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(54) **Title:** A PHARMACEUTICAL COMPOSITION COMPRISING A COMBINATION OF BETA BLOCKER AND AN ACE INHIBITOR

(57) **Abstract:** A once a day pharmaceutical composition for use in the treatment of cardiovascular disorders includes (a) a first active ingredient comprising a beta blocker; (b) a second active ingredient comprising an ACE inhibitor; and (c) optionally one or more pharmaceutically acceptable excipients. The beta blocker is present in an extended release form and the ACE inhibitor is present in an immediate release form.

A PHARMACEUTICAL COMPOSITION COMPRISING A COMBINATION OF BETA BLOCKER AND AN ACE INHIBITOR

Field of the Invention

This invention relates to a combination of a beta blocker and an ACE inhibitor or their pharmaceutically acceptable salts; pharmaceutical compositions comprising such combinations; processes for their preparation; and methods of using such compositions to treat subjects suffering from cardiovascular disorders, in particular hypertension and heart failure.

Background of the Invention

Combination therapy affords the physician and patient the opportunity to more effectively treat diseases that may stem from more than one cause. When used correctly and appropriately, combination therapy can lead to better outcomes than monotherapy by treating more than one cause of the disease and/or by synergistically enhancing the action of one of the component drugs. Combination therapy also can lead to a better outcome by reducing noncompliance by the patient to a particular regimen.

Compliance is highly important for treating hypertension. However, there are several reasons associated with the noncompliance in case of hypertensives, namely lack of motivation to comply with prescribed medication due to asymptomatic nature of the disease at initial stages, multiple medications and adverse effects associated with the same, and the chronic therapy associated with these medications. This noncompliance to a particular regimen in the case of hypertension may lead to serious complications including sudden cardiac death, cardiac failure, and renal failure; hypertension is the strongest risk factor for atherosclerotic progression, ischaemic heart disease and stroke. Thus, a combination of two anti-hypertensive drugs would make disease management easier for the physician and make the dosage regimen more patient compliant.

A single drug acts mainly on a single pathophysiological mechanism, whereas it is widely known that hypertension is a multifactorial pathology, in which many mechanisms interact. It is also known that when a particular system is blocked, other systems are activated that reduce the initial therapeutic effect. Hence, two classes of medications,

which can act on different physiological systems and could be combined into a single dosage unit, would have an additive effect.

The U.S. application 2005/0032879 describes a combination of metoprolol tartarate and enalapril maleate. According to the applicants, the invention reduces the number of pills a patient is required to ingest on a daily basis from 7-8 pills per day to 2-3 pills per day.

Summary of the Invention

In one general aspect there is provided a once a day pharmaceutical composition for use in the treatment of cardiovascular disorders. The composition includes (a) a first active ingredient comprising a beta blocker; (b) a second active ingredient comprising an ACE inhibitor; and (c) optionally one or more pharmaceutically acceptable excipients. The beta blocker is present in an extended release form and the ACE inhibitor is present in an immediate release form.

Embodiments of the pharmaceutical composition may include one or more of the following features. For example, the cardiovascular disorders may be heart failure and hypertension.

The beta blocker may be one or more of acebutolol, atenolol, betaxolol, bisoprolol, carteolol, carvedilol, esmolol, labetalol, metoprolol, nadolol, penbutolol, pindolol, propranolol, sotalol, timolol and pharmaceutically acceptable salts thereof. The ACE inhibitor may be one or more of benazepril, captopril, enalapril, fosinopril, lisinopril, moexipril, perindopril, quinapril, ramipril, trandolapril and pharmaceutically acceptable salts thereof. The beta blocker may be metoprolol or a pharmaceutically acceptable salt thereof and the ACE inhibitor may be ramipril or a pharmaceutically acceptable salt thereof.

The pharmaceutically acceptable salts of metoprolol may include succinate, fumarate, benzoate, hydrochloride and tartarate. The metoprolol may be present in a dosage range of 20-200 mg and ramipril is present in a dosage range of 1-15 mg.

The extended release form may be an extended release polymer selected from water soluble and water insoluble polymers. The water-soluble polymers may be selected from the group consisting of polyvinylpyrrolidine, hydroxypropylcellulose, hydroxypropyl methylcellulose, methylcellulose, vinyl acetate copolymers, polysaccharides, polyethylene oxide and mixtures thereof. The water-insoluble polymers may be selected from acrylates, cellulose derivatives, polyethylene, high molecular weight polyvinylalcohols and mixtures thereof.

