Title: SOFT GELATIN CAPSULES COMPRISING ACETYLSALICYLIC ACID

Abstract: The present invention concerns a new soft gelatin capsule comprising a shell of gelatinous material, said shell being in direct contact with the liquid or pasty lipophilic phase present within the capsule, in which the lipophilic phase comprises aspirin, characterized in that the internal lipophilic phase also comprises substances chosen from the group consisting of pharmaceutically acceptable solid polyhydroxylated organic compounds and water-soluble hygroscopic salts.
SOFT GELATIN CAPSULES COMPRISING ACETYSALICYLIC ACID

FIELD OF THE INVENTION
The present invention relates to a new pharmaceutical formulation of acetylsalicylic acid.

STATE OF THE ART
Soft gelatin capsules are a pharmaceutical form used for the, mainly oral, administration of a wide variety of active principles also including poorly water-soluble active principles.

The soft gelatin capsules used for the administration of poorly water-soluble active principles consist of a shell comprising plasticized gelatin which encloses an often lipophilic-type filling material (fill phase), which can have a liquid or a pasty consistency.

Although soft gelatin capsules are a widely used pharmaceutical form, their use is not however possible in the case of active principles that are unstable in the presence of even moderate amounts of water. Indeed, the technique of gelatin shell formation involves the presence of water which cannot be completely removed in subsequent stages of the process so as to ensure the shell has the correct plasticity. This residual water, initially present in the capsule wall, tends to partly diffuse into the fill phase, compromising the chemical stability of those active principles which by their nature are unstable in the presence of even moderate amounts of water, such as aspirin (acetylsalicylic acid, ASA).

For other lipophilic active principles, belonging to the same therapeutic class (so-called NSAIDs or Non Steroidal Anti Inflammatory Drugs) and in particular for ibuprofen, specific formulations in soft capsules have instead been proposed (see for example US 4,690,823, US 6,251,426, US 6,551,615). Given the considerable advantages of these formulations in terms of ease of ingestion and hence patient compliance, besides the bioavailability of the active principle carried, NSAID formulations in soft capsules have had a considerable market success and are today available on a vast scale (e.g. Aktren® by Bayer or Buscofen® by Boehringer Ingelheim). To the applicant's knowledge, however, formulations in
soft capsules of acetylsalicylic acid or aspirin, being by far the oldest of the NSAIDs, do not as yet exist on the market.

Aspirin is a widely used active principle which possesses analgesic, anti-inflammatory and anti-fever properties as well as being useful, given its platelet anti-aggregation activity, in the therapy and prevention of cardiovascular diseases. In chronic applications especially, as in the case of cardiopathic patients, the notorious gastrolesivity of aspirin requires special pharmaceutical forms for an administration that allows these undesirable effects to be minimized. Soft gelatin capsules, whether in the stomach or intestine soluble form, could be an advantageous administration form of aspirin as they could comprise the presence of lipophilic compounds in the fill phase not only as pharmaceutical excipients but also as coadjuvants of the pharmacological action of aspirin, as in the case of omega 3 and omega 6 polyunsaturated fatty acids and their derivatives esterified with biocompatible alcohols.

The traditional soft capsule pharmaceutical form has been hitherto precluded due to the known instability of aspirin in environments with even moderate amounts of water. In this respect, when introduced into soft capsules of conventional type, this active principle tends to hydrolyse rapidly to form salicylic acid (SA).

In an attempt to overcome the apparent difficulties of formulating active principles susceptible to hydrolysis in soft capsules, US 5,814,338 presents a modified formulation in which, underneath the traditional gelatinous shell, there is a further hydrophobic silicon polymer-based layer and in which the lipophilic internal phase is supplemented with silicon resins. In this way the internal phase is isolated from the gelatinous wall and hence from the water contained within it. However, this arrangement is rather laborious because the inclusion of an intermediate hydrophobic layer, situated underneath the traditional gelatinous layer, requires considerable modifications to the processes and equipment normally employed.

