Abstract:

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Title: CAPSULES OF ACTIVE PHARMACEUTICAL INGREDIENTS AND POLYUNSATURATED FATTY ACID ESTERS FOR THE TREATMENT OF CARDIOVASCULAR DISEASES

Abstract: Pharmaceutical composition in the form of a capsule which contains polyunsaturated fatty acid alkyl esters (PUFA) and active pharmaceutical ingredients for the treatment and/or prevention of cardiovascular diseases.
CAPSULES OF ACTIVE PHARMACEUTICAL INGREDIENTS AND POLYUNSATURATED FATTY ACID ESTERS FOR THE TREATMENT OF CARDIOVASCULAR DISEASES

FIELD OF THE INVENTION

This invention relates to a pharmaceutical composition in the form of a capsule which comprises a suspension of polymeric microcapsules suspended in an oil which contains polyunsaturated fatty acid alkyl esters (PUFA), wherein the microcapsules contain at least one polymer and one active pharmaceutical ingredient, and its use for the treatment and/or prevention of cardiovascular diseases.

BACKGROUND OF THE INVENTION

Among the most used active pharmaceutical ingredients for the treatment of cardiovascular diseases, in particular for the treatment of hypertension, there are the angiotensin-converting enzyme inhibitors (ACE inhibitors) and the angiotensin II receptor blockers (ARB, angiotensin II receptor antagonists). ACE inhibitors and ARBs act on the renin-angiotensin system. ACE inhibitors inhibit the angiotensin-converting enzyme, preventing the conversion of angiotensin I to angiotensin II. They are very effective anti-hypertensive agents which are also used for the treatment of heart failure and myocardial infarction. The majority of ACE inhibitors are administered with the carboxyl group in alpha position with regards to the secondary amino group in the form of diethyl ester, although its acids are the biologically active form.

The ARBs act by blocking the angiotensin II receptor in the arteries, preventing its action. Therefore, the ARBs are also a first-line treatment for hypertension, particularly in the case of patients who develop cough due to ACE inhibitors. ARBs are also used for the treatment of heart failure and diabetic nephropathy.

Polyunsaturated fatty acids (PUFA) also possess a known beneficial effect on the prevention of cardiovascular events and are often used in combination therapy in patients who have suffered some type of cardiovascular episode. There are numerous studies on anti-hypertensive, reduction of serum cholesterol, anti-hypertriglyceridemic, antiarrhythmic, antiplatelet and anti-inflammatory effects of PUFAs [Bucher H.C. et al. Am. J. Med. 112: 298-304 (2002); Benatti P. et al. J. Am. Coll. Nutr. 23: 281-302]
PUFAs are essential fatty acids and should be obtained from a person's diet. They are divided into omega-3 and omega-6 fatty acids depending on the position of the first unsaturation (n-3 and n-6 respectively). The principal omega-3 fatty acids are found in fish oils, such as eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA). PUFAs can be found in the form of triglycerides or alkyl esters. Commercial compositions of omega-3 fatty acid alkyl esters vary in purity and content of fatty acids and are normally expressed in relation to the content in EPA and DHA.

PUFAs, in any of their forms, are easily oxidized and should be stored under an inert atmosphere and protected from light. Commercial compositions contain antioxidants to minimize their degradation.

The great instability of the aforementioned pharmaceutical antihypertensive active ingredients is also known, particularly of the ACE inhibitors. ACE inhibitors can suffer from three types of degradation: a) internal cyclization to form diketopiperazines, b) hydrolysis of the ester group of the side chain to give the diacid, and c) oxidation that produces unwanted colored products. Degradation occurs both in liquid and solid state.

According to WO 2006/050533 A2, EP 0317878 B1, US 5442008 A, US 5151433 A, WO 2004/064809 A1 and EP 1429748 B1, the instability of the known formulations of ramipril is influenced by different factors, such as mechanical stress (compression), the manufacturing process, excipients, storage conditions, heat and moisture. As a consequence, ramipril needs very controlled formulation conditions to minimize the decomposition and avoid the formation of the aforementioned degradation products (diketopiperazine and diacid). According to WO 2008/000040 A1 and WO 2008/001 184 A2, the choice of the different excipients can affect the stability of ramipril and other ACE inhibitors such as quinapril, enalapril or spirapril, accelerating their degradation; furthermore, a significant cause of decomposition is mechanical stress associated with the manufacturing process.

According to US 2007281000 A1, to improve the stability of the active pharmaceutical ingredients sensitive to moisture, water scavenger compounds can be incorporated in the formulation, such as copovidone in the case of cilazapril. Fosinopril is unstable since it is susceptible to hydrolytic degradation in the ester and phosphodiester groups, and the same occurs with the trandolapril ester group; in EP 1906931 B1 the
compositions of these two active ingredients are stabilized with dimethicone, so that cyclization, hydrolysis and/or oxidation are inhibited.

