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PHARMACEUTICAL COMPOSITIONS CONTAINING IRBESARTAN

The present invention relates to pharmaceutical compositions containing irbesartan, preferably in the form of a tablet. The present invention also relates to tablets prepared from these compositions.

Irbesartan, 2-n-butyl-4-spirocyclopentane-1-[(2'-(tetrazol-5-yl)biphenyl-4-yl)methyl]-2-imidazolin-5-one, is a potent, long-acting angiotensin II receptor antagonist which is particularly useful in the treatment of cardiovascular ailments such as hypertension and heart failure. Irbesartan has the following structure:

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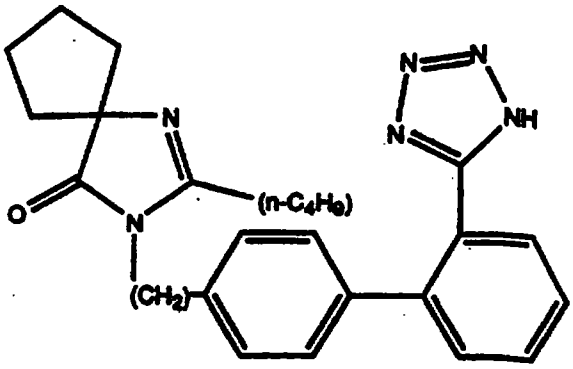
ACTION



and is described in Bernhart et al., U.S. Patent No. 5,270,317, incorporated herein by reference.

Preferred pharmaceutical compositions of this drug contain, as active ingredient(s), irbesartan alone or in combination with a diuretic such as hydrochlorothiazide.

Irbesartan may be administered in dosages containing a substantial quantity of the active agent (e.g., 75 - 300 mg). Certain physical properties of the drug present a challenge in developing formulations suitable for preparing a tablet having both a substantial quantity of active agent and a small enough tablet mass to allow ease of swallowing.

Irbesartan is, for example, a fluffy material, with relatively low bulk and tap densities. These properties make it difficult to formulate a large amount of the drug into a small tablet with uniformity of weight, hardness, and other desirable tablet properties. In addition, irbesartan has certain undesirable flow characteristics, for example, is sticky and can adhere to surfaces such as tablet punch faces and dies, causing problems in tableting, especially on a high speed tablet press. The low aqueous solubility of irbesartan also

presents a challenge, since, to keep the tablet mass small, only limited amounts of excipients may be added to facilitate wetting, disintegration, and ultimately, rapid and complete drug release. The addition of a diuretic such as hydrochlorothiazide, which is also a fluffy material exhibiting poor flow and low aqueous solubility, can further contribute to tableting problems.

Thus, there is a need in the art for pharmaceutical compositions containing irbesartan, alone or in combination with a diuretic, which have good properties for tablet formation, and yet which contain a low mass of excipients so that small, easily swallowed tablets with a high content of active agent may be prepared.

The present invention provides pharmaceutical compositions containing irbesartan, alone or in combination with a diuretic, which (1) have a minimal mass of added excipients, thereby allowing preparation of small, easily swallowed tablets which enhance patient acceptance and compliance, and yet which (2) have excellent properties for tablet formation, and (3) provide tablets with excellent wetting, disintegration, and ultimately, rapid and complete drug release properties.

In particular, the present invention provides pharmaceutical compositions, especially suitable for forming tablets, comprising from about 20 to about 70% by weight irbesartan or pharmaceutically acceptable salts thereof, and pharmaceutically acceptable excipients, wherein a tablet formed from said composition has a dissolution performance such

that about 80% or greater, preferably 85% or greater, of the irbesartan or salts thereof contained in said tablet dissolve within 30 minutes. The present compositions optionally also comprise from about 2 to about 33% diuretic, wherein the combined amount of irbesartan and diuretic does not exceed about 85%.

Preferred compositions containing irbesartan comprise, based on a total of 100% by weight: (a) from about 20 to about 70% (preferably, about 50%) irbesartan, (b) from about 1 to about 70% diluent, (c) from about 2 to about 20% binder, (d) from about 1 to about 10% disintegrant, (e) from about 0.1 to about 5% antiadherent, and (f) from about 0.2 to about 5% lubricant, and, optionally (g) from about 0.2 to about 6% surfactant, and/or (h) up to about 2% (preferably, from about 0.1 to about 1%) coloring agent.

Preferred compositions containing irbesartan and diuretic comprise, based on a total of 100% by weight: (a) from about 20 to about 70% (preferably, about 50%) irbesartan, (b) from about 2 to about 33% diuretic, wherein the combined loading of (a) and (b) does not exceed about 85%, (c) from about 1 to about 70% diluent, (d) from about 2 to about 20% binder, (e) from about 1 to about 10% disintegrant, (f) from about 0.1 to about 5% antiadherent, and (g) from about 0.2 to about 5% lubricant, and, optionally, (h) up to about 2% (preferably, from about 0.1 to about 1%) coloring agent.

The present compositions may contain up to about 70% w/w irbesartan, or up to about 85% w/w irbesartan and diuretic, and yet can be employed in the reproducible manufacture of tablets on a large scale. The present compositions can, for example, be

compressed on high speed tableting equipment (especially, a high speed tablet press) to form tablets which are uniform in both weight and content and which exhibit desirable physical properties, including elegant appearance, low friability, and fast disintegration time. Tablets prepared from the present compositions are capable of releasing the active component(s), by dissolution, in a fast and reproducible manner.

Unless otherwise indicated, mention of irbesartan herein also includes pharmaceutically acceptable salts thereof.

The present invention is described in further detail as follows. The components employed in the compositions of the present invention should be pharmaceutically acceptable, particularly as described in the National Formulary (NF) or United States Pharmacopeia (USP).

The "dissolution performance" of a tablet, as used herein with respect to irbesartan, refers to the weight % of irbesartan, based on the total weight of irbesartan contained in the tablet, which dissolves within 30 minutes under the following conditions: using a tablet having a total weight of from 150 to 600 mg and a USP Apparatus 2, placing the tablet in 1000 mL of 0.1 N hydrochloric acid at 37°C, with a paddle speed of 50 rpm, and measuring the amount of irbesartan dissolved (especially, using UV at 244 nm or, when hydrochlorothiazide is also present, using HPLC, wavelength 272 nm) at 30 minutes. (If desired, the progress of dissolution may also be monitored at various time points.)

The "dissolution performance" of a tablet, as used herein with respect to a diuretic (preferably, hydrochlorothiazide), refers to the weight % of diuretic, based on the total weight of diuretic contained in the tablet, which dissolves within 30 minutes under the conditions described above for irbesartan dissolution. The dissolution performance for the diuretic preferably meets the USP dissolution specification for the diuretic (for hydrochlorothiazide, greater than 60% dissolution at 30 minutes). The dissolution performance of a tablet containing hydrochlorothiazide is most preferably such that about 90% or greater of the hydrochlorothiazide is dissolved at 30 minutes.

The "diuretic" employed in a composition of the present invention may be any suitable diuretic, or combination of two or more diuretics, such as hydrochlorothiazide, bendroflumethiazide, benzthiazide, chlorothiazide, chlorthalidone, cyclothiazide, hydroflumethiazide, methyclothiazide, metolazone, polythiazide, quinethazone, and trichlormethiazide. Preferably, the diuretic is hydrochlorothiazide.

The "diluent" employed in a composition of the present invention may be one or more compounds which are capable of providing bulk to obtain a desired tablet mass. It is desirable to employ the diluent in an amount at the lower end of the weight range for the diluent. Preferred diluents are inorganic phosphates such as dibasic calcium phosphate; sugars such as lactose hydrous or lactose anhydrous; and cellulose or cellulose derivatives such as microcrystalline cellulose.

The "binder" employed in a composition of the present invention may be one or more compounds which are capable of facilitating granulation of the irbesartan and/or diuretic into larger, denser, and/or more free-flowing particles. Preferred binders are alginic acid (most preferably employed in the range of 2 - 5% by weight) or sodium alginate (most preferably employed in the range of 2 - 3% by weight); cellulose or cellulose derivatives such as carboxymethylcellulose sodium (most preferably employed in the range of 2 - 6% by weight), ethylcellulose (most preferably employed in the range of 2 - 3% by weight), hydroxyethyl cellulose (most preferably employed in the range of 2 - 5% by weight), hydroxypropyl cellulose (most preferably employed in the range of 2 - 6% by weight), hydroxypropyl methylcellulose (most preferably employed in the range of 2 - 5% by weight), or methylcellulose (most preferably employed in the range of 2 - 6% by weight); gelatin (most preferably employed in the range of 2 - 10% by weight); povidone (polyvinylpyrrolidone, i.e., 1-ethenyl-2-pyrrolidinone homopolymer) (e.g., povidone K-30) (most preferably employed in the range of 2 - 20% by weight); or starch (most preferably employed in the range of 5 - 20% by weight) or pregelatinized starch (most preferably employed in the range of 2 - 20, such as 5 - 20% by weight).

