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(54) **Title:** ORAL PHARMACEUTICAL COMPOSITIONS OF IRBESARTAN AND HYDROCHLOROTHIAZIDE AND PROCESSES FOR THEIR PREPARATION

(57) **Abstract:** The invention relates to stable oral pharmaceutical compositions of irbesartan and hydrochlorothiazide, and processes for their preparation, wherein the two active ingredients are present as distinct portions within the composition.

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ORAL PHARMACEUTICAL COMPOSITIONS OF IRBESARTAN AND HYDROCHLOROTHIAZIDE AND PROCESSES FOR THEIR PREPARATION

Technical field of the invention

The present inventions relate to stable oral pharmaceutical compositions of irbesartan and hydrochlorothiazide, and processes for their preparation, wherein the two active ingredients are present as distinct portions within the composition.

Background of the invention

Antihypertensive drugs given as monotherapy normalize blood pressure in only a fraction of hypertensive patients and, hence, treatment with two or more agents from different pharmacological classes is often necessary to achieve adequate blood pressure control. The rationale for using combination therapy is to obtain increased blood pressure control by employing two antihypertensive agents with different modes of action and to enhance compliance by using a single tablet that is taken once or twice daily.

Fixed dose combinations of an angiotensin-receptor blocker (AT1-receptor blocker) and diuretics are very effective in controlling blood pressure in cases where monotherapy fails to provide adequate control. Administration of diuretics alone results in sodium depletion that results in the compensatory rise in renin secretion. Simultaneous blockade of the renin-angiotensin system, with an AT1-receptor blocker, makes this compensatory hyper-reninemia ineffective and allows maximum benefit from sodium depletion.

Irbesartan, a long-acting angiotensin-II receptor antagonist, is useful in the treatment of cardiovascular ailments such as hypertension and heart failure. Sanofi Synthelabo is marketing a combination of irbesartan and a diuretic, hydrochlorothiazide, in the form of oral tablets under the brand name AVALIDE®.

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, either actives or non-actives, is not without drawbacks. For

example, the stability of a composition might be compromised due to incompatibility between the two actives or an active with an essential excipient.

US 6,342,247, assigned to Sanofi, discloses that certain physical properties of irbesartan 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 a fluffy material having 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 '247 patent also discloses that the poloxamer (poly (oxypropylene) block co-polymer) 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.

US 5,994,348, also assigned to Sanofi, describes a pharmaceutical composition comprising irbesartan or a pharmaceutically acceptable salt thereof, and hydrochlorothiazide. The composition is disclosed as being free of povidone and poloxamer. The inventors have emphasized that under certain conditions, hydrochlorothiazide can undergo hydrolysis to form, as by-products, a free amine degradant (4-amino-6-chloro-1,3-benzenedisulfonamide) and formaldehyde. The degradation of hydrochlorothiazide in a dosage form is undesirable since the US Pharmacopoeia sets a limit for the free amine content of not more than 1% of hydrochlorothiazide potency due to toxicological reasons. The selection of excipients can affect the stability of hydrochlorothiazide. The use of poloxamer was found to increase the degradation of hydrochlorothiazide and, therefore, while employed as a preferred

component in compositions of irbesartan, poloxamer was not utilized for the irbesartan/hydrochlorothiazide compositions.

Our scientists have prepared a stable dosage form for orally administering irbesartan and hydrochlorothiazide, wherein the dosage form comprises poloxamer. This dosage form is particularly advantageous since the dissolution of irbesartan is not compromised and hydrochlorothiazide does not undergo degradation.

Summary of the Invention

The present invention relates to a stable oral pharmaceutical composition comprising irbesartan and hydrochlorothiazide, wherein the two actives are present as distinct portions within the composition.

Therefore, it is one of the aspects to provide a stable oral pharmaceutical composition comprising irbesartan and hydrochlorothiazide, in form of a tablet or pellet, wherein one active is present intragranularly and the other active is present extra granularly.

It is another aspect to provide a stable oral pharmaceutical composition comprising irbesartan and hydrochlorothiazide, in form of a multiple compression tablet, wherein the multiple compression tablet is a layered tablet, compression coated tablet or an inlay tablet.

It is another aspect to provide a stable oral pharmaceutical composition comprising irbesartan and hydrochlorothiazide, in the form of a coated tablet, wherein one active is present in the core and the other active is present in the coat.

