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(54) Title: CAPSULES OF ACTIVE PHARMACEUTICAL INGREDIENTS AND POLYUNSATURATED FATTY ACIDS FOR THE TREATMENT OF PROSTATE DISEASES

(57) Abstract: Pharmaceutical composition in capsule form which contains polyunsaturated fatty acids (PUFA) and active pharmaceutical ingredients for the treatment and/or prevention of prostate diseases and/or hyperandrogenic disorders.

CAPSULES OF ACTIVE PHARMACEUTICAL INGREDIENTS AND POLYUNSATURATED FATTY ACIDS FOR THE TREATMENT OF PROSTATE DISEASES

FIELD OF THE INVENTION

This invention relates to a pharmaceutical composition in capsule form which comprises a suspension of polymeric microcapsules suspended in an oil which contains 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 prostate diseases and/or hyperandrogenic disorders.

BACKGROUND OF THE INVENTION

Prostate diseases include benign prostatic hyperplasia (BPH), prostate cancer, prostatitis, chronic prostatitis and prostatodynia.

BPH refers to an increase in size of the prostate due to proliferation of cells and is common among middle-aged and elderly men. Medical treatments for BPH include surgery, treatment with alpha-adrenergic blockers, with 5-alpha-reductase inhibitors, or phytosterol therapy.

Alpha-adrenergic blockers, such as tamsulosin, doxazosin, terazosin, prazosin, alfuzosin, bunazosin, silodosin or indoramin, are used to alleviate urinary obstruction in BPH and for the treatment of hypertension.

The other approach for the treatment of BPH is that which involves altering testosterone metabolism. 5-alpha-Reductase is an enzyme which catalyzes the conversion of testosterone to dihydrotestosterone (DHT), a hormone which stimulates the growth of the prostate tissue. 5-alpha-Reductase inhibitors, such as finasteride or dutasteride, block the action of this enzyme and prevent the increase in the size of the prostate.

The growth of the prostate can also be treated by reducing the quantity of estrogens; this is the way of action of mepartricin, used in the treatment of BPH and chronic prostatitis. For the treatment of BPH antiandrogens such as oxendolone, have been

used, and other compounds such as the selective androgen receptor modulators are being studied, e.g. andarine. Vitamin D analogues such as elocalcitol (or BXL-628) are also under study for the treatment of BPH, overactive bladder and male infertility [Colli, E. *et al. Eur. J. Urol.* 49: 82-86 (2006)].

5-alpha-Reductase inhibitors are also used for the treatment of hyperandrogenic disorders, as well as some antiandrogens such as spironolactone. Among these hyperandrogenic disorders are androgenic alopecia, acne, seborrhea, hirsutism and polycystic ovary syndrome.

Prostate cancer is the second most common cancer among men. The type of treatment depends on the stage at which the cancer is. As well as surgery and radiotherapy or brachytherapy, in the case of a locally advanced or metastatic disease, hormone therapy and/or chemotherapy is used. Hormone therapy for prostate cancer involves the use of medication and/or surgery to achieve androgen deprivation and block the production of DHT, required for the growth and spread of the cancerous cells of the prostate.

Among the most used active pharmaceutical ingredients for hormone treatment of prostate cancer are:

- Antiandrogens or androgen antagonists, which block the androgen receptors, such as flutamide, bicalutamide, nilutamide, cyproterone acetate, chlormadinone acetate, medroxyprogesterone acetate and megestrol acetate. These active ingredients directly block the action of testosterone and DHT in the prostate cancer cells.

- Adrenal androgen synthesis inhibitors, such as ketoconazole and aminoglutethimide. Since the adrenal glands only produce between 5 and 10% of the body's androgens, these active ingredients are generally used in combination with other methods to obtain a complete androgen blockade. They are used as a second-line hormone treatment in advanced prostate cancer.

- Gonadorelin analogues or gonadotropin-releasing hormone analogues (GnRH analogues), also called lubirelin analogues or luteinizing hormone-releasing hormone analogues (LHRH analogues). They are in turn divided into:

- LHRH antagonists: they directly suppress the production of luteinizing hormone; examples are abarelix, cetrorelix, ganirelix and degarelix.
- LHRH agonists: they suppress the production of luteinizing hormone through a process of sub-regulation after an initial stimulation effect, and include leuprolide, goserelin, triptorelin and buserelin, among others.

Epidemiological studies which link vitamin D deficiency with a greater risk of suffering from prostate cancer have lead to clinical trials of administration of this vitamin, its metabolites and analogues in animals and patients with cancer. The principal active metabolite of vitamin D, calcitriol, has pro-differentiating, antiproliferative, noninvasive and antimetastatic effects in the prostate cells. The greatest obstacle shown by calcitriol is the risk of hypercalcemia. To reduce this risk, as well as with pulse dose administration of calcitriol, numerous less-calcemic vitamin D analogues are subject to study [Schwartz G.G. *Ann. Epidemiol.* 19: 96-102 (2009); Skowronski, R. J. *et al. Endocrinology* 136: 20-26 (1995); Lokeshwar, B.L. *et al. Cancer Epidemiol. Biomarkers Prev.* 8: 241-248 (1999); Chen, T.C. *et al. Clin. Cancer. Res.* 6: 901-908 (2000); Blutt, S.E. *et al. Cancer Res.* 60: 779-782 (2000)].

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. The principal essential fatty acids in the omega-6 series are gamolenic acid (or gamma-linolenic acid, GLA) and linolenic acid, and are present in many vegetable seed oils.

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.

Different epidemiological studies suggest that diets rich in omega-3 polyunsaturated fatty acids reduce cancer levels, including prostate cancer [Norrish A.E. *et al. Br. J. Cancer* 81: 1238-1242 (1999); Leitzmann *et al. Am. J. Clin. Nutr.* 80: 204-216 (2004)].

In US 6656969 B2 the administration of EPA and DHA is proposed for the treatment and prevention of prostate cancer.

