Title: ACTIVE PHARMACEUTICAL INGREDIENT CAPSULES AND POLYUNSATURATED FATTY ACID ESTERS

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

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 alkyl esters of polyunsaturated fatty acids (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 and/or inflammatory processes.

BACKGROUND OF THE INVENTION

Among the most used active pharmaceutical ingredients for the treatment of cardiovascular diseases are the calcium channel blockers or antagonists, beta blockers or beta-adrenergic antagonists, the platelet antiaggregants and/or anticoagulants.

The main use of the calcium channel blockers in the treatment of angina pectoris, hypertension and cardiac dysrhythmia.

Beta blockers are competitive antagonists of the beta-adrenergic receptors and are used for the treatment of cardiovascular disorders such as hypertension, angina pectoris, cardiac dysrhythmia, myocardial infarction and heart failure.

Platelet antiaggregants reduce platelet aggregation and are used to prevent thromboembolic episodes in patients who have suffered a myocardial infarction, ischemic cerebral infarction or transitory ischemic attacks, unstable angina and for primary prevention of thromboembolic episodes in patients at risk. Some of them are used for the prevention of reocclusion or restenosis after an angioplasty or a coronary bypass.

Anticoagulant drugs are used for the treatment and profilaxis of thromboembolic disorders.

Non-steroidal anti-inflammatory drugs are drugs with analgesic and anti-inflammatory properties, of generalized use. They are particularly suitable for the treatment of illnesses or processes involving inflammation and/or pain, such as rheumatic disorders, among others.

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 instability of many of the aforementioned active pharmaceutical ingredients is also known. The photolability of calcium channel blockers which possess a 1,4-dihydropyridine ring is known and there are numerous studies on its photostability in the literature. The dihydropyridine ring easily oxidizes and aromatizes to give a pyridine as a product of photodegradation.

Amiodipine presents formulation problems due to the fact that it is hygroscopic and can degrade in the presence of moisture by a process of oxidation which leads to, among others, an impurity with the dihydropyridine ring aromatized to pyridine [WO 2008/062435 A2]. Amiodipine besylate is photosensitive and degrades both in solution and in solid state forming pyridine derivatives which lack therapeutic activity. The degradation studies show that amiodipine degrades slowly under heat stress, but it degrades quicker under photo-stress and even in acidic, alkaline and oxidative conditions, with the highest level of degradation in alkaline conditions [Aryal, S. et al. Acta Pharm. 58: 299-308 (2008)]. Another known pharmaceutical problem is that in solid pharmaceutical compositions of amiodipine besylate the mixtures of lactose, basic excipients (magnesium stearate) and water induce a certain instability in the

In a comparative study of photostability between amlodipine, nilvadipine and nifedipine, this latter active ingredient proved to be the most photosensitive. The photodegradation reactions involved include aromatization of the dihydropyridine ring and conversion of the nitro group of the benzene ring to nitroso group [Kawabe, Y. et al. J. Pharm. Biomed. Anal. 47: 618-624 (2008)]. The high photosensitivity of nifedipine makes necessary to protect it from the light during manufacturing, storage and handling of the pharmaceutical compositions [Aman, W. et al. Int. J. Pharm. 243: 33-41 (2002)]. US 4954346 A mentions the photosensitivity of the commercial preparation of nifedipine in Procardia® soft gelatin capsules (or Adalat®); this patent proposes the improvement of the stability of these type of compositions by adding solubilizing agents such as cyclic carbonate diester to the liquid content of the capsule.

Since these derivatives of dihydropyridine are instable due to oxidation catalyzed by light or heat or by the interaction with some excipients, there are limitations in the preparation of pharmaceutical compositions which contain them. As well as proposing the preparation of new amlodipine salts which are photochemically more stable [WO 2008/010659 A1], in EP 1813274 A1 the photostabilization of the dihydropyridines by adding iron oxide and carrageenans is proposed, and in WO 2008/062435 A2 through the addition of polyols; other alternatives studied are, for example, the protection by forming inclusion complexes with cyclodextrins [Bayomi, M.A. et al. Int. J. Pharm. 243: 107-117 (2002)].

In the case of beta blockers, the presence of the secondary amino group in alpha position with relation to the hydroxyl group affords them chemical instability, due to possible interactions with the excipients. This represents a problem during their storage. Thus, the amino group of carvedilol, for example, can react with aldehyde or ester functional groups [WO 2005/051383 A1], and degrades in the presence of polyvinylpyrrolidone and moisture [Galanopoulou, O. et al. J. Pharm. Biomed. Anal. 48: 70-77 (2008)]. A study of the stability of atenolol with different common excipients in the pharmaceutical industry concludes that atenolol is incompatible with some of them, such as ascorbic acid, citric acid or butylated hydroxyanisole [Kumar, V. et al. J. Pharm. Biomed. Anal. 49: 880-888 (2009)].
The ester group of esmolol hydrochloride is unstable in aqueous medium due to its great susceptibility to hydrolytic degradation [EP 0403578 B1; EP 1368019 B1], therefore, the presence of water in the formulation should be avoided.