It is yet another aspect to provide a stable oral pharmaceutical composition comprising irbesartan and hydrochlorothiazide, in the form of multiparticulates comprising first particulate phase of one active and second particulate phase of the other active.

The multiparticulates are in the form selected from the group consisting of pellets, beads, granules, slugs, powder and particles. These multiparticulates are filled into capsules or are compressed into tablets.

The two distinct portions of the stable oral pharmaceutical composition are separated by a barrier to reduce or eliminate the physical contact between the two portions.

It is yet another aspect to provide a method for the treatment of hypertension in a patient in need thereof, comprising administering a stable oral pharmaceutical composition comprising irbesartan and hydrochlorothiazide, wherein the two actives are present as distinct portions within the composition.

The details of one or more embodiments are set forth in the description below. Other features, objects and advantages of the invention will be apparent from the description and claims.

Detailed Description of the Invention

Stability is 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: Each active ingredient retains its chemical integrity and labeled potency within the specified limits.

Physical: The original physical properties, including appearance, palatability, uniformity, dissolution, etc. are retained.

Microbiological: Sterility or resistance to microbial growth is retained according to the specified requirements.

Therapeutic: The therapeutic effect remains unchanged.

Toxicological: No significant increase in toxicity occurs.

The use of poloxamer and polyvinyl pyrrolidone increases the degradation of hydrochlorothiazide. In order to avoid degradation, one can simply eliminate poloxamer and polyvinylpyrrolidone from the composition. This may be the case when only hydrochlorothiazide compositions are to be formulated. However, for a combination of irbesartan and hydrochlorothiazide, the addition of poloxamer is important for complete and rapid dissolution and satisfactory compression of irbesartan. Therefore, we have

prepared a composition wherein the contact between hydrochlorothiazide and poloxamer is minimized.

Irbesartan, 2-n-butyl-4-spiro cyclopentane-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 is described in Bernhart et al., U.S. 5,270,317, incorporated herein by reference.

Hydrochlorothiazide is a thiazide diuretic and an antihypertensive. It is the 3,4-dihydro derivative of chlorothiazide. Its chemical name is 6-chloro-3,4-dihydro-2*H*-1,2,4-benzothiadiazine-7-sulfonamide 1,1-dioxide. The thiazides comprise a 1,2,4 benzothiazine class of compounds. Their use and methods for their preparation are described in U.S. Patent Nos. 2,809,194, 3,025,292, 2,937,169, 3,164,588 and 3,043,840, incorporated herein by reference.

Poloxamer is a nonionic polyoxyethylene-polyoxypropylene block co-polymer with the general formula $HO(C_2H_4O)_a(-C_3H_6O)_b(C_2H_4O)_cH$. It is available in different grades which vary from liquids to solids. It is used as an emulsifying agent, solubilizing agent, surfactant, and wetting agent for antibiotics. Poloxamer is also used as a tablet binder. In the present invention, poloxamer is the preferred binder for irbesartan.

The present invention provides a stable oral pharmaceutical composition comprising irbesartan and hydrochlorothiazide, wherein the two actives are present as distinct portions within the composition. In addition to the actives, the composition may contain other pharmaceutically acceptable excipients, which act in one or more capacities as diluents, binders, disintegrants, lubricants, glidants, colorants or flavoring agents.

Suitable diluents may be selected from amongst one or more compounds which are capable of providing bulk to the dosage form. Examples of diluents include dibasic calcium phosphate, sugars such as lactose hydrous or lactose anhydrous, and cellulose or cellulose derivatives such as microcrystalline cellulose.

Suitable binders may be selected from amongst alginic acid; sodium alginate; cellulose derivatives such as hydroxypropyl methylcellulose, hydroxy propyl cellulose, hydroxy ethyl cellulose, methylcellulose and ethyl cellulose; gelatin; and starch or starch derivatives.

Suitable disintegrants may be selected from one or more compounds that are capable of promoting moisture penetration and dispersion of the dosage form in dissolution fluid to expose the drug particles. Examples of disintegrants include carboxymethyl cellulose sodium (cross-linked), sodium starch glycolate, pregelatinized starch, cross-linked polyvinyl pyrrolidone and low-substituted hydroxy propyl cellulose.

Suitable lubricants may be selected from one or more compounds which are capable of reducing friction between tablet surfaces and die wall. Examples of lubricants include fatty acids or fatty acid derivatives such as calcium stearate, magnesium stearate, glyceryl monostearate, glyceryl palmitostearate, zinc stearate, sodium stearyl fumarate and stearic acid; sodium lauryl sulphate, polyethylene glycol, hydrogenated vegetable oil, talc and sodium benzoate.