Omega-3 fatty acids, especially those of marine origin, EPA and DHA, inhibit the proliferation of cancerous prostate cells, both *in vitro* and *in vivo* [Rose, D.P. *et al. Prostate* 18: 243-254 (1991); US 6656969 B2; Kobayashi, N. *et al. Clin. Cancer Res.* 12: 4662-4670 (2006); Kelavkar, U.P. *et al. Neoplasia 8*: 112-124 (2006)]. A study by Berquin *et al.* [*J. Clin. Inv.* 117: 1866-1875 (2007)] asserts that omega-3 fatty acids reduce the growth of prostate tumors, slow down their histopathological progression and increase survival in PTEN knockout mice.

Different extracts of vegetable seeds rich in omega-6 fatty acids, in particular in gamma-linolenic acid, such as borage, evening primrose or blackcurrant, are used to treat disorders associated with 5-alpha-reductase, such as alopecia or acne. In a study by Liao *et al.* [*Biochem. J.* 285: 557-562 (1992)] the inhibition of 5-alpha-reductase with different PUFA from the two series is tested, the gamma-linolenic acid, from the omega-6 series, being the most effective inhibitor. In EP 0201159 A2 the use of gelatin capsules containing evening primrose and borage oil for the treatment of BPH is claimed, due to their high content in the omega-6 fatty acids gamma-linolenic acid and dihomo-gamma-linolenic acid.

Oral administration is the most convenient form of drug administration. However, the majority of alpha-adrenergic blockers, 5-alpha-reductase inhibitors, mepartricin, andarine, antiandrogens, adrenal androgen synthesis inhibitors and vitamin D analogues are hydrophobic active ingredients and mostly very insoluble, and therefore show a low bioavailability. Administration in the form of tablets is not, in these cases, appropriate. In general, to improve the bioavailability of active ingredients, they are usually administered as a solution, emulsion or dispersion.

Among the forms of oral administration, gelatin capsules, in particular soft capsules which contain liquids, are among those preferred by patients, due to their easy administration. However, many of the aforementioned active ingredients which are habitually used for the treatment of prostate diseases show problems for formulation as 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 filling 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.

Furthermore, the external layer of the capsule contains a certain amount of water as a component. 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 water from 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 additives and the active ingredient. These additives can facilitate the oxidation, degradation or hydrolysis processes, causing a loss of activity of the formulated active ingredient. Another factor to take into account is the possible chemical interaction between the filling and the gelatin in the capsule, which may favor cross-linking and thus reduce the solubility of the capsule in aqueous medium; cross-linking leads to the formation of an insoluble membrane, called film, on the inner side of the gelatin coating which delays the speed of disintegration of the capsule. Thus for example, dutasteride is marketed as a solution in soft gelatin capsules with a limited stability due to cross-linking in the capsule coating; the result is a decrease in the solubility of the gelatin capsule coating and a decrease in the speed of release of the active ingredient [EP 2050436 A1].

If the liquid formulation is to be administered in the form of a gelatin (hard or soft) or a hydroxypropyl methylcellulose (HPMC) capsule, for example, for oral administration, solvents used inside the capsule must be compatible with its coating. One of the greatest limitations is the amount of active ingredient that can be encapsulated as a solution. Often it is necessary to use solubilizing agents and cosolvents. As a result of this a problem arises concerning the lack of integrity of the capsule coating in the presence of non-aqueous solubilizing agents such as *N*-methyl-2-pyrrolidone (NMP) and other derivatives of pyrrolidone. This also occurs with a common cosolvent in soft gelatin capsules, such as ethanol: ethanol spreads easily through the soft gelatin capsule coatings during the drying process, which could cause a reduction in the solubility of the dissolved active ingredient. Furthermore, the partial migration of water occurring from the gelatin capsule coating towards the inside of the capsule during the drying and equilibration process must be taken into account. This can lead to a decrease in the solubility and precipitation of the sparingly soluble hydrophobic active ingredients [Serajuddin, A.T. *et al. J. Pharm. Sci.* 75: 62-4 (1986)].

The use of surfactants for the formation of micelles only permits the preparation of low doses of the active ingredients, and the emulsions are thermodynamically unstable. Although microemulsions are more stable, their inclusion in gelatin capsules is problematic: there may exist interaction between the water in the capsule coating and the water in the microemulsion, varying the proportion of water in both; furthermore, the surfactants necessary for the formation of any type of emulsion or microemulsion (including self-emulsifying mixtures or preconcentrated microemulsions) can react with the capsule coating [US 6280770 B1].

When the active ingredients cannot be dissolved, they can be administered in the form of dispersions or suspensions. Suspensions are thermodynamically unstable systems, and the active ingredient can deposit forming more insoluble aggregates. To improve the stability of any type of suspension it is advisable for the active ingredient to be fully insoluble in the suspension medium; thus, possible recrystallizations leading to crystalline forms of different solubility which affect its bioavailability are avoided. In the case of suspensions in oily vehicles it is normal to micronize the active ingredients during the preparation and include suspension agents to prevent sedimentation and to achieve homogenous mixtures. In any event, the handling of very fine solids is complicated at an industrial scale. In US 2006/204588 A1 compositions of

nanoparticles with a size smaller than 2 μm of finasteride, dutasteride, tamsulosin hydrochloride, or combinations thereof, are proposed in order to improve their bioavailability. In addition to the drawbacks associated with the preparation and handling of these fine particle-sized and potentially teratogenic solids, the presence of excipients such as surface stabilizers is necessary.

Finasteride shows bioavailability problems due to its insolubility; furthermore, as many steroids, it is susceptible to oxidization by the oxygen in the air. Vitamin D derivatives also degrade on contact with the air.

In WO 99/08666 A2 the bioavailability of azasteroids such as finasteride is increased by preparing solutions in mixtures of polyethylene glycol and propylene glycol, and oxidation of the active ingredient is limited by encapsulating it in gelatin capsules. However, due to its permeability, the capsule coating is not sufficient to protect the active ingredient.

In US 5952003 A terazosin capsules stable under accelerated stability studies are prepared, in which the liquid inside is replaced by a solid vehicle, which does not favor bioavailability due to its physical state.

It is known, furthermore, that the formulations based on lipids increase the bioavailability, both of the low soluble hydrophobic drugs [Charman, W.N. *J. Pharm. Sci.* 89: 967-978 (2000); Fatouros, D.G. *et al. Ther. Clin. Risk Manag.* 3: 591-604 (2007), as well as the hydrophilic drugs, such as peptides and/or proteins [Rawat, M. *et al. Yakugaku Zasshi* 128: 269-280 (2008)].