In a further attempt to provide soft capsules by which to administer NSAIDs and COX-2 inhibitors, including aspirin, the inventors of US 6,383,515 proposed particular solvent systems comprising polycarboxylic acid salts. The problems identified in this patent, however – in a similar manner to the efforts undertaken for ibuprofen - concern obtaining a stable solution (i.e. does not form precipitates) of
the active principle used. However, the authors of US 6,383,515 did not study the stability of the active principle as such, which remains dissolved. Indeed in these systems, water is used to solubilize the carboxylic acid salts, and therefore their suitability for formulating aspirin remains doubtful. Incidentally US 6,383,515 does not give any examples of aspirin formulations.

Of the efforts undertaken in attempts to provide formulations of the type in question herein, mention should be made of WO 98/17673 in which the inventors, in an attempt to overcome the known instability of aspirin in its various administration forms including capsules with an oil-based fill, propose the actual modification of the aspirin itself which they use in the form of esters with various alcohols.

Given the aforesaid situation and given the consequent absence on the market of aspirin formulations in soft capsules, the problem remains of developing alternative soft capsules to those described in US 5,814,338, US 6,383,515 or WO 98/17673, i.e. obtainable without modifying traditional processes or equipment, or without modifying the active principle used, hence allowing this advantageous pharmaceutical form to be also extended to aspirin.

**SUMMARY OF THE INVENTION**

Surprisingly it has been found that the above drawback can be overcome by the provision of new soft gelatin capsules comprising a shell of gelatinous material, said shell being in direct contact with a liquid or pasty lipophilic phase present within the capsule, in which the lipophilic phase comprises aspirin, characterized in that the internal lipophilic phase also comprises substances chosen from the group consisting of pharmaceutically acceptable solid polyhydroxylated organic compounds and water-soluble hygroscopic salts. The term "aspirin" according to the present invention means both acetylsalicylic acid as such and its pharmaceutically acceptable salts such as, purely by way of example, a lysine salt or a Na salt or others. Biocompatible polyhydroxylated compounds such as sugars, polysaccharides and polyols are useable as the solid polyhydroxylated organic compounds within the lipophilic fill phase of the soft gelatin capsules. Otherwise, biocompatible salts in anhydrous form can be used as the water-soluble hygroscopic salts to be added to the lipophilic fill of the capsule. The solid
polyhydroxylated organic compounds and the water-soluble hygroscopic compounds can both be used singly or synergistically in a mixture thereof in the lipophilic fill phase of the capsule of the invention.

This innovative formulation for the soft gelatin capsule lipophilic fill phase enables the use of the soft capsule pharmaceutical form in its traditional form i.e. composed of a gelatinous shell in direct contact with the lipophilic fill, to be extended for the first time to aspirin, not having yet been administered in this manner due to its excessive instability in the presence even of traces of water.

DETAILED DESCRIPTION OF THE INVENTION

The soft capsule pharmaceutical form offers a number of advantages for the oral administration of drugs, and its use is in continuous expansion through the development of well-established production methods and through the possibility of continuously modulating the dissolution process and release of the active principle which can take place either at the gastric or intestinal level.

For forming the capsule walls, the known methods of soft gelatin capsule preparation use pasty systems consisting primarily of gelatin as the structuring matrix, polyols such as glycerin with plasticizer function, and water as the solvent. In general the mix for preparing the capsule walls contains from 30 to 70% w/w of water, from 20 to 50% w/w of gelatin and from 10 to 20% w/w of plasticizer. Optionally other components with different functions can be provided such as colouring, modulating capsule dissolution rate or improving the rheology of the mix during the production process. In the capsule wall construction stage, some of the water is removed by drying under critically controlled conditions, but a quantity up to 5-7% of the weight of the finished capsule remains. This residual moisture, initially localized in the wall, tends to enter into equilibrium over time with the rest of the capsule and therefore tends to partly diffuse into the fill phase.