There are numerous examples in the literature which confirm that different ACE inhibitors decompose during the formulation of the active pharmaceutical ingredient, even during the process of preparation of the tablet. This problem is attempted to be solved, for example, by adding acid stabilizers [EP 0264888 B1; EP 0468929 B1; US 4830853 A], the formation of enalapril salts [WO 01/32689], with meglumine [WO 2005/041940 A1], by mixing the ACE inhibitor with a metal dispersion in alcohol [WO 04/071526 A1], through the use of alkali carbonates or alkaline earth metals to inhibit the cyclization or changes in color and a saccharide to inhibit hydrolysis [US 4743450 A], or with magnesium oxide as a stabilizer against the cyclization and means of moisture control [EP 1083931 B1; WO 2008/000040 A1].

The approaches to the stabilization of pharmaceutical compositions which contain ACE inhibitors that do not use the addition of stabilizing excipients would be those which use polymer coatings, such as polymer coatings of agglomerate [US 5151433 A] or of individual particles of ramipril in the final solid formulation [WO 2006/050533 A2], or coating an inert nucleus with the active ingredient itself [US 2005202081 A1] that would avoid degradation induced both by the mechanical stress of compression and the contact of the active ingredient with potentially incompatible excipients.

Some ARBs also show formulation problems, it being necessary to avoid the presence of water according to that deduced from the formulations described in the literature for valsartan [EP 1674080 A1].

Irbesartan, valsartan (both bulky powders) and candesartan cilexetil (sticky), for example, are very difficult to formulate in tablets or capsules due to the physical properties of the solids [EP 0747050 B1, EP 1774967 A1, WO 2008/012372 A1].

Formulations as suspensions of the losartan potassium salt degrade in the presence of light, resulting in the destruction of the imidazole ring [Seburg R.A. et al. J. Pharm. Biomed. Anal. 42: 411-422 (2006)]. Losartan potassium salt, furthermore, is not stable in the amorphous form and tends to turn into the less soluble and less bioactive crystalline forms. This amorphous form can be stabilized by using polymers for its subsequent formulation into tablets WO 2004/064834 A1, US 2006160871 A1]. This is also the case for valsartan [US 2007166372 A1, US 2008152717 A1].
Candesartan cilexetil is stable with regards to temperature, moisture and light when it is isolated, but it decomposes over time when it is formulated with excipients in tablets. The principal product of degradation is the derivative O-desethy. This degradation caused by pressure, abrasion and heat applied during the granulation or high pressure molding process can be reduced through the incorporation in the formulation prior to the compression of oily substances with a low melting point [EP 0546358 B1], of lipids or phospholipids [WO 2005/079751 A2], of different co-solvents [WO 2005/070398 A2], of carbohydrates for the formation of adsorbates of the active ingredient [EP 1952806 A1], of water soluble polymers [WO 2005/084648 A1] or of methacrylate polymers with the amorphous active ingredient [EP 1997479 A1].

Compressive forces that promote degradation are inevitable in the preparation of tablet type solid oral formulations. An alternative to this type of solid oral formulations are gelatin capsules.

Gelatin capsules, whether they are hard or soft, allow the active pharmaceutical ingredients to be incorporated into their interior, but the protection of the active ingredient is not satisfactory in the event that the substance is degradable or unstable in the presence of moisture or oxidizing agents.

Conventional gelatin capsules possess an external layer whose basic ingredient is gelatin, and in general this capsule can be hard or soft, the latter containing plasticizers. The coating of the conventional gelatin capsules consists of a single external layer, with a uniform thickness and composition, which covers the inside, which contains the active pharmaceutical ingredient mixed with the appropriate excipients. The content of the soft gelatin capsules is normally liquid or semi-liquid: oils, polar liquids, microemulsions, suspensions, waxes or colloids. The content in water of the liquid inside cannot exceed 20% so that it does not dissolve the gelatin layer.

The external layer of the capsule contains a certain amount of water as an ingredient. However, the presence of water in the coating of the conventional gelatin capsules constitutes a serious problem, in the case that the active pharmaceutical ingredients or their salts to be formulated are water soluble, degradable in the presence of moisture or unstable in contact with water. In fact, using the usual ingredients and techniques to produce the soft gelatin capsules, it is impossible to avoid the active pharmaceutical ingredient contained in the capsule coming into contact with the moisture of the gelatin mass of the outside layer, whether this is during the production process or during the storage process of the finished capsules, due to the partial diffusion of the water of the
coating towards the inside of the capsule, or due to the contact of a part of the active ingredient with the capsule walls. Since the outer coating of the capsule contains, as well as water, a notable quantity of conventional additives such as plasticizers, colorants, opacifiers and preservatives, it is also very difficult to satisfactorily prevent or control the possible incompatibilities between these and the active ingredient. These additives can facilitate the oxidation, degradation or hydrolysis processes, causing a loss of activity of the active ingredient formulated [EP 0769938 B1]. Another factor to take into account is the possible chemical interaction between the content and gelatin in the capsule, which may favor cross-linking and thus reduce the capsule's solubility in the aqueous medium (delaying its speed of disintegration).

Therefore, although soft gelatin capsules are widely used in the pharmaceutical industry, their use is not recommended in the case of active ingredients which are unstable in the presence of moderate quantities of water.