Atenolol, nadolol and sotalol present, furthermore, formulation problems since they are solids with a sticky nature and difficult to compress; therefore, they require the addition of high quantities of excipients [EP 0454396 A1].

An antiplatelet drug, clopidogrel, is marketed in salt form. The most used, clopidogrel hydrogen sulfate, is a very acidic salt. This leads to incompatibilities of the salt with many additives or excipients, influencing the stability of the pharmaceutical compositions. Furthermore, it presents many problems in the manufacturing processes of tablets, such as corrosion of equipment, and in the preparation of gelatin capsules, since it constitutes a very aggressive filling that perforates the coating. Clopidogrel hydrogen sulfate is, furthermore, very hygroscopic and degrades on contact with the atmosphere which leads to racemization and impurities such as the hydrolysis product of the ester group. Several examples of formulations to solve these problems are described in the literature, as well as variations in the pharmaceutical excipients of the tablets: in EP 1903046 A1 the problem is attempted to be solved through the formation of a new, more stable and less corrosive salt, in WO 2008/072939 A1 the formation of inclusion complexes with cyclodextrins is proposed which provide stability against temperature and moisture during storage, and in WO 2008/122994 A2 more stable and soluble tablets are obtained by using a hydrophilic polymer. In WO 2005/048992 A1, particles, granules or agglomerates of the active ingredient coated by a vinyl polymer in the preparation of tablets are used to overcome the problem of the hygroscopic nature of different clopidogrel salts.

During the preparation of compositions of another antiplatelet drug, dipyridamol, significant proportions of impurities are generated, it seems due incompatibilities of dipyridamol with acid excipients. In EP 1894561 A1 dipyridamol is stabilized in tablets by including it in an isolated, intermediate layer with consecutive tablet coatings.

With regards to the anticoagulants, both warfarin sodium salt and clathrate are hygroscopic. Warfarin sodium salt tends to decompose in the presence of water and excessive alkalinity, particularly if the temperature rises [US 6673944 B2].

The most widely known and used NSAID, ibuprofen, is very soluble, it has a low melting point and is not directly compressible, since it leads to tablets which stick to the press and easily disintegrate or break. To avoid this problem, ibuprofen is normally
subjected to a process of wet granulation as a prior step to compression [US 20080131507 A1]. But the compositions obtained by wet granulation often age during storage, causing a reduction in the speed of dissolution of ibuprofen. This aging is influenced by factors such as temperature and moisture, and causes the ibuprofen particles to become compressed together, reducing their solubility. A way of minimizing this problem is to increase the level or percentage of excipients or diluents to isolate the individual particles as much as possible, but this leads to tablets or capsules which are too large [EP 0172014 B1].

Examples of ibuprofen, naproxen and flurbiprofen formulations in soft gelatin capsule form are described in the literature; in them, suspensions of these active pharmaceutical ingredients are stabilized by the addition of different excipients [US6251426 B1; WO 2008/070950 A1; EP 1365749 B1; WO 97/03655 A1]. In EP 1321140 B1 the use of surfactants is considered indispensable, but this compromises the integrity of the capsule due to the interaction of the surfactant with the coating’s membrane.

Compositions of other NSAIDs also present problems of stability, such as ketoprofen and pranoprofen, which are photolabile [US 5856345; EP 1688129 A1; EP 1526849 A1], or pirprofen, which tends to decompose oxidatively due to exposure to heat, light or air [US 4565807 A]. Ketoprofen salt tablets present a great instability due to its great hygroscopicity, which forces storage in an environment with a strict control of moisture [EP 0523153 B1].

The aim of using polymeric coatings in NSAIDs is to mask their bitter taste [EP 524180 B1; WO 95/05166 A1], to increase the bioavailability [US 5653993 A] and to improve the properties of compression of solids for their formulation in tablets [Palmieri G.F. et al. Int. J. Pharm. 242: 175-178 (2002)].

Compressive forces that promote degradation are inevitable in the preparation of solid oral formulations such as tablets. An alternative to these types of solid oral formulations are gelatin capsules.

Gelatin capsules, whether they are hard or soft, allow 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 one containing plasticizers. The coating of the conventional gelatin capsules consists of an external layer, with a uniform thickness and composition, which covers the inside, which contains the active pharmaceutical ingredient mixed with suitable 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 interior liquid cannot exceed 20% so it does not dissolve the gelatin layer.