This water migration from the shell to the internal fill has hitherto been a considerable limitation in the use of the soft capsule pharmaceutical form in the case of drugs characterized by susceptibility to hydrolysis including where the fill used in the capsules was of a lipophilic nature, for example consisting of an oil phase. An important example of an active principle susceptible to hydrolysis is aspirin whose stability is notoriously connected to the presence of a strictly
anhydrous environment. Surprisingly it has been found that locking or trapping the water present in the lipophilic fill phase of traditional soft gelatin capsules by substances chosen from the group consisting of solid polyhydroxylated organic compounds and water-soluble hygroscopic salts incorporated within said lipophilic phase, enables this pharmaceutical form to be effectively used also in the case of aspirin.

Consequently, the capsules of the invention obtained according to traditional procedures in pharmaceutics, of which the Rotary Die Process is preferred, are distinct from traditional capsules due to the presence, in the lipophilic fill phase, of substances chosen from the group consisting of solid polyhydroxylated organic compounds and water-soluble hygroscopic salts.

Without intending to be limiting, the belief is that the substances identified above, under the conditions described herein, interact with water either by forming hydrogen bridge bonds of co-operative type as in the case of polyhydroxylated organic compounds, or by strong electrostatic interactions as in the case of anhydrous salts which hydrate by coordinating water around the ions. With this presumed strategy, water present in the lipophilic fill phase is continuously and competitively removed from reacting with the drug. Preferably biocompatible solid polyhydroxylated organic compounds such as sugars, polysaccharides or polyols and biocompatible water-soluble salts are usable as substances present in the lipophilic fill phase of soft gelatin capsules.

Without intending to be limiting, some examples usable in the oil-based fill which characterize the capsules of the invention are given hereinafter. Examples of usable sugars are: monosaccharides, such as glucose and fructose; disaccharides, such as saccharose, maltose and trehalose; polysaccharides such as chondroitin sulphate; hyaluronic acid, guar gum, carrageenans, chitosan, alginate, agar and starch. Examples of polyols are: erythritol, sorbitol, inositol, polyvinyl alcohol. Examples of water-soluble hygroscopic salts are: calcium sulphate hemihydrate which traps 1 mole of water per mole of salt; anhydrous calcium chloride which traps up to six moles of water per mole of salt. The aforesaid substances can be used in the lipophilic fill phase either singly or mixed together synergistically.
The capsules of the invention are of gastro-soluble type but can also be produced in the gastroresistant form when active principle release at the intestinal level is required. In this case a gastro-resistant and enterosoluble coating is applied to the capsule surface using techniques known in the art for conferring these selective solubilization properties of orally consumed pharmaceutical forms.

The substances chosen from the group consisting of solid polyhydroxylated organic compounds and water-soluble hygroscopic salts are used in the lipophilic fill phase in quantities suitable for enabling the aspirin within to be stabilized against hydrolysis. This quantity is determinable by an expert of the art by way of experimentation, taking into account the residual moisture in the capsule, the nature of the substance chosen from the group consisting of solid polyhydroxylated organic compounds and water-soluble hygroscopic salts, and the quantity of aspirin used in the formulation. In particular, the inventors of the present application have discovered that the substances chosen from solid polyhydroxylated organic compounds and water-soluble hygroscopic salts can be used within the oil phase preferably in a quantity ranging from 1 to 7, more preferably from 1.5 to 6 equivalents relative to the water theoretically available in the whole capsule, stabilizing in this manner formulations of aspirin in the lipophilic phase. Generally, substances chosen from the solid polyhydroxylated organic compounds and water-soluble hygroscopic salts constitute from 10 to 70% by weight (w/w) of the internal lipophilic phase, being preferably from 20 to 50% w/w. As components of the internal lipophilic phase, pharmaceutically acceptable lipids or oils of natural or synthetic origin or mixtures thereof can be used. For example, mixtures of fatty acids as such or esterified with glycerin or another biocompatible alcohol can be used. In particular saturated, unsaturated and/or polyunsaturated fatty acids (or their esters) can be used as present in some vegetable or fish oils. The use of unsaturated or polyunsaturated fatty acids (or their esters) of the omega 3 and omega 6 series is preferred. The use of EPA (C20:5 ω-3) and/or DHA (C22:6 ω-3) fatty acids, and most particularly the triglycerides thereof, or their methyl or ethyl esters, are particularly preferred.