In an attempt to overcome this difficulty of formulating active ingredients susceptible to hydrolysis in soft gelatin capsules, in EP 0769938 B1 there are described one or more hydrophobe polymer layers under the gelatin layer, as well as silicone resins in the inside of the capsule. The active ingredient, which can be an ACE inhibitor, or an anticholesterol agent such as omega-3 fatty acid eicosapentaenoic acid (EPA) or docosahexaenoic acid (DHA), among others, are found on the inside, mixed, dissolved, suspended or bound in the silicone resin. However, the processes and manufacturing equipment require significant modifications with regards to the usual ones.

It is also known that formulations based on lipids increase the bioavailability of certain active pharmaceutical ingredients. Examples of formulations which increase bioavailability of the active ingredients through the use of PUFA are described in the literature, generally by the formation of emulsions. Therefore, in US 5447729 A a release system is proposed which consists of an emulsion or dispersion of particles of an active ingredient, which can be an ACE inhibitor, among others, that alternate different hydrophobic and hydrophilic layers; the emulsion can be incorporated onto capsules or tablets, and for its formulation long chain fatty acids such as linolenic, linoleic or arachidonic acids are used. In WO 2006/135415 A2 the preparation of microemulsions formed by nanoparticles of acids such as eicosapentaenoic acid (EPA) are described, which contain active pharmaceutical ingredients such as ACE inhibitors or ARBs, among others. In all these cases the contact with water or excipients of the formulation would not be avoided, which is a cause of degradation for many active ingredients.
As well as the examples discussed regarding formulations specifically aimed at minimizing the degradation of ACE inhibitors and ARBs, there are other examples in the literature of formulations with the same objective and that can also incorporate PUFA.

As has been stated previously, in WO 2005/079751 A2 candesartan cilexetil is stabilized in tablets through the addition of lipids or phospholipids to the composition. The lipids can be fatty acids such as linoleic and/or arachidonic acid, or their glycercyl esters.

In WO 2007/103557 A2 it proposed as a solution to the problems of chemical incompatibilities in compositions with two or more active pharmaceutical ingredients, the physical separation of the components in a gelatin capsule, hard or soft, which contains a first active ingredient such as the omega-3 fatty acids, with one or more capsule coatings wherein at least one of them consists of a polymer combined with another active ingredient such as enalapril, and the coating which contains this active ingredient is isolated from the capsule and optionally from the outside by additional coatings. The manufacturing process is complex due to the fragility and solubility in water of the gelatin coatings and requires a rigorous control of the temperature and speed of deposition during coating.

In WO 2006/081518 A2, in order to achieve a modified release of multiple active ingredients, among them antihypertensive agents, complexes of the active ingredients with ion exchange resins are prepared, with or without polymeric coatings, suspended in a non-ionic and non-aqueous vehicle ("NINA" vehicle) such as alcohols, polyols, oils, triglycerides or waxes, among them omega-3. The active pharmaceutical ingredient must contain an acid or basic functional group in order to be able to form the complex.

In the examples in this document, furthermore, the application of these formulations is solely by topical route. The use of resinate for oral administration is controversial, since the administration of large quantities of ion exchange resins or their prolonged use in chronic treatments can change the ionic force of the gastrointestinal fluids and cause electrolyte imbalances.

Although many of the references described represent an attempt to solve the problems of instability associated with the pharmaceutical compositions which contain ACE inhibitors and/or ARBs, the problem arising from the technique is the need to improve the stability of these pharmaceutical compositions, especially in the presence of moisture. The solution proposed by this invention is a pharmaceutical capsule which
incorporates alkyl esters of PUFA and microcapsules of the desired active ingredient which is isolated by means of a polymer.

The subject-matter of this invention is a pharmaceutical composition in the form of a capsule which provides a greater protection for active pharmaceutical ingredients against moisture, oxidizing agents and/or the possible chemical interactions with the additives of the exterior coating. The pharmaceutical capsule of the invention allows active pharmaceutical ingredients known for their instability to be conveniently formulated, such as the angiotensin-converting enzyme inhibitors (ACE inhibitors) and/or the angiotensin II receptor blockers (ARB), avoiding its degradation through the isolation provided by the combination of a polymer coating of the active pharmaceutical ingredient and its suspension in alkyl esters of PUFA.

**DESCRIPTION OF THE INVENTION**

Therefore, this invention relates to a new pharmaceutical composition which avoids the problems of degradation of active pharmaceutical ingredients such as the angiotensin-converting enzyme inhibitors (ACE inhibitors) and/or the angiotensin II receptor blockers (ARB) when they are formulated in pharmaceutical capsules for oral administration.

In a first aspect, this invention relates to a pharmaceutical capsule which comprises a suspension of polymer microcapsules which comprise at least one polymer and active pharmaceutical ingredient selected from the group formed by the ACE inhibitors and the ARBs, these microcapsules are suspended in an oil which contains polyunsaturated fatty acid alkyl esters. The polymer of the microcapsules constitutes their external part and provides a complete coating for the active pharmaceutical ingredient in the capsule.