The one or more pharmaceutically inert excipients may be selected from diluents, binders, desiccants, disintegrants, coloring agents, flavoring agents, stabilizers, surfactants, lubricants/glidants, plasticizers and preservatives. The composition may be a tablet or a capsule. The tablet may be an inlay tablet, a compression coated tablet or a bilayer tablet. The capsule may be a beta blocker being present in the form of tablet, granules, minitablet or pellets and an ACE inhibitor being present in the form of a powder, minitablets, pellets, granules or beads.

In another general aspect there is provided a process for the preparation of a pharmaceutical composition that includes the steps of

a) coating an inert core with a drug layer comprising a beta blocker,

b) coating the core with an extended release polymer layer,

c) optionally coating the core with a seal coat,

d) preparing a blend of an ACE inhibitor with one or more pharmaceutically inert excipients,

e) filling the blend of step d) into capsules, and

f) filling the beads of step c) or d) and the ACE inhibitor capsules into capsules.

In another general aspect there is provided a process for the preparation of a pharmaceutical composition that includes the steps of:

a) extruding a beta blocker with suitable excipients,

b) breaking the extruded cylinders into an appropriate length and transforming them into spheroids,

c) coating the spheroids with an extended release polymer coating,

d) optionally, seal coating the spheroids of step c),

e) coating the spheroid of step c) or d) with a drug layer comprising an ACE inhibitor, and

f) filling the spheroids into capsules or compressing them into tablets.

In another general aspect there is provided a process for the preparation of a pharmaceutical composition that includes the steps of:

a) extruding a beta blocker and an extended release polymer with one or more suitable excipients,

b) breaking the extruded cylinders into an appropriate length and transforming them into spheroids,

c) optionally, seal coating the spheroids of step c),

d) coating the spheroid of step c) or d) with a drug layer comprising an ACE inhibitor, and

e) filling the spheroids into capsules or compressing them into tablets.

In another general aspect there is provided a process for the preparation of a pharmaceutical composition that includes the steps of:

i) preparing beta blocker granules in steps comprising

a) blending a beta blocker with one or more pharmaceutically inert excipients;

b) optionally granulating the blend of step a); and

c) lubricating the blend or granules of step a) or step b);

ii) preparing ACE inhibitor granules in steps comprising

a) blending ACE inhibitor and one or more pharmaceutically inert excipients;

b) optionally granulating the blend of step a); and

c) lubricating the blend of step a) or granules of step b); and

iii) compressing the granules of step i) and step ii) to form a bilayer tablet.

In another general aspect there is provided a medicament for the treatment of cardiovascular disorders in a mammal, by administering to the mammal a pharmaceutical composition that includes (a) a first active ingredient comprising a beta blocker; (b) a second active ingredient comprising an ACE inhibitor; and (c) optionally one or more pharmaceutically acceptable excipients. The beta blocker is present in an extended release form and the ACE inhibitor is present in an immediate release form.

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

Description of the Invention

In the instant application, the inventors have developed a process for preparing a once a day pharmaceutical composition for use in the treatment of cardiovascular disorders which comprises combining together:

a) a first active ingredient which is a beta blocker, or a pharmaceutically acceptable salt thereof; and

b) a second active ingredient which is an ACE inhibitor, or a pharmaceutically acceptable salt thereof.

The first and second active ingredients are optionally combined with pharmaceutically acceptable excipients wherein the beta blocker is present as an extended release form and the ACE inhibitor is present as an immediate release form.

According to another aspect, there is provided a once a day pharmaceutical composition for use in the treatment of cardiovascular disorders which includes:

a) a first active ingredient which is a beta blocker, or a pharmaceutically acceptable salt thereof;

b) a second active ingredient which is an ACE inhibitor, or a pharmaceutically acceptable salt thereof;

The pharmaceutical composition optionally includes the first and second active ingredients combined with one or more pharmaceutically acceptable excipients and the beta blocker being present as an extended release form and the ACE inhibitor being present as an immediate release form.