On the other hand, the hydrophilic active ingredients such as LHRH analogue oligopeptides, orally administered as aqueous formulations, show low bioavailability due to their low permeability through the biological membranes and their susceptibility to enzyme degradation by different proteases.

The formulations in gelatin capsules which include hydrophilic components also represent a challenge, since the components can interact with the coating. During the preparation and drying, the hydrophilic components from the filling of the capsule can migrate towards the coating and vice versa, thus changing the initial composition of both. During storage, these processes can continue until they reach a state of balance.

As a result, the capsule coating becomes brittle or sticky and the composition of the filling can decompose.

The hydrophilic and/or hygroscopic active ingredients suspended in an oily vehicle and formulated in gelatin capsules can attract and retain water from the coating and/or migrate towards it [Armstrong, N.A. *et al. J. Pharm. Pharmacol.* 36: 361-5 (1984)]. This can lead to stability problems such as hydrolysis or oxidation of the active ingredient and/or discoloration of the coating.

Hydrophilic active ingredients, such as leuprolide acetate, show low solubility in lipids; therefore, their use in oily formulations is limited. In WO 99/43299 A2 and a subsequent study [Zheng, J.Y. *et al. Int. J. Pharm.* 307: 209-215 (2006)] its solubilization in fatty acids and water is described, increasing its membrane permeability and reducing its enzyme degradation; by this way, its bioavailability improves and the oral administration becomes appropriate. To that end, microemulsions which comprise leuprolide acetate dissolved in a fatty acid such as oleic acid and water are prepared; the addition of cosolvents such as ethanol is necessary, as well as high proportions of other excipients, such as polysorbates, which would limit their formulation in gelatin capsules. Some excipients habitually used in microemulsions, such as polysorbates, among others, can self-oxidize to give rise to peroxides [Donbrow, M. *et al. J. Pharm. Sci.* 67: 1676-1681 (1978)] which favor the cross-linking of the gelatin in the coating.

Therefore, although the soft gelatin capsules are widely used in the pharmaceutical industry, many active ingredients show problems for their formulation in them. Although some of the described references represent an attempt to solve the formulation problems associated with the pharmaceutical compositions in capsule form which contain insoluble hydrophobic active ingredients, or hydrophilic active ingredients, the problem arising from the state of the art is the need to improve the stability of these pharmaceutical compositions, overcoming the solubilization or dispersion problems shown by highly hydrophobic and insoluble compounds, as well as the hydrophilic compounds, and which affect their bioavailability. The solution proposed by this invention is a pharmaceutical capsule which incorporates oils containing PUFA and microcapsules of the desired active ingredient isolated by means of a polymer.

In the case of peptides, furthermore, the use of polymer release systems can improve the bioavailability by oral route, limiting its proteolytic degradation [Delie, F. *et al. Molecules* 10: 65-80 (2005)].

The subject-matter of this invention is a pharmaceutical composition in capsule form, which permits the formulation of active pharmaceutical ingredients for the treatment and/or prevention of prostate diseases and/or hyperandrogenic disorders, solving the problems of stability and bioavailability described in the prior art, both regarding insoluble hydrophobic compounds and hydrophilic compounds, without the need to add cosolvents, surfactants or other excipients which could damage the capsule coating. The pharmaceutical capsule of this invention allows active pharmaceutical ingredients for the treatment and/or prevention of prostate diseases and/or hyperandrogenic disorders to be conveniently formulated, such as alpha-adrenergic blockers, 5-alpha-reductase inhibitors, mepartricin, andarine, antiandrogens, adrenal androgen synthesis inhibitors, vitamin D analogues and/or LHRH analogues, in combination with oils which contain PUFA in one single composition. Thus greater comfort and reliability is achieved with regards to the patient following the treatment, as it reduces the risk of the patient forgetting to administer any of the drugs. Likewise, the pharmaceutical composition of this invention provides protection for the active pharmaceutical ingredients against moisture, oxidizing agents and/or possible chemical interactions with additives in the outside coating, by the isolation provided by the combination of a polymeric coating of the active pharmaceutical ingredient and its suspension in oils which contain PUFA.

DESCRIPTION OF THE INVENTION

This invention, therefore, relates to a new pharmaceutical composition which avoids problems associated with the formulation of active pharmaceutical ingredients for the treatment and/or prevention of prostate diseases and/or hyperandrogenic disorders, such as alpha-adrenergic blockers, 5-alpha-reductase inhibitors, mepartricin, andarine, antiandrogens, adrenal androgen synthesis inhibitors, vitamin D analogues and/or LHRH analogues, 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 polymeric microcapsules which comprise at least one polymer and at

least one active pharmaceutical ingredient for the treatment and/or prevention of prostate diseases and/or hyperandrogenic disorders, these microcapsules being suspended in an oil which contains polyunsaturated fatty acids. 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 this invention, the active pharmaceutical ingredients are found inside the polymeric microcapsules in suspension in an oil which contains PUFA. The active pharmaceutical ingredients are isolated from the exterior medium as well as the oils which contain PUFA by the polymer, which disintegrates easily in the gastrointestinal medium. The pharmaceutical capsule of this 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 additives of the capsule coating, outer moisture, light and oxygen, as well as from the direct contact with oils which contain PUFA in the suspension. The polymeric coating isolates the active pharmaceutical ingredients and affords them stability.