In the pharmaceutical capsule of the invention, the active pharmaceutical ingredients are found inside the polymer microcapsules in suspension in an oil which contains alkyl esters of PUFA. The active pharmaceutical ingredients are isolated both from the exterior medium and the alkyl esters of PUFA through the polymer, which disintegrates easily in the gastrointestinal medium. The pharmaceutical capsule of the invention allows, as well as the joint administration of active pharmaceutical ingredients in a combination therapy, the active pharmaceutical ingredient to be isolated from moisture and capsule coating additives, as well as moisture and oxygen from the outside. The polymer coating provides stability to the active pharmaceutical ingredients, avoiding the
formation of degradation products caused by moisture, compression and high temperatures during the preparation process of the final composition in the form of pharmaceutical capsules.

Preferably, the fatty acids of the alkyl esters of PUFA belong to the omega-3 series. Preferably, the PUFAs are selected from the group formed by the (all-cis)-5,8,11,14,17-eicosapentaenoic or eicosapentaenoic (EPA) or timnodonic acid or icosapent (C20:5 n-3), the (a/-o/s)-4,7,10,13,16,19-docosahexaenoic or docosahexaenoic (DHA) or cervonic acid or doconexent (C22:6 n-3), and/or mixtures thereof, such as Omacor®, Lovaza® or Zodin®, among others. In a preferred embodiment, the EPA:DHA relationship can range between 100:0 and 0:100, preferably between 4:1 and 1:4, and more preferably between 1:2 and 2:1. The PUFAs can comprise just EPA or just DHA.

Preferably, the alkyl radical of the alkyl esters of PUFA is selected from the group formed by short chain alkyl radicals, with from 1 to 8 carbon atoms. Preferably, the alkyl radical is selected from the group formed by ethyl, methyl, propyl, butyl and/or mixtures thereof. More preferably, the alkyl radical is an ethyl group.

Preferably, the oil containing alkyl esters of PUFA is an oil enriched in alkyl esters of PUFA, preferably, the oil contains more than 50% of alkyl esters of PUFA, more preferably more than 60% of alkyl esters of PUFA and even more preferably, more than 85% of alkyl esters of PUFA.

In a preferred embodiment, the quantity of alkyl esters of PUFA contained in the pharmaceutical capsule of the invention is comprised between 0.01 and 4 g, preferably between 0.1 and 2 g.

In a particular embodiment, the active pharmaceutical ingredient is an angiotensin-converting enzyme inhibitor, selected, without restriction, from the group formed by captopril, enalapril, enalaprilat, ramipril, quinapril, perindopril, lisinopril, benazepril, fosinopril, spirapril, trandolapril, moexipril, cilazapril, imidapril, renipril, temocapril, alacepril, delapril, moveltipril, zofenopril, pentopril, libenazapril, pivopril, ceronapril, indolapril, teprotide, their pharmaceutically acceptable salts and their acids.

In another particular embodiment, the active pharmaceutical ingredient is an angiotensin II receptor blocker, selected, without restriction, from the group formed by candesartan, eprosartan, irbesartan, losartan, olmesartan, telmisartan, valsartan, tasosartan, pratosartan, azilsartan, saralasin, ripisartan, elisartan, milfasartan, embusatran, fonsartan, saprisartan, zolasartan, forasartan, pomisartan, abitesartan,
fimasartan, W-benzyl-losartan, enoltasosartan, glycyl-losartan, opomisartan, trityl-
losartan, sarmesin, isoteolin and their pharmaceutically acceptable salts.

The polymer of the microcapsules of the pharmaceutical capsule of this invention is
selected, without restriction, from the group formed by proteins, polysaccharides,
polyesters, polyacrylates, polycyanoacrylates, polyethylene glycol and/or mixtures
thereof. Preferably, the polymer of the microcapsules is selected from the group formed
by gelatin, albumin, alginites, carrageenans, pectins, gum arabic, chitosan,
carboxymethylcellulose, ethylcellulose, hydroxypropyl methylcellulose (HPMC),
nitrocellulose, cellulose acetate butyrate, cellulose acetate phthalate, hydroxypropyl
methylcellulose phthalate, hydroxypropyl methylcellulose acetate-succinate, polyvinyl
acetate phthalate, poly(E-caprolactone), poly(p-dioxanone), poly(5-valerolactone),
poly(p-hydroxybutyrate), poly(p-hydroxybutyrate) copolymers and β-hydroxyvalerate,
poly(p-hydroxypropionate), methacrylic acid copolymers (Eudragit® L and S),
dimethylaminoethyl methacrylate copolymers (Eudragit® E), trimethylammonium ethyl
methacrylate copolymers (Eudragit® RL and RS), polymers and copolymers of lactic
and glycolic acids, polymers and copolymers of lactic and glycolic acids and
polyethylene glycol and/or mixtures thereof. More preferably, the polymer is formed by
copolymers of methacrylic acid (Eudragit® L and S), polymers and copolymers of lactic
and glycolic acids, polymers and copolymers of lactic and glycolic acids and
polyethylene glycol, and/or mixtures thereof.