Without intending to be limiting a series of examples which better describe the invention and its field of application is given below.
EXAMPLES

EXAMPLE 1 – Preparation of soft capsules containing acetylsalicylic acid and trehalose dihydrate in a lipophilic fill

a) Preparation of the shell mix – 17.2 kg of anhydrous glycerin are added to 46.2 L of purified water under agitation. The solution is then heated to 70°C and 36.6 kg of gelatin are added, maintaining the solution under agitation for 30-60 minutes. The mass is subsequently deaerated, applying a progressive vacuum until 0.8-0.9 bar is attained.

b) Preparation of the fill material – Acetylsalicylic acid 1.0 kg; trehalose dihydrate (British Sugar plc, Oundle Road, Peterborough, UK) 1.5 kg; Epax 5500 TG (triglyceride mixture containing 33% EPA and 22% DHA, Pronova Biocare) 1.5 kg; soya lecithin 0.5 kg; beeswax 0.2 kg; hydrogenated coconut oil 0.2 kg; refined palm oil 0.1 kg; delta tocopherol 10 g.

c) Soft gelatin capsules of size 7.5 oval were prepared in accordance with the Rotary Die Process.

The capsules obtained present the following characteristics:
- average weight per capsule 639 mg
- residual moisture 5.3% w/w using the Karl Fischer method
- acetylsalicylic acid content 88.6 mg/capsule
- dissolution time, measured according to the European Pharmacopeia method: 15 minutes.

EXAMPLE 2 – Preparation of soft capsules containing acetylsalicylic acid and trehalose in a lipophilic fill

a) Preparation of the shell mix – The mix for the shell is obtained as described in example 1.

b) Preparation of the fill material - Acetylsalicylic acid 1.0 kg; trehalose (British Sugar plc, Oundle Road, Peterborough, UK; the trehalose is brought to a constant weight by heating at 80°C under vacuum at 0.8 bar with about 10% w/w weight loss) 1.3 kg; Epax 5500 TG (triglyceride mixture containing 33% EPA and 22% DHA, Pronova Biocare) 1.7 kg; soya lecithin 0.5 kg; beeswax 0.2 kg; hydrogenated coconut oil 0.2 kg; refined palm oil 0.1 kg; delta tocopherol 10 g.

c) Soft gelatin capsules of size 7.5 oval were prepared in accordance with the
Rotary Die Process.
The capsules obtained present the following characteristics:
- average weight per capsule 645 mg
- residual moisture 5.2% w/w using the Karl Fischer method
- acetylsalicylic acid content 89.8 mg/capsule
- dissolution time, measured according to the European Pharmacopeia method: 15 minutes.

EXAMPLE 3 - Preparation of soft capsules containing acetylsalicylic acid and sorbitol in a lipophilic fill

a) Preparation of the shell mix – 9.1 kg of anhydrous glycerin are added to 28 L of purified water under agitation. The solution is then heated to 70 ºC and 21.7 kg of gelatin are added, maintaining the solution under agitation for 30-60 minutes. The mass is subsequently deaerated, applying a progressive vacuum until 0.8-0.9 bar is attained.

b) Preparation of the fill material – Acetylsalicylic acid 1.0 kg; anhydrous sorbitol 1.4 kg; Epax 5500 TG (triglyceride mixture containing 33% EPA and 22% DHA, Pronova Biocare) 1.6 kg; soya lecithin 0.5 kg; beeswax 0.2 kg; hydrogenated coconut oil 0.2 kg; refined palm oil 0.1 kg; delta tocopherol 10 g.

c) Soft gelatin capsules of size 7.5 oval were prepared in accordance with the Rotary Die Process.
The capsules obtained present the following characteristics:
- average weight per capsule 639 mg
- residual moisture 5.6% w/w using the Karl Fischer method
- acetylsalicylic acid content 88.8 mg/capsule
- dissolution time, measured according to the European Pharmacopeia method: 15 minutes.