The beta blocker is selected from the group consisting of acebutolol, atenolol, betaxolol, bisoprolol, carteolol, carvedilol, esmolol, labetalol, metoprolol, nadolol, penbutolol, pindolol, propranolol, sotalol, timolol and pharmaceutically acceptable salts thereof. In particular, the beta blocker is metoprolol or pharmaceutically acceptable salts thereof.

Metoprolol, which is a beta adrenoreceptor antagonist, is indicated for the treatment of hypertension. It may be used alone or in combination with other antihypertensive agents. It is also indicated in the long-term treatment of angina pectoris and stable, symptomatic (NYHA Class II or III) heart failure of ischemic, hypertensive, or cardiomyopathic origin.

Metoprolol is rapidly and completely absorbed, however, the plasma levels achieved are highly variable after oral administration. In addition, it also has a relatively short elimination half-life of about 3-7 hours in adults. Frequent dosing is thus necessary to maintain reasonably stable plasma concentrations. However, frequent dosing results in inconvenience to the patient, leading to poor compliance. Moreover, widely fluctuating plasma concentrations of the drug also result in availability of erratic therapeutic response. Hence metoprolol is present in the composition as an extended release form.

The ACE inhibitor is selected from group consisting of benazepril, captopril, enalapril, fosinopril, lisinopril, moexipril, perindopril, quinapril, ramipril, trandolapril and pharmaceutically acceptable salts thereof. In particular, the ACE inhibitor is ramipril or pharmaceutically acceptable salts thereof.

Ramipril is a 2-aza-bicyclo [3.3.0]-octane-3-carboxylic acid derivative. Ramiprilat, the diacid metabolite of ramipril, is a non-sulfhydryl angiotensin converting enzyme inhibitor. Ramipril is converted to ramiprilat by hepatic cleavage of the ester group. Ramipril and ramiprilat are angiotensin-converting enzyme (ACE) inhibitors. Ramipril is indicated for the treatment of hypertension and in stable patients who have demonstrated clinical signs of congestive heart failure within the first few days after sustaining acute myocardial infarction. The preparation and pharmaceutical use of ramipril and its salts are described in EP 79,022 B1.

According to one particular aspect, there is provided a process for preparing a pharmaceutical composition for use in the treatment of cardiovascular disorders which comprises combining together:

a) a first active ingredient which is metoprolol, or a pharmaceutically acceptable salt thereof; and

b) a second active ingredient which is ramipril, or a pharmaceutically acceptable salt thereof.

The process further includes optionally combining the first and second active ingredients with one or more pharmaceutically acceptable excipients wherein metoprolol is present as an extended release form and ramipril as an immediate release form.

According to another aspect, there is provided a pharmaceutical composition for use in the treatment of cardiovascular disorders which comprises combining together:

a) a first active ingredient which is metoprolol, or a pharmaceutically acceptable salt thereof; and

b) a second active ingredient which is ramipril, or a pharmaceutically acceptable salt thereof.

The pharmaceutical composition optionally further includes one or more pharmaceutically acceptable excipients wherein metoprolol is present as an extended release form and ramipril as an immediate release form.

According to another aspect, there is provided a pharmaceutical composition comprising metoprolol and ramipril and pharmaceutically acceptable salts thereof in a

single dosage unit wherein metoprolol is present as an extended release component of the composition and ramipril is present as an immediate release component.

According to another aspect, there is provided a process for preparing a pharmaceutical composition comprising metoprolol and ramipril and pharmaceutically acceptable salts thereof in a single dosage unit wherein metoprolol is present as an extended release component of the composition and ramipril is present as an immediate release component of the composition.

In another aspect, there is provided a process for the preparation of a pharmaceutical composition comprising metoprolol and ramipril or pharmaceutically acceptable salts thereof in a single dosage unit comprising the steps of

a) coating an inert core with a drug layer comprising metoprolol,

b) coating the core with a polymeric coating to provide for extended release of the drug,

c) optionally, coating the core of step b) with a seal coat,

d) coating cores of step b) or c) with a drug layer comprising ramipril,

e) optionally, coating the cores of step d) with a seal coat, and

f) filling the beads of step d) or e) into capsules or compressing into tablets.

According to another aspect, there is provided a method of treating cardiovascular disorders such as hypertension and heart failure by administering to said patient a therapeutically effective amount of metoprolol and pharmaceutically acceptable salts thereof and ramipril and pharmaceutically acceptable salts thereof in a single dosage unit, wherein metoprolol is present as extended release component in the composition and ramipril is present as an immediate release component.