The "disintegrant" employed in a composition of the present invention may be one or more compounds which are capable of facilitating the break up of a tablet prepared from the composition when placed in contact with an aqueous medium. Preferred disintegrants are alginic acid (most preferably

employed in the range of 2 - 5% by weight) or sodium alginate (most preferably employed in the range of 2.5 - 10% by weight); cellulose or cellulose derivatives such as carboxymethylcellulose sodium (most preferably employed in the range of 2 - 6% by weight), microcrystalline cellulose (most preferably employed in the range of 5 - 15% by weight), powdered cellulose (most preferably employed in the range of 5 - 15% by weight), or croscarmellose sodium (cross-linked polymer of carboxymethylcellulose sodium) (most preferably employed in the range of 2 - 5% by weight); crospovidone (cross-linked homopolymer of N-vinyl-2-pyrrolidinone, i.e., cross-linked 1-ethenyl-2-pyrrolidinone) (most preferably employed in the range of 2 - 5% by weight); pregelatinized starch (most preferably employed in the range of 5 - 10% by weight), sodium starch glycolate (most preferably employed in the range of 2 - 8% by weight), or starch (most preferably employed in the range of 3 - 15% by weight).

The "antiadherent" employed in a composition of the present invention may be one or more compounds which are capable of reducing the stickiness of the formulation, for example, preventing adherence to metal surfaces. Preferred antiadherents are silicon-containing compounds such as silicon dioxide (most preferably employed in the range of 0.25 - 5% (such as 0.5 - 2 or 2.5 to 3.0%) by weight), magnesium trisilicate (most preferably employed in the range of 0.5 - 2% by weight), or talc (most preferably employed in the range of 1 - 5% by weight).

The "lubricant" employed in a composition of the present invention may be one or more compounds which are capable of preventing tableting problems.

such as those relating to the release of a tablet prepared from the composition from the apparatus on which it is formed, for example, preventing adherence to the face of the upper punch (picking) or lower punch (sticking) of a tableting apparatus. Preferred lubricants are fatty acids or fatty acid derivatives such as calcium stearate (most preferably employed in the range of 0.5 - 2% by weight), glyceryl monostearate (most preferably employed in the range of 0.5 - 2% by weight), glyceryl palmitostearate (most preferably employed in the range of 0.5 - 2% by weight), magnesium stearate (most preferably employed in the range of 0.2 - 2% by weight), sodium lauryl sulfate (most preferably employed in the range of 1 - 2% by weight), sodium stearyl fumarate (most preferably employed in the range of 0.5 - 2% by weight), zinc stearate (most preferably employed in the range of 0.5 - 1.5% by weight) or stearic acid (most preferably employed in the range of 1 - 3% by weight); hydrogenated vegetable oil (most preferably employed in the range of 1 - 5% by weight); polyalkylene glycols such as polyethylene glycol (most preferably employed in the range of 1 - 5% by weight); sodium benzoate (most preferably employed in the range of 2 - 5% by weight); or talc (most preferably employed in the range of 1 - 5% by weight).

The "surfactant" employed in a composition of the present invention may be one or more compounds which are capable of improving the wetting of the tablets and/or enhancing dissolution. Preferred surfactants are sodium lauryl sulfate (most preferably employed in the range of 0.2 - 6% by weight), and poly(oxyethylene),poly(oxypropylene)

block co-polymers such as poloxamers, especially poloxamer 188 (most preferably employed in the range of 1 - 6% by weight).

The "coloring agent" (or "colorant") employed in a composition of the present invention may be one or more compounds which impart a desired color to a tablet prepared from the composition. Addition of a coloring agent may be used, for example, so that tablets of different potencies may be easily distinguished. Preferred coloring agents are ferric oxides, which are universally accepted.

As can be seen from the above, a single compound may perform two or more functions. Calculation of weight percent is preferably on the basis of the primary function of a compound in a given composition. The present compositions preferably consist essentially of, most preferably, consist of the above-described components.

Preferred Compositions

Preferred compositions of the present invention contain one or more of the following components in the indicated concentration range (% by weight): irbesartan, 20 to 60 (e.g., 25 to 60), such as 30 to 60, most preferably, 30 to 50, especially about 50%; diuretic, 2 to 20, most preferably 2 to 17, especially 4 to 9%; diluent, 1 to 70, most preferably 1 to 60, especially 1 to 40%; binder, 5 to 20, most preferably 5 to 15%; disintegrant, 4 to 8, most preferably about 5%; antiadherent, 0.25 to 5.0% (such as 0.25 to 1.5, most preferably 0.7 to 0.8%, for example, when a diuretic is present or 2.5 to 3.0%, for example, when a diuretic is not present);

lubricant, 0.5 to 1.5, most preferably about 1%; and surfactant, 1 to 3, most preferably, about 3%.

The following tables recite preferred compositions of the present invention which produce tablets of especially high quality and superior performance. Table A recites preferred compositions containing irbesartan; Table B recites preferred compositions containing irbesartan in combination with a diuretic.

TABLE A

IRBESARTAN

Preferred Ingredient	Component	Concentration Range (% w/w)
irbesartan	active drug	20 - 50
lactose hydrous	diluent	1 - 70
microcrystalline cellulose (e.g., Avicel® PH 102+)	diluent	5 - 20
pregelatinized starch (e.g., Starch® 1500+)	binder	10 - 20
croscarmellose sodium (e.g., Ac-Di-Sol®+)	disintegrant	4 - 8
poloxamer,* especially poloxamer 188 (e.g., Pluronic® F68+)	surfactant	1 - 6
silicon dioxide (e.g., Syloid® 244+)	antiadherent	0.25 - 5.0 (0.25 to 1.5 or, especially, 2.5 to 3.0)
magnesium stearate	lubricant	0.5 - 1.5
TOTAL		100

* Optional, but preferred, component.

\+ These exemplary compounds may be used as desired throughout this specification as appropriate. For example, Starch® 1500 may be used as desired wherever pregelatinized starch appears in this specification.

In the above compositions of Table A, the combination of magnesium stearate and silicon dioxide provides a superior lubrication effect while

minimizing any decline in tablet dissolution performance; the intragranular:extragranular placement ratio of the disintegrant croscarmellose sodium is superior (e.g., 1:1); and the poloxamer surfactant improves the aqueous granulation of irbesartan (which is hydrophobic), eases the ejection of tablets after compression and accelerates the dissolution of the irbesartan active agent.

TABLE B

IRBESARTAN IN COMBINATION WITH DIURETIC

Preferred Ingredient	Component	Concentration Range (% w/w)
irbesartan	active drug	20 - 50
hydrochlorothiazide	diuretic, active drug	2 - 20*
lactose hydrous	diluent	1 - 70
microcrystalline cellulose (e.g., Avicel® PH 102)	diluent	10 - 20
croscarmellose sodium (e.g., Ac-Di-Sol®)	disintegrant	4 - 6
pregelatinized starch (e.g., Starch® 1500)	binder	10 - 20
silicon dioxide (e.g., Syloid® 244)	antiadherent	0.5 - 1.0
magnesium stearate	lubricant	0.5 - 1.5
TOTAL		100

* The concentration of hydrochlorothiazide can vary according to the hydrochlorothiazide potency sought in the combination tablet, which preferably ranges from 6.25 mg to 25 mg per tablet.

The compositions of Tables A and B preferably also contain 0.08 to 0.12% by weight ferric oxide, red and 0.08 to 0.12% by weight ferric oxide, yellow as a colorant.