EXAMPLE 4 – Preparation of soft capsules containing acetylsalicylic acid and chondroitin in a lipophilic fill

a) Preparation of the shell mix – The mix for shell is obtained as described in example 3.

b) Preparation of the fill material - Acetylsalicylic acid 1.0 kg; chondroitin sulphate (IBSA Lugano-CH) 1.8 kg; Epax 5500 TG (triglyceride mixture containing 33%
EPA and 22% DHA, Pronova Biocare) 1.4 kg; soya lecithin 0.5 kg; beeswax 0.2 kg; hydrogenated coconut oil 0.1 kg; delta tocopherol 10 g.

c) Soft gelatin capsules of size 5 oval were prepared in accordance with the Rotary Die Process.

The capsules obtained present the following characteristics:
- average weight per capsule 425 mg
- residual moisture 5.6% w/w using the Karl Fischer method
- acetylsalicylic acid content 59.8 mg/capsule
- dissolution time, measured according to the European Pharmacopeia method: 15 minutes.

EXAMPLE 5 - Preparation of soft capsules containing acetylsalicylic acid and carrageenan in a lipophilic fill

a) Preparation of the shell mix – The mix for shell is obtained as described in example 1.

b) Preparation of the fill material - Acetylsalicylic acid 1.0 kg; carrageenan (Hainan Kaiyang Trade Co. Ltd, email kaiyangco@yahoo.com.cn) 1.7 kg; Epax 2050 TG (triglyceride mixture containing 20% EPA and 50% DHA, Pronova Biocare) 1.5 kg; soya lecithin 0.5 kg; beeswax 0.2 kg; refined palm oil 0.1 kg; delta tocopherol 10 g.

c) Soft gelatin capsules of size 5 oval were prepared in accordance with the Rotary Die Process.

The capsules obtained present the following characteristics:
- average weight per capsule 426 mg
- residual moisture 5.5% w/w using the Karl Fischer method
- acetylsalicylic acid content 61.0 mg/capsule
- dissolution time, measured according to the European Pharmacopeia method: 15 minutes.

EXAMPLE 6 – Preparation of soft capsules containing acetylsalicylic acid and anhydrous calcium chloride in a lipophilic fill

a) Preparation of the shell mix – The mix for the shell is obtained as described in example 1.

b) Preparation of the fill material - Acetylsalicylic acid 1.0 kg; anhydrous calcium
chloride 1.8 kg; Epax 5500 TG (triglyceride mixture containing 33% EPA and 22% DHA, Pronova Biocare) 1.5 kg; soya lecithin 0.5 kg; beeswax 0.1 kg; hydrogenated coconut oil 0.1 kg; delta tocopherol 10 g.

c) Soft gelatin capsules of size 5 oval were prepared in accordance with the Rotary Die Process.

The capsules obtained present the following characteristics:
- average weight per capsule 429 mg
- residual moisture 5.6% w/w using the Karl Fischer method
- acetylsalicylic acid content 61.2 mg/capsule
- dissolution time, measured according to the European Pharmacopeia method: 15 minutes.

EXAMPLE 7 – Analytical method for determining acetylsalicylic acid stability in soft gelatin capsules

Determination of acetylsalicylic acid (ASA) stability in the capsules obtained in accordance with examples 1 to 6 is undertaken by evaluating the quantity of salicylic acid (SA) which forms over time and the corresponding decrease in ASA.