Preferably, the polyunsaturated fatty acids or PUFA include the omega-3 and omega-6 series, their alkyl esters and/or triglycerides. Examples of omega-3 fatty acids include, without restriction, *(all-cis)*-7,10,13-hexadecatrienoic or roughanic acid (C16:3 *n*-3), *(all-cis)*-9,12,15-octadecatrienoic or alpha-linolenic acid (ALA) (C18:3 *n*-3), *(all-cis)*-6,9,12,15-octadecatetraenoic or stearidonic or moroctic acid (C18:4 *n*-3), *(all-cis)*-11,14,17-eicosatrienoic or homo-alpha-linolenic or eicosatrienoic acid (ETE) (C20:3 *n*-3), *(all-cis)*-8,11,14,17-eicosatetraenoic or eicosatetraenoic or bishomostearidonic acid (C20:4 *n*-3), *(all-cis)*-5,8,11,14,17-eicosapentaenoic or timnodonic or eicosapentaenoic acid (EPA) or icosapent (C20:5 *n*-3), *(all-cis)*-6,9,12,15,18-heneicosapentaenoic or heneicosapentaenoic acid (C21:5 *n*-3), *(all-cis)*-7,10,13,16,19-docosapentaenoic or clupanodonic or docosapentaenoic acid (DPA) (C22:5 *n*-3), *(all-cis)*-4,7,10,13,16,19-docosahexaenoic or cervonic or docosahexaenoic acid (DHA) or doconexent (C22:6 *n*-3), *(all-cis)*-9,12,15,18,21-tetracosapentaenoic or tetracosapentaenoic acid (C24:5 *n*-3) and *(all-cis)*-6,9,12,15,18,21-tetracosahexaenoic or tetracosahexaenoic or nisinic acid (C24:6 *n*-3), their alkyl esters, triglycerides and/or mixtures thereof, such as Omacor®, Lovaza® or Zodin®, among others. Preferably, the omega-3 fatty acid is ALA, DHA, EPA, DPA, their alkyl esters, triglycerides and/or mixtures thereof. In a preferred embodiment, the EPA:DHA ratio can range between 100:0 and 0:100, preferably

between 4:1 and 1:4, and more preferably between 1:2 and 2:1. Examples of omega-6 fatty acids include, without restriction, *(all-cis)*-9,12-octadecadienoic acid or linoleic acid (C18:2 *n*-6), *(all-cis)*-6,9,12-octadecatrienoic or gamolenic or gamma-linolenic acid (GLA) (C18:3 *n*-6), *(all-cis)*-11,14-eicosadienoic or eicosadienoic or bishomolinoleic acid (C20:2 *n*-6), *(all-cis)*-8,11,14-eicosatrienoic or dihomo-gamma-linolenic acid (DGLA) (C20:3 *n*-6), *(all-cis)*-5,8,11,14-eicosatetraenoic or arachidonic acid (AA) (C20:4 *n*-6), *(all-cis)*-13,16-docosadienoic or docosadienoic acid (C22:2 *n*-6), *(all-cis)*-7,10,13,16-docosatetraenoic or adrenic acid (C22:4 *n*-6) and *(all-cis)*-4,7,10,13,16-docosapentaenoic or docosapentaenoic or osbond acid (C22:5 *n*-6), their alkyl esters and/or mixtures thereof. Preferably, the omega-6 fatty acid is linoleic acid or gamma-linolenic acid, their alkyl esters, triglycerides and/or mixtures thereof.

Preferably, the alkyl radical of the omega-3 and omega-6 fatty acid alkyl esters 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.

As an example and without restriction, the oil contained in PUFA is selected from the group formed by fish oil, cod liver oil, salmon oil, mackerel oil, herring oil, anchovy oil, sardine oil, vegetable oils, algae oils, linseed oil, evening primrose oil, borage oil, blackcurrant oil, stinging nettle oil, safflower oil, sunflower oil, corn oil, pumpkin seed oil, soybean oil, hemp seed oil and/or mixtures thereof.

Preferably, the oil containing PUFA is an oil enriched in PUFA, preferably, the oil contains more than 40% of PUFA, more preferably more than 60% of PUFA and even more preferably, more than 85% of PUFA.

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

In a particular embodiment, the active pharmaceutical ingredient is an alpha-adrenergic blocker. The alpha-adrenergic blocker is selected, without restriction, from the group formed by tamsulosin, doxazosin, terazosin, prazosin, alfuzosin, bunazosin, silodosin,

indoramin, abanoquil, naftopidil, trapizosin, fiduxosin, parvosin, GYKI-16084, L-771688, UK-294315, AIO-8507L, RBx-2258 and/or their pharmaceutically acceptable salts.

In another particular embodiment, the active pharmaceutical ingredient is a 5-alpha-reductase inhibitor, selected, without restriction, from the group formed by finasteride, dutasteride, izonsteride, turosteride, TF-505, AS-601811, FK-143 and/or their pharmaceutically acceptable salts.

In another particular embodiment, the active pharmaceutical ingredient is mepartricin.

In another particular embodiment, the active pharmaceutical ingredient is andarine.

In another particular embodiment, the active pharmaceutical ingredient is an antiandrogen. The antiandrogen is selected, without restriction, from the group formed by flutamide, bicalutamide, nilutamide, cyproterone acetate, chlormadinone acetate, medroxyprogesterone acetate, abiraterone acetate, spironolactone, MDV3100, osaterone acetate, oxendolone and/or their pharmaceutically acceptable salts.

In another particular embodiment, the active pharmaceutical ingredient is an adrenal androgen synthesis inhibitor, selected, without restriction, from the group formed by ketoconazole, aminoglutethimide and/or their pharmaceutically acceptable salts.

In another particular embodiment, the active pharmaceutical ingredient is a vitamin D analogue, selected, without restriction, from the group formed by vitamin D2 or ergocalciferol, vitamin D3 or colecalciferol, calcitriol, calcifediol, doxercalciferol, paricalcitol, calcipotriol or MC-903, seocalcitol or EB-1089, 22-oxacalcitriol or maxacalcitol, ercalcitriol or Ro 17-6218, 1,24,25 trihydroxyvitamin D3, MC-1288, KH-1060, GS-1558, CB-1093, Ro 23-7553 or BXL-353, Ro 24-2637, Ro 25-4020, Ro 25-6760, Ro 26-9114, LG-190119, alfacalcidol, falecalcitriol, elocalcitol and/or their pharmaceutically acceptable salts.

