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(57) Abstract: The present invention relates to an oral, stable pharmaceutical composition of angiotensin converting enzyme (ACE) inhibitor in combination with a diuretic, and to a process for preparation thereof.

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SOLID COMPOSITION

FIELD OF THE INVENTION

The present invention relates to an oral, stable pharmaceutical composition of angiotensin converting enzyme (ACE) inhibitor in combination with a diuretic, and to a process for preparation thereof.

BACKGROUND OF THE INVENTION

ACE inhibitors have achieved widespread usage in the treatment of cardiovascular and renal disease. ACE inhibitors have been reported to alter the balance between the vasoconstrictive, salt-retentive, and hypertrophic properties of angiotensin II and the vasodilatory and natriuretic properties of bradykinin and alter the metabolism of a number of other vasoactive substances. Chemically, three different classes of ACE inhibitors are well known viz., a) Sulfhydryl containing ACE inhibitors structurally related to captopril such as fentiapril, pivalopril, zofenopril, alacepril; b) di-carboxyl-containing ACE inhibitors structurally related to enalapril such as lisinopril, benzapril, quinapril. c) Phosphorus containing ACE inhibitors structurally related to fosinopril. Therapeutically and commercially important ACE inhibitors can be selected from the group consisting of ramipril (US 5,061,722), quinapril (US 4,344,949), enalapril (US 4,374,829), spirapril (US 4,470,972) and lisinopril (US 4,374,829).

Ramipril, (2S, 3aS, 6aS)-1 [(S) – N – [(S) – 1– carboxy – 3 – phenyl propyl] alanyl] octahydrocyclopenta [b] pyrrole-2-carboxylic acid, 1-ethyl ester, is available in the United States and elsewhere under the brand name of Altace® in the form of capsule in strengths of 1.25 mg, 2.5 mg, 5 mg and 10 mg. Marketed capsule formulation is a two-piece hard gelatin capsule filled with a mixture of ramipril and pregelatinized starch and has found wide applicability in the treatment of hypertension, heart failure, stroke, myocardial infarction, diabetes and cardiovascular disease (Prescribing Information for Altace® available at http://kingpharm.com/kingpharm/uploads/ pdf_inserts/Altace_Web _PI.pdf).

The preparation of a stable pharmaceutical composition of ACE inhibitors such as ramipril, has vexed researchers since long because of the difficulty to formulate into

dosage forms as for most ACE inhibitors, contact with many of the excipients commonly used in pharmaceutical products accelerates the rate of degradation of the ACE inhibitors rendering such product unstable and devoid of long shelf-life. Moreover, it has been found that a significant cause of degradation can be the mechanical stress associated with the manufacturing process of pharmaceutical compositions such as compression. It is thus generally difficult to select the excipients that enable dosage forms with adequate stability (US 4,743,450; US 5,562,921; US 6,790,861; US 2005/0202081).

Moreover, the preparation of stable pharmaceutical composition of ACE inhibitors, such as ramipril, is complicated since it is susceptible to certain types of degradation. Ramipril can undergo cyclization via internal nucleophilic attack to form substituted diketopiperazines and also degrade via hydrolysis and oxidation. Similarly, quinapril, enalapril and spirapril degrade readily in dosage from to a diketopiperazines and diacids. It is believed that one or more of these types of degradation including oxidation causes the discoloration in pharmaceutical compositions containing ACE inhibitors (US 2005/0142196).

Various methods/attempts of improving the stability of certain ACE inhibitors have been disclosed. To name a few:

i) Harris et. al. in US 4, 743, 450 discloses a pharmaceutical composition of ACE inhibitors, stabilized by addition of suitable alkali or alkaline earth metal carbonate to inhibit cyclization and discoloration, and a suitable amount of a saccharide to inhibit hydrolysis. The examples of suitable alkaline stabilizers include the inorganic salts of metals of Groups I and II of the Periodic Table;

ii) Sherman et. al. in US 5, 562, 921 has disclosed that stable tablets can be made using anhydrous lactose as filler and zinc stearate as lubricant. It is also mentioned that enalapril maleate is particularly unstable in the presence of microcrystalline cellulose and calcium phosphates, and also in the presence of magnesium stearate, which is the most commonly used lubricant;

iii) Murthy et. al. in US 4, 830, 853 discloses that the composition of ACE inhibitors can be stabilized against oxidation and discolourants by including