Methods of Manufacture

Tablets may be prepared from the present compositions by any suitable method for forming tablets. Preferably, tablets are prepared from the present compositions by a wet granulation process. An exemplary such method comprises the following steps:

(a) preparing an intragranular composition by:

(i) mixing the irbesartan, diuretic (for combined tablets), a portion of the diluent (preferably, from about 5 to about 80% by weight of the total diluent), a portion of the disintegrant (preferably, from about 50 to about 80% by weight of the total disintegrant), the binder, and, optionally, a portion of the antiadherent (preferably, from about 50 to about 80% by weight of the total antiadherent), to form a powder blend and, optionally, sizing the blend (e.g., milling the blend to break up aggregates);

(ii) re-mixing the blend;

(iii) granulating the blend with a granulating fluid, preferably water and/or an aqueous solution of the surfactant, to form granules (e.g., using a high shear mixer/granulator);

(iv) drying the granules (e.g., in an oven or, preferably, in a fluid bed dryer); and

(v) sizing the dried granules (e.g., by milling or screening);

(b) preparing a mixture of the sized granules of step (a)(v) with an extragranular composition by:

(i) mixing the remainder of the diluent, the remainder of the disintegrant, the antiadherent or the remainder of the antiadherent, and, optionally, the coloring agent, where one or more of these may be pre-blended, sized (e.g., milled to break up aggregates) and re-mixed prior to this step, with the sized granules from step (a)(v) to form a granule blend; and

(ii) mixing the lubricant with the granule blend; and

(c) compressing the mixture from step (b)(ii) to form tablets (for example, employing a tablet press).

The solid starting materials of the present compositions are preferably screened prior to use. The weight ratio of water (preferably, purified water, USP or water for injection, USP) to solids employed in step (a)(iii) is preferably within the range of from about 0.25:1 to about 0.6:1.

The tablets may, optionally, be finished or coated such as by methods known in the art.

The tablets prepared from the compositions of the present invention preferably contain (per tablet) from about 25 to about 300 mg of irbesartan, most preferably from about 75 to 300 mg of irbesartan and, for the combined tablets, an additional amount of from about 1 to about 25 mg of diuretic, most preferably from about 6.25 to about 25 mg of hydrochlorothiazide. The total weight of the tablets prepared is preferably from about 50 to about 600 mg. In addition to tablets, the compositions of the present invention may be used to prepare beads,

granules for dispersion or capsules, the latter, for example, filled with powder or the aforementioned beads or granules. Methods such as those well known in the art may be used to prepare these dosage forms.

The compositions and tablets of the present invention may be used to treat or prevent disorders such as those described in U.S. Patent No. 5,270,317, incorporated herein by reference. Such disorders include cardiovascular disorders, for example, hypertension or heart failure, venous insufficiency, as well as glaucoma, diabetic retinopathy, renal insufficiency and various complaints of the central nervous system. The present compositions or tablets are preferably administered orally, in an effective amount, to a mammalian (especially, human) subject to treat or prevent the aforementioned disorders. For human subjects, preferred dosages of from about 75 mg to about 300 mg of irbesartan (alone or in combination with a diuretic) may be administered, for example, 1 to 2 times per day.

The following Examples are provided to illustrate preferred embodiments of the invention, and are not intended to limit the scope of the present claims.

EXAMPLE 1

PREPARATION OF TABLETS CONTAINING IRBESARTAN

Tablets containing irbesartan were prepared in three potencies from the composition of the present invention described in the following Table 1: (1) 75 mg irbesartan with a total weight of 150 mg per tablet; (2) 150 mg irbesartan with a total weight of 300 mg per tablet; and (3) 300 mg irbesartan with a total weight of 600 mg per tablet.

TABLE 1

Ingredient	Component	Concentration (% w/w)
INTRAGRANULAR		
irbesartan	active drug	50
lactose hydrous, NF	diluent	10.25
pregelatinized starch, NF	binder	15.0
croscarmellose sodium, NF	disintegrant	2.5
poloxamer 188, NF	surfactant	3.0
EXTRAGRANULAR		
microcrystalline cellulose, NF	diluent	15.0
croscarmellose sodium, NF	disintegrant	2.5
silicon dioxide, NF	antiadherent	0.75
magnesium stearate, USP	lubricant	1.0
TOTAL	100.00	100.00

Using the above formulation, the tablets were prepared by a wet granulation process as follows. In this process, the total amount of water employed (by weight) was up to 50% of the total solids weight.

The irbesartan, lactose, pregelatinized starch, and a portion (1/2) of the croscarmellose sodium were mixed in a mixer. The powder blend prepared was passed through sizing equipment (cone mill or oscillator), and mixed in a mixer. The poloxamer 188 was dissolved in water (purified, USP or water for injection, USP) (25% of the weight of total solids), and used to wet granulate (with the further addition of water in an amount which was up to 25% of the weight of total solids as needed) the mixed powder. The granules obtained were dried (tray or fluid bed dryer) until the loss-on-drying (LOD) was 2% or less. The dried granules were passed through a screen or milled to obtain the proper size (1 to 3 mm).

The sized granules were mixed with the silicon dioxide, the microcrystalline cellulose and the remaining croscarmellose sodium in a mixer. The blend obtained was then mixed with the magnesium stearate. By compressing the mixture using tableting equipment, tablets were prepared for each potency having the compositions indicated in the following Table 2.

TABLE 2

Ingredient	75 mg Potency (mg)	150 mg Potency (mg)	300 mg Potency (mg)
irbesartan	75.00	150.00	300.00
lactose hydrous, NF	15.38	30.75	61.50
microcrystalline cellulose, NF	22.50	45.00	90.00
pregelatinized starch, NF	22.50	45.00	90.00
croscarmellose sodium, NF	7.50	15.00	30.00
poloxamer 188, NF (or Pluronic F68, NF)	4.50	9.00	18.00
silicon dioxide, NF	1.12	2.25	4.50
magnesium stearate, USP	1.50	3.00	6.00
Tablet Weight	150.00	300.00	600.00

EXAMPLE 2

PREPARATION OF TABLETS CONTAINING IRBESARTAN: ALTERNATIVE FORMULATION

Tablets were prepared having the composition of the following Table 3 by a method analogous to that of Example 1.

TABLE 3

Ingredient	Amount mg/tablet (% w/w)
INTRAGRANULAR	
irbesartan	300.0 (50)
lactose hydrous, NF (diluent)	121.5 (20.25)
povidone K-30, USP (binder)	30.0 (5)
croscarmellose sodium (disintegrant)	24.0 (4)
Pluronic F68, NF (poloxamer, surfactant)	18.0 (3)
EXTRAGRANULAR	
microcrystalline cellulose, NF (diluent)	90.0 (15)
croscarmellose sodium (disintegrant)	6.0 (1)
silicon dioxide, NF (antiadherent)	4.5 (0.75)
magnesium stearate (lubricant)	6 (1)
TOTAL WEIGHT	600.00 (100)

EXAMPLE 3

PREPARATION OF COMBINATION TABLETS: IRBESARTAN AND HYDROCHLOROTHIAZIDE

Tablets containing a combination of irbesartan and hydrochlorothiazide were prepared in two potencies from the composition of the present invention described in the following Table 4: (1) 75

mg irbesartan/12.5 mg hydrochlorothiazide with a total weight of 150 mg per tablet; and (2) 150 mg irbesartan/12.5 mg hydrochlorothiazide with a total weight of 300 mg per tablet.

TABLE 4

Ingredient	Amount (% w/w) in 75 mg/12.5 mg Tablets	Amount (% w/w) in 150 mg/12.5 mg Tablets
INTRAGRANULAR		
irbesartan	50.00	50.00
hydrochlorothiazide, USP	8.33	4.17
lactose hydrous NF (diluent)	4.72	8.88
pregelatinized starch, NF (binder)	15.00	15.00
croscarmellose sodium, NF (disintegrant)	4.00	4.00
EXTRAGRANULAR		
microcrystalline cellulose, NF (diluent)	15.00	15.00
croscarmellose sodium, NF (disintegrant)	1.00	1.00
silicon dioxide, NF (antiadherent)	0.75	0.75
ferric oxide, NF, red (colorant)	0.10	0.10
ferric oxide, NF, yellow (colorant)	0.10	0.10
magnesium stearate, NF (lubricant)	1.00	1.00
TOTAL	100.00	100.00

Tablets having the above compositions were prepared using a wet granulation process as follows. The irbesartan and hydrochlorothiazide drug substances, the lactose hydrous, the pregelatinized starch, and a portion (4/5 of the total amount) of the croscarmellose sodium were weighed out and mixed. This powder blend was then milled to break up aggregates of the drug(s). The milled powder blend was then mixed again, followed by granulation with water (in an amount which was about 55% of the weight of total solids), in a mixer/granulator. The wet granules were then dried in drying equipment (tray or fluid bed dryer) until the LOD was 2% or less, followed by milling of the dried granules.