The external layer of the capsule contains a certain amount of water as a component. However, the presence of water in the coating of the conventional gelatin capsules constitutes a serious problem, in the event 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 for the production of soft gelatin capsules, it is impossible to avoid contact between the active pharmaceutical ingredient contained in the capsule with the moisture of the mass of gelatin of the exterior stratum, 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 one part of the active ingredient with the walls of the capsule. 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 any possible incompatibilities between them and the active ingredient. These additives can facilitate oxidation, degradation or hydrolysis processes, causing a loss of activity of the active ingredient formulated [EP 0769393 B1]. Another factor to take into account is the possible chemical interaction between the content and the gelatin of the capsule, which may favor cross-linking and thus reduce the solubility in aqueous medium of the capsule (delaying its speed of disintegration). Certain active pharmaceutical ingredients favor cross-linking in the capsule's coating, such as nifedipine [US 5874106 A].

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.

With the objective of avoiding degradation due to moisture in ketoprofen salt tablets, in EP 0523153 B1 gelatin capsules which contain ketoprofen salts in an oily solution of polyethoxylated vegetable oils, ricin oil, or fatty acid or polyol esters are prepared.
However, as has been mentioned, gelatin capsules do not establish proper isolation from moisture for the active ingredients contained in its interior.

It is also known that formulations based on lipids increase the bioavailability of certain active pharmaceutical ingredients. Examples of formulations which increase the bioavailability of the active ingredients by using PUFA are described in the literature, generally by formation of emulsions. Therefore, in US 5447729 A a delivery system is proposed which consists of an emulsion or dispersion of particles of an active ingredient which may be nifedipine, indometacin or naproxen, among others, which alternate different hydrophobic and hydrophilic layers; the emulsion can be incorporated into capsules and tablets, and for its formation long-chain hydrophobic fatty acid agents such as linolenic, linoleic or arachidonic acids are used. In WO 01/021154 A2 is proposed as a delivery system based on the formation of particles of 0.01 to 10 micrometers in diameter and with a modified surface which comprise an active ingredient insoluble in water such as nifedipine or piroxicam, among others, dissolved in a non-aqueous medium such as fish oil or PUFA, with phospholipids such as surfactants and an alcohol or polyol. In WO 2006/135415 A2 the preparation of microemulsions formed by nanoparticles of biocompatible oils such as eicosapentaenioc acid (EPA), which contain active pharmaceutical ingredients such as calcium channel blockers, beta blockers or anti-inflammatory drugs, among others, is described. US 2007009559 A1 proposes an improvement of the bioavailability of different active pharmaceutical ingredients poorly water soluble, such as carvedilol, felodipine or amlodipine, among others, through their incorporation into compositions which contain unsaturated fatty acids, such as linoleic acid or ethyl linoleate, as well as water, a surfactant, a polyol and phospholipids. In all these cases contact with water or with excipients of the formulation would not be avoided, which is a cause of degradation for many of the active ingredients.

As well as the aforementioned examples of formulations specifically aimed at minimizing degradation of the calcium channel blockers, beta blockers, antiplatelet drugs, anticoagulants and NSAIDs, there are other examples in the literature of formulations with the same objective and which can also incorporate PUFA.

As a solution to the problems of chemical incompatibilities of compositions with two or more active ingredients WO 2007/103557 A2 proposes the physical separation of the components in a hard or soft gelatin capsule which contains a first active ingredient such as omega-3 fatty acids, with one or more internal coatings of the capsule wherein at least one of them consists of a polymer combined with another active ingredient, and
the coating which contains this active ingredient is isolated from the capsule and
optionally from the outside through additional coatings. In WO 2007/016256 A2 and
WO 2008/063323 A2 the combination therapy is achieved by consecutive internal
coatings of a capsule which contains omega-3 fatty acids with coatings which comprise
antiarrhythmic active ingredients. In WO 2008/088808 A1 the consecutive coatings
comprise one or more NSAID. 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 the coating.

In WO 2006/081518 A2, with the aim of achieving a modified release of multiple active
ingredients, among them antiarrhythmic drugs, beta blockers or anti-inflammatory
drugs, 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, polyethers, 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 resinates 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.

In US 2003161884 A1 formulations of anticoagulants, such as heparins,
glycosaminoglycans and heparinoids are prepared by mixing the active ingredients with
lipids, polymers and other excipients by hot extrusion. The lipids can be unsaturated
fatty acids, among them linoleic acid. The formation temperatures of these plastic
mixtures normally exceed 100°C, and in them the active ingredient is not completely
isolated, but mixed with the polymer, the lipid and the excipients. However, it is evident
that the high temperatures used favor degradation of unstable active pharmaceutical
ingredients.