ascorbic acid or sodium ascorbate in the composition. The effect of the ascorbic acid is maximized when certain lubricants, e.g., Sterotex.RTM., and/or talc, are used in combination therewith;

iv) Jerzewski et. al. in US 5, 006, 344 teaches that compositions are relatively unstable if they comprise magnesium stearate as lubricant, but stability can be improved by use of sodium stearyl fumarate or hydrogenated vegetable oil as lubricant;

v) Vivilecchia et. al. in US 6, 790, 861 discloses that a pharmaceutical composition of ACE inhibitor could be stabilized by the use of certain acid donors and, more particularly, a select group of hydrochloric acid donors. Preferred acid donors include amino acid hydrochlorides and Lewis acid chlorides, whereas the most preferred acid donor is glycine hydrochloride;

vi) Hrakovsky et. al. in a published Application, US 2005/0069586 discloses that a pharmaceutical composition of ACE inhibitors could be stabilized by using an effective amount of lubricant, preferably sodium stearyl fumarate;

vii) Patel et. al. in US 2005/0009806 discloses that a pharmaceutical composition of an ACE inhibitor could be stabilized by utilizing an alkali or alkaline earth metal carbonate, and a low-substituted hydroxypropyl cellulose;

viii) Eyjolfsson et. al. in US 2005/0118259 discloses that a stable pharmaceutical composition of an ACE inhibitor could be prepared by using alkali or alkaline earth metal carbonate; and an alkaline-earth metal salt of hydrogen phosphate and keeping such formulation free of any stabilizing amount of a saccharide compound;

ix) Bahl et. al. in US 2005/0202081 discloses when ACE inhibitor is applied as a coat to the core, preferably to a compressed core, avoids degradation (such as cyclization to diketopiperazine) induced by mechanical stress, which builds up during compression. Such an arrangement also avoids the direct contact of the tabletting auxiliaries with the ACE inhibitor, thereby avoiding degradation by any incompatible tablet auxiliaries; and

x) Fulbreth et. al. in US 5, 151, 433 discloses that a stable formulation of ACE inhibitors could be obtained by applying a polymeric protective coating to an agglomerate of ACE inhibitor, particularly ramipril.

Thus, all the abovementioned approaches for stabilization of a pharmaceutical composition of an ACE inhibitor could be classified in various categories, such as:

i) Addition of a stabilizing amount of an excipient; and
ii) Utilization of coating technology.

However, both these methodologies suffer from one or more of the following drawbacks:

a) Most of the teachings disclose addition of a stabilizing amount of an excipient in order to render a pharmaceutical composition of ACE inhibitors sufficiently stable for pharmaceutically acceptable duration. Commonly used excipients are lubricants and/or fillers. However, teachings of the prior art is often conflicting and many times are poles apart from each other, thereby leaving a practitioner bewildered. For e.g. Sherman et al in US 5 562 921 teach addition of lactose as filler to a composition of an ACE inhibitor, whereas Eyjolfsson et al in US 2005/0118259 teach to make a composition of an ACE inhibitor free of sugars to render them stable.
b) Further, utilization of an additional excipient, as stabilizer can produce unwanted pharmacological effects. Health Authorities all over the world are concerned regarding the safety and toxicity profile of excipients used in pharmaceutical compositions and regulatory norms, all over the world are very stringent and may require additional data for pharmacological effects of such excipients.

Further, in US 5, 256, 687, Becker et al has disclosed that the antihypertensive action of an angiotensin converting enzyme inhibitor is potentiated by the addition of effective amounts of a diuretic. The used diuretics are known in the prior art for example furosemide, diuril, amiloride, hydrochlorothiazide or hydrodiuril. Similar synergistic effects of angiotensin converting enzyme inhibitor and diuretic have been reported in US 6, 653, 336 by Guez et al.

Accordingly, a fixed-dose combination of ramipril (angiotensin converting enzyme inhibitor) and hydrochlorothiazide (thiazide diuretic) is available in India under the

brand name of Ramipres-H®, Ramipro-H®, Rampri-H® (http://www.cipladoc.com /html/cardiology/newintrocipla.htm; http://www.emcure.co.in/html/product_range2.htm). This fixed-dose combination provides a balanced and synergistic antihypertensive effect in controlling blood pressure in hypertension along with a significant regression of left ventricular hypertrophy. Also, this combination is efficacious in a wide range of patient population - young as well as the elderly and in patients with low as well as high levels of renin. The efficacy of ramipril and hydrochlorothiazide combination has been well established over the monotherapy in various trials. The combination of ramipril-hydrochlorothiazide is reported to be well tolerated and the efficacy is maintained over 1-year period. Normally, the fixed dose combination of ramipril and hydrochlorothiazide contains Ramipril 2.5 mg and Hydrochlorothiazide 12.5 mg.