A color blend was made by mixing the ferric oxides with a portion (1/3 of the total amount) of the microcrystalline cellulose, milling the color blend, then mixing again. The remaining microcrystalline cellulose, the remaining croscarmellose sodium, the color blend, and the silicon dioxide were then weighed, screened, and mixed in a mixer with the dried, milled granules. In a final step, the magnesium stearate was weighed, screened and mixed with the above granule blend. This final blend was then compressed into tablets using a suitable tablet press.

Tablets Prepared

For the irbesartan/hydrochlorothiazide 75 mg/12.5 mg tablets, the tablet weight was 150 mg and the tablet hardness was 10 - 14 SCU (Strong Cobb Units). For the 150 mg/12.5 mg potency tablets, the tablet weight was 300 mg and the tablet hardness was 14 - 18 SCU. For both potency tablets, the

friability was less than 0.5%, the disintegration time was under 7 minutes, and the coefficient of variation for tablet weight was under 2%. In addition, the dissolution of these tablets meets the specification for irbesartan dissolution of 85% or greater in 30 minutes and easily meets the USP dissolution specification for hydrochlorothiazide of 60% in 30 minutes.

The tablets of this formulation were found to have good stability. Under certain conditions, hydrochlorothiazide can hydrolyze to form, as by-products, a free amine degradant and formaldehyde (D.S. Desai et al., *International Journal of Pharmaceutics*, 107(2), 141-47 (1994)). The selection of excipients can impact the stability of hydrochlorothiazide. The use of pregelatinized starch as a binder in the present compositions was found to impart greater stability to hydrochlorothiazide than, for example, povidone (which resulted in the formation of quantities of the free amine degradant). Poloxamer was also found to increase the degradation of hydrochlorothiazide, and therefore, while employed as a preferred component in compositions without hydrochlorothiazide, poloxamer is not a preferred component for the irbesartan/hydrochlorothiazide compositions of the present invention. The aforementioned preferred compositions of the present invention containing irbesartan and hydrochlorothiazide are thus further advantageous since the excipients employed therein minimize or eliminate hydrochlorothiazide degradation.

EXAMPLE 4

PREPARATION OF COMBINATION TABLETS: IRBESARTAN AND HYDROCHLOROTHIAZIDE: ALTERNATIVE FORMULATIONS

Tablets were prepared having the compositions 4(A), 4(B), 4(C) or 4(D) of the following Table 5 by methods analogous to those of Example 3.

TABLE 5

Ingredient	4(A) mg per tablet (% w/w)	4(B) mg per tablet (% w/w)	4(C) mg per tablet (% w/w)	4(D) mg per tablet (% w/w)
INTRAGRANULAR				
irbesartan (active drug)	75.0 (50)	75.0 (50)	150.0 (50)	150.0 (50)
hydrochlorothiazide (diuretic, active drug)	12.5 (8.33)	12.5 (8.33)	12.5 (4.17)	12.5 (4.17)
lactose hydrous, NF (diluent)	2.575 (1.72)	17.575 (11.72)	17.65 (5.88)	47.65 (15.88)
pregelatinized starch, NF (binder)	22.5 (15)	---	45.0 (15)	---
povidone K-30, USP (binder)	---	7.5 (5)	---	15.0 (5)
croscarmellose sodium (disintegrant)	6.0 (4)	6.0 (4)	12.0 (4)	12.0 (4)
Pluronic F68, NF (poloxamer, surfactant)	4.5 (3)	4.5 (3)	9.0 (3)	9.0 (3)
EXTRAGRANULAR				
microcrystalline cellulose, NF (diluent)	22.5 (15)	22.5 (15)	45.0 (15)	45.0 (15)
croscarmellose sodium (disintegrant)	1.5 (1)	1.5 (1)	3.0 (1)	3.0 (1)
ferric oxide, NF red (colorant)	0.15 (0.1)	0.15 (0.1)	0.3 (0.1)	0.3 (0.1)
ferric oxide, NF yellow (colorant)	0.15 (0.1)	0.15 (0.1)	0.3 (0.1)	0.3 (0.1)
silicon dioxide (antiadherent)	1.125 (0.75)	1.125 (0.75)	2.25 (0.75)	2.25 (0.75)

magnesium stearate (lubricant)	1.5 (1)	1.5 (1)	3.0 (1)	3.0 (1)
TOTAL WEIGHT	150.0 (100)	150.0 (100)	300.0 (100)	300.0 (100)

EXAMPLE 5
PREPARATION OF TABLETS CONTAINING IRBESARTAN

Tablets containing irbesartan were prepared in three potencies from the composition of the present invention described in the following Table 6: (1) 75 mg irbesartan with a total weight of 150 mg per tablet; (2) 150 mg irbesartan with a total weight of 300 mg per tablet; and (3) 300 mg irbesartan with a total weight of 600 mg per tablet.

TABLE 6

Ingredient	Component	Concentration (% w/w)
INTRAGRANULAR		
irbesartan	active drug	50
lactose hydrous, NF	diluent	10.25
pregelatinized starch, NF	binder	15.0
croscarmellose sodium, NF	disintegrant	2.5
poloxamer 188, NF	surfactant	3.0
silicon dioxide, NF	antiadherent	2.0
EXTRAGRANULAR		
microcrystalline cellulose, NF	diluent	13.0
croscarmellose sodium, NF	disintegrant	2.5
silicon dioxide, NF	antiadherent	0.75
magnesium stearate, USP	lubricant	1.0
TOTAL	100.00	100.00

Using the above formulation, the tablets were prepared by a wet granulation process as follows. In this process, the total amount of water employed (by weight) was up to 50% of the total solids weight.

The irbesartan, lactose, pregelatinized starch, a portion (1/2) of the croscarmellose sodium, and a portion (about 73%) of the silicon dioxide were mixed in a mixer. The powder blend prepared was passed through sizing equipment (cone mill or oscillator), and mixed in a mixer. The poloxamer 188 was dissolved in water (purified, USP or water for injection, USP) (25% of the weight of total solids), and used to wet granulate (with the further addition of water in an amount which was up to 25% of the weight of total solids as needed) the mixed powder. The granules obtained were dried (tray or fluid bed dryer) until the loss-on-drying (LOD) was 2% or less. The dried granules were passed through a screen or milled to obtain the proper size (1 to 3 mm).

The sized granules were mixed with the remaining silicon dioxide, the microcrystalline cellulose and the remaining croscarmellose sodium in a mixer. The blend obtained was then mixed with the magnesium stearate. By compressing the mixture using tableting equipment, tablets were prepared for each potency having the compositions indicated in the following Table 7.

TABLE 7

Ingredient	75 mg Potency (mg)	150 mg Potency (mg)	300 mg Potency (mg)
irbesartan	75.00	150.00	300.00
lactose hydrous, NF	15.38	30.75	61.50
microcrystalline cellulose, NF	19.50	39.00	78.00
pregelatinized starch, NF	22.50	45.00	90.00
croscarmellose sodium, NF	7.50	15.00	30.00
poloxamer 188, NF (or Pluronic F68, NF)	4.50	9.00	18.00
silicon dioxide, NF	4.12	8.25	16.50
magnesium stearate, USP	1.50	3.00	6.00
Tablet Weight	150.00	300.00	600.00

Tablets comprising irbesartan or a pharmaceutically acceptable salt thereof, prepared (such as is described herein) by mixing an extragranular composition with granules comprising an antiadherent (preferably, silicon dioxide), may dissolve more rapidly and/or completely, and thus may exhibit an improved dissolution performance.

EXAMPLE 6
PREPARATION OF TABLETS CONTAINING IRBESARTAN: ALTERNATIVE FORMULATION

Tablets were prepared having the composition of the following Table 8 by a method analogous to that of Example 5.

TABLE 8

Ingredient	Amount mg/tablet (% w/w)
INTRAGRANULAR	
irbesartan	300.0 (50)
lactose hydrous, NF (diluent)	121.5 (20.25)
povidone K-30, USP (binder)	30.0 (5)
croscarmellose sodium (disintegrant)	24.0 (4)
Pluronic F68, NF (poloxamer, surfactant)	18.0 (3)
silicon dioxide, NF (antiadherent)	12.0 (2)
EXTRAGRANULAR	
microcrystalline cellulose, NF (diluent)	78.0 (13)
croscarmellose sodium (disintegrant)	6.0 (1)
silicon dioxide, NF (antiadherent)	4.5 (0.75)
magnesium stearate (lubricant)	6 (1)
TOTAL WEIGHT	600.00 (100)

What we claim is:

1. A pharmaceutical composition, wherein said composition comprises from about 20 to about 70% by weight irbesartan or a pharmaceutically acceptable salt thereof, and one or more pharmaceutically acceptable excipients, wherein a tablet formed from said composition has a dissolution performance such that about 80% or greater of the irbesartan or salt thereof contained in said tablet dissolves within 30 minutes.