Although many of the described references represent an attempt to solve the problems
of instability associated with the pharmaceutical compositions which contain calcium
channel blockers, beta blockers, antiplatelet drugs, anticoagulants and/or non-steroidal
anti-inflammatory drugs, the problem arising from the technique is the need to improve
the stability of these pharmaceutical compositions, especially in the presence of
moisture, oxygen and/or light. The solution proposed by this invention is a
pharmaceutical capsule which incorporates alkyl esters of PL)FA 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 the 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 the active pharmaceutical ingredients known for their instability to be conveniently formulated, such as the calcium channel blockers, beta blockers, antiplatelet drugs, anticoagulants and NSAID, 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 problems of degradation of active pharmaceutical ingredients such as the calcium channel antagonists, beta blockers, antiplatelet drugs, anticoagulants and NSAID, 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 at least one active pharmaceutical ingredient selected from the group formed by the calcium channel antagonists, beta blockers, antiplatelet drugs, anticoagulants and non-steroidal anti-inflammatory drugs, 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 by 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 the active pharmaceutical ingredients with stability, 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 fa/-c/sj-5,8,11,14,17-eicosapentaenoic or eicosapentaenoic (EPA) or timnodonic acid or icosapent (C20:5 n-3), the fa/-c/sj-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 Omacer®, 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 a calcium channel blocker, selective or non-selective, and/or its pharmaceutically acceptable salts. The selective calcium channel blocker is selected, without restriction, from the group formed by the dihydropyridine calcium channel blockers, such as amlodipine, arandipine, azelnidipine, azodipine, barnidipine, benidipine, cilnidipine, clevidipine, dazodipine, efondipine, felodipine, flordipine, iodipine, isradipine, lacidipine, lercanidipine, manidipine, mesudipine, nicardipine, nifedipine, nilvadipine, nimodipine, nisoldipine, nitrendipine, oxodipine, pranidipine, riodipine or ryosidine, phenylalkylamine calcium channel blockers, such as verapamil, galopamil, tiapamil, emopamil, fulpamil, ronipamil or anipamil, benzothiazepine calcium channel blockers such as diltiazem, clentiazem or fostedil, and others such as ziconotide. Among the non-selective calcium channel blockers are, among others, flunarizine, cinarizine, prenilamine, fendiline, mibefradil, bepridil, caroverine, lidoflazine and perhexiline.

In another particular embodiment, the active pharmaceutical ingredient is a beta blocker, selected, without restriction, from the group formed by acebutolol, alprenolol,
amosulalol, arotinolol, atenolol, betaxolol, bevantolol, bisoprolol, bopindolol, bucindolol, bupranolol, carazolol, carteolol, carvedilol, celirolol, satenolol, esmolol, indenolol, labetalol, landiolol, levobunolol, mepindolol, metipranolol, metoprolol, nadolol, nebivolol, oxprenolol, penbutolol, pindolol, propranolol, sotalol, talinolol, tertatolol, tilisolol, timolol, butoxamine, and/or their pharmaceutically acceptable salts.

In another particular embodiment, the active pharmaceutical ingredient is an antiplatelet drug. The antiplatelet drug is selected from the group formed by the glycoprotein IIb/IIIa inhibitors, such as abciximab, eptifibatide, tirolibiban, lamifiban, sibrafiban, orbofiban, and/or their pharmaceutically acceptable salts. Examples of such antiplatelet drugs include dabigatran, fondaparinux, danaparoid, idraparinux, or ximelagatran.

In another particular embodiment, the active pharmaceutical ingredient is an anticoagulant. The anticoagulant is selected, without restriction, from the group formed by direct anticoagulants such as heparins, direct inhibitors of factor Xa, direct inhibitors of thrombin (II) and indirect coagulants such as vitamin K antagonists, and/or their pharmaceutically acceptable salts. Heparins include unfractioned heparins, low molecular weight heparins such as ardeparin, bemiparin, certoparin, dalteparin, enoxaparin, nadroparin, naranparin, reviparin or tinzaparin, oligosaccharides such as fondaparinux or idraparinux, and heparinoids such as danaparoid, sulodexide or dermatan sulfate. Direct inhibitors of factor Xa include xabans such as apixaban, otamixaban or rivaroxaban. Direct inhibitors of thrombin II include bivalents such as hirudin, bivalirudin, lepirudin or desirudin, and univalents such as argatroban, dabigatran, melagatran or ximegalagatran. Vitamin K antagonists include coumarins such as acenocoumarol, dicoumarol, ethyl biscoxicamate, phenprocoumon or warfarin, 1,3-indanodiones such as clorindione, anisindione, fluindione or phenindione, and ticloplamor, among others. Another compound with anticoagulant activity is defibrotide.