However, again preparation of a pharmaceutical combination comprising fixed doses of an angiotensin converting enzyme inhibitor and a diuretic is challenging. The disclosed methods for preparation of pharmaceutical compositions containing an angiotensin converting enzyme inhibitor and a diuretic either utilizes coating of angiotensin converting enzyme inhibitor on a core comprising diuretic (US 2005/0202081) or take recourse to multilayer tabletting process and therefore, suffers from the abovementioned disadvantages in each case with regard to formulation of angiotensin converting enzyme inhibitor.

In view of the above, a great need, if not imperative, exists for more simple, economical and commercially viable methods which would utilize proper blend of selected excipients for stabilizing the ACE inhibitor formulations in combination with a diuretic.

OBJECTS OF THE INVENTION

It is therefore, an object of the present invention to provide a novel, stabilized pharmaceutical composition of ACE inhibitor in combination with diuretics.

Another object of the present invention is to provide a stabilized pharmaceutical composition of an ACE inhibitor and hydrochlorothiazide.

A further object of the present invention is to provide a stabilized pharmaceutical composition of ramipril and hydrochlorothiazide.

Yet another object of the present invention is to provide a process for preparation of stabilized pharmaceutical composition of ACE inhibitor in combination with a diuretic, particularly ramipril and hydrochlorothiazide.

SUMMARY OF THE INVENTION

The present invention relates to a pharmaceutical composition of ACE inhibitors, which are susceptible to degradation. More particularly, the present invention provides a novel pharmaceutical composition of an ACE inhibitor and a diuretic.

Thus, according to the present invention, angiotensin converting enzyme inhibitor and diuretic are formulated separately and then are provided in single pharmaceutical dosage form, preferably, hard gelatin capsule.

Further, according to present invention, it is not only separate formulating strategy but also judicious selection of proper excipients, leads to a stable formulation comprising a fixed dose combination of an angiotensin converting enzyme inhibitor and a diuretic.

Thus, ACE inhibitor, in particular ramipril, is formulated preferably as a blend containing compatible excipients. Magnesium stearate and Anhydrous Lactose are preferred as excipients.

Flow of blend and weight variation depends on the bulk density of the excipients used. If Bulk Density is on lower side, flow of the powder from hopper to the capsule will be poor and will lead to the weight variation. Even the bulk density affects the selection of the size of the capsules. Tapped Bulk density of Anhydrous Lactose is 0.85g/cc.

Further, in another embodiment of the present invention, the above formulation of ACE inhibitor is free of any disintegrating agent. Since, ACE inhibitor is provided in powder/blend form, it rapidly dissolves in the gastro-intestinal fluids and is readily absorbed.

In yet another embodiment of the invention, diuretic, in particular, hydrochlorothiazide is separately subjected to tabletting process and compression. The tablet of diuretic is prepared according to known methods in the art and employing commonly used excipients. Such tablet may be further coated to provide suitable attribute to the formulation.

Subsequently, both the formulation viz., a coated tablet of hydrochlorothiazide prepared by using tabletting process involving compression and a blend of ramipril containing excipients are presented in a suitable pharmaceutical dosage form, preferably in hard gelatin capsule.

The pharmaceutical compositions disclosed above have, not only good storage stability and dissolution characteristics, but also are prepared by a simple, economical process and are suitable for use in treatment of various clinical applications.

Thus, in one aspect, the present invention provides a stable pharmaceutical composition comprising an ACE inhibitor and a diuretic.

In another aspect, the present invention provides a pharmaceutical composition, comprising an ACE inhibitor and hydrochlorothiazide.

In still another aspect, the present invention provides a pharmaceutical composition, comprising ramipril and hydrochlorothiazide.

In yet another aspect the present invention provides a pharmaceutical composition, wherein the blend of ramipril has not been prepared by employing high compression.