Metoprolol and ramipril may be present in the same matrix or may be separated by one or more pharmaceutically inert excipients.

The term 'extended released component' as used herein includes those components of the pharmaceutical composition that achieve the slow release of drug over an extended period of time, and includes both prolonged and sustained release compositions.

Single dosage unit as used herein includes tablet, capsule, pills and the like. This single dosage unit is suitable for once a day administration.

The present invention incorporates extended release metoprolol and an immediate release ramipril. Metoprolol reduces blood pressure (BP) by competitive antagonism of catecholamines peripherally and through suppression of renin activity. Ramipril reduces BP by inhibition of the angiotensin converting enzyme. Because the two active ingredients act on two different physiological systems, additive effects and enhanced BP reduction would result. The metoprolol component (extended release) and ramipril both have a duration of action of about 24 hours so that once daily dosing with this combination is rational and appropriate for each of the ingredients. Also, this combination does not have any pharmacokinetic interaction.

Acting by differing mechanisms, metoprolol and ramipril in combination would produce an additive antihypertensive effect. Although an enhanced antihypertensive effect can be obtained by using a larger dose of a single drug, this may increase the incidence of side effects. Using low doses of the two drugs in combination would achieve better BP reduction without compromising tolerability. As indicated in Table 1, although they both may have the adverse event of dizziness, there does not appear to be overlap of any severe or serious adverse reaction profile of the two drugs.

Table 1: Adverse event profile of Metoprolol and Ramipril

Metoprolol	Ramipril
Bradycardia	Headache
Dizziness, Tiredness	Cough
Wheezing (Bronchospasm)	Dizziness
Depression	Angioneurotic edema

Metoprolol and ramipril have been shown to be capable of regressing left ventricular hypertrophy, independent of their BP lowering effects. When used in combination, therefore, an additive beneficial effect is expected.

Therapeutically effective amount of metoprolol or pharmaceutically acceptable salt thereof ranges from 20-200 mg equivalent to metoprolol. Therapeutically effective amount of ramipril or pharmaceutically acceptable salt thereof ranges from 1-15 mg

equivalent to ramipril. The combination may comprise strengths such as Metoprolol (extended release) and ramipril – 25 and 2.5 mg; 50 and 2.5 mg; and 100 and 2.5 mg, respectively.

Metoprolol is available in various salt forms such as tartarate, fumarate, succinate, hydrochloride, benzoate, etc. These salts differ in their solubility e.g. succinate, fumarate and benzoate salts have solubility less than 600 mg/ml in water at 25°C, whereas hydrochloride and tartarate are very soluble in water. Generally salts with less solubility are preferred for the preparation of extended release pharmaceutical composition.

Examples of salts of the ACE inhibitors include acid addition salts with organic or inorganic acids. Suitable organic carboxylic acids include salicylic acid, maleic acid, tartaric acid, citric acid, adipic acid, sorbic acid, malonic acid, 1,4-butanedioic acid, malic acid, pivalic acid, succinic acid, nicotinic acid, isonicotinic acid, furan-2-carboxylic acid, acetic acid, benzoic acid, fatty acids such as, for example, lauric acid, myristic acid or oleic acid, and suitable inorganic acids include, for example, hydrochloric acid, hydrobromic acid, hydriodic acid, nitric acid, sulfuric acid and/or phosphoric acid.

The ACE inhibitors have a tendency to undergo decomposition reactions such as hydrolysis, cyclization or oxidation (cf., EP 280,999 B1), which are accelerated by acids or bases. They may be stabilized using buffer substances such as sodium dihydrogen phosphate, sodium citrate, sodium carbonate, sodium hydrogen carbonate or tris(hydroxymethyl)aminomethane and/or by addition of saccharides; cf., EP 317,878 B1.

The pharmaceutical composition may be provided in the form of capsules wherein the capsule comprises beads comprising metoprolol and ramipril.

In one of the embodiments, there is provided a pharmaceutical composition comprising a beta blocker and an ACE inhibitor or pharmaceutically acceptable salts thereof. The composition is formulated by:

a) coating an inert core with a drug layer comprising a beta blocker (e.g., metoprolol),

b) coating the core (of step a) with an extended release polymer layer,

c) coating the metoprolol extended release core of step b) with a seal coat,

d) coating cores of step c) with a drug layer comprising ACE inhibitor,

e) coating the cores of step d) with a seal coat,

f) filling the beads of step e) into capsules.