1) Extraction of ASA and SA from capsules – The extraction process is based on the division of ASA and SA between an oil phase (esters of the omega 3 acids present in ASA softgels) and an aqueous phase. In order to ensure a total separation, the aqueous phase volume is about 5,000 times greater than that of the oil phase. The consequent dilution of ASA and SA does not constitute a problem at the analytical level, due to the strong absorption in the ultraviolet ($\lambda_{max}$ of ASA = 236nm; $\lambda_{max}$ of SA = 241nm) of the two compounds which, at this wavelength, have the following $\varepsilon_{mM}$ (mM$^{-1}$cm$^{-1}$) values: $ASA_{cmM}$ 236nm = 4.4; SA $cmM$ 236nm = 6.1; $ASA_{cmM}$ 241nm = 2.7; SA $cmM$ 241nm = 5.7). As a preliminary, a sample of pure ASA was tested to see if the extraction procedures caused the hydrolysis conditions of the product. Under the established conditions degradation of ASA was not detected. The various stages of the process for extracting ASA and SA from soft gelatin capsules are given below:

- the capsule is homogenized (Homogenizer: DIAX 900, Heidolph; speed: 18,000 revs/min; shaft diameter: 25 mm) for 1 hour in H$_2$O (1 litre H$_2$O /100 mg ASA) while keeping the sample at 0°C in a bath of water and ice;
- the resulting emulsion is centrifuged at 1,800xg for 30 minutes at a temperature of 4°C to separate the aqueous phase from the oil contained in the capsule;
- within 2 hours of obtaining it the clear aqueous solution was analysed by HPLC for quantitative determination of ASA and SA. All the samples prepared are maintained at 4°C.

2) Chromatographic separation of ASA/SA and quantitative analysis – The aqueous phase is analysed by reverse phase chromatography (HPLC, P580 DIONEX) for the separation and quantitative determination of ASA and SA. The chromatographic system used is: Column C18, 5μm, 120 Å, 4.6 x 250 mm; eluent 60% v/v (CH₃COOH 5% w/w in H₂O), 40% v/v CH₃OH, pH 2.65; isocratic elution; flow 0.5 ml/min; spectrophotometric reader UV-VIS; acquisition at 236 and 241 nm. Under these chromatographic conditions ASA exhibits a retention time of 18 minutes and SA one of 32.5 minutes.

EXAMPLE 8 - Stability of the acetylsalicylic acid in soft gelatin capsules containing one of the substances of the invention in the lipophilic fill phase

The capsules, obtained in accordance with examples 1 to 6, are packaged in blister packs and maintained at 30°C in a controlled humidity environment. Over a period of time, the capsules are analysed following the procedures described in example 7.

The table shows the test results of the capsules obtained in accordance with examples 1 to 6 compared with a control sample consisting of a batch of capsules prepared in accordance with example 1, but without adding the substance of the invention (trehalose) to the lipophilic fill. The analyses are carried out in triplicate, using 5 capsules for each analysis. Putting the total milligrams of ASA and SA equal to 100, calculated on the basis of the areas of the two chromatographic peaks and the calibration curves of the two compounds, the percentage of SA is a measure of the instability of ASA in the capsule microenvironment.
<table>
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<td>2</td>
<td>trehalose</td>
<td>1.23 ± 0.18</td>
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<tr>
<td>3</td>
<td>sorbitol</td>
<td>0.93 ± 0.07</td>
</tr>
<tr>
<td>4</td>
<td>chondroitin sulphate</td>
<td>1.06 ± 0.11</td>
</tr>
<tr>
<td>5</td>
<td>carrageenan</td>
<td>1.13 ± 0.20</td>
</tr>
<tr>
<td>6</td>
<td>sulphate hemihydrate</td>
<td>0.98 ± 0.15</td>
</tr>
</tbody>
</table>

As can be ascertained from the data in the table, a conventional soft gelatin capsule (the control) without the substances of the invention described herein is not suitable for pharmaceutical use due to excessive ASA degradation. Instead, the presence of substances chosen from solid polyhydroxylated organic compounds and water-soluble hygroscopic salts (trehalose, cyclodextrin, sorbitol, chondroitin sulphate, carrageenan, anhydrous calcium chloride) leads to a significant reduction in the hydrolysis process of the acetylsalicylic acid within the internal lipophilic fill, thus rendering the new soft gelatin capsules comprising aspirin described herein suitable for use in the pharmaceutical field.
CLAIMS

1. Soft gelatin capsule comprising a shell of gelatinous material, said shell being in direct contact with a liquid or pasty lipophilic phase present within the capsule, in which the lipophilic phase comprises aspirin, characterized in that the internal lipophilic phase also comprises substances chosen from the group consisting of pharmaceutically acceptable solid polyhydroxylated organic compounds and water-soluble hygroscopic salts.