DETAILED DESCRIPTION OF THE INVENTION:

The pharmaceutical composition of the present invention comprises typically a combination of:

a) ACE inhibitor in the form of a blend; and

b) Diuretic in the form of tablet

in a unit dosage form.

Eventhough, the commercially marketed products of ramipril and hydrochlorothiazide are available in the form of tablet, wherein the two APIs are mixed and processed together, our attempts to make a single stable tablet formulation by mixing two APIs have failed, suggesting an existence of incompatibility in two APIs According to the present invention it is found that if both the Active Pharmaceutical Ingredients i.e. API, viz., an angiotensin converting enzyme inhibitor and a diuretic, are mixed and compressed together with certain excipients, a stable formulation is not obtained. For example, a series of formulation containing 2.5 mg Ramipril and 12.5 mg hydrochlorothiazide with excipients is prepared, the details of which are summarized in Table- 1.

Table: 1: Details Of Various Tablet Formulation Containing Ramipril And Hydrochlorothiazide Along With Their Stability Data

Sr. No.	Ingredients	F – 1 (mg/tab)	F – 2 (mg/tab)	F – 3 (mg/tab)	F – 4 (mg/tab)
1	Ramipril	2.5	2.5	2.5	2.5
2	DCL-21 Lactose anhydrous	29.58	-	-	-
3	Starch 1500 LM	34.62	29.58	41.2	-
4	Hydrochlorothiazide	12.5	12.5	12.5	12.5
5	Mg- stearate	0.8	0.8	0.8	1.5
6	silica (Cabosil)	3	3	3	3
7	Perlitol SD 200	-	24.58	-	-
8	MCC PH 112	-	10	20	-
9	Sodium starch glycolate	-	-	3	-
10	L HPC-21	-	-	-	60
11	Anhydrous DCP	-	-	-	10.5
12	Croscarmellose sodium	-	-	-	5
13	Mg-carbonate	-	-	-	55
	Tablet wt. [mg]	**83**	**82.96**	**83**	**150**
	Granulation	**Dry mix**	**Dry mix**	**Dry mix**	**Granulation with water**
Stability Evaluation Data:					
1	**Assay (Initial)**				
	Ramipril	107.59%	105.69%	95.83%	106.85%
	HCTZ	103.01%	99.81%	96.78%	103.39%
2	**30°C/65%RH (1Month)**				
	Ramipril	75.68 %	78.44%	81.83	79.85
	HCTZ	97.34%	99.02%	97.60	99.73

3	**40°C/75%RH (1 Month)**				
	Ramipril	29.51%	39.11%	76.42	43.22
	HCTZ	97.81%	100.24%	91.56	100.66

F – Formulation; MCC - Microcrystalline cellulose; RH – Relative Humidity; HCTZ – Hydrochlorothiazide

Thus, from the above Table -1, it would be abundantly evident that the initial assay of ramipril is well within the limits of acceptance for Regulatory Health Authorities. Generally, the acceptance limit given by the most of the Pharmacopoeias for assay of active ingredient is 90 -110 %. However, when these formulations were subjected to stability evaluation at a temperature of 30 ^{0}C and relative humidity (RH) of 65 % for 1-month, it was observed that the ramipril component is decomposed by about 20 to 25 %, whereas when the same formulations were subjected to stability evaluation at a temperature of 40 ^{0}C and relative humidity (RH) of 75 % for 1-month, even higher extent of degradation i.e. from about 25 % to about 75% were observed in above formulation. Moreover, the angiotensin converting enzyme inhibitor is more susceptible to degradation than the diuretics, when the two agents are formulated together. Thus, form above, if an angiotensin converting enzyme inhibitor and a diuretic are mixed and compressed together with excipients, a stable formulation is not at all obtained.

The reasons for above observed degradation in the two APIs could vary from improper selection of excipients to instability due to mechanical stress associated with the manufacturing process. However, the more susceptibility of ramipril towards degradation is attributed to the mechanical stress associated with the manufacturing process.

Thus, according to present invention, the two APIs viz., an ACE inhibitor and a diuretic are formulated separately with judiciously selected excipients and then the two formulations are placed in a suitable dosage unit.

In a preferred embodiment of the present invention, the ACE inhibitor, preferably ramipril is presented as blend along with suitable excipients. However, it could also be presented in other suitable forms such as pellets or tablet prepared by direct compression, which do not require higher amount of mechanical force for compression.