Optionally, the polymer of the microcapsules of the pharmaceutical capsule of this
invention can comprise a plasticizer additive. The plasticizer additive is selected,
without restriction, from the group formed by alkyl esters of the citric acid such as
triethyl citrate, tributyl citrate, acetyl tributyl citrate and acetyl triethyl citrate, phthalates
such as butyl phthalate and diethyl phthalate, glycerin, sorbitol, maltitol, propylene
glycol, polyethylene glycol, glucose, sucrose, lanolin, palmitic acid, oleic acid, stearic
acid, metal salts of fatty acids such as stearic acid or palmitic acid, sodium stearate,
potassium stearate, propylene glycol monostearate, acetylated monoglycerides such as
monoacetylated glycerin and glyceryl triacetate or triacetin, glyceryl lecithin, glyceryl
monostearate, alkyl sebacates such as dibutyl sebacate or diethyl sebacate, alkyl
fumarates, alkyl succinates, medium chain triglycerides (MCT), ricin oil, hydrogenated
vegetable oils, wax and/or mixtures.

Optionally other technical additives of the polymer can be incorporated which improve
or facilitate the encapsulation process such as fluidifying agents, such as talc, colloidal
silicon dioxide, glycerin, polyethylene glycol, glycerin monostearate and/or metal stearate salts.

Optionally, the pharmaceutical capsule of this invention comprises at least one antioxidant, such as and not restricted to, butylhydroxytoluene (BHT), butylhydroxyanisole (BHA), tert-butylhydroquinone (TBHQ), gallic acid esters such as propyl gallate, tocopherols such as vitamin E acetate, ascorbic acid esters such as ascorbyl palmitate and ascorbyl acetate, carnitine and/or mixtures thereof. Preferably, the antioxidant is vitamin E acetate.

In a particular embodiment, the microcapsules represent between 0.001% and 80% of the total weight of the pharmaceutical capsule of this invention, preferably between 0.01% and 60%, and more preferably between 0.1% and 50% of the total weight of the pharmaceutical capsule of this invention.

The amount of active pharmaceutical ingredient incorporated in these microcapsules is comprised between 1% and 80% in weight, preferably between 1% and 60% in weight with respect to the total weight of the microcapsules. The total amount of active pharmaceutical ingredient included in the pharmaceutical capsule of this invention depends on the recommended daily doses.

The pharmaceutical capsule of this invention can be a hard or soft capsule, of gelatin or any usual polymer in the preparation of capsules in the pharmaceutical industry, such as and not restricted to, hydroxypropyl methylcellulose (HPMC), pullulan, modified starches, carrageenans and/or mixtures thereof. Preferably, it is a gelatin capsule. More preferably, this capsule is made of soft gelatin. Optionally, the capsule has an enteric coating. The capsule coating can contain other additives such as plasticizers, colorants, pigments, opacifiers, preservatives, moisturizers, surfactants, sweeteners and/or flavorings. The preparation of the capsule is carried out through the usual procedures in the pharmaceutical industry, and can be any form and size known by the person skilled in the art.

The preparation of the microcapsules can be carried out by following any of the procedures described in the literature. As a description and not restricted to them, the different procedures for obtaining microcapsules can be grouped in the following sections:

A) Simple coacervation procedure
A solution of the polymer together with its possible additives is prepared in an appropriate solvent. In this solution of the polymer the active pharmaceutical ingredient to be encapsulated is suspended and a solvent in which the polymer is not soluble is added to force the polymer deposition on the crystals of the active ingredient. Examples of these procedures can be found in documents such as ES 2009346 A6, EP 0052510 A2 and EP 0346879 A1.

B) Complex coacervation procedure

It is based on the interaction between two colloids with an opposite electrical charge to generate an insoluble complex which is deposited on the particles of the active pharmaceutical ingredient to be encapsulated forming a membrane which isolates it. Examples of these procedures can be found in documents such as GB 1393805 A.

C) Double emulsion procedure

The active pharmaceutical ingredient to be encapsulated is dissolved in water or in a solution of another coadjuvant and is emulsified in a solution of the polymer and additives in an appropriate solvent such as dichloromethane. The resulting emulsion is in turn emulsified in water or in an aqueous solution of an emulsifier such as polyvinyl alcohol. Once this second emulsion has been carried out the solvent in which the polymer and the plasticizer were dissolved in is eliminated by evaporation or extraction. The resulting microcapsules are directly obtained by filtration or evaporation. Examples of these procedures can be found in documents such as US 4652441 A.

D) Simple emulsion procedure

The active pharmaceutical ingredient to be encapsulated, the polymer and the additives are jointly dissolved in an appropriate organic solvent. This solution is emulsified in water or in a solution of an emulsifier such as polyvinyl alcohol and the organic solvent is eliminated by evaporation or extraction. The resulting microcapsules are recovered by filtration or drying. Examples of these procedures can be found in documents such as US 5445832 A.

E) Solvent evaporation procedure

The active pharmaceutical ingredient to be encapsulated, the polymer and the additives are jointly dissolved in an appropriate solvent. This solution is evaporated
and the resulting residue is micronized to obtain the suitable size, or it is dried by spray-drying. Examples of this procedure can be found in documents such as GB 2209937 A.