The pharmaceutical composition may be provided in the form of capsules wherein the capsule comprises two beads *viz.* one of metoprolol and another of ramipril.

In another embodiment, there is provided a pharmaceutical composition comprising metoprolol and ramipril or pharmaceutically acceptable salts thereof. The pharmaceutical composition is formulated by:

a) coating inert cores with a drug layer comprising ramipril,

b) coating separate inert cores with a drug layer comprising metoprolol,

c) coating the cores of step b) with an extended release layer, and

d) filling the beads of step a) and c) into capsules.

The inert core described here can be water insoluble, soluble or swellable.

The pharmaceutical composition may be provided in the form of capsules or tablets wherein the capsule or tablet comprises spheroids.

In another embodiment, there is a provided a pharmaceutical composition comprising metoprolol and ramipril or pharmaceutically acceptable salts thereof comprising the steps of:

a) extruding metoprolol with suitable excipients,

b) breaking the extruded cylinders into an appropriate length and transforming them into spheroids,

c) coating the spheroids with an extended release polymer coating,

d) optionally, seal coating the spheroids of step c),

e) coating the spheroid of step c) or d) with a drug layer comprising ramipril, and

f) filling these spheroids into capsules or compressing them into tablets.

In another embodiment, there is provided a pharmaceutical composition comprising metoprolol and ramipril or pharmaceutically acceptable salts thereof comprising the steps of:

a) extruding metoprolol and extended release polymer with suitable excipients,

b) breaking the extruded cylinders into an appropriate length and transforming them into spheroids,

c) optionally, seal coating the spheroids of step b),

d) coating the spheroid of step b) or c) with a drug layer comprising ramipril, and

e) filing these spheroids into capsules or compressing them into tablets.

The pharmaceutical composition may be provided in the form of tablets wherein metoprolol and ramipril are separated by a layer or a membrane of a physiologically acceptable inert material.

In another embodiment, there is provided a process for the preparation of a pharmaceutical composition comprising metoprolol and ramipril or pharmaceutically acceptable salts thereof comprising the steps of

a) blending metoprolol with one or more pharmaceutically inert excipients,

b) optionally granulating the blend,

c) lubricating the blend or granules,

d) compressing the lubricated blend of step c) into tablet,

e) optionally coating the core with suitable inert excipients,

f) dispersing or dissolving ramipril and other inert excipients in a suitable solvent system, and

g) coating the cores of step e) with a drug layer of ramipril from step f).

The pharmaceutical composition may be provided in the form of tablets wherein metoprolol and ramipril are processed to form a bilayer/multilayer tablet or inlay tablet.

In another embodiment, there is provided a process for the preparation of a pharmaceutical composition comprising metoprolol and ramipril or pharmaceutically acceptable salts thereof comprising the steps of

i) preparation of metoprolol granules

a) blending metoprolol, with one or more pharmaceutically inert excipients,

b) optionally granulating the blend of step a),

c) lubricating the blend or granules of step a) or step b),

ii) preparation of ramipril granules

a) blending ramipril and one or more pharmaceutically inert excipients,

b) optionally granulating the blend of step a),

c) lubricating the blend or granules of step a) or step b), and

iii) compressing the granules of step i) and step ii) to form a bilayer tablet.

In another embodiment, there is provided a process for the preparation of a pharmaceutical composition comprising metoprolol and ramipril or pharmaceutically acceptable salts thereof comprising the steps of

i) preparation of metoprolol tablets

a) blending metoprolol with one or more pharmaceutically inert excipients,

b) optionally granulating the blend of step a), and

c) lubricating the blend or granules of step a) or step b),

ii) preparation of ramipril granules

a) blending ramipril and one or more pharmaceutically inert excipients,

b) optionally granulating the blend of step a), and

c) lubricating the blend or granules of step a) or step b), and

d) compressing the blend of step c) into tablet

iii) compressing the granules of step i) and the tablets of step ii) to form an inlay tablet.

The pharmaceutical composition may be provided in the form of capsules wherein the metoprolol composition is in the form of tablets, minitablets, granules or pellets and the ramipril composition is in the form of the powder, granules, minitablets or pellets.