In another particular embodiment, the active pharmaceutical ingredient is a LHRH analogue. The LHRH analogue can be a LHRH antagonist or a LHRH agonist. The LHRH antagonist is selected, without restriction, from the group formed by abarelix, cetrorelix, ganirelix, degarelix, teverelix, ramorelix, azaline B, acyline, ozarelix, detirelix, ramorelix, antide, orntide, ORF 21243, LXT-101, RS-68439, A-75998 and/or their pharmaceutically acceptable salts. The LHRH agonist is selected, without restriction,

from the group formed by leuprolide, buserelin, goserelin, triptorelin, nafarelin, deslorelin, histrelin, avorelin and/or 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, copolymers of all of them and/or mixtures thereof. Preferably, the polymeric coating of the microcapsules is selected from the group formed by gelatin, albumin, soy protein, pea protein, broad bean protein, potato protein, wheat protein, whey protein, β-lactoglobulin, caseinates, wheat starch, corn starch, zein, alginates, carrageenans, pectins, arabinogalactans, gum arabic, xanthan gum, mesquite gum, tragacanth gum, galactomannans, guar gum, locust bean gum, chitosan, agar, poly(L-lysine), sodium dextran sulfate, carboxymethyl galactomannan, carboxymethyl cellulose, ethyl cellulose, hydroxypropyl methylcellulose (HPMC), nitrocellulose, cellulose acetate butyrate, cellulose acetate phthalate, hydroxypropyl methylcellulose phthalate, hydroxypropyl methylcellulose acetate succinate, polyvinyl acetate phthalate, poly(ε-caprolactone), poly(*p*-dioxanone), poly(δ-valerolactone), poly(β-hydroxybutyrate), poly(β-hydroxybutyrate) and β-hydroxyvalerate copolymers, poly(β-hydroxypropionate), methacrylic acid copolymers (Eudragit® L and S), dimethylaminoethyl methacrylate copolymers (Eudragit® E), trimethylamonium ethyl methacrylate copolymers (Eudragit® RL and RS), poly(*n*-butyl)cyanoacrylate polymers and copolymers, poly(isobutyl)cyanoacrylate polymers and copolymers, poly(*n*-hexyl)cyanoacrylate polymers and copolymers, poly(2-octyl)cyanoacrylate polymers and copolymers, lactic and glycolic acid polymers and copolymers, lactic and glycolic and polyethylene glycol acid polymers and copolymers and and/or mixtures thereof. More preferably, the polymeric coating is made of gelatin, alginates, pectins, gum arabic, carboxymethyl cellulose, hydroxypropyl methylcellulose, cellulose acetophthalate, methacrylic acid copolymers (Eudragit® L and S), lactic and glycolic and polyethylene glycol acid polymers and copolymers and and/or mixtures thereof.

Optionally, the microcapsules of the pharmaceutical capsule of this invention can be coated by several layers of additional polymers, whether this is the same polymer as the first layer, different polymer or mixtures of polymers.

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, waxes and/or mixtures thereof.

Optionally other technical additives of the polymer can be incorporated to 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 0.0001% and 80% of the total weight of the pharmaceutical capsule of this invention, preferably between 0.001% and 60%, and more preferably between 0.01% 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 a 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 prostate diseases. Preferably, prostate diseases are selected from the group formed by benign prostatic hyperplasia (BPH), prostate cancer, prostatitis, chronic prostatitis and prostatodynia, among others.

Another aspect of this invention relates to the pharmaceutical capsule of this invention for the treatment and/or prevention of hyperandrogenic disorders. Preferably, the hyperandrogenic disorders are selected from the group formed by androgenic alopecia, acne, seborrhea, hirsutism and polycystic ovary syndrome, among others.

Another aspect of this invention is a method of treatment and/or prevention of prostate diseases which comprises the administration of the pharmaceutical capsule of this invention. Preferably, the prostate diseases are selected from the group formed by

benign prostatic hyperplasia (BPH), prostate cancer, prostatitis, chronic prostatitis and prostatodynia, among others.

Another aspect of this invention is a method of treatment and/or prevention of hyperandrogenic disorders which comprises the administration of the pharmaceutical capsule of this invention. Preferably, the hyperandrogenic disorders are selected from the group formed by androgenic alopecia, acne, seborrhea, hirsutism and polycystic ovary syndrome, among others.

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 construed as limitations on the invention claimed herein.

EXAMPLES

Example 1. Preparation of pharmaceutical capsules which contain microcapsules of tamsulosin hydrochloride with gelatin, gum Arabic and pectin prepared by a complex coacervation procedure and which contain a second polymer coating of polysaccharides.

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

Solution B: Another 2% solution of gum Arabic and pectin in water was prepared (ratio 1.2:1) and the pH was adjusted so that it was 7 or greater.

100 mL of solution A and 100 mL of solution B were mixed together and were heated to 40 °C. 1.0 g of tamsulosin hydrochloride powder was 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. 0.5 mL of 50% glutaraldehyde solution in water were added.

The microcapsules obtained were recovered by filtration, and the filtered product was washed with water to eliminate the excess of glutaraldehyde. 16.0 g of wet product were obtained, which presented a 6% concentration of tamsulosin hydrochloride and a 75% content in water.

Next, a solution of mannitol (1.44 g) and hydroxypropyl methylcellulose (0.95 g) in 25 mL of water was prepared. The microcapsules were dispersed in the solution of polysaccharides and the dispersion obtained was dried by spray drying to obtain a microcapsule powder which contained 15% of tamsulosin hydrochloride.

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 (0.267 g of microcapsule powder obtained per 100 g of oil). Next, 1.00 g of the dispersion of microcapsules in oil was incorporated into a soft gelatin capsule to obtain a dose of 0.4 mg of tamsulosin hydrochloride per capsule.

Example 2. Preparation of pharmaceutical capsules which contain microcapsules of prazosin hydrochloride with gelatin by a simple coacervation process.

A 1% solution of gelatin in water was prepared.

500 mL of this solution were taken and 5.0 g of prazosin hydrochloride powder were dispersed in it. Next, 150 mL of saturated sodium sulfate solution in water were added. The mixture was stirred for 1 hour and 2.5 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 prazosin hydrochloride content of these microcapsules was 36%.

The resulting microcapsule powder 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. Next, the dispersion of microcapsules in oil was incorporated into a soft gelatin capsule. The quantities used to prepare capsules of different doses of prazosin are shown in Table 1.