Suitable anti-adherents may be selected from 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 pharmaceutically acceptable excipients may be similar or different for the two regions.

Several approaches may be utilized to design these portions within the composition. The two actives may be present in a single unit dosage form, such as tablets or pellets, in which irbesartan is present along with poloxamer intragranularly and hydrochlorothiazide is added extragranularly. Alternatively, hydrochlorothiazide can be incorporated into an exterior coating for a tablet containing irbesartan and poloxamer.

Tablets or pellets containing irbesartan, poloxamer and optionally one or more pharmaceutically acceptable excipients may be prepared by any pharmaceutically acceptable technique that achieves uniform blending, e.g., dry blending, wet granulation and dry granulation. In embodiments in which the tablet is prepared by direct compression, the active ingredient and excipients are blended together and compressed. For dry granulation, any suitable compacting apparatus may be used including, for example, a roller compactor such as a chilsonator or drop roller; or a conventional tablet press. In the wet-granulation method, the active ingredient and excipients, and a solution or dispersion of a wet binder are mixed and granulated. The resulting granulated material

is dried, and blended with other excipients, for example lubricants and colorants. The final blend is then compressed. Pellets can be prepared using techniques like extrusion-spheronization, drug layering, and granulation.

Hydrochlorothiazide can be incorporated into the dosage form in a variety of ways. For example, it can be incorporated into an exterior coating for a tablet from which it releases substantially immediately upon ingestion. Such a coating can similarly be applied to each of the particles comprising a multiparticulate, i.e., granules, beads, etc.. The coating composition may comprise water-soluble polymers such as hydroxypropyl cellulose, polyvinyl alcohol, and hydroxypropyl methylcellulose. The polymer may be applied as a solution in an organic solvent or as an aqueous dispersion. The solvent may be selected from water; alcohols such as ethyl alcohols or isopropyl alcohol; ketones such as acetone or ethylmethyl ketone; and chlorinated hydrocarbons such as dichloroethane and trichloroethane. The coating composition may also comprise plasticizers, opacifiers and colorants. Any conventional coating equipment may be employed to facilitate coating such as centrifugal fluidized bed coating apparatus, pan coating apparatus, or fluidized bed granulating coating apparatus. The coating may also be applied over the tablets or pellets by compression coating.

The two actives in the oral pharmaceutical composition are brought together into a form of a multiple-compression tablet for oral administration. A multiple-compression tablet of the present invention can exist as a layered tablet, as a compression-coated tablet, or as an inlay tablet.

A layered tablet is a tablet which is made up of two or more distinct layers or discrete zones of granulation compressed together with the individual layers lying one on top of another. Such conventional layered tablets are generally prepared by compressing a granulation onto a previously compressed granulation. The operation may be repeated to produce multilayered tablets of more than two layers. A layered tablet has at least two layers or discrete zones, one of which is made from irbesartan and another of which is made from hydrochlorothiazide.

A compression-coated tablet is a tablet which is made up of an inner core and one or more outer coats, wherein the inner core is completely surrounded by the outer coat or coats. These tablets have at least two discrete zones of granulation compressed together,

i.e., an inner core zone and an outer coat zone. Such tablets are prepared by feeding a previously compressed inner core into a special tableting machine and compressing one or more other granulation coats around the preformed inner core.

A variation of the compression-coated tablet is the inlay tablet, also referred to as a dot, or bull's-eye tablet. Instead of an inner core zone being completely surrounded by an outer coat, one surface of the zone corresponding to an inner core zone is exposed. These tablets have at least two discrete zones of granulation compressed together. The preparation of inlay tablets is similar to the preparation of compression-coated tablets except that a surface of coating is eliminated.

The two actives may be present in the form of multiparticulates, such as particles, pellets, slugs, powder, beads or granules. The coated or uncoated multiparticulates of irbesartan and hydrochlorothiazide can be filled into capsules. Alternatively, the multiparticulates can be compressed into tablets.

Inclusion of a barrier between the two actives may also improve the stability of the formulation. The barrier is a physical barrier around one or both of the actives. In one of the embodiments, the barrier is a coating around at least one of the two active ingredients. The coating serves to reduce or eliminate the physical contact between the coated ingredient and the other ingredients.