Another aspect of this invention relates to the pharmaceutical capsule of this invention for the treatment and/or prevention of cardiovascular diseases. Preferably, the cardiovascular diseases are selected from the group formed by hypertension, heart failure and myocardial infarction.

Another aspect of this invention relates to a method of treatment and/or prevention of cardiovascular diseases which comprises the administration of the pharmaceutical capsule of the invention. Preferably, the cardiovascular diseases are selected from the group formed by hypertension, heart failure and myocardial infarction.

The following specific examples provided here serve to illustrate the nature of this invention. These examples are included solely for illustrative purposes and should not be interpreted as a limitation to the invention claimed herein.

**EXAMPLES**

**Example 1. Preparation of pharmaceutical capsules which contain ramipril microcapsules with gelatin through simple coacervation procedures.**

A 1% solution of gelatin in water was prepared.

100 ml of this solution were taken and 1 g of ramipril powder was dispersed in it. Then 30 ml of saturated sodium sulfate solution in water were added. The mixture was stirred for 1 hour and 0.5 mL of 50% glutaraldehyde solution in water were added.

The microcapsules formed by filtration were collected, washed with water and dried in a vacuum drying oven. The ramipril content of these microcapsules was 35%.

The resulting microcapsule powder was dispersed directly in oil containing a minimum of 90% of ethyl esters of PUFA, with a minimum EPA/DHA content of 85% in a ratio of 1.2:1 (719 mg of the suspension of microcapsules obtained per 100 g of oil). Next, 1.00 g of the dispersion of microcapsules in oil was incorporated to a soft gelatin capsule to obtain a dose of 2.5 mg of ramipril per capsule.
Example 2. Preparation of pharmaceutical capsules which contain trandolapril microcapsules with poly(lactic-co-glycolic acid) (PLGA) and vitamin E. Preparation of the microcapsules by the simple emulsion method (oil in water).

Solution A: A 10% solution in dichloromethane (DCM) of PLGA with an intrinsic viscosity (I.V.) of 0.17 and a lactic/glycolic ratio of 1:1 was prepared.

Solution B: 5 g of trandolapril and 1 g of vitamin E acetate were dissolved in 100 mL of solution A.

Solution C: A 1% solution of polyvinyl alcohol (PVA) in water was prepared.

100 mL of solution B were added slowly and under intense stirring to 1000 mL of solution C until a milky emulsion was obtained. During this stirring, a nitrogen current was passed through the previous emulsion for two hours to eliminate most of the DCM. Subsequently the resulting suspension was frozen and lyophilized. A powder was obtained which was washed with a great amount of water to eliminate the excess of PVA and was dried under reduced pressure.

The microcapsule powder obtained contained 31% of trandolapril, and was directly dispersed in oil containing a minimum of 60% of ethyl esters of PUFA, with a minimum DHA content of 40%. Next, the dispersion of microcapsules in oil obtained was incorporated to a soft gelatin capsule. The quantities used to prepare capsules of different sizes and doses of trandolapril are shown in Table 1.

<table>
<thead>
<tr>
<th>Dispersion:</th>
<th>Dose of trandolapril</th>
</tr>
</thead>
<tbody>
<tr>
<td>g microcapsules/100 g oil</td>
<td>Weight of dispersion/capsule</td>
</tr>
<tr>
<td>0.65 g</td>
<td>0.50 g</td>
</tr>
<tr>
<td>0.43 g</td>
<td>0.75 g</td>
</tr>
<tr>
<td>1.31 g</td>
<td>0.50 g</td>
</tr>
<tr>
<td>0.65 g</td>
<td>1.00 g</td>
</tr>
</tbody>
</table>

Table 1

Example 4. Preparation of pharmaceutical capsules which contain lisinopril microcapsules with poly(lactic-co-glycolic acid) (PLGA) prepared by the triple emulsion method.
Solution A: 5 g of PLGA with an intrinsic viscosity (I.V.) of 0.4 dL/g and a lactic/glycolic ratio of 1:1 were dissolved in 50 mL of dichloromethane (DCM).

Solution B: 1.08 g of lisinopril dihydrate were dissolved in 10 mL of water.

Solution C: A 0.5% p/v concentration solution of polyvinyl alcohol (PVA) in water was prepared.

The aqueous phase (solution B) was emulsified in the solution of PLGA (solution A) with the help of an Ultra Turrax homogenizer (W/O emulsion).

The previously prepared W/O emulsion was added to 1 L of the PVA solution (solution C) under intense stirring. The new emulsion formed was stirred whilst a nitrogen current was passed through the reactor at a flow no less than 50L/minute to evaporate the DCM. The microcapsules were recovered by filtration through a membrane with a pore diameter of 5 μm, they were washed with abundant water to eliminate the excess of PVA and were dried by lyophilization.

The microcapsule powder obtained contained 16% of lisinopril, and was directly dispersed in oil containing a minimum of 90% of ethyl esters of PUFA, with a minimum EPA/DHA content of 85% in a ratio of 1.2:1 (1.59 g of the microcapsule suspension obtained per 100 g of oil). Next, 1.00 g of the microcapsule dispersion in oil was incorporated to a soft gelatin capsule, to obtain a dose of 2.5 mg of lisinopril per capsule.