2. The pharmaceutical composition of claim 1, wherein a tablet formed from said composition has a dissolution performance such that about 85% or greater of the irbesartan or salt thereof contained in said tablet dissolves within 30 minutes.

3. A pharmaceutical composition of claim 1 comprising, based on weight: (a) from about 20 to about 70% irbesartan, (b) from about 1 to about 70% diluent, (c) from about 2 to about 20% binder, (d) from about 1 to about 10% disintegrant, (e) from about 0.1 to about 5% antiadherent, and (f) from about 0.2 to about 5% lubricant, and, optionally (g) from about 0.2 to about 6% surfactant, and/or (h) up to about 2% coloring agent.

4. A pharmaceutical composition of claim 3, wherein

the diluent is one or more compounds selected from the group consisting of dibasic calcium phosphate, lactose hydrous, lactose anhydrous, and microcrystalline cellulose;

the binder is one or more compounds selected from the group consisting of alginic acid, sodium alginate, carboxymethylcellulose sodium, ethylcellulose, hydroxyethyl cellulose, hydroxypropyl cellulose, hydroxypropyl methylcellulose, methylcellulose, gelatin, povidone, starch and pregelatinized starch;

the disintegrant is one or more compounds selected from the group consisting of alginic acid, sodium alginate, carboxymethylcellulose sodium, microcrystalline cellulose, powdered cellulose, croscarmellose sodium, crospovidone, pregelatinized starch, sodium starch glycolate, and starch;

the antiadherent is one or more compounds selected from the group consisting of silicon dioxide, magnesium trisilicate, and talc;

the lubricant is one or more compounds selected from the group consisting of calcium stearate, glyceryl monostearate, glyceryl palmitostearate, magnesium stearate, sodium lauryl sulfate, sodium stearyl fumarate, zinc stearate, stearic acid, hydrogenated vegetable oil, polyethylene glycol, sodium benzoate, and talc;

when present, the surfactant is one or more compounds selected from the group consisting of sodium lauryl sulfate, and poloxamers; and

when present, the coloring agent is one or more ferric oxides.

5. A pharmaceutical composition of claim 3, comprising, based on weight, about 20 to 50% irbesartan; about 1 to 70% diluent; about 10 to 20% binder; about 4 to 8% disintegrant; about 0.25 to

5.0% antiadherent; about 0.5 to 1.5% lubricant; and about 1 to 6% surfactant.

6. The pharmaceutical composition of claim 5, wherein said diluent is lactose hydrous and microcrystalline cellulose; said binder is pregelatinized starch; said disintegrant is croscarmellose sodium; said antiadherent is silicon dioxide; said lubricant is magnesium stearate; and said surfactant is poloxamer 188.

7. A pharmaceutical composition of claim 1, comprising, based on weight, about 50% irbesartan; about 10.25% lactose hydrous; about 15.0% pregelatinized starch; about 5.0% croscarmellose sodium; about 3.0% poloxamer 188; about 15% microcrystalline cellulose; about 0.75% silicon dioxide; and about 1.0% magnesium stearate.

8. A pharmaceutical composition of claim 1, comprising, based on weight, about 50% irbesartan; about 10.25% lactose hydrous; about 15.0% pregelatinized starch; about 5.0% croscarmellose sodium; about 3.0% poloxamer 188; about 13% microcrystalline cellulose; about 2.75% silicon dioxide; and about 1.0% magnesium stearate.

9. A pharmaceutical composition of claim 1, comprising, based on weight, about 50% irbesartan; about 20.25% lactose hydrous; about 5.0% povidone K-30; about 5.0% croscarmellose sodium; about 3.0% poloxamer; about 15% microcrystalline cellulose; about 0.75% silicon dioxide; and about 1.0% magnesium stearate.

10. A pharmaceutical composition of claim 1, comprising, based on weight, about 50% irbesartan; about 20.25% lactose hydrous; about 5.0% povidone K-30; about 5.0% croscarmellose sodium; about 3.0% poloxamer; about 13% microcrystalline cellulose; about 2.75% silicon dioxide; and about 1.0% magnesium stearate.

11. A pharmaceutical composition of claim 1, further comprising about 2 to about 33% diuretic, wherein the total weight % of irbesartan or salt thereof and diuretic does not exceed about 85%.

12. A pharmaceutical composition of claim 11, wherein said diuretic is one or more compounds selected from the group consisting of hydrochlorothiazide, bendroflumethiazide, benzthiazide, chlorothiazide, chlorthalidone, cyclothiazide, hydroflumethiazide, methyclothiazide, metolazone, polythiazide, quinethazone, and trichlormethiazide.

13. A pharmaceutical composition of claim 12, wherein said diuretic is hydrochlorothiazide.

14. A pharmaceutical composition of claim 11 comprising, based on weight: (a) from about 20 to about 70% irbesartan, (b) from about 2 to about 33% diuretic, wherein the combined loading of (a) and (b) does not exceed about 85%, (c) from about 1 to about 70% diluent, (d) from about 2 to about 20% binder, (e) from about 1 to about 10% disintegrant, (f) from about 0.1 to about 5% antiadherent, and (g) from

about 0.2 to about 5% lubricant, and, optionally (h) up to about 2% coloring agent.

15. A pharmaceutical composition of claim 14, wherein

the diuretic is hydrochlorothiazide;

the diluent is one or more compounds selected from the group consisting of dibasic calcium phosphate, lactose hydrous, lactose anhydrous, and microcrystalline cellulose;

the binder is one or more compounds selected from the group consisting of alginic acid, sodium alginate, carboxymethylcellulose sodium, ethylcellulose, hydroxyethyl cellulose, hydroxypropyl cellulose, hydroxypropyl methylcellulose, methylcellulose, gelatin, povidone, starch and pregelatinized starch;

the disintegrant is one or more compounds selected from the group consisting of alginic acid, sodium alginate, carboxymethylcellulose sodium, microcrystalline cellulose, powdered cellulose, croscarmellose sodium, crospovidone, pregelatinized starch, sodium starch glycolate, and starch;

the antiadherent is one or more compounds selected from the group consisting of silicon dioxide, magnesium trisilicate, and talc;

the lubricant is one or more compounds selected from the group consisting of calcium stearate, glyceryl monostearate, glyceryl palmitostearate, magnesium stearate, sodium lauryl sulfate, sodium stearyl fumarate, zinc stearate, stearic acid, hydrogenated vegetable oil, polyethylene glycol, sodium benzoate, and talc; and

when present, the coloring agent is one or more ferric oxides.

16. A pharmaceutical composition of claim 14, comprising, based on weight, about 20 to 50% irbesartan; about 2 to 20% diuretic; about 1 to 70% diluent; about 10 to 20% binder; about 4 to 6% disintegrant; about 0.5 to 1.0% antiadherent; and about 0.5 to 1.5% lubricant.

17. The pharmaceutical composition of claim 16, wherein said diuretic is hydrochlorothiazide; said diluent is lactose hydrous and microcrystalline cellulose; said binder is pregelatinized starch; said disintegrant is croscarmellose sodium; said antiadherent is silicon dioxide; and said lubricant is magnesium stearate.

18. A pharmaceutical composition of claim 11, comprising, based on weight, about 50% irbesartan; about 8.33% hydrochlorothiazide; about 4.72% lactose hydrous; about 15.0% pregelatinized starch; about 5.0% croscarmellose sodium; about 15% microcrystalline cellulose; about 0.75% silicon dioxide; about 1.0% magnesium stearate; about 0.1% ferric oxide, red; and about 0.1% ferric oxide, yellow.

19. A pharmaceutical composition of claim 11, comprising, based on weight, about 50% irbesartan; about 4.17% hydrochlorothiazide; about 8.88% lactose hydrous; about 15.0% pregelatinized starch; about 5.0% croscarmellose sodium; about 15% microcrystalline cellulose; about 0.75% silicon

dioxide; about 1.0% magnesium stearate; about 0.1% ferric oxide, red; and about 0.1% ferric oxide, yellow.