In another particular embodiment, the active pharmaceutical ingredient is a nonsteroidal anti-inflammatory drug (NSAID). The NSAID is selected from the group formed by arylalkanoic acids, 2-arylpropionic acids or profens, N-aryl-anthranilic acids, derivatives of pyrazolidin, oxicams, cycloxygenase-2 inhibitors (COX-2), sulfonanilides, ClINOD ("COX-inhibiting nitric oxide donors") and flupiruroazone, and/or their pharmaceutically acceptable salts. Examples of arylalkanoic acids are diclofenac, aceclofenac, acemetacin, alclofenac, bromfenac, etodolac, indomethacin, nabumetone, oxametacin, proglumetacin, sulindac and tolmetin, among others. Examples of 2-
arylpropionic acids or profens include ibuprofen, dexibuprofen, alminoprofen, carprofen, fenbufen, fenoprofen, flunoxaprofen, flurbiprofen, tarenflurbil, ibuproxam, ketoprofen, dexketoprofen, ketorolac, loxoprofen, miroprofen, naproxen, oxaprozin, pranoprofen, tiaprofenic acid and suprofen, among others. Examples of /V-arylantranilic acids are mefenamic acid, meclofenamic acid, flufenamic acid and tolfenamic acid, among others. Examples of derivatives of pyrazolidin include phenylbutazone, azapropazone, clofezone, kebuzone, metamizole, mofebutazone, oxyphenbutazone, phenazone and sulfinpyrazone, among others. Examples of oxicams include piroxicam, lornoxicam, meloxicam and tenoxicam, among others. Examples of COX-2 inhibitors are celecoxib, etoricoxib, firocoxib, lumiracoxib, parecoxib, rofecoxib, and valdecoxib, among others. An example of sulfonamide is nimesulide, and an example of CINOD is naproxcinod.

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, polycyanacrylates, polyethylene glycol and/or mixtures thereof. Preferably, the polymer of the microcapsules is selected from the group formed by gelatin, albumin, alginates, 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(6-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 into these microcapsules is comprised between 1% and 80% in weight, preferably between 1% and 60% in weight with regards 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, made from 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 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 cardiac dysrhythmia, hypertension, angina pectoris, myocardial infarction, heart failure and/or thromboembolic disorders, among others.

Another aspect of this invention relates to the pharmaceutical capsule of this invention for the treatment of diseases and/or processes involving inflammation and/or pain, preferably rheumatic diseases, among others.

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 cardiac dysrhythmia, hypertension, angina pectoris, myocardial infarction, heart failure and/or thromboembolic disorders.

Another aspect of this invention relates to a method of treatment of diseases and/or processes involving inflammation and/or pain, preferably rheumatic diseases, which comprises the administration of the pharmaceutical capsule of this invention.

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

EXAMPLES
Example 1. Preparation of pharmaceutical capsules which contain amiodipine besylate microcapsules and a methacrylic acid copolymer.

10 g of amiodipine besylate was 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 20% of amiodipine besylate.

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. (3.57 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 5 mg of amiodipine base (equivalent to 6.9 mg of besylate) per capsule.

Example 2. Preparation of pharmaceutical capsules which contain diltiazem microcapsules with poly(lactic-co-glycolic acid) and vitamin E. Preparation of the microcapsules by the simple emulsion method (oil in water).

Solution A: A 10% solution in dichloromethane 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 diltiazem hydrochloride 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 PVA and was dried under reduced pressure.

The microcapsule powder obtained contained 21% of diltiazem, and was directly dispersed in oil containing a minimum of 65% of ethyl esters of PUFAi with a minimum
EPA/DHA content of 45% in a ratio of 1.2:1 (2.35 g of the microcapsule suspension obtained per 10 g of oil). Next, 1.50 g of the microcapsule dispersion in oil was incorporated to a soft gelatin capsule, obtaining a dose of 60 mg of diltiazem per capsule.

Example 3. Preparation of pharmaceutical capsules which contain microcapsules of carvedilol with gelatin through a simple coacervation procedure.

A 1% solution of gelatin in water was prepared.

100 mL of this solution were taken and 1 g of carvedilol powder was dispersed in it. Next, 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 in water solution were added.

The microcapsules formed by filtration were collected, washed with water and dried in a vacuum drying oven. The carvedilol content of these microcapsules was 39%.

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 (1.63 g 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 6.25 mg of carvedilol per capsule.

Example 4. Preparation of pharmaceutical capsules which contain atenolol microcapsules with polyethylene glycol.

A 10% solution of polyethylene glycol with a molecular weight of 35000 (PEG-35000) in water was prepared.