Further, according to present invention, the preferred excipient for the preparation of ramipril blend includes lactose, preferably direct compressible lactose. The preferred amount of Lactose for a unit formulation of ramipril varies from 250.0 mg to 350.0 mg, preferably ranging from 280.0 mg to 305.0 mg. The typical ramipril blend further contains a lubricant, preferably magnesium stearate, which is present in an amount of about 3 mg per capsule.

However, the present ramipril blend formulation may also contain one or more excipients that are normally employed in such pharmaceutical compositions, the only qualifications being that they must not deleteriously affect the stability of the pharmaceutical composition. Examples of such excipients are diluents, binders, disintegrant, lubricant, glidants. A combination of excipients may also be used. Such excipients are known to those skilled in the art, and thus, only few representative examples for each class of excipient are mentioned herein below:

The diluent may be, for example, any pharmaceutically acceptable, non-toxic diluent. Particular examples include lactose, dextrose, sucrose, maltose, microcrystalline cellulose, starch, calcium hydrogen phosphate, mannitol and the like.

Binders may be, for example, starch, sugars, gums, hydroxypropyl methyl cellulose, hydroxyl propyl cellulose or the like. Disintegrant may be, for example, croscarmellose sodium, crospovidone, sodium starch glycolate, bentonite, sodium alginate, hydroxypropylmethyl cellulose or the like. Lubricants may be, for example, talc, magnesium stearate, calcium stearate, or the like. Glidants may be, for example, colloidal silicone dioxide, talc or the like.

The pharmaceutical composition may additionally contain a hydrophilic base such as polyethylene glycol, polyvinyl pyrrolidone, sugar alcohols, such as D-sorbitol, saccharides, such as sucrose, maltose, surfactants, such as polyoxyethylene-hydrogenated castor oil, polyoxyethylene-polyoxypropylene glycol, aminosaccharides, such as meglumine, etc, and the like.

A typical procedure for preparation of ramipril blend comprises of following steps:

1. Mixing of active agent and suitable excipients such as lactose in geometrical proportion;
2. Lubricating the above blend with suitable lubricant; and
3. Filling appropriate amount of the blend of step 2 into suitable unit dosage form.

In the above process, active agent and excipients such as lactose can be passed through appropriate mesh size either independently or collectively. The mixing is done according to process known in the prior art such as by using blender or mixer etc.

A typical hydrochlorothiazide tablet is prepared by using hydrochlorothiazide and lactose; preferably direct compressible lactose, sodium stearyl fumarate, microcrystalline cellulose, magnesium stearate as excipients. However, the present tablet formulation may also contain one or more excipients that are normally employed in pharmaceutical compositions, the only qualifications being that they must not deleteriously affect the stability of the pharmaceutical composition. Examples of such excipients are surfactants, diluents, binders, aminoacids, solubilizers, disintegrants, fillers, lubricants, buffers, stabilizers, colorants, dyes, antioxidants, anti-adherents, preservatives, and glidants. A combination of excipients may also be used. Such excipients are known to those skilled in the art, and thus, only few representative examples for each class of excipient are mentioned herein below:

Examples of fillers include microcrystalline cellulose, dibasic calcium phosphate dihydrate, calcium sulfate trihydrate and calcium sulfate dehydrate. A combination of fillers may also be used. Most preferred filler is microcrystalline cellulose.

Examples of lubricants include magnesium stearate, sodium stearate, calcium stearate, zinc stearate, talc. A combination of lubricants may also be used. A preferred lubricant is magnesium stearate.

Examples of glidants include silica, magnesium trisilicate, powdered cellulose, talc, calcium silicate, and tribasic calcium phosphate. Colloidal silica, e.g., Aerosil.

Examples of disintegrants include:

(i) cross-linked polyvinylpyrrolidones, e.g., crospovidones, such as Polyplasdone® and Kollidon® CL;

(ii) alginic acid and sodium alginate;

(iii) methacrylic acid-divinylbenzene co-polymer salts, e.g., Amberlite® IRP-88; and

(iv) cross-linked sodium carboxymethylcellulose, available as, e.g., Ac-di-sol®, Primellose®, Pharmacel® XL, Explocel® and Nymcel®

Additional disintegrants also include hydroxypropylmethyl cellulose, croscarmellose sodium, polacrillin potassium, polyacrylates, such as Carbopol®, magnesium aluminium silicate and bentonite.