20. A pharmaceutical composition of claim 11, comprising, based on weight, about 50% irbesartan; about 8.33% hydrochlorothiazide; about 1.72% lactose hydrous; about 15.0% pregelatinized starch; about 5.0% croscarmellose sodium; about 3% poloxamer; about 15% microcrystalline cellulose; about 0.75% silicon dioxide; about 1.0% magnesium stearate; about 0.1% ferric oxide, red; and about 0.1% ferric oxide, yellow.

21. A pharmaceutical composition of claim 11, comprising, based on weight, about 50% irbesartan; about 8.33% hydrochlorothiazide; about 11.72% lactose hydrous; about 5.0% povidone K-30; about 5.0% croscarmellose sodium; about 3% poloxamer; about 15% microcrystalline cellulose; about 0.75% silicon dioxide; about 1.0% magnesium stearate; about 0.1% ferric oxide, red; and about 0.1% ferric oxide, yellow.

22. A pharmaceutical composition of claim 11, comprising, based on weight, about 50% irbesartan; about 4.17% hydrochlorothiazide; about 5.88% lactose hydrous; about 15.0% pregelatinized starch; about 5.0% croscarmellose sodium; about 3% poloxamer; about 15% microcrystalline cellulose; about 0.75% silicon dioxide; about 1.0% magnesium stearate; about 0.1% ferric oxide, red; and about 0.1% ferric oxide, yellow.

23. A pharmaceutical composition of claim 11, comprising, based on weight, about 50% irbesartan; about 4.17% hydrochlorothiazide; about 15.88% lactose hydrous; about 5.0% povidone K-30; about 5.0% croscarmellose sodium; about 3% poloxamer; about 15% microcrystalline cellulose; about 0.75% silicon dioxide; about 1.0% magnesium stearate; about 0.1% ferric oxide, red; and about 0.1% ferric oxide, yellow.

24. A tablet formed from the composition of claim 1.

25. A tablet formed from the composition of claim 7.

26. A tablet formed from the composition of claim 8.

27. A tablet formed from the composition of claim 9.

28. A tablet formed from the composition of claim 10.

29. A tablet formed from the composition of claim 18.

30. A tablet formed from the composition of claim 19.

31. A tablet formed from the composition of claim 20.

32. A tablet formed from the composition of claim 21.

33. A tablet formed from the composition of claim 22.

34. A tablet formed from the composition of claim 23.

35. A tablet of claim 24, wherein the total weight of said tablet is from about 50 to about 600 mg.

36. A pharmaceutical composition comprising irbesartan or a pharmaceutically acceptable salt thereof, hydrochlorothiazide, and a binder which is starch and/or pregelatinized starch.

37. A pharmaceutical composition of claim 36, wherein said binder is pregelatinized starch.

38. A tablet formed from the composition of claim 37.

39. A tablet formed from the composition of claim 1, wherein said tablet is prepared by mixing an extragranular composition with granules comprising an antiadherent.

40. The tablet of claim 39, wherein said antiadherent is silicon dioxide.

41. A pharmaceutical composition, wherein said composition is prepared by mixing components

comprising from about 20 to about 70% by weight irbesartan or a pharmaceutically acceptable salt thereof with one or more pharmaceutically acceptable excipients, wherein a tablet formed from said composition has a dissolution performance such that about 80% or greater of the irbesartan or salt thereof contained in said tablet dissolves within 30 minutes.

42. The pharmaceutical composition of claim 41, wherein a tablet formed from said composition has a dissolution performance such that about 85% or greater of the irbesartan or salt thereof contained in said tablet dissolves within 30 minutes.

43. A pharmaceutical composition of claim 41, prepared by mixing components comprising, based on weight: (a) from about 20 to about 70% irbesartan, (b) from about 1 to about 70% diluent, (c) from about 2 to about 20% binder, (d) from about 1 to about 10% disintegrant, (e) from about 0.1 to about 5% antiadherent, and (f) from about 0.2 to about 5% lubricant, and, optionally (g) from about 0.2 to about 6% surfactant, and/or (h) up to about 2% coloring agent.

44. A pharmaceutical composition of claim 43, wherein

the diluent is one or more compounds selected from the group consisting of dibasic calcium phosphate, lactose hydrous, lactose anhydrous, and microcrystalline cellulose;

the binder is one or more compounds selected from the group consisting of alginic acid, sodium alginate, carboxymethylcellulose sodium, ethylcellulose, hydroxyethyl cellulose, hydroxypropyl cellulose, hydroxypropyl methylcellulose, methylcellulose, gelatin, povidone, starch and pregelatinized starch;

the disintegrant is one or more compounds selected from the group consisting of alginic acid, sodium alginate, carboxymethylcellulose sodium, microcrystalline cellulose, powdered cellulose, croscarmellose sodium, crospovidone, pregelatinized starch, sodium starch glycolate, and starch;

the antiadherent is one or more compounds selected from the group consisting of silicon dioxide, magnesium trisilicate, and talc;

the lubricant is one or more compounds selected from the group consisting of calcium stearate, glyceryl monostearate, glyceryl palmitostearate, magnesium stearate, sodium lauryl sulfate, sodium stearyl fumarate, zinc stearate, stearic acid, hydrogenated vegetable oil, polyethylene glycol, sodium benzoate, and talc;

when present, the surfactant is one or more compounds selected from the group consisting of sodium lauryl sulfate, and poloxamers; and

when present, the coloring agent is one or more ferric oxides.

45. A pharmaceutical composition of claim 43, prepared by mixing components comprising, based on weight, about 20 to 50% irbesartan; about 1 to 70% diluent; about 10 to 20% binder; about 4 to 8%

disintegrant; about 0.25 to 5.0% antiadherent; about 0.5 to 1.5% lubricant; and about 1 to 6% surfactant.

46. The pharmaceutical composition of claim 45, wherein said diluent is lactose hydrous and microcrystalline cellulose; said binder is pregelatinized starch; said disintegrant is croscarmellose sodium; said antiadherent is silicon dioxide; said lubricant is magnesium stearate; and said surfactant is poloxamer 188.

47. A pharmaceutical composition of claim 41, prepared by mixing components comprising, based on weight, about 50% irbesartan; about 10.25% lactose hydrous; about 15.0% pregelatinized starch; about 5.0% croscarmellose sodium; about 3.0% poloxamer 188; about 15% microcrystalline cellulose; about 0.75% silicon dioxide; and about 1.0% magnesium stearate.

48. A pharmaceutical composition of claim 41, prepared by mixing components comprising, based on weight, about 50% irbesartan; about 10.25% lactose hydrous; about 15.0% pregelatinized starch; about 5.0% croscarmellose sodium; about 3.0% poloxamer 188; about 13% microcrystalline cellulose; about 2.75% silicon dioxide; and about 1.0% magnesium stearate.

49. A pharmaceutical composition of claim 41, prepared by mixing components comprising, based on weight, about 50% irbesartan; about 20.25% lactose hydrous; about 5.0% povidone K-30; about 5.0% croscarmellose sodium; about 3.0% poloxamer; about 15% microcrystalline cellulose; about 0.75% silicon dioxide; and about 1.0% magnesium stearate.

50. A pharmaceutical composition of claim 41, prepared by mixing components comprising, based on weight, about 50% irbesartan; about 20.25% lactose hydrous; about 5.0% povidone K-30; about 5.0% croscarmellose sodium; about 3.0% poloxamer; about 13% microcrystalline cellulose; about 2.75% silicon dioxide; and about 1.0% magnesium stearate.

51. A pharmaceutical composition of claim 41, prepared by mixing components comprising, in addition, about 2 to about 33% diuretic, wherein the total weight % of irbesartan or salt thereof and diuretic mixed does not exceed about 85%.

52. A pharmaceutical composition of claim 51, wherein said diuretic is one or more compounds selected from the group consisting of hydrochlorothiazide, bendroflumethiazide, benzthiazide, chlorothiazide, chlorthalidone, cyclothiazide, hydroflumethiazide, methyclothiazide, metolazone, polythiazide, quinethazone, and trichlormethiazide.