5 g of atenolol were dispersed in 100 mL of this solution through intense stirring. Once a fine dispersion without lumps was obtained the solution was dried by spray-drying.

The microcapsule powder obtained showed a concentration of atenolol of 33%, and was dispersed directly 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 (17.9 g 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 50 mg of atenolol per capsule.

**Example 5. Preparation of pharmaceutical capsules which contain dipyridamole microcapsules with cellulose acetate phthalate.**

A 2% solution in water of cellulose acetate sodium phthalate was prepared. 2 g of dipyridamole powder was suspended in 100 mL of this solution. The resulting suspension was dried by *spray-drying*.

The resulting microcapsule powder contained 50% of dipyridamole, and 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 (2.5 g of the microcapsule suspension obtained per 10 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 100 mg of dipyridamole per capsule.

**Example 6. Preparation of pharmaceutical capsules which contain sodium warfarin microcapsules with poly(lactic-co-glycolic acid) (PLGA) prepared by the triple emulsion method.**

Solution A: 2.5 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 10 mL of dichloromethane (DCM).

Solution B: 1 g of sodium warfarin was dissolved in 20 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 250 mL 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 28% of sodium warfarin, 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. Next, the microcapsule dispersion in oil obtained was incorporated into a soft gelatin capsule. The quantities used to prepare capsules of different doses of sodium warfarin are shown in Table 1.

<table>
<thead>
<tr>
<th>Dispersion: mg microcapsules/10 g oil</th>
<th>Weight of dispersion/capsule</th>
<th>Dose sodium warfarin/capsule</th>
</tr>
</thead>
<tbody>
<tr>
<td>35.8 mg</td>
<td>1.00 g</td>
<td>1 mg</td>
</tr>
<tr>
<td>108.3 mg</td>
<td>1.00 g</td>
<td>3 mg</td>
</tr>
<tr>
<td>181.8 mg</td>
<td>1.00 g</td>
<td>5 mg</td>
</tr>
<tr>
<td>370.4 mg</td>
<td>1.00 g</td>
<td>10 mg</td>
</tr>
</tbody>
</table>

Table 1

Ejemplo 7. Preparation of pharmaceutical capsules which contain acenocoumarol microcapsules with alginate prepared by a simple coacervation procedure.

A 1.5% solution of sodium alginate in water was prepared.

1 g of acenocoumarol powder was dispersed in 100 ml of this solution. Next, the dispersion was added to a 2% dispersion of calcium chloride in water.

The microcapsules formed by filtration were collected, washed with water and dried in a vacuum drying oven. The acenocoumarol content of these microcapsules was 40%.

The resulting 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 microcapsule dispersion in oil obtained was incorporated to a soft gelatin capsule. The quantities used to prepare capsules of different doses of acenocoumarol 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 acenocoumarol / capsule</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.502 g</td>
<td>0.50 g</td>
<td>1 mg</td>
</tr>
</tbody>
</table>
Example 8. Preparation of pharmaceutical capsules which contain dabigatran etexilate microcapsules with gelatin, gum arabic and pectin 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 the same or higher than 7.

Solution B: Another 2% solution of gum arabic and pectin in water (ratio 1.2:1) and the pH was adjusted so it was the same or higher than 7.

100 mL of solution A and 100 mL of solution B were mixed and heated to 40 °C. 2 g of dabigatran etexilate powder 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. 1 mL of 50% glutaraldehyde solution in water was added.

The resulting suspension was dried by spray-drying, obtaining a microcapsule powder which contained 20% of dabigatran etexilate.

This microcapsule powder was directly dispersed in oil containing a minimum of 60% of ethyl esters of PUFA, with a minimum DHA content of 40% (4.58 g of the microcapsule suspension obtained per 10 g of oil). Next, 1.00 g of the microcapsule dispersion in oil was incorporated to a soft gelatin capsule, obtaining a dose of 110 mg of dabigatran etexilate per capsule.

Example 9. Preparation of pharmaceutical capsules that contain ibuprofen microcapsules 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 the same 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 the same 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 ibuprofen 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, obtaining a microcapsule powder which contained 38% of ibuprofen.

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 (5.40 g of the microcapsule suspension obtained per 10 g of oil). Next, 1.50 g of the dispersion of microcapsules in oil was incorporated to a soft gelatin capsule, obtaining a dose of 200 mg of ibuprofen per capsule.

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Example 10. Preparation of pharmaceutical capsules which contain ketoprofen microcapsules and a methacrylic acid copolymer.

10 g of ketoprofen 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 achieved. 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 ketoprofen.