The barrier layer or coating comprises one or more film-formers or binders, such as a hydrophilic polymer like hydroxyl -propyl methyl cellulose (HPMC) or a hydrophobic polymer like ethyl cellulose, cellulose acetate, polyvinyl alcohol-maleic anhydride copolymers, acrylic copolymers and one or more plasticizers, such as polyethylene glycol, triethyl citrate, diethyl phthalate, propylene glycol, glycerin, butyl phthalate, and castor oil.

The film formers are applied from a solvent system containing one or more solvents including water, alcohols like methyl alcohol, ethyl alcohol or isopropyl alcohol, ketones like acetone, or ethylmethyl ketone, chlorinated hydrocarbons like methylene chloride, dichloroethane, and 1,1,1-trichloroethane.

The oral pharmaceutical compositions of the present invention were subjected to accelerated stability studies at 40°±2°C and 75±5% relative humidity. These were evaluated on the basis of assay, in vitro dissolution, moisture content and related

substances measured between initial and 3-month time points for irbesartan as well as hydrochlorothiazide.

The following examples describe compositions of the present invention containing irbesartan and hydrochlorothiazide, but they are not to be interpreted as limiting the scope of the claims.

EXAMPLES

Example 1. Preparation of Tablets Containing Irbesartan Intragranularly and Hydrochlorothiazide Extragranularly

S.No.		Ingredients	Percent w/w
1.	Intragranular	Irbesartan	50
2.		Lactose monohydrate	8.33
3.		Pregelatinized starch	3
4.		Croscarmellose sodium	2
5.		Colloidal silicon dioxide	0.5
6.		Microcrystalline cellulose	8.33
7.		Poloxamer	3
8.		Ferric oxide (red)	0.03
9.		Ferric oxide (yellow)	0.008
10.		Purified water	qs
11.	Extragranular	Hydrochlorothiazide	2.08
12.		Croscarmellose sodium	2.022
13.		Colloidal silicon dioxide	0.5
14.		Microcrystalline cellulose	18.95
15.		Calcium stearate	1.25

Process:

Intragranular portion

1. Ferric oxide (red) and ferric oxide (yellow) were sieved through ASTM* sieve # 60 along with a portion of the microcrystalline cellulose.

2. Irbesartan, lactose monohydrate, colloidal silicon dioxide, croscarmellose sodium, pregelatinized starch and the remaining portion of microcrystalline cellulose were sifted together with the materials of step 1 through ASTM sieve # 35.

3. The mixture of step 2 was mixed in a rapid mixer granulator.

4. Poloxamer was sifted through ASTM sieve # 18 and dissolved in purified water under stirring.

5. The mixture of step 3 was granulated with poloxamer solution and the granules were dried in a fluid bed drier at 50° to 60°C until the loss on drying was not more than 2.5% w/w.

6. The dried granules of step 5 were sifted through ASTM sieve # 30.

Extragranular portion

7. Hydrochlorothiazide was sieved along with a portion of the microcrystalline cellulose through ASTM sieve # 60.

8. The remaining portion of microcrystalline cellulose, croscarmellose sodium and colloidal silicon dioxide were sifted along with the material of step 7 through ASTM sieve # 35.

9. The materials of step 6 and 8 were blended in a low-shear blender for 15 minutes.

10. Calcium stearate was sifted through ASTM sieve # 45 and added to the mixture of step 9 and the blend was compressed into tablets.

*ASTM: American Society of Testing and Materials

Example 2. Tablet within a tablet

S.No.		Ingredients	Percent w/w
1.	Irbesartan layer	Irbesartan	50
2.		Lactose monohydrate	8.33
3.		Pregelatinized starch	3.0
4.		Croscarmellose sodium	2.0
5.		Colloidal silicon dioxide	0.5
6.		Microcrystalline cellulose	8.33
7.		Poloxamer	3.0
8.		Ferric oxide (red)	0.03
9.		Ferric oxide (yellow)	0.0083
10.		Purified water	q.s
11.	Hydrochlorothiazide layer	Hydrochlorothiazide	2.08
12.		Croscarmellose sodium	2.025
13.		Colloidal silicon dioxide	0.5
14.		Microcrystalline cellulose	18.93
15.		Calcium stearate	1.25

Process:

Irbesartan layer

1. Ferric oxide (red) and ferric oxide (yellow) were sieved through ASTM* sieve # 60 along with a portion of the microcrystalline cellulose.

2. Irbesartan, lactose monohydrate, colloidal silicon dioxide, croscarmellose sodium, pregelatinized starch and the remaining portion of the microcrystalline cellulose were sifted together with the materials of step 1 through ASTM sieve # 35.