Dispersion: mg of microcapsules per 100 g of oil	**Weight of dispersion per capsule**	Dose of prazosin per capsule
153.0 mg	1.00 g	0.5 mg
306.5 mg	0.50 g	0.5 mg
558.7 mg	1.00 g	2 mg

Table 1

Example 3. Preparation of pharmaceutical capsules which contain microcapsules of dutasteride and a methacrylic acid copolymer.

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

The resulting suspension was dried by spray drying to obtain a microcapsule powder which contained 10.0% of dutasteride.

The resulting microcapsule powder was directly dispersed in borage oil containing 0.1% of vitamin E acetate (502.5 mg of microcapsule powder obtained per 100 g of oil). Next, 1.00 g the dispersion of microcapsules in oil obtained was incorporated to a soft gelatin capsule to obtain a dose of 0.5 mg of dutasteride per capsule.

Example 4. Preparation of pharmaceutical capsules which contain microcapsules of finasteride 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 of PLGA in dichloromethane with an intrinsic viscosity (I.V.) of 0.17 and a lactic:glycolic ratio of 1:1 was prepared.

Solution B: 5.0 g of finasteride 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 stream

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 abundant water to eliminate the excess of PVA and was dried under reduced pressure.

The microcapsule powder obtained contained 24% of finasteride, 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 dispersion of microcapsules in oil obtained was incorporated into a soft gelatin capsule. The quantities used to prepare capsules of different doses of finasteride are shown in Table 2.

Dispersion: g of microcapsules per 100 g of oil	**Weight of dispersion per capsule**	**Dose of finasteride per capsule**
0.418 g	1.00 g	1 mg
2.13 g	1.00 g	5 mg

Table 2

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

A 2% solution of sodium cellulose acetate phthalate in water was prepared. 1.5 g of mepartricin powder were suspended in 100 mL of this solution. The resulting suspension was dried by spray drying.

The resulting microcapsule powder contained 38% of mepartricin, and was directly dispersed in oil containing a minimum of 60% of ethyl esters of PUFA, with a minimum DHA content of 40% and 0.1% of vitamin E acetate (1.18 g of microcapsule powder 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 40 mg of mepartricin per capsule.

Example 6. Preparation of pharmaceutical capsules which contain microcapsules of cyproterone acetate with alginate prepared by a simple coacervation procedure.

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

100 mL of this solution were taken and 1.0 g of cyproterone acetate powder was dispersed in them. 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 cyproterone acetate content of these microcapsules was 38%.

The resulting microcapsule powder was dispersed directly in evening primrose oil which contained 0.1% of vitamin E acetate (1.61 g of microcapsule powder obtained per 10 g of oil). Next, 1.00 g of the dispersion of microcapsules in oil was incorporated into a soft gelatin capsule to obtain a dose of 50 mg of cyproterone acetate per capsule.

Example 7. Preparation of pharmaceutical capsules which contain microcapsules of bicalutamide 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 that it was 7 or greater.

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

100 mL of solution A and 100 mL of solution B were mixed together and heated to 40°C. 1.5 g of bicalutamide 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 to obtain a microcapsule powder which contained 37% of bicalutamide.

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 (1.56 g of microcapsule powder obtained per 10 g of oil). Next, 1.00 g of the dispersion of microcapsules in oil was incorporated into a soft gelatin capsule to obtain a dose of 50 mg of bicalutamide per capsule.

Example 8. Preparation of pharmaceutical capsules which contain microcapsules of buserelin acetate with poly(lactic-co-glycolic acid) (PLGA) prepared by a simple coacervation procedure.

1.45 g of lactic-co-glycolic polymer (molecular weight 50000 and ratio of lactic:glycolic monomers of 1:1) were dissolved in 50 mL of dichloromethane . Once all of the polymer had dissolved, 70 mg of buserelin acetate were added and suspended by sonication. Under intense stirring, 65 g of silicon of 350 cts (centistokes) were slowly added. Next, the content of the reactor was poured onto 2.5 L of *n*-heptane and the mixture was stirred for 1 hour. The microcapsules were recovered by filtration and dried under vacuum.

The microcapsule powder obtained presented a concentration of buserelin acetate of 4.5%, and 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 (118.0 mg of microcapsule powder obtained per 10 g of oil). Next, 1.00 g of the microcapsule dispersion in oil was incorporated into a soft gelatin capsule to obtain a dose of 0.5 mg of buserelin per capsule (corresponding to 0.525 mg of buserelin acetate).

Example 9. Preparation of pharmaceutical capsules which contain microcapsules of leuprolide acetate with poly(lactic-co-glycolic acid) (PLGA) prepared by a simple coacervation procedure.

1.45 g of lactic-co-glycolic polymer (molecular weight= 50000 and ratio of lactic:glycolic monomers of 1:1) were dissolved in 50 mL of dichloromethane . Once all of the

polymer had dissolved, 75 mg of leuprolide acetate were added and suspended by sonication. Under intense stirring, 63 g of silicon of 350 cts (centistokes) were slowly added. Next, the content of the reactor was poured onto 2.5 L of *n*-heptane and the mixture was stirred for 1 hour. The microcapsules were recovered by filtration and dried under vacuum for 48 hours.

The microcapsule powder obtained presented a concentration of leuprolide acetate of 4.8%, 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 (212.8 mg of microcapsule powder obtained per 10 g of oil). Next, 1.00 g of the microcapsule dispersion in oil was incorporated into a soft gelatin capsule to obtain a dose of 1 mg of leuprolide acetate per capsule.

Example 10. Preparation of pharmaceutical capsules that contain microcapsules of degarelix acetate 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: 0.7 g of degarelix acetate 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 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 stream was passed through the reactor at a flow of not 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 plenty of water to eliminate the excess of PVA and were dried by lyophilization.

The microcapsule powder obtained contained 19% of degarelix acetate, and was directly dispersed in oil containing a minimum of 60% of ethyl esters of PUFA, with a

minimum content of DHA of 40% and 0.1% of vitamin E acetate. Next, the microcapsule dispersion in oil was incorporated into a soft gelatin capsule. The quantities used to prepare capsules of different doses of degarelix acetate are shown in Table 3.