The resulting microcapsule powder was directly dispersed in oil containing a minimum of 60% of ethyl esters of PUFA, with a minimum DHA content of 40% (12.8 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 25 mg of ketoprofen per capsule.
Example 11. Studies of stability of the soft gelatin capsules which contain amlodipine besylate, diltiazem, carvedilol, atenolol, dipyridamole, warfarin, acenocoumarol, dabigatran etexilate, ibuprofen and ketoprofen 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>
<th>Initial</th>
<th>1 month</th>
<th>2 months</th>
<th>3 months</th>
<th>4 months</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amlodipine besylate (example 1)</td>
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<td></td>
<td></td>
<td></td>
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<tr>
<td>a</td>
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<td>96.0</td>
<td>90.3</td>
<td>85.1</td>
<td>77.8</td>
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</tr>
<tr>
<td>b</td>
<td>98.5</td>
<td>98.3</td>
<td>-</td>
<td>98.2</td>
<td>98.2</td>
<td></td>
</tr>
<tr>
<td>Diltiazem (example 2)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>a</td>
<td>98.0</td>
<td>96.2</td>
<td>90.9</td>
<td>86.6</td>
<td>81.8</td>
<td></td>
</tr>
<tr>
<td>b</td>
<td>98.3</td>
<td>98.2</td>
<td>-</td>
<td>98.1</td>
<td>98.2</td>
<td></td>
</tr>
<tr>
<td>Carvedilol (example 3)</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
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<td>93.3</td>
<td>89.6</td>
<td>84.1</td>
<td></td>
</tr>
<tr>
<td>b</td>
<td>98.9</td>
<td>99.0</td>
<td>-</td>
<td>99.1</td>
<td>99.0</td>
<td></td>
</tr>
<tr>
<td>Atenolol (example 4)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>a</td>
<td>98.5</td>
<td>96.9</td>
<td>93.4</td>
<td>90.3</td>
<td>86.6</td>
<td></td>
</tr>
<tr>
<td>b</td>
<td>98.6</td>
<td>98.5</td>
<td>-</td>
<td>98.3</td>
<td>98.2</td>
<td></td>
</tr>
<tr>
<td>Dipyridamole (example 5)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>a</td>
<td>99.0</td>
<td>97.2</td>
<td>94.5</td>
<td>91.6</td>
<td>88.2</td>
<td></td>
</tr>
<tr>
<td>b</td>
<td>99.2</td>
<td>99.3</td>
<td>-</td>
<td>99.2</td>
<td>99.1</td>
<td></td>
</tr>
<tr>
<td>Warfarin (example 6; dose 5 mg, capsule 1 g)</td>
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<td></td>
<td></td>
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<td></td>
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<tr>
<td>a</td>
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<td></td>
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<tr>
<td>b</td>
<td>98.3</td>
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<td>-</td>
<td>98.1</td>
<td>98.2</td>
<td></td>
</tr>
<tr>
<td>Acenocoumarol (example 7; dose 4 mg, capsule 1 g)</td>
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<td></td>
</tr>
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<td>95.2</td>
<td>92.6</td>
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</tr>
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</tr>
<tr>
<td>Dabigatran etexilate (example 8)</td>
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<tr>
<td>Ibuprofen (example 9)</td>
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<td></td>
</tr>
<tr>
<td>b</td>
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<td>98.4</td>
<td>-</td>
<td>98.3</td>
<td>98.2</td>
<td></td>
</tr>
<tr>
<td>Ketoprofen (example 10)</td>
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<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
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<td>97.1</td>
<td>95.3</td>
<td>93.5</td>
<td></td>
</tr>
<tr>
<td>b</td>
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<td>99.0</td>
<td>-</td>
<td>98.9</td>
<td>98.9</td>
<td></td>
</tr>
</tbody>
</table>

Table 3
1. Pharmaceutical capsule which comprises a suspension of polymeric microcapsules which comprise at least one polymer and at least one active pharmaceutical ingredient selected from the group formed by the calcium channel blockers, beta blockers, antiplatelet drugs, anticoagulants and non-steroidal anti-inflammatory drugs, these microcapsules being suspended in an oil which contains alkyl esters of polyunsaturated fatty acids.

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 calcium channel blocker is selected from the group formed by selective calcium channel blockers, dihydropyridine calcium channel blockers, amlodipine, aranidipine, azelnidipine, azodipine, barnidipine, benidipine, cilnidipine, clevidipine, dazodipine, efonidipine, felodipine, flordipine, iodipine, isradipine, lacidipine, lercanidipine, manidipine, mesudipine, nicardipine, nifedipine, nilvadipine, nimodipine, nisoldipine, nitrendipine, oxodipine, pranidipine, riodipine, ryosidine phenylalkylamine, calcium channel blockers, verapamil, gallopamil, tiapamil, emopamil, falipamil, ronipamil, anipamil benzothiazepine calcium channel blockers, diltiazem, clentiazem, fostedil, ziconotide, non-selective calcium channel blockers, flunarizine, cinnarizine, prenylamine, fendiline, mibefradil.
bepridil, caroverine, lidoflazine, perhexiline, and/or their pharmaceutically
acceptable salts.