53. A pharmaceutical composition of claim 52, wherein said diuretic is hydrochlorothiazide.

54. A pharmaceutical composition of claim 51 prepared by mixing components comprising, based on weight: (a) from about 20 to about 70% irbesartan, (b) from about 2 to about 33% diuretic, wherein the combined loading of (a) and (b) does not exceed about 85%, (c) from about 1 to about 70% diluent, (d) from about 2 to about 20% binder, (e) from about 1 to

about 10% disintegrant, (f) from about 0.1 to about 5% antiadherent, and (g) from about 0.2 to about 5% lubricant, and, optionally (h) up to about 2% coloring agent.

55. A pharmaceutical composition of claim 54, wherein

the diuretic is hydrochlorothiazide;

the diluent is one or more compounds selected from the group consisting of dibasic calcium phosphate, lactose hydrous, lactose anhydrous, and microcrystalline cellulose;

the binder is one or more compounds selected from the group consisting of alginic acid, sodium alginate, carboxymethylcellulose sodium, ethylcellulose, hydroxyethyl cellulose, hydroxypropyl cellulose, hydroxypropyl methylcellulose, methylcellulose, gelatin, povidone, starch and pregelatinized starch;

the disintegrant is one or more compounds selected from the group consisting of alginic acid, sodium alginate, carboxymethylcellulose sodium, microcrystalline cellulose, powdered cellulose, croscarmellose sodium, crospovidone, pregelatinized starch, sodium starch glycolate, and starch;

the antiadherent is one or more compounds selected from the group consisting of silicon dioxide, magnesium trisilicate, and talc;

the lubricant is one or more compounds selected from the group consisting of calcium stearate, glyceryl monostearate, glyceryl palmitostearate, magnesium stearate, sodium lauryl sulfate, sodium stearyl fumarate, zinc stearate,

stearic acid, hydrogenated vegetable oil, polyethylene glycol, sodium benzoate, and talc; and

when present, the coloring agent is one or more ferric oxides.

56. A pharmaceutical composition of claim 54, prepared by mixing components comprising, based on weight, about 20 to 50% irbesartan; about 2 to 20% diuretic; about 1 to 70% diluent; about 10 to 20% binder; about 4 to 6% disintegrant; about 0.5 to 1.0% antiadherent; and about 0.5 to 1.5% lubricant.

57. The pharmaceutical composition of claim 56, wherein said diuretic is hydrochlorothiazide; said diluent is lactose hydrous and microcrystalline cellulose; said binder is pregelatinized starch; said disintegrant is croscarmellose sodium; said antiadherent is silicon dioxide; and said lubricant is magnesium stearate.

58. A pharmaceutical composition of claim 51, prepared by mixing components comprising, based on weight, about 50% irbesartan; about 8.33% hydrochlorothiazide; about 4.72% lactose hydrous; about 15.0% pregelatinized starch; about 5.0% croscarmellose sodium; about 15% microcrystalline cellulose; about 0.75% silicon dioxide; about 1.0% magnesium stearate; about 0.1% ferric oxide, red; and about 0.1% ferric oxide, yellow.

59. A pharmaceutical composition of claim 51, prepared by mixing components comprising, based on weight, about 50% irbesartan; about 4.17% hydrochlorothiazide; about 8.88% lactose hydrous;

about 15.0% pregelatinized starch; about 5.0% croscarmellose sodium; about 15% microcrystalline cellulose; about 0.75% silicon dioxide; about 1.0% magnesium stearate; about 0.1% ferric oxide, red; and about 0.1% ferric oxide, yellow.

60. A pharmaceutical composition of claim 51, prepared by mixing components comprising, based on weight, about 50% irbesartan; about 8.33% hydrochlorothiazide; about 1.72% lactose hydrous; about 15.0% pregelatinized starch; about 5.0% croscarmellose sodium; about 3% poloxamer; about 15% microcrystalline cellulose; about 0.75% silicon dioxide; about 1.0% magnesium stearate; about 0.1% ferric oxide, red; and about 0.1% ferric oxide, yellow.

61. A pharmaceutical composition of claim 51, prepared by mixing components comprising, based on weight, about 50% irbesartan; about 8.33% hydrochlorothiazide; about 11.72% lactose hydrous; about 5.0% povidone K-30; about 5.0% croscarmellose sodium; about 3% poloxamer; about 15% microcrystalline cellulose; about 0.75% silicon dioxide; about 1.0% magnesium stearate; about 0.1% ferric oxide, red; and about 0.1% ferric oxide, yellow.

62. A pharmaceutical composition of claim 51, prepared by mixing components comprising, based on weight, about 50% irbesartan; about 4.17% hydrochlorothiazide; about 5.88% lactose hydrous; about 15.0% pregelatinized starch; about 5.0% croscarmellose sodium; about 3% poloxamer; about 15%

microcrystalline cellulose; about 0.75% silicon dioxide; about 1.0% magnesium stearate; about 0.1% ferric oxide, red; and about 0.1% ferric oxide, yellow.

63. A pharmaceutical composition of claim 51, prepared by mixing components comprising, based on weight, about 50% irbesartan; about 4.17% hydrochlorothiazide; about 15.88% lactose hydrous; about 5.0% povidone K-30; about 5.0% croscarmellose sodium; about 3% poloxamer; about 15% microcrystalline cellulose; about 0.75% silicon dioxide; about 1.0% magnesium stearate; about 0.1% ferric oxide, red; and about 0.1% ferric oxide, yellow.

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Abstract

PHARMACEUTICAL COMPOSITIONS CONTAINING IRBESARTAN

Pharmaceutical compositions containing irbesartan, alone or in combination with a diuretic, providing tablets with a high relative amount of active agent and excellent wetting and disintegration properties

THIS SHEET HAS BEEN REPLACED

Abstract

PHARMACEUTICAL COMPOSITIONS CONTAINING IRBESARTAN

Pharmaceutical compositions containing irbesartan, alone or in combination with a diuretic, providing tablets with a high relative amount of active agent and excellent wetting and disintegration properties.

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03 FEB 1997

What we claim is :

1. A pharmaceutical composition wherein said composition comprises, based on weight : (a) from about 20 to about 70 % irbesartan, (b) from about 1 to about 70 % diluent, (c) from about 2 to about 20 % binder, (d) from about 1 to about 10 % disintegrant, (e) from about 0.1 to about 5 % antiadherent, and (f) from about 0.2 to about 5 % lubricant, and, optionally (g) from about 0.2 to about 6 % surfactant, and/or (h) up to about 2 % coloring agent, wherein a tablet formed from said composition has a dissolution performance such that about 80 % or greater of the irbesartan or salt thereof contained in said tablet dissolves within 30 minutes.

2. The pharmaceutical composition of claim 1, wherein a tablet formed from said composition has a dissolution performance such that about 85 % or greater of the irbesartan of salt thereof contained in said tablet dissolves within 30 minutes.

3. A pharmaceutical composition of claim 2, wherein the diluent is one or more compounds selected from the group consisting of dibasic calcium phosphate, lactose hydrous, lactose anhydrous , and microcrystalline cellulose ;

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the binder is one or more compounds selected from the group consisting of alginic acid, sodium alginate, carboxymethylcellulose sodium, ethylcellulose, hydroxyethyl cellulose, hydroxypropyl cellulose, hydroxypropyl methylcellulose, methylcellulose, gelatin, povidone, starch and pregelatinized starch;

the disintegrant is one or more compounds selected from the group consisting of alginic acid, sodium alginate, carboxymethylcellulose sodium, microcrystalline cellulose, powdered cellulose, croscarmellose sodium, crospovidone, pregelatinized starch, sodium starch glycolate, and starch;

the antiadherent is one or more compounds selected from the group consisting of silicon dioxide, magnesium trisilicate, and talc;

the lubricant is one or more compounds selected from the group consisting of calcium stearate, glyceryl monostearate, glyceryl palmitostearate, magnesium stearate, sodium lauryl sulfate, sodium stearyl fumarate, zinc stearate, stearic acid, hydrogenated vegetable oil, polyethylene glycol, sodium benzoate, and talc;

when present, the surfactant is one or more compounds selected from the group consisting of sodium lauryl sulfate, and poloxamers; and

when present, the coloring agent is one or more ferric oxides.

4. A pharmaceutical composition of claim 1., comprising, based on weight, about 20 to 50% irbesartan; about 1 to 70% diluent; about 10 to 20% binder; about 4 to 8% disintegrant; about 0.25 to

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5.0% antiadherent; about 0.5 to 1.5% lubricant; and about 1 to 6% surfactant.