The pharmaceutical compositions of the invention can be prepared by any of the conventionally employed tablet processing techniques such as dry granulation or wet granulation process. A typical process comprises of the following steps:

1. Mixing of active agents along with all the ingredients;
2. Lubricating the above blend with suitable lubricant; and
3. Compressing the blend of step 2 on suitable punches.

In the above process, active agents and excipients can be passed through the appropriate mesh size either independently or collectively. Mixing can be done by using the process known in the art such as by using blender or mixer. Punches used for compression could be used from those known in the art such as standard compression punches of 5.5 mm and the like.

A typical hydrochlorothiazide tablet obtained by abovementioned procedure has weight of about 80 mg, thickness of 2.8 and hardness not less than 3 Kg.

The prepared tablet of diuretic could optionally be further coated to incorporate specific attributes to the formulation. Coating could be employed by using coating agents and methods known in the art. For example coating agent could be selected from the group comprising polymethacrylates, cellulose polymers such as ethyl celluloses, hydroxypropyl-methyl celluloses, hydroxypropyl celluloses and cellulose

acetophthalates and combinations of these polymers with each other optionally combined with plasticizers or soluble agents, such as polyols. A typical hydrochlorothiazide is preferably seal coated using suitable coating agents such as Opadry®. Preferably, tablets are coated with the Opadry coating solution to get 2% weight gain.

The above two formulations, which are separately prepared are filled in a capsule, preferably by using semiautomatic capsule filling machine. The preferred capsules, which could be used for filling of formulations are of size '1' and has weight of about 80 mg and typically contains ramipril blend of about 320 mg and a hydrochlorothiazide tablet weighting 80 mg.

Since ACE inhibitors are susceptible to certain types of degradation, there are several impurities formed during the manufacturing process and storage of the formulation. It is of high importance to minimize this degradation. The provided formulation is found to be sufficiently stable and show minimized decomposition rendering such formulation acceptable by Health Authorities.

Thus, according to present invention, active agents viz., ACE inhibitor present in the form of blend, and diuretic present in the form of tablet, are present in therapeutically effective amount in the final formulation. For example a typical formulation comprising ramipril and hydrochlorothiazide, provided in the form of a hard gelatin capsule, would contain ramipril in the range of about Ramipril 1.25, 2.5, 5.0 mg, 10 mg per unit dosage formulation. The amount of hydrochlorothiazide would be about 12.5 mg.

The principles, preferred embodiments, and modes of operation of the present invention have been described in the foregoing specification. The invention which is intended to be protected herein, however, is not to be construed limited to the particular forms disclosed, since these are to be regarded as illustrative rather than restrictive. Variations and changes may be made by those skilled in the art, without departing from the spirit of the invention.

The invention is further explained with the help of following illustrative examples, however, in no way these examples should be construed as limiting the scope of the invention.

EXAMPLES

Example- 1: Comparison of composition of invention with marketed samples

Table – 2: ***Comparison of Different Marketed Samples of Ramipril and Hydrochlorothiazide Product with Emcure's developed Product***

Parameters	Marketed Sample			Composition of invention
	Cardace -H	**Ramcor –H5**	**Ecator -H**	
Physical separation of Ramipril and HCTZ	No	No	No	**Yes**
Dosage form	Capsule shaped **uncoated Tablet**	**Uncoated round Tablet**	**Uncoated round Tablet**	Capsule containing **blend** of Ramipril and **Coated Tablet** of HCTZ
Processing manner	Mixing of Ramipril and HCTZ	Mixing of Ramipril and HCTZ	Mixing of Ramipril and HCTZ	**NO** Mixing of Ramipril and HCTZ
Label Claim	Ramipril 5.0mg HCTZ 12.5mg	Ramipril …5.0mg HCTZ 12.5mg	Ramipril …5.0mg HCTZ 12.5mg	Ramipril …5.0mg HCTZ …12.5mg

The above table shows that the three marketed samples of ramipril and hydrochlorothiazide combination formulation are available as either capsule shaped tablet or round tablet. In preparation of such formulation, ramipril and hydrochlorothiazide are mixed together and then formulated into suitable dosage form.

As against this, in the composition of the invention, ramipril and hydrochlorothiazide are never mixed during preparation of pharmaceutical dosage form. In fact, in the formulation according to present invention the two APIs are processed separately and ramipril is presented as a blend and hydrochlorothiazide is presented as tablet, preferably coated tablet. By such a presentation, the contact of the two APIs is minimized. To say in other words, physical separation of the two APIs is achieved.