2. Capsule as claimed in claim 1 wherein the substances chosen from the group consisting of solid polyhydroxylated organic compounds and water-soluble hygroscopic salts are chosen from the group consisting of sugars, polysaccharides, polyols and inorganic salts.

3. Capsule as claimed in claim 2 wherein the solid polyhydroxylated organic compounds are chosen from the group consisting of: maltose, trehalose, chondroitin sulphate, hyaluronic acid, guar gum, carrageenans, chitosan, alginate, agar, starch, erythritol, sorbitol, inositol and polyvinyl alcohol, and the inorganic salts are chosen from the group consisting of anhydrous calcium chloride and hemihydrated calcium sulphate.

4. Capsules as claimed in claims 1 to 3 wherein the quantity of substances chosen from the group consisting of solid polyhydroxylated organic compounds and water-soluble hygroscopic salts accounts for 10 to 70% by weight of the internal lipophilic phase.

5. Capsules as claimed in claim 4 wherein the quantity of substances chosen from the group consisting of solid polyhydroxylated organic compounds and water-soluble hygroscopic salts accounts for 20 to 50% by weight of the internal lipophilic phase.

6. Capsule as claimed in one or more of the preceding claims wherein aspirin is present in the form of one of its salts.

7. Capsule as claimed in claim 6 wherein the acetylsalicylic acid or one of its salts is present in the internal lipophilic phase in a quantity from 1 to 400 mg.

8. Capsule as claimed in claim 7 wherein the acetylsalicylic acid or one of its salts is present in the internal lipophilic phase in a quantity from 40 to 150 mg.

9. Capsule as claimed in one or more of the preceding claims wherein the internal
lipophilic phase comprises mixtures of polyunsaturated fatty acids or their esters with a biocompatible alcohol.

10. Capsule as claimed in claim 9 wherein the polyunsaturated fatty acids belong to the omega 3 or omega 6 series, or to the omega 3 and omega 6 series.

11. Capsule as claimed in claims 9 and 10 wherein in the internal lipophilic phase, compounds are present with antioxidant activity to prevent the peroxidation of unsaturated lipids.

12. Capsule as claimed in one or more of the preceding claims wherein the shell is coated with a gastroresistant or enterosoluble material.

13. Use of the capsules as claimed in preceding claims for the treatment of cardiopathies, rheumatic pathologies and febrile states.
A. CLASSIFICATION OF SUBJECT MATTER

A61K47/26 A61K47/36 A61K47/44

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic database consulted during the international search (name of data base and where practical, search terms used)
EPO-Internal, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

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</table>

Relevant to claim No.

- 1-13

Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier document but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"P" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
"Z" document member of the same patent family

Date of the actual completion of the international search 13 March 2008

Date of mailing of the international search report 27/03/2008

Name and mailing address of the ISA European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx 31 651 epi nl, Fax: (+31-70) 340-3016

Authorized officer Giménez Miralles, J
INTERNATIONAL SEARCH REPORT

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. X Claims Nos.: 13
   because they relate to subject matter not required to be searched by this Authority, namely:
   see FURTHER INFORMATION sheet PCT/ISA/210

2. Claims Nos.
   because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. Claims Nos.
   because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. As all searchable claims could be searched without effort justifying an additional fees, this Authority did not invite payment of additional fees.

3. As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.: 

4. No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.: 

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.

☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.

☐ No protest accompanied the payment of additional search fees.

Form PCT/ISA/210 (continuation of first sheet (2)) (April 2005)
Continuation of Box II.1

Although claim 13 is directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

Claims Nos.: 13

Rule 39.1(iv) PCT - Method for treatment of the human or animal body by therapy
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