Dispersion: g of microcapsules per 10 g of oil	*Weight of dispersion* per capsule	Dose of degarelix (as acetate) per capsule
2.79 g	1.00 g	40 mg
1.70 g	1.50 g	40 mg

Table 3

Example 11. Preparation of pharmaceutical capsules which contain microcapsules of bicalutamide and leuprolide acetate for combination therapy in prostate cancer .

The bicalutamide microcapsule powder prepared according to example 7 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 (3.70 g of microcapsule powder obtained per 10 g of oil).

In the same way, 434.8 mg of microcapsules of leuprolide acetate, prepared according to example 9, were dispersed, in 10 g of 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 two dispersions were mixed under stirring until a homogenous mixture was obtained, and 1.00 g of the final dispersion of microcapsules in oil was incorporated into a soft gelatin capsule to obtain a dose of 50 mg of bicalutamide + 1 mg of leuprolide acetate per capsule.

Example 12. Stability studies of the soft gelatin capsules which contain suspensions of microcapsules with tamsulosin, prazosin, dutasteride,

finasteride, mepartricin, cyproterone acetate, bicalutamide, buserelin, leuprolide, degarelix and bicalutamide+leuprolide in an oil which contained PUFA.

Accelerated stability studies (40±2 °C, 75±5 % RH) of the soft gelatin capsules which contained suspensions of microcapsules of the active pharmaceutical ingredients in an oil which contained PUFA were carried out.

The percentages of the active pharmaceutical ingredient in the capsules were determined by HPLC after storage in amber glass containers for 2 months. The subsequent analysis of the capsule and its content allowed to conclude that, as well as the exterior aspect was correct, no deposits or agglomerates of solid or film (insoluble membrane) had formed in the inner side of the coating. The results of the analyses are shown in Table 4.

The stability of PUFAs was also studied by gas chromatography, although no variations were observed in their composition.

Example	Stability: % of active ingredient		Stability after 2 months		
	Initial	2 months	External aspect	Deposits	Formation of film
Example 1	98.4	98.2	Correct	No	No
Example 2 (dose 2 mg, capsule 1 g)	98.9	99.0	Correct	No	No
Example 3	98.4	98.2	Correct	No	No
Example 4 (dose 5 mg, capsule 1 g)	98.6	98.4	Correct	No	No
Example 5	99.2	99.3	Correct	No	No
Example 6	98.3	98.2	Correct	No	No
Example 7	98.5	98.6	Correct	No	No
Example 8	98.1	98.1	Correct	No	No
Example 9	98.2	98.0	Correct	No	No
Example 10 (capsule 1 g)	99.1	98.8	Correct	No	No
Example 11 (Bicalutamide/leuprolide)	99.1/98.4	99.0/98.1	Correct	No	No

Table 4

CLAIMS

1. Pharmaceutical capsule which comprises a suspension of polymeric microcapsules which comprise at least one polymer and at least one active pharmaceutical ingredient for the treatment and/or prevention of prostate diseases and/or hyperandrogenic disorders, these microcapsules being suspended in an oil which contains polyunsaturated fatty acids.

2. Pharmaceutical capsule according to claim 1, wherein the active pharmaceutical ingredient is selected from the group formed by alpha-adrenergic blockers, 5-alpha-reductase inhibitors, mepartricin, andarine, antiandrogens, adrenal androgen synthesis inhibitors, vitamin D analogues, LHRH analogues and/or mixtures thereof.

3. Pharmaceutical capsule according to claim 1, wherein the polyunsaturated fatty acids belong to the omega-3 series.

4. Pharmaceutical capsule according to claim 3, wherein the polyunsaturated fatty acids of the omega-3 series are selected from the group formed by *(all-cis)*-7,10,13-hexadecatrienoic or roughanic acid (C16:3 *n*-3), *(all-cis)*-9,12,15-octadecatrienoic or alpha-linolenic acid or ALA (C18:3 *n*-3), *(all-cis)*-6,9,12,15-octadecatetraenoic or stearidonic or moroctic acid (C18:4 *n*-3), *(all-cis)*-11,14,17-eicosatrienoic or homo-alpha-linolenic or eicosatrienoic acid or ETE (C20:3 *n*-3), *(all-cis)*-8,11,14,17-eicosatetraenoic or eicosatetraenoic or bishomo-stearidonic acid (C20:4 *n*-3), *(all-cis)*-5,8,11,14,17-eicosapentaenoic or timnodonic or eicosapentaenoic acid or EPA or icosapent (C20:5 *n*-3), *(all-cis)*-6,9,12,15,18-heneicosapentaenoic or heneicosapentaenoic acid (C21:5 *n*-3), *(all-cis)*-7,10,13,16,19-docosapentaenoic or clupanodonic or docosapentaenoic acid or DPA (C22:5 *n*-3), *(all-cis)*-4,7,10,13,16,19-docosahexaenoic or cervonic or docosahexaenoic acid or DHA or doconexent (C22:6 *n*-3), *(all-cis)*-9,12,15,18,21-tetracosapentaenoic or tetracosapentaenoic acid (C24:5 *n*-3) and *(all-cis)*-6,9,12,15,18,21-tetracosahexaenoic or tetracosahexaenoic or nisinic acid (C24:6 *n*-3), their alkyl esters, triglycerides and/or mixtures thereof.

5. Pharmaceutical capsule according to claim 4, wherein the polyunsaturated fatty acids of the omega-3 series are selected from the group formed by ALA, DHA, EPA, DPA, their alkyl esters, triglycerides and/or mixtures thereof.

6. Pharmaceutical capsule according to claim 1, wherein the polyunsaturated fatty acids belong to the omega-6 series.

7. Pharmaceutical capsule according to claim 6, wherein the polyunsaturated fatty acids of the omega-6 series are selected from the group formed by *(all-cis)*-9,12-octadecadienoic acid or linoleic acid (C18:2 *n*-6), *(all-cis)*-6,9,12-octadecatrienoic or gamolenic or gamma-linolenic acid (C18:3 *n*-6), *(all-cis)*-11,14-eicosadienoic or eicosadienoic or bishomolinoleic acid (C20:2 *n*-6), *(all-cis)*-8,11,14-eicosatrienoic or dihomo-gamma-linolenic acid (C20:3 *n*-6), *(all-cis)*-5,8,11,14-eicosatetraenoic or arachidonic acid (C20:4 *n*-6), *(all-cis)*-13,16-docosadienoic or docosadienoic acid (C22:2 *n*-6), *(all-cis)*-7,10,13,16-docosatetraenoic or adrenic acid (C22:4 *n*-6) and *(all-cis)*-4,7,10,13,16-docosapentaenoic or docosapentaenoic or osbond acid (C22:5 *n*-6), their alkyl esters, triglycerides and/or mixtures thereof.