In another embodiment there is provided a process for the preparation of a pharmaceutical composition comprising metoprolol and ramipril or pharmaceutically acceptable salts thereof comprising the steps of

a) blending metoprolol with one or more pharmaceutically inert excipients;

b) optionally granulating the blend of step a;

c) lubricating the blend or granules of step b;

d) compressing the lubricated blend of step c into suitable size tablet;

e) blending ramipril and one or more pharmaceutically inert excipients; and

f) filling the tablet and ramipril powder blend into a capsule.

The beads or tablets as described above may have an additional non-functional coating such as polyethylene glycol for protection or to improve the aesthetic appeal of the product. The non functional coating may also help in overcoming a common problem of the rupturing or cracking of release controlling layers/membrane or fragmentation of the core due to mechanical stress generated during compression of cores to tablet or filling into a capsule/sachet.

The term "pharmaceutically inert excipient" as used herein includes substances known in the art as diluents, binders, disintegrants, coloring agents, flavoring agents, stabilizers, extended release polymers, surfactants, lubricants/glidants, plasticizers and preservatives for pharmaceutical compositions.

Examples of disintegrants include sodium starch glycolate, croscarmellose sodium, crospovidone, low substituted hydroxypropyl cellulose, and the like.

Examples of binders include methyl cellulose, hydroxypropyl cellulose, hydroxypropyl methylcellulose, polyvinylpyrrolidone, gelatin, gum arabic, ethyl cellulose, polyvinyl alcohol, pullulan, pregelatinized starch, agar, tragacanth, sodium alginate, copolvidone and the like.

Examples of diluents include powdered cellulose, microcrystalline cellulose, dextrates, dextrins, dextrose excipients, fructose, kaolin, lactitol, lactose, mannitol, sorbitol, starch, starch pregelatinized, sucrose, sugar compressible, sugar confectioners, dicalcium phosphate and the like.

Examples of lubricants and glidants include magnesium stearate, sodium stearyl fumarate, colloidal anhydrous silica, stearic acid, magnesium stearate, calcium stearate, talc, hydrogenated castor oil, sucrose esters of fatty acid, microcrystalline wax, yellow beeswax, white beeswax, zinc stearate, silicon dioxide, sodium chloride and the like.

Water insoluble core includes silicon dioxide, small particles of glass, or plastic resin particles such as polypropylene or polyethylene. Water-soluble core includes sugar spheres such as glucose, mannitol, lactose, xylitol, dextrose, sucrose and salt cores such as sodium chloride, potassium chloride. Water swellable core may be made up of hydroxypropyl methylcellulose, microcrystalline cellulose or starch. Inert core may have a diameter ranging from about 150-600 μm, preferably about 250-425 μm.

Examples of extended release polymers include water soluble polymers and water insoluble polymers. Specific examples of water-soluble polymers include polyvinylpyrrolidone, hydroxy propylcellulose, hydroxypropyl methylcellulose, methylcellulose, vinyl acetate copolymers, polysaccharides (such as alginate, xanthum gum), polyethylene oxide, maleic anhydride , methyl vinyl ether copolymers and derivatives and mixtures thereof. Specific example of water-insoluble polymers include acrylates such as methacrylates, methacrylic acid copolymers, acrylic acid copolymers; cellulose derivatives such ethylcellulose or cellulose acetate; polyethylene, and high molecular weight polyvinylalcohols.

Coating may be performed by applying one or more film forming polymers, with or without other pharmaceutically inert excipients, as a solution/dispersion in a suitable

solvent system using any conventional coating technique known in the art, such as spray coating in a conventional coating pan or fluidized bed processor; or dip coating.

Examples of plasticizers include polyethylene glycol, triethyl citrate, triacetin, diethyl phthalate, dibutyl phthalate, dibutyl sebacate and the like.