3. The mixture of step 2 was mixed in a rapid mixer granulator.

4. Poloxamer was sifted through ASTM sieve # 18 and dissolved in purified water under stirring.

5. The mixture of step 3 was granulated with poloxamer solution and the granules were dried in a fluid bed drier at 50° to 60°C until the loss on drying was not more than 2.5% w/w.

6. The dried granules of step 5 were sifted through ASTM sieve # 30.

Hydrochlorothiazide layer:

7. Hydrochlorothiazide was sieved along with microcrystalline cellulose through ASTM sieve # 60.

8. The remaining portion of microcrystalline cellulose, croscarmellose sodium and colloidal silicon dioxide were sifted along with material of step 7 through ASTM sieve # 35.

9. Calcium stearate was sifted through ASTM sieve # 45 and added to the mixture of step 8.

10. The blends of step 6 and step 9 were compressed

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While several particular forms of the invention have been illustrated and described, it will be apparent that various modifications and combinations of the invention detailed in the text can be made without departing from the spirit and scope of the invention. For

example, irbesartan granules and hydrochlorothiazide granules can be prepared separately and filled into capsules or alternatively, the granules can be compressed into tablets or the two set of granules can be compressed into bilayered tablets. Further aspects of this invention, together with additional features contributing thereto and advantages accruing there from will be apparent from the following hypothetical examples.

Example 3. Bilayered Tablet

S.No.		Ingredients
1.	Irbesartan layer	Irbesartan
2.		Lactose monohydrate
3.		Pregelatinized starch
4.		Croscarmellose sodium
5.		Colloidal silicon dioxide
6.		Microcrystalline cellulose
7.		Poloxamer
8.		Ferric oxide (red)
9.		Ferric oxide (yellow)
10.		Purified water
11.	Hydrochlorothiazide layer	Hydrochlorothiazide
12.		Croscarmellose sodium
13.		Microcrystalline cellulose
14.		Calcium stearate

Process:

Irbesartan layer

1. Sift Iron oxide (Red) and Iron Oxide (Yellow) through ASTM # 60 sieve along with a portion of microcrystalline cellulose.

2. Sift together Irbesartan, Lactose monohydrate, Colloidal Silicon Dioxide, Croscarmellose Sodium, Pregelatinized Starch and remaining portion of microcrystalline cellulose along with materials of step 1 through ASTM # 35.

3. Transfer the material of step 2 to a Rapid Mixer Granulator and mix for 10 minutes.

4. Sift Poloxamer through mesh # 18 ASTM and dissolve in purified Water under stirring.

5. Granulate the material of step 3 with poloxamer solution of step 4 in the Rapid Mixer Granulator.

6. Dry the material of step 5 in a Fluid Bed Drier at 50° - 60°C until the loss on drying is not more than 2.5% w/w.

7. Sift the dried granules through ASTM # 30.

Hydrochlorothiazide layer

8. Sift hydrochlorothiazide along with a portion of the microcrystalline cellulose through ASTM sieve # 60.

9. Sift the remaining portion of microcrystalline cellulose, croscarmellose sodium and colloidal silicon dioxide along with the material of step 8 through ASTM sieve # 35.

10. Sift calcium stearate through ASTM sieve # 45 and blend with the mixture of step 9.

11. Compress the blends of steps 7 and 10 using appropriate tooling on a bilayered tablet machine.

*ASTM: American Society of Testing and Materials

Example 4. Irbesartan Granules and HydrochlorothiazideTablets in a Capsule

S.No.		Ingredients
1.	Irbesartan granules	Irbesartan
2.		Lactose monohydrate
3.		Pregelatinized starch
4.		Croscarmellose sodium
5.		Colloidal silicon dioxide
6.		Microcrystalline cellulose
7.		Poloxamer
8.		Ferric oxide (red)
9.		Ferric oxide (yellow)
10.		Purified water
11.	Hydrochlorothiazide tablet	Hydrochlorothiazide
12.		Purified water
13.		Opadry
14.		Microcrystalline cellulose
15.		Calcium stearate

Process:

Irbesartan granules

Similar to the process described in Example 3.

Hydrochlorothiazide tablet

1. Sift hydrochlorothiazide along with a portion of the microcrystalline cellulose through ASTM sieve # 60.

2. Sift the remaining portion of microcrystalline cellulose, croscarmellose sodium and colloidal silicon dioxide along with material of step 1 through ASTM sieve # 35.