Example 4. Preparation of pharmaceutical capsules that contain microcapsules of candesartan cilexetil with gelatin and carboxymethyl cellulose prepared by a complex coacervation procedure.

Solution A: A 1% solution of gelatin in water was prepared and the pH was adjusted so it was equal or higher than 7.

Solution B: Another 1% solution of sodium carboxymethyl cellulose in water was prepared and the pH was adjusted so it was equal or higher than 7.

250 mL of solution A and 250 mL of solution B were mixed and heated to 40 °C. 4 g of powdered candesartan cilexetil were dispersed in the mixture. When all the powder was dispersed and there were no lumps the pH was adjusted to 4-4.5 by adding acetic acid. The mixture was stirred for 1 hour at 40°C and afterwards the solution was cooled.
to 10 °C, maintaining this temperature for another hour. 2 mL of 50% glutaraldehyde solution in water were added.

The resulting suspension was dried by spray-drying, to give a microcapsule powder which contained 40% of candesartan cilexetil.

This microcapsule powder was directly dispersed in oil containing a minimum of 90% of ethyl esters of PUFA, with a minimum EPA/DHA content of 85% in a ratio of 1.2:1. Next, the dispersion of microcapsules in oil obtained was incorporated to a soft gelatin capsule. The quantities used to prepare the capsules of different size and doses of candesartan cilexetil are shown in Table 2.

<table>
<thead>
<tr>
<th>Dispersion: g microcapsules/100 g oil</th>
<th>Weight of dispersion/capsule</th>
<th>Dose of candesartan cilexetil / capsule</th>
</tr>
</thead>
<tbody>
<tr>
<td>2.04 g</td>
<td>1.00 g</td>
<td>8 mg</td>
</tr>
<tr>
<td>1.35 g</td>
<td>1.50 g</td>
<td>8 mg</td>
</tr>
<tr>
<td>4.17 g</td>
<td>1.00 g</td>
<td>16 mg</td>
</tr>
<tr>
<td>2.74 g</td>
<td>1.50 g</td>
<td>16 mg</td>
</tr>
</tbody>
</table>

Table 2

Example 5. Preparation of pharmaceutical capsules which contain valsartan microcapsules and a methacrylic acid copolymer.

10 g of valsartan were suspended in 100 mL of a suspension of Eudragit FS 30D® (suspension in water of 30% methacrylic acid, methyl methacrylate and methyl acrylate copolymers) until a fine suspension was obtained. Triethyl citrate was added to this suspension (polymer plasticizer) until a concentration of 5%.

The resulting suspension was dried by spray-drying, to give a microcapsule powder which contained 22% of valsartan.

The resulting microcapsule powder was directly dispersed in oil containing a minimum of 65% of ethyl esters of PUFA, with a minimum EPA/DHA content of 45% in a ratio of 1.2:1 (25.0 g of the suspension of microcapsules obtained per 100 g of oil). Next, 1.00 g of the microcapsule dispersion in oil was incorporated to a soft gelatin capsule, to obtain a dose of 40 mg of valsartan per capsule.
Example 6. Studies of stability of the soft gelatin capsules which contain ramipril, trandolapril, lisinopril, candesartan cilexetil and valsartan microcapsule suspensions in an oil which contains alkyl esters of PUFA.

Studies of accelerated stability (40±2 °C, 75±5 % RH) were carried out on the soft gelatin capsules which contained suspensions of the active pharmaceutical ingredients in an oil which contained alkyl esters of PUFA, wherein:

a) The active pharmaceutical ingredient does not have a polymer coating (control composition).

b) The active pharmaceutical ingredient is in microcapsules prepared according to the previous examples (composition of the invention).

The percentages of the active pharmaceutical ingredient in the capsules were determined through HPLC after storage in amber glass containers for 1 month, 2 months, 3 months and 4 months. The percentages of the active pharmaceutical ingredient are shown in Table 3.

The stability of PUFAs was also studied (concentration of alkyl esters of EPA and DHA, as well as the EPA/DHA ratio) through gas chromatography, although no variations were observed in the composition.

<table>
<thead>
<tr>
<th>Active ingredient (%)</th>
<th>Stability (40±2 °C, 75±5 % RH)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Initial</td>
</tr>
<tr>
<td>Ramipril (example 1)</td>
<td></td>
</tr>
<tr>
<td>a</td>
<td>99.2</td>
</tr>
<tr>
<td>b</td>
<td>98.9</td>
</tr>
<tr>
<td>Trandolapril (example 2; dose 2 mg, capsule 1 g)</td>
<td></td>
</tr>
<tr>
<td>a</td>
<td>99.1</td>
</tr>
<tr>
<td>b</td>
<td>99.2</td>
</tr>
<tr>
<td>Lisinopril (example 3; dose 2.5 mg, capsule 1 g)</td>
<td></td>
</tr>
<tr>
<td>a</td>
<td>99.0</td>
</tr>
<tr>
<td>b</td>
<td>99.1</td>
</tr>
<tr>
<td>Candesartan cilexetil (example 4; dose 16 mg, capsule 1 g)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>a</td>
</tr>
<tr>
<td>-----</td>
<td>-----</td>
</tr>
<tr>
<td></td>
<td>98.8</td>
</tr>
<tr>
<td></td>
<td>94.8</td>
</tr>
<tr>
<td></td>
<td>91.9</td>
</tr>
</tbody>
</table>