8. Pharmaceutical capsule according to claim 1 wherein this beta blocker is
selected from the group formed by acebutolol, alprenolol, amosulalol, arotinolol,
atenolol, betaxolol, bevantolol, bisoprolol, bopindolol, bucindolol, bupranolol,
carazolol, carteolol, carvedilol, celiprolol, satenolol, esmolol, indenolol, labetalol,
landiolol, levobunolol, mepindolol, metipranolol, metoprolol, nadolol, nebivolol,
oxprenolol, penbutolol, pindolol, propranolol, sotalol, talinolol, tertatolol, tilisolol,
timolol, butoxamine, and/or their pharmaceutically acceptable salts.

9. Pharmaceutical capsule according to claim 1, wherein this antiplatelet drug is
selected from the group formed by glycoprotein IIb/IIIa inhibitors, abciximab,
eptifibatide, tirofiblan, orbofiban, lamifiban, sibrafiban, xemilofiban,
thienopyridines, clopidogrel, ticlopidine, prasugrel, cilostazol, cloricromen,
dipyridamole, ditazole, indobufen, picotamide, sarpogrelate, trapidil, triflusal,
and/or their pharmaceutically acceptable salts.

10. Pharmaceutical capsule according to claim 1, wherein this anticoagulant is
selected from the group formed by direct anticoagulants, indirect
anticoagulants, heparins, unfractioned heparin, low molecular weight heparins,
ardeparin, bemiparin, certoparin, dalteparin, enoxaparin, nadroparin,
parnaparin, reviparin, tinzaparin, oligosaccharides, fondaparinux, idraparinux,
heparinoids, danaparoid, sulodexide, dermatan sulfate, direct inhibitors of factor
Xa, xabans, apixaban, otamixaban, rivaroxaban, direct inhibitors of thrombin II,
hirudin, bivalirudin, lepirudin, desirudin, argatroban, dabigatran, melagatran,
ximelagatran, vitamin K antagonists, coumarins, acenocoumarol, dicumarol,
etyl bismacacetate, phenprocoumon, warfarin, 1,3-indanodiones, clorindione,
anisindione, fluindione, phenindione, ticloparin, defibrotide and/or their
pharmaceutically acceptable salts.

11. Pharmaceutical capsule according to claim 1, wherein this non-steroidal anti-
inflammatory drug is selected from the group formed by arylalkanoic acids,
diclofenac, aceclofenac, acemetacin, alclofenac, bromfenac, etodolac,
indometacin, nabumetone, oxametacin, proglumetacin, sulindac, tolmetin, 2-
arylpropionic acids or profens, ibuprofen, dexibuprofen, alminoprofen,
carprofen, fenbufen, fenoprofen, flunoxaprofen, flurbiprofen, tarenflurbil,
ibuproxam, ketoprofen, dexketoprofen, ketorolac, loxoprofen, miroprofen,
naproxen, oxaprozin, pranoprofen, tiaprofenic acid, /V-arylantranilic acids, mefenamic acid, meclofenamic acid, flufenamic acid and tolfenamic acid, derivatives of pyrazolidin, phenylbutazone, azapropazone, clofezone, kebuzone, metamizole, mofebutazone, oxyphenbutazone, phenazone, sulfonpyrazone, oxicams, piroxicam, lornoxicam, meloxicam, tenoxicam, COX-2 inhibitors, celecoxib, etoricoxib, firocoxib, lumiracoxib, parecoxib, rofecoxib, valdecoxib, sulfonamides, nimesulide, CINOD, naproxcinod, fluproquazone, and/or their pharmaceutically acceptable salts.

12. 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.

13. Pharmaceutical capsule according to claim 12, 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 polymers, polymers and copolymers of the lactic and glycolic acids, polymers and copolymers of the lactic and glycolic acids and polyethylene glycol and/or mixtures thereof.

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

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

16. Pharmaceutical capsule according to claim 1, wherein the polymer of these microcapsules contains at least one plasticizer, a fluidifying agent and/or an antioxidant.
17. 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.

18. Pharmaceutical capsule according to claim 17, wherein this coating is made of soft gelatin.

19. Pharmaceutical capsule according to claim 1, wherein this capsule comprises an enteric coating.

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

21. Pharmaceutical capsule according to claim 1, for the treatment of diseases and/or processes involving inflammation and/or pain.