Example 2: Storage stability

Different formulations of ramipril blend as well as hydrochlorothiazide tablet were prepared for determining the effects of various excipients as well as their amount, when present in formulation together with drug, on storage stability of drug. Accordingly, several formulations of ramipril blend and hydrochlorothiazide tablet were prepared, the details of which are summarized in Table- 3 and 4.

Table -3: Different Trials For Preparing Ramipril Blend And Determining The Effects On Stability Of Ramipril

Ingredients	F – 1 (mg/cap)	F – 2 (mg/cap)	F – 3 (mg/cap)	F– 4 (mg/cap)	F – 5 (mg/cap)	F – 6 (mg/cap)
Ramipril	2.5	2.5	2.5	2.5	2.5	2.5
Lactose (DCL -21)	293.25	294.5	0	0	0	0
Meglumine	1.25	0	0	1.25	0	1.25
Perlitol SD 200	0	0	294.5	293.25	0	0
Starch 1500LM	0	0	0	0	294.5	293.25
Mg-stearate	3	3	3	3	3	3

F – Formulation; RH – Relative Humidity;

Table -4: Different Trials For Preparing Hydrochlorothiazide Tablet

Ingredients	F – 1	F – 2	F – 3	F– 4	F – 5	F – 6
HCTZ	12.5	12.5	12.5	12.5	12.5	12.5
(DCL-11) Lactose	41.75	41.75	21.75	21.75	21.75	21.75
Sodium stearyl fumarate	3	3	3	3	3	3
MCC (PH 102)	10	35.75	35.75	35.75	35.75	35.75
silica (Cabosil)	.2	1	1	1	1	1
SSG	5	5	5	5	5	5
Mg-Stearate	0.75	1	1	1	1	1

F – Formulation; HCTZ – Hydrochlorothiazide; MCC – microcrystalline cellulose; SSG – sodium starch glycolate

All hydrochlorothiazide tablets were prepared by dry mix process. Above ramipril formulation blend and hydrochlorothiazide tablets are placed in size '1' hard gelatin capsule and are subjected to one-month stability studies at 30 ^{0}C/65% RH and at 40 ^{0}C /

75%RH. The result of the same along with evaluation of dissolution and content uniformity are presented in Table- 5:

Table – 5: Stability Data For Different Trials Of Ramipril And Hydrochlorothiazide Tablet.

Tests	F – 1 (mg/ cap)	F – 2 (mg/cap)	F – 3 (mg/cap)	F – 4 (mg/cap)	F – 5 (mg/cap)	F- 6 (mg/cap)
Assay (Initial)						
Blend (Ramipril)	100.83%	102.09%	103.98%	99.26%	113.345	107.16%
Tablet (HCTZ)	103.21%	98.13%	103.29%	102.83%	100.05%	105.95%
Assay (30°C/65%RH)						
Blend (Ramipril)	93.48	104.79	96	91	90.39	98.14
Tablet (HCTZ)	119.81	99.05	99.64	103.53	100.04	99.12
Assay (40°C/75%RH)						
Blend (Ramipril)	91.87	101.75	96.13	83.11	91.85	95.54
Tablet (HCTZ)	98.4	103.24	100.11	100.37	105.7	102.66
Dissolution (Initial)						
Ramipril						
a. Min.	97.89%	98.23%	88.87%	86.93%	83.04%	91.43%
b. Max.	112.23%	105.21%	93.87%	117.90%	107.12%	98.36%
c. Avg.	99%	101.33%	91.33%	89%	95.57%	95.95%
HCTZ						
a. Min.	94.01%	96.23%	94.12%	94.01%	86.60%	71.77%
b. Max.	111.54%	109.13%	101.73%	102.64%	98.58%	109.10%
c. Avg.	103.57%	101.34%	98.48%	100.97%	94.45%	92.49%
Content Uniformity (Initial)						
Ramipril						
Min.	92%	100.05%	94.13%	88.78%	91.17%	92.05%
Max.	106.70%	110.56%	98.33%	98.83%	115.42%	104.86%
HCTZ						
Min.	94.33%	98.44%	93.03%	94.47%	94.05%	94.37%
Max.	105.02%	103.83%	108.73%	108.13%	112.27%	121.36%