3. Sift calcium stearate through ASTM sieve # 45 and blend with the mixture of step 2 and compress the blend into tablets.

4. Film-coat the tablets prepared in step 3 using a 10% w/w dispersion of opadry.

5. Fill the hydrochlorothiazide tablets of step 4 and irbesartan blend capsules using an appropriate filling machine.

*ASTM: American Society of Testing and Materials

Example 5. Hydrochlorothiazide Coating on Irbesartan Tablet

S.No.		Ingredients
1.	Irbesartan layer	Irbesartan
2.		Lactose monohydrate
3.		Pregelatinized starch
4.		Croscarmellose sodium
5.		Colloidal silicon dioxide
6.		Microcrystalline cellulose
7.		Poloxamer
8.		Ferric oxide (red)
9.		Ferric oxide (yellow)
10.		Purified water
11.	Hydrochlorothiazide coating dispersion	Hydrochlorothiazide
12.		Hydroxy propyl methyl cellulose 5 cps
13.		Hydroxy propyl cellulose
14.		Purified water
15.	Barrier coat	Opadry white
16.		Purified water

Process:

Irbesartan layer

Prepare irbesartan granules according to the process followed in Example 3 and compress using appropriate tooling.

Barrier Coat

Coat irbesartan tablets using opadry dispersion to a weight build up of 2% w/w.

Hydrochlorothiazide layer

1. Disperse hydroxypropyl methylcellulose and hydroxy propyl cellulose in purified water and stir until a clear solution is obtained.

2. Disperse hydrochlorothiazide in the solution of step 1 with continuous stirring to obtain a uniform dispersion.

3. Film coat the barrier coated irbesartan tablets using the hydrochlorothiazide dispersion of step 2.

*ASTM: American Society of Testing and Materials

Example 6: Irbesartan and Hydrochlorothiazide Multiparticulates in a Tablet

Hydrochlorothiazide granules

1.	Hydrochlorothiazide
2.	Microcrystalline cellulose
3.	Hydroxypropyl methylcellulose 5cps
4.	Calcium Stearate
5.	Purified Water

Process

1. Sift Hydrochlorothiazide and Microcrystalline cellulose.

2. Blend premix of step 1 for 10 min.

3. Dissolve hydroxypropyl methylcellulose in purified water under stirring.

4. Granulate premix of step 2 using binder solution of step 3, and then dry the granules

and sift.

5. Sift Calcium Stearate and blend with materials of step 4.

Barrier coat

Hydrochlorothiazide granules coated using the following dispersion.

6. Opadry White

7. Purified Water

Irbesartan Granules

1.	Irbesartan
2.	Lactose monohydrate
3.	Pregelatinized starch
4.	Croscarmellose sodium
5.	Colloidal silicon dioxide
6.	Microcrystalline cellulose
7.	Poloxamer
8.	Ferric oxide (red)
9.	Ferric oxide (yellow)
10.	Purified water

Process:

8. Sift Iron oxide (Red) and Iron Oxide (Yellow) through ASTM # 60 sieve along with a portion of the microcrystalline cellulose.

9. Sift together Irbesartan, Lactose monohydrate, Colloidal Silicon Dioxide, Croscarmellose Sodium, Pregelatinized Starch and the remaining portion of microcrystalline cellulose along with the materials of step 8 through ASTM # 35.

10. Transfer the material of step 9 to a Rapid Mixer Granulator and mix for 10 minutes.

11. Sift Poloxamer through mesh # 18 ASTM and dissolve in purified water under stirring.

12. Granulate the material of step 10 with the poloxamer solution of step 11 in the Rapid Mixer Granulator.

13. Dry the material of step 12 in a Fluid Bed Drier at 50° - 60°C until the loss on drying is not more than 2.5% w/w.

14. Sift the dried granules through ASTM # 30.

15. Compress using appropriate tooling.

Accelerated Stability Studies of Irbesartan-Hydrochlorothiazide tablets, 150/12.5 mg

The chemical and physical stability of packaged irbesartan and hydrochlorothiazide tablets under accelerated stability conditions of 40°±2°C and 75±5% relative humidity, were evaluated on the basis of assay, in vitro dissolution, moisture content and related substances measured between initial and 3-month time points. The tablets were prepared according to Example 1.

Container: 60CC HDPE bottle with Child resistant (CR) closure, Pack: 30's.