8. Pharmaceutical capsule according to claim 7, wherein the polyunsaturated fatty acids of the omega-6 series are selected from the group formed by linoleic acid, gamma-linolenic acid, their alkyl esters, triglycerides, and/or mixtures thereof.

9. Pharmaceutical capsule according to claims 4 and 7, wherein the alkyl radical of these alkyl esters of the fatty acids is selected from the group formed by short chain alkyl radicals, with from 1 to 8 carbon atoms.

10. Pharmaceutical capsule according to claim 9, wherein the alkyl radical of these alkyl esters is selected from the group formed by ethyl, methyl, propyl, butyl and/or mixtures thereof.

11. Pharmaceutical capsule according to claim 1, wherein this oil contains more than 40% of polyunsaturated fatty acids.

12. Pharmaceutical capsule according to claim 2, wherein this alpha-adrenergic blocker is selected from the group formed by tamsulosin, doxazosin, terazosin, prazosin, alfuzosin, bunazosin, silodosin, indoramin, abanoquil, naftopidil,

trapizosin, fiduxosin, parvosin, GYKI-16084, L-771688, UK-294315, AIO-8507L, RBx-2258 and/or their pharmaceutically acceptable salts.

13. Pharmaceutical capsule according to claim 2, wherein this 5-alpha-reductase inhibitor is selected from the group formed by finasteride, dutasteride, izonsteride, turosteride, TF-505, AS-601811, FK-143 and/or their pharmaceutically acceptable salts.

14. Pharmaceutical capsule according to claim 2, wherein this antiandrogen is selected from the group formed by flutamide, bicalutamide, nilutamide, cyproterone acetate, chlormadinone acetate, medroxyprogesterone acetate, abiraterone acetate, spironolactone, MDV3100, osaterone acetate, oxendolone and/or their pharmaceutically acceptable salts.

15. Pharmaceutical capsule according to claim 1, wherein this adrenal androgen synthesis inhibitor is selected from the group formed by ketoconazole, aminoglutethimide and/or their pharmaceutically acceptable salts.

16. Pharmaceutical capsule according to claim 2, wherein this vitamin D analogue is selected from the group formed by vitamin D2 or ergocalciferol, vitamin D3 or colecalciferol, calcitriol, calcifediol, doxercalciferol, paricalcitol, calcipotriol or MC-903, seocalcitol or EB-1089, 22-oxacalcitriol or maxacalcitol, ercalcitriol or Ro 17-6218, 1,24,25-trihydroxyvitamin D3, MC-1288, KH-1060, GS-1558, CB-1093, Ro 23-7553 or BXL-353, Ro 24-2637, Ro 25-4020, Ro 25-6760, Ro 26-9114, LG-190119, alfacalcidol, falecalcitriol, elocalcitol and/or their pharmaceutically acceptable salts.

17. Pharmaceutical capsule according to claim 2, wherein this LHRH analogue is selected from the group formed by LHRH antagonists, abarelix, cetrorelix, ganirelix, degarelix, teverelix, ramorelix, azaline B, acyline, ozarelix, detirelix, ramorelix, antide, orntide, ORF 21243, LXT-101, RS-68439, A-75998, LHRH agonists, leuprolide, buserelin, goserelin, triptorelin, nafarelin, deslorelin, histrelin, avorelin and/or their pharmaceutically acceptable salts.

18. 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, copolymers of all of them and/or mixtures thereof.

19. Pharmaceutical capsule according to claim 18, wherein the polymer of these microcapsules is selected from the group formed by gelatin, albumin, soy protein, pea protein, broad bean protein, potato protein, wheat protein, whey protein, β-lactoglobulin, caseinates, wheat starch, corn starch, zein, alginates, carrageenans, pectins, arabinogalactans, gum arabic, xanthan gum, mesquite gum, tragacanth gum, galactomannans, guar gum, locust bean gum, chitosan, agar, poly(L-lysine), sodium dextran sulfate, carboxymethyl galactomannan, carboxymethyl cellulose, ethyl cellulose, hydroxypropyl methylcellulose, nitrocellulose, cellulose acetate butyrate, cellulose acetate phthalate, hydroxypropyl methylcellulose phthalate, hydroxypropyl methylcellulose acetate succinate, polyvinyl acetate phthalate, poly(ε-caprolactone), poly(*p*-dioxanone), poly(δ-valerolactone), poly(β-hydroxybutyrate), poly(β-hydroxybutyrate) and β-hydroxyvalerate copolymers, poly(β-hydroxypropionate), methacrylic acid copolymers, dimethylaminoethyl methacrylate copolymers, trimethylamonium ethyl methacrylate copolymers, poly(*n*-butyl)cyanoacrylate polymers and copolymers, poly(isobutyl)cyanoacrylate polymers and copolymers, poly(*n*-hexyl)cyanoacrylate polymers and copolymers, poly(2-octyl)cyanoacrylate polymers and copolymers, lactic and glycolic acid polymers and copolymers, lactic and glycolic and polyethylene glycol acid polymers and copolymers and/or mixtures thereof.

20. Pharmaceutical capsule according to claim 1, wherein these microcapsules represent between 0.0001% and 80% of the total weight of the capsule.

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

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

23. Pharmaceutical capsule according to claim 1, wherein the composition of the coating of this capsule is selected from the group formed by gelatin,

hydroxypropyl methyl cellulose, pullulan, modified starches, carrageenans and/or mixtures thereof.

24. Pharmaceutical capsule according to claim 23, wherein this coating is made from soft gelatin.

25. Pharmaceutical capsule according to claim 1, wherein this capsule has an enteric coating.

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

27. Pharmaceutical capsule according to claim 1, for the treatment and/or prevention of hyperandrogenic disorders.