F – Formulation; RH – Relative Humidity; HCTZ – Hydrochlorothiazide

From the above example, it would be evident that, when ramipril is formulated with direct compressible lactose and magnesium stearate as excipient (formulation -2), the active agent showed minimum degradation and the formulation is found to be highly stable. However, when meglumine is added to above formulation in an amount equivalent to 50 % of active agent (formulation -1), there is a 7-8% decrease in the content of active agent when stored at mentioned conditions. Further, when ramipril is formulated with starch (formulation -5) or with perlitol (formulation - 3) a reduction in the content of active agent is observed. Similar results were obtained when meglumine is added to formulation 3 and 5 (formulation - 4 and 6).

Example 3: Stability of tablet and capsule formulations

The Applicant has also carried out a stability test, wherein the Applicant has compared the stability of following two formulations:

a) A Tablet formulation prepared by mixing ramipril and hydrochlorthiaizide representing marketed formulation (formulation -1); and

b) A capsule formulation as disclosed in the present invention, wherein ramipril is provided as blend and hydrochlorothiazide is provided as Tablet (formulation - 2).

The above formulations are then subjected to stability testing at a temperature of 30 ^{0}C and relative humidity (RH) of 65 % as well as at a temperature of 40 ^{0}C and relative humidity (RH) of 75 % for 6-months. The results of this study are presented in Table – 6.

Table -6: Stability study of Formulation 1 and 2

	Formulation -1		Formulation -2	
Assay	**Ramipril**	**HCTZ**	**Ramipril**	**HCTZ**
Initial	104.96	100.38	100.04	106.91
30°C/65%RH (6-month)	88.20	104.95	109.17	106.46
40°C/75%RH (6-month)	19.20	103.50	104.96	107.10

Thus, form the above, it would be abundantly evident that the two APIs are required to be processed separately and when provided as physically separated from each other, it results in a stable formulation (Formulation -2, according to present invention).

However, when the two APIs are mixed and formulated (formulation -1), as in the case of marketed samples, the stability is very poor (Assay 88.20 % and 19.20 %).

Example 4: Comparison of impurity profile

The impurity profile on storage of the formulation as claimed in the instant application was compared with that of marketed sample, namely Cardace –H 2.5. The comparative impurity profile after storage for 9 months on at cool place (temperature of 4 °C) of the two samples is presented in Table –7.

Table -7: Comparative impurity profile of formulation according to present invention with that of marketed sample of Cardace – H, when stored at 4 °C for 9 months

Impurity	Formulation according to instant invention	Marketed sample of Cardace – H 2.5
Ramipril impurity -A	Not Detected	0.242 %
Ramipril impurity -B	Not Detected	Not Detected
Ramipril impurity -C	Not Detected	Not Detected
Ramipril impurity -D	0.632 %	0.816 %
Ramipril impurity -K	Not Detected	0.046 %

Thus, form the Table – 7, it would be evident that, the formulation according to present invention is also superior in terms of impurity profile.

WE CLAIM:

1. A pharmaceutical composition for oral administration comprising:
    a. a first component of ACE inhibitor, with at least one excipients, in the form of blend or pellets; and
    b. a second component of a diuretic in the form of tablet.
2. A pharmaceutical composition according to claim -1, which is provided in the form of capsules.
3. A pharmaceutical composition according to claim -1, wherein the ACE inhibitor is present along with lactose.
4. A pharmaceutical composition according to claim -3, wherein the lactose is anhydrous lactose.
5. A pharmaceutical composition according to claim -1, wherein the ACE inhibitor is ramipril.
6. A pharmaceutical composition according to claim -1, wherein the diuretic is hydrochlorothiazide.
7. A pharmaceutical composition for oral administration comprising:
    a. a first component of ramipril along with at least one excipients, prepared without conventional tabletting techniques involving high mechanical force; and
    b. a second component of a hydrochlorothiazide in the form of tablet.
8. A pharmaceutical composition according to claim -8, wherein the ramipril along with at least one excipient is present as blend or pellets.
9. A pharmaceutical composition according to claim -1, comprising:
    a. Ramipril along with lactose in the form of blend;
    b. Hydrochlorothiazide in the form of tablet

    wherein the final formulation is provided in the form of capsule.
10. A solid oral dosage formulation of ramipril and hydrochlorothiazide as described herein with the help of Examples.