EXAMPLES

Example 1

		mg/Capsule			
Stage	Ingredients	100 + 2.5 mg	50 + 5.0 mg	50 + 2.5 mg	25 + 2.5 mg
CORE	Sugar spheres	23.75	11.88	11.88	5.94
Metoprolol Layer	Metoprolol Succinate	95.00	47.50	47.50	23.75
	Opadry	9.50	4.75	4.75	2.38
	Purified Water	q.s.	q.s.	q.s.	q.s.
ER Coat	Ethyl Cellulose	11.29	5.64	5.64	2.82
	Opadry	2.82	1.41	1.41	0.71
	Isopropyl Alcohol	q.s.	q.s.	q.s.	q.s.
	Purified Water	q.s.	q.s.	q.s.	q.s.
Seal coating	HPMC	4.27	2.14	2.14	1.07
	Isopropyl alcohol	q.s.	q.s.	q.s.	q.s.
	Water	q.s.	q.s.	q.s.	q.s.
Ramipril layer	Ramipril	2.5	5.0	2.5	2.5
	HPMC	2.25	4.5	2.25	2.25
	HPC	0.25	0.5	0.25	0.25
	Purified Water	q.s.	q.s.	q.s.	q.s.
Overcoat	HPMC	4.55	2.5	2.35	1.25
	Purified Water	q.s.	q.s.	q.s.	q.s.
Lubrication	Talc	1.56	0.86	0.81	0.43

Procedure:

1. A dispersion of Metoprolol succinate and Opadry was prepared in purified water.
2. The dispersion of step-1 was used to coat the sugar spheres to a desired weight gain.
3. A dispersion of Opadry and ethylcellulose was prepared in IPA/ purified water mix.
4. The drug layered beads of step-2 were coated with dispersion of step 3.

5. The coated beads of step-4 were then seal coated with a solution of HPMC in IPA/water mixture.
6. A dispersion of Ramipril was prepared with HPMC and HPC in purified water
7. The beads obtained in step-5 were coated with the ramipril dispersion of step 6.
8. Ramipril coated beads of step-7 were coated with an overcoat as indicated in the table above.
9. The beads obtained in step 8 were lubricated and filled into suitable size capsules.

Example 2

		mg/capsule	
Stage	Ingredients	50 + 5.0 mg	50 + 2.5 mg
CORE	Sugar spheres	11.88	11.88
Metoprolol Layer	Metoprolol Succinate	47.50	47.50
	Opadry	4.75	4.75
	Purified Water	q.s.	q.s.
ER Coat	Ethyl Cellulose	6.41	6.41
	Opadry	1.60	1.60
	Isopropyl Alcohol	q.s.	q.s.
	Purified Water	q.s.	q.s.
Seal coating	HPMC	2.16	2.16
	Isopropyl alcohol	q.s.	q.s.
	Water	q.s.	q.s.
Ramipril Blend	Ramipril	5.0	2.5
	Pregelatinized Starch	125	62.5
	Hard gelatin Capsule	Size 4	Size 4
Hard Gelatin Capsule		Size 1	Size 1

Procedure:

1. A dispersion of Metoprolol succinate and Opadry was prepared in purified water.
2. The dispersion of step-1 was used to coat the sugar spheres to a desired weight gain.
3. A dispersion of Opadry and ethylcellulose was prepared in IPA/ purified water mix.
4. The drug layered beads of step 2 were coated with dispersion of step 3.
5. The coated beads of step-4 were then seal coated with a solution of HPMC in IPA/water mixture.

6. A blend of ramipril and pregelatinized starch was obtained and filled into capsules.

7. The metoprolol beads of step 5 and ramipril capsules of step 6 were filled into capsules.

While several particular forms of the inventions have been described, it will be apparent that various modifications and combinations of the inventions detailed in the text can be made without departing from the spirit and scope of the inventions. Accordingly, it is not intended that the inventions be limited, except as by the appended claims.

CLAIMS

1. A once a day pharmaceutical composition for use in the treatment of cardiovascular disorders, the composition comprising:

a) a first active ingredient comprising a beta blocker;

b) a second active ingredient comprising an ACE inhibitor; and

c) optionally one or more pharmaceutically acceptable excipients,

wherein the beta blocker is present in an extended release form and the ACE inhibitor is present in an immediate release form.

2. The pharmaceutical composition according to claim 1 wherein the cardiovascular disorders comprises heart failure and hypertension.

3. The pharmaceutical composition according to claim 1 wherein the beta blocker comprises one or more of acebutolol, atenolol, betaxolol, bisoprolol, carteolol, carvedilol, esmolol, labetalol, metoprolol, nadolol, penbutolol, pindolol, propranolol, sotalol, timolol and pharmaceutically acceptable salts thereof.