Table 3
1. Pharmaceutical capsule which comprises a suspension of polymeric microcapsules which comprise at least one polymer and an active pharmaceutical ingredient selected from the group formed by the angiotensin-converting enzyme inhibitors and the angiotensin receptor blockers, these microcapsules being suspended in an oil which contains polyunsaturated fatty acid alkyl esters.

2. Pharmaceutical capsule according to claim 1, wherein the polyunsaturated fatty acids of these alkyl esters belong to the omega-3 series.

3. Pharmaceutical capsule according to claim 2, wherein the polyunsaturated fatty acids of these alkyl esters are selected from the group formed by eicosapentaenoic acid, docosahexaenoic acid, and/or mixtures thereof.

4. Pharmaceutical capsule according to claim 1, wherein the alkyl radical of these alkyl esters is selected from the group formed by short chain alkyl radicals, with from 1 to 8 carbon atoms.

5. Pharmaceutical capsule according to claim 4, wherein the alkyl radical of these alkyl esters is selected from the group formed by ethyl, methyl, propyl, butyl and/or mixtures thereof.

6. Pharmaceutical capsule according to claim 1, wherein this oil contains more than 50% of polyunsaturated fatty acid alkyl esters.

7. Pharmaceutical capsule according to claim 1 wherein this angiotensin-converting enzyme inhibitor is selected from the group formed by captopril, enalapril, enalaprilat, ramipril, quinapril, perindopril, lisinopril, benazepril, fosinopril, spirapril, trandolapril, moexipril, cilazapril, imidapril, reniatpril, temocapril, alacepril, delapril, moventipril, zofenopril, pentopril, libenzapril, pivopril, ceronapril, indolapril, teprotide, their pharmaceutically acceptable salts and their acids.

8. Pharmaceutical capsule according to claim 1 wherein this angiotensin II receptor blocker is selected from the group formed by candesartan, eprosartan, irbesartan, losartan, olmesartan, telmisartan, valsartan, tasosartan, pratosartan, azilsartan, saralasin, ripisartan, elisartan, milfasesartan, embusartan, fonsartan, saprisartan, zolasartan, forasartan, pomisartan, abitesartan, fimasartan, N-
benzyl-losartan, enoltasosartan, glycyl-losartan, opomisartan, trityl-losartan, sarmesin, isoteolin and their pharmaceutically acceptable salts.

9. Pharmaceutical capsule according to claim 1, wherein the polymer of these microcapsules is selected from the group formed by proteins, polyesters, polyacrylates, polycyanoacrylates, polysaccharides, polyethylene glycol and/or mixtures thereof.

10. Pharmaceutical capsule according to claim 9 wherein the polymer of these microcapsules is selected from the group formed by gelatin, albumin, alginates, carrageenans, pectins, gum arabic, chitosan, carboxymethyl cellulose, ethyl cellulose, hydroxypropyl methylcellulose, nitrocellulose, cellulose acetate butyrate, cellulose acetate phthalate, hydroxypropyl methylcellulose phthalate, hydroxypropyl methylcellulose acetate-succinate, polyvinyl acetate phthalate, poly(e-caprolactone), poly(p-dioxanone), poly(6-valerolactone), poly(p-hydroxybutyrate), poly(p-hydroxybutyrate) and β-hydroxyvalerate copolymers, poly(p-hydroxypropionate), methacrylic acid copolymers, dimethylaminoethyl methacrylate copolymers, trimethylammonium ethyl methacrylate copolymers, polymers and copolymers of lactic and glycolic acids, polymers and copolymers of lactic and glycolic acids and polyethylene glycol and/or mixtures thereof.

11. Pharmaceutical capsule according to claim 1, wherein these microcapsules represent between 0.001% and 80% of the total weight of the capsule.

12. Pharmaceutical capsule according to claim 1, wherein the quantity of the active pharmaceutical ingredient incorporated in these microcapsules is comprised between 1% and 80% in weight.

13. Pharmaceutical capsule according to claim 1, wherein the polymer of these microcapsules contains at least one plasticizer, a fluidifying agent and/or an antioxidant.

14. Pharmaceutical capsule according to claim 1, wherein the composition of the coating of this capsule is selected from the group formed by gelatin, hydroxypropyl methylcellulose, pullulan, modified starches, carrageenans and/or mixtures thereof.

15. Pharmaceutical capsule according to claim 14, wherein this coating is made of soft gelatin.
16. Pharmaceutical capsule according to claim 1, wherein this capsule comprises an enteric coating.

17. Pharmaceutical capsule according to claim 1, for the treatment and/or prevention of cardiovascular diseases.