5. The pharmaceutical composition of claim 4., wherein said diluent is lactose hydrous and microcrystalline cellulose; said binder is pregelatinized starch; said disintegrant is croscarmellose sodium; said antiadherent is silicon dioxide; said lubricant is magnesium stearate; and said surfactant is poloxamer 188.

6. A pharmaceutical composition of claim 1, comprising, based on weight, about 50% irbesartan; about 10.25% lactose hydrous; about 15.0% pregelatinized starch; about 5.0% croscarmellose sodium; about 3.0% poloxamer 188; about 15% microcrystalline cellulose; about 0.75% silicon dioxide; and about 1.0% magnesium stearate.

7. A pharmaceutical composition of claim 1, comprising, based on weight, about 50% irbesartan; about 10.25% lactose hydrous; about 15.0% pregelatinized starch; about 5.0% croscarmellose sodium; about 3.0% poloxamer 188; about 13% microcrystalline cellulose; about 2.75% silicon dioxide; and about 1.0% magnesium stearate.

8. A pharmaceutical composition of claim 1, comprising, based on weight, about 50% irbesartan; about 20.25% lactose hydrous; about 5.0% povidone K-30; about 5.0% croscarmellose sodium; about 3.0% poloxamer; about 15% microcrystalline cellulose; about 0.75% silicon dioxide; and about 1.0% magnesium stearate.

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9. A pharmaceutical composition of claim 1, comprising, based on weight, about 50% irbesartan; about 20.25% lactose hydrous; about 5.0% povidone K-30; about 5.0% croscarmellose sodium; about 3.0% poloxamer; about 13% microcrystalline cellulose; about 2.75% silicon dioxide; and about 1.0% magnesium stearate.

10. A pharmaceutical composition of claim 1, further comprising about 2 to about 33% diuretic, wherein the total weight % of irbesartan or salt thereof and diuretic does not exceed about 85%.

11. A pharmaceutical composition of claim 10, wherein said diuretic is one or more compounds selected from the group consisting of hydrochlorothiazide, bendroflumethiazide, benzthiazide, chlorothiazide, chlorthalidone, cyclothiazide, hydroflumethiazide, methyclothiazide, metolazone, polythiazide, quinethazone, and trichlormethiazide.

12. A pharmaceutical composition of claim 11, wherein said diuretic is hydrochlorothiazide.

13. A pharmaceutical composition of claim 10 comprising, based on weight: (a) from about 20 to about 70% irbesartan, (b) from about 2 to about 33% diuretic, wherein the combined loading of (a) and (b) does not exceed about 85%, (c) from about 1 to about 70% diluent, (d) from about 2 to about 20% binder, (e) from about 1 to about 10% disintegrant, (f) from about 0.1 to about 5% antiadherent, and (g) from

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about 0.2 to about 5% lubricant, and, optionally (h) up to about 2% coloring agent.

14. A pharmaceutical composition of claim 13, wherein

the diuretic is hydrochlorothiazide;

the diluent is one or more compounds selected from the group consisting of dibasic calcium phosphate, lactose hydrous, lactose anhydrous, and microcrystalline cellulose;

the binder is one or more compounds selected from the group consisting of alginic acid, sodium alginate, carboxymethylcellulose sodium, ethylcellulose, hydroxyethyl cellulose, hydroxypropyl cellulose, hydroxypropyl methylcellulose, methylcellulose, gelatin, povidone, starch and pregelatinized starch;

the disintegrant is one or more compounds selected from the group consisting of alginic acid, sodium alginate, carboxymethylcellulose sodium, microcrystalline cellulose, powdered cellulose, croscarmellose sodium, crospovidone, pregelatinized starch, sodium starch glycolate, and starch;

the antiadherent is one or more compounds selected from the group consisting of silicon dioxide, magnesium trisilicate, and talc;

the lubricant is one or more compounds selected from the group consisting of calcium stearate, glyceryl monostearate, glyceryl palmitostearate, magnesium stearate, sodium lauryl sulfate, sodium stearyl fumarate, zinc stearate, stearic acid, hydrogenated vegetable oil, polyethylene glycol, sodium benzoate, and talc; and

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when present, the coloring agent is one or more ferric oxides.

15. A pharmaceutical composition of claim 13, comprising, based on weight, about 20 to 50% irbesartan; about 2 to 20% diuretic; about 1 to 70% diluent; about 10 to 20% binder; about 4 to 6% disintegrant; about 0.5 to 1.0% antiadherent; and about 0.5 to 1.5% lubricant.

16. The pharmaceutical composition of claim 15, wherein said diuretic is hydrochlorothiazide; said diluent is lactose hydrous and microcrystalline cellulose; said binder is pregelatinized starch; said disintegrant is croscarmellose sodium; said antiadherent is silicon dioxide; and said lubricant is magnesium stearate.

17. A pharmaceutical composition of claim 10, comprising, based on weight, about 50% irbesartan; about 8.33% hydrochlorothiazide; about 4.72% lactose hydrous; about 15.0% pregelatinized starch; about 5.0% croscarmellose sodium; about 15% microcrystalline cellulose; about 0.75% silicon dioxide; about 1.0% magnesium stearate; about 0.1% ferric oxide, red; and about 0.1% ferric oxide, yellow.

18. A pharmaceutical composition of claim 10, comprising, based on weight, about 50% irbesartan; about 4.17% hydrochlorothiazide; about 8.88% lactose hydrous; about 15.0% pregelatinized starch; about 5.0% croscarmellose sodium; about 15% microcrystalline cellulose; about 0.75% silicon

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dioxide; about 1.0% magnesium stearate; about 0.1% ferric oxide, red; and about 0.1% ferric oxide, yellow.

19. A pharmaceutical composition of claim 10, comprising, based on weight, about 50% irbesartan; about 8.33% hydrochlorothiazide; about 1.72% lactose hydrous; about 15.0% pregelatinized starch; about 5.0% croscarmellose sodium; about 3% poloxamer; about 15% microcrystalline cellulose; about 0.75% silicon dioxide; about 1.0% magnesium stearate; about 0.1% ferric oxide, red; and about 0.1% ferric oxide, yellow.

20. A pharmaceutical composition of claim 10, comprising, based on weight, about 50% irbesartan; about 8.33% hydrochlorothiazide; about 11.72% lactose hydrous; about 5.0% povidone K-30; about 5.0% croscarmellose sodium; about 3% poloxamer; about 15% microcrystalline cellulose; about 0.75% silicon dioxide; about 1.0% magnesium stearate; about 0.1% ferric oxide, red; and about 0.1% ferric oxide, yellow.

21. A pharmaceutical composition of claim 10, comprising, based on weight, about 50% irbesartan; about 4.17% hydrochlorothiazide; about 5.88% lactose hydrous; about 15.0% pregelatinized starch; about 5.0% croscarmellose sodium; about 3% poloxamer; about 15% microcrystalline cellulose; about 0.75% silicon dioxide; about 1.0% magnesium stearate; about 0.1% ferric oxide, red; and about 0.1% ferric oxide, yellow.

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22. A pharmaceutical composition of claim 10, comprising, based on weight, about 50% irbesartan; about 4.17% hydrochlorothiazide; about 15.88% lactose hydrous; about 5.0% povidone K-30; about 5.0% croscarmellose sodium; about 3% poloxamer; about 15% microcrystalline cellulose; about 0.75% silicon dioxide; about 1.0% magnesium stearate; about 0.1% ferric oxide, red; and about 0.1% ferric oxide, yellow.

23. A tablet formed from the composition of claim 1.

24. A tablet formed from the composition of claim 6.

25. A tablet formed from the composition of claim 7.

26. A tablet formed from the composition of claim 8.

27. A tablet formed from the composition of claim 9.

28. A tablet formed from the composition of claim 17.

29. A tablet formed from the composition of claim 18.

30. A tablet formed from the composition of claim 19.

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31. A tablet formed from the composition of claim 20.

32. A tablet formed from the composition of claim 21.

33. A tablet formed from the composition of claim 22.

34. A tablet of claim 23, wherein the total weight of said tablet is from about 50 to about 600 mg.

35. A tablet formed from the composition of claim 1, wherein said tablet is prepared by mixing an extragranular composition with granules comprising an antiadherent.

36. The tablet of claim 35, wherein said antiadherent is silicon dioxide.

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Abstract

PHARMACEUTICAL COMPOSITIONS
CONTAINING IRBESARTAN

Pharmaceutical compositions containing irbesartan, alone or in combination with a diuretic, providing tablets with a high relative amount of active agent and excellent wetting and disintegration properties.

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