4. The pharmaceutical composition according to claim 1 wherein ACE inhibitor comprises one or more of benazepril, captopril, enalapril, fosinopril, lisinopril, moexipril, perindopril, quinapril, ramipril, trandolapril and pharmaceutically acceptable salts thereof.

5. The pharmaceutical composition according to claim 1 wherein the beta blocker comprises metoprolol or a pharmaceutically acceptable salt thereof and the ACE inhibitor comprises ramipril or a pharmaceutically acceptable salt thereof.

6. The pharmaceutical composition according to claim 5 wherein the pharmaceutically acceptable salts of metoprolol include succinate, fumarate, benzoate, hydrochloride and tartarate.

7. The pharmaceutical composition according to claim 5 wherein the metoprolol is present in a dosage range of 20-200 mg and ramipril is present in a dosage range of 1-15 mg.

8. The pharmaceutical composition according to claim 1 wherein the extended release form comprises an extended release polymer selected from water soluble and water insoluble polymers.

9. The pharmaceutical composition according to claim 8 wherein the water-soluble polymers are selected from the group consisting of polyvinylpyrrolidine, hydroxypropylcellulose, hydroxypropyl methylcellulose, methylcellulose, vinyl acetate copolymers, polysaccharides, polyethylene oxide and mixtures thereof.

10. The pharmaceutical composition according to claim 8 wherein the water-insoluble polymers are selected from acrylates, cellulose derivatives, polyethylene, high molecular weight polyvinylalcohols and mixtures thereof.

11. The pharmaceutical composition according to claim 1 wherein the one or more pharmaceutically inert excipients are selected from diluents, binders, desiccants, disintegrants, coloring agents, flavoring agents, stabilizers, surfactants, lubricants/glidants, plasticizers and preservatives.

12. The pharmaceutical composition according to claim 1 wherein the composition is a tablet or a capsule.

13. The pharmaceutical composition according to claim 12 wherein the tablet is an inlay tablet, a compression coated tablet or a bilayer tablet.

14. The pharmaceutical composition according to claim 14 wherein the capsule comprises a beta blocker being present in the form of tablet, granules, minitablet or pellets and an ACE inhibitor being present in the form of a powder, minitablets, pellets, granules or beads.

15. A process for the preparation of a pharmaceutical composition of claim 1 comprising the steps of

a) coating an inert core with a drug layer comprising a beta blocker,

b) coating the core with an extended release polymer layer,

c) optionally coating the core with a seal coat,

d) preparing a blend of an ACE inhibitor with one or more pharmaceutically inert excipients,

e) filling the blend of step d) into capsules, and

f) filling the beads of step c) or d) and the ACE inhibitor capsules into capsules.

16. A process for the preparation of a pharmaceutical composition of claim 1 comprising the steps of:

a) extruding a beta blocker with suitable excipients,

b) breaking the extruded cylinders into an appropriate length and transforming them into spheroids,

c) coating the spheroids with an extended release polymer coating,

d) optionally, seal coating the spheroids of step c),

e) coating the spheroid of step c) or d) with a drug layer comprising an ACE inhibitor, and

f) filling the spheroids into capsules or compressing them into tablets.

17. A process for the preparation of a pharmaceutical composition of claim 1 comprising the steps of:

a) extruding a beta blocker and an extended release polymer with one or more suitable excipients,

b) breaking the extruded cylinders into an appropriate length and transforming them into spheroids,

c) optionally, seal coating the spheroids of step c),

d) coating the spheroid of step c) or d) with a drug layer comprising an ACE inhibitor, and

e) filling the spheroids into capsules or compressing them into tablets.

18. A process for the preparation of a pharmaceutical composition of claim 1 comprising the steps of:

i) preparing beta blocker granules in steps comprising

a) blending a beta blocker with one or more pharmaceutically inert excipients;

b) optionally granulating the blend of step a); and

c) lubricating the blend or granules of step a) or step b);

ii) preparing ACE inhibitor granules in steps comprising

a) blending ACE inhibitor and one or more pharmaceutically inert excipients;

b) optionally granulating the blend of step a); and

c) lubricating the blend of step a) or granules of step b); and

iii) compressing the granules of step i) and step ii) to form a bilayer tablet.

19. A medicament for the treatment of cardiovascular disorders in a mammal, by administering to the mammal a pharmaceutical composition according to any of the preceding claims.