TABLE 1

Time (Months)	Parameters		
	Assay (mg/tablet)		Moisture content (% w/w)
	Irbesartan	Hydrochlorothiazide	
0	151.6	12.5	2.8
1	150.1	12.1	2.3
2	149.2	12.3	1.8
3	148.5	12.8	2.1

Container: 300CC HDPE bottle with CR closure, Pack: 500's.

TABLE 2

Time (Months)	Parameters		
	Assay (mg/tablet)		Moisture content (% w/w)
	Irbesartan	Hydrochlorothiazide	
0	151.6	12.5	2.8
1	150.5	12.2	2.5
2	149.7	12.5	2.3
3	145.2	12.5	2.5

TABLE 3

In vitro dissolution (900 ml, 0.1 N Hydrochloric acid, 50 rpm, USP Apparatus, paddle type, 37°C)

Time (Months)	Percent release (%)			
	Irbesartan		Hydrochlorothiazide	
	Amount of irbesartan dissolved in 45 minutes		Amount of hydrochlorothiazide dissolved in 45 minutes	
	30's pack	500's pack	30's pack	500's pack
0	99	99	98	98
1	98	97	96	97
2	98	98	97	96
3	96	97	93	94

TABLE 4

Related substances (% w/w): 30's pack

Period (Months)	Related substances (% w/w)					
	Irbesartan related compound A	Any other known impurity of Irbesartan	Chloro-thiazide	4-amino-6-chloro-1, 3-benzene disulphonamide	Any Unknown impurity of HCTZ	Total impurity
0	ND	0.017	0.010	0.017	0.070	0.231
1	0.013	0.022	0.016	0.017	0.018	0.112
2	0.009	0.014	0.035	0.021	ND	0.168
3	0.011	0.017	0.030	0.035	ND	0.145

ND = Not detected

TABLE 5

Related substances (% w/w): 500's pack

Period (Months)	Related substances (% w/w)					
	Irbesartan related compound A	Any other known impurity of Irbesartan	Chloro-thiazide	4-amino-6-chloro-1, 3-benzene disulphonamide	Any Unknown impurity of HCTZ	Total impurity
0	ND	0.017	0.010	0.017	0.070	0.231
1	0.011	0.015	0.016	0.017	0.019	0.117
2	0.008	0.013	0.034	0.021	ND	0.156
3	0.020	0.020	0.030	0.037	ND	0.142

ND = Not detected

Pharmacokinetic studies under fed and fasting conditions:

The drug release was evaluated in vivo in a randomized, two treatment, two period, single dose, crossover bioavailability study. The study was conducted in healthy, adult, male, human subjects under fed and fasting conditions. A single dose of Irbesartan 300 mg and Hydrochlorothiazide 12.5 mg tablets was compared with Irbesartan 300 mg and Hydrochlorothiazide 12.5 mg tablets (AVALIDE tablets; Bristol Myers Squibb – Sanofi Synthelabo).

Values for pharmacokinetic parameters, including observed C_{max}, AUC_{0-t} and $AUC_{0-\infty}$, were calculated using standard non-compartmental methods. The results as indicated by ratio of test to reference are shown in Tables 6 and 7.

Reference **R**: Avalide® (300 mg/12.5 mg) tablets, Manufactured by Bristol Myers Squibb and Sanofi

Test **T**: Irbesartan hydrochlorothiazide tablets (prepared according to Example 1)

Table 6. Summary of pharmacokinetic parameters for irbesartan

		Parameters		
		C_{max} (ng/ml)	**AUC $_{(0-t)}$ (ng.hr /ml)**	**AUC $_{(0-\infty)}$ (ng.hr /ml)**
Fasting conditions	Ratio % (T/R)	107.92 (101.4 – 114.87)	101.7 (96.89 -106.75)	102.26 (97.4 – 107.37)
Fed conditions	Ratio % (T/R)	99.54 (91.27 – 108.56)	96.17 (90.38 – 102.33)	98.25 (93.39 – 103.35)

Table 7. Summary of pharmacokinetic parameters for hydrochlorothiazide

		Parameters		
		C_{max} (ng/ml)	**AUC $_{(0-t)}$ (ng.hr /ml)**	**AUC $_{(0-\infty)}$ (ng.hr /ml)**
Fasting conditions	Ratio % (T/R)	96.7 (91.08 – 102.66)	103.29 (98.22 – 108.62)	103.32 (98.3 – 108.6)
Fed conditions	Ratio % (T/R)	97.95 (90.98 – 105.45)	97.65 (94.42 – 100.99)	99.16 (95.24 - 103.24)

While several particular forms of the invention have been illustrated and described, it will be apparent that various modifications and combinations of the invention detailed in the text can be made without departing from the spirit and scope of the invention.

WE CLAIM:

1. A stable oral pharmaceutical composition comprising irbesartan and hydrochlorothiazide, wherein the irbesartan and hydrochlorothiazide are present as distinct portions within the composition.

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

3. The composition according to claim 2, wherein the ibesartan is present intragranularly and the hydrochlorothiazide is present extragranularly.

4. The composition according to claim 2, wherein the ibesartan is present extragranularly and the hydrochlorothiazide is present intragranularly.

5. The composition according to claim 2 wherein the tablet is a multiple compression tablet.

6. The composition according to claim 5 wherein the multiple compression tablet is a layered tablet, compression coated tablet or an inlay tablet.

7. The composition according to claim 6 wherein the layered tablet is prepared by compressing the granules of one active onto tablet of the other active.

8. The composition of claim 6 wherein the compression-coated tablet is prepared by compressing the granules of one active ingredient around all the surfaces of the tablet or pellet of the other active ingredient.

9. The composition according to claim 6 wherein the inlay tablet is prepared by compressing the granules of one active ingredient around all except one surface of the tablet of the other active ingredient.

10. The composition according to claim 2 wherein the tablet is coated.

11. The composition according to claim 10 wherein one active ingredient is present in the core and the other active ingredient is present in the coat.

12. The composition according to claim 1 wherein the composition is in the form of multiparticulates comprising a first particulate phase of one active ingredient and a second particulate phase of the other active ingredient.

13. The composition according to claim 12 wherein the multiparticulates are in the form of one or more of pellets, beads, granules, slugs, powder and particles.

14. The composition according to claim 12 wherein the multiparticulates are filled into capsules.

15. The composition according to claim 12 wherein the multiparticulates are compressed into tablets.

16. The composition according to claim 1 wherein the irbesartan comprises between 20 and about 70% by weight of the composition.

17. The composition according to claim 1 wherein the hydrochlorothiazide comprises between 2 and about 30% by weight of the composition.

18. The composition according to claim 1 wherein the two distinct portions are separated by a barrier layer.

19. A process for the preparation of a stable oral pharmaceutical composition comprising irbesartan and hydrochlorothiazide, wherein the process comprises the steps of:

(i) granulating irbesartan and one or more pharmaceutically acceptable excipients with an aqueous surfactant solution to form granules,

(ii) separately blending hydrochlorothiazide with pharmaceutically acceptable excipients,

(iii) mixing the irbesartan granules with the hydrochlorothiazide blend; and

(iv) compressing the mixture into tablets.

20. A method for the treatment of hypertension in a patient in need thereof, the method comprising administering a stable oral pharmaceutical composition comprising irbesartan and hydrochlorothiazide, wherein the two actives are present as distinct portions within the composition.

INTERNATIONAL SEARCH REPORT

Inter nal application No
PCT/IB2005/003861

A. CLASSIFICATION OF SUBJECT MATTER
INV. A61K9/20 A61K9/24 A61K31/54 A61K31/4178 A61P9/12
A61K9/28 A61K9/54

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

B. FIELDS SEARCHED

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

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

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

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 6 342 247 B1 (KU CATHY C ET AL) 29 January 2002 (2002-01-29) cited in the application page 4, line 62 - page 5, line 3 column 10 - column 11; example 4	1-20
X	US 2004/242567 A1 (COSNIER-PUCHEU SYLVIE ET AL) 2 December 2004 (2004-12-02) page 3; examples 4,5	1,2,12, 13, 15-17,20
E,X	WO 2006/025566 A (TOYOTA JIDOSHA KABUSHIKI KAISHA; ASADA, TOSHIAKI; EZAKI, SHUICHI; TATE) 9 March 2006 (2006-03-09) claim 1 page 10; example 3	1,2,12, 13, 15-17,20

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

☒ See patent family annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

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

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

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

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

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

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

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
11 April 2006	25/04/2006

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

International application No.
PCT/IB2005/003861

Box II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claim 20 is directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. [ ] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/IB2005/003861

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 6342247 B1	29-01-2002	NONE	
US 2004242567 A1	02-12-2004	BR 0213479 A	03-11-2004
		CA 2461625 A1	01-05-2003
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WO 2006025566 A	09-03-2006	NONE	