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(54) **Title:** A PROCESS FOR PREPARING IBUPROFEN SOFT GELATIN CAPSULES

(57) **Abstract:** The present invention relates to a process for manufacturing pharmaceutical composition comprising poorly soluble pharmaceutical ingredient, particularly ibuprofen, encapsulated into a soft gelatin capsule. The solvent system of the present invention is useful in that it provides a highly concentrated clear aqueous solution of ibuprofen in a volume that is small enough to permit easy swallowing.

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A PROCESS FOR PREPARING IBUPROFEN SOFT GELATIN CAPSULES

Field of Invention

The present invention relates to a process for manufacturing pharmaceutical compositions comprising poorly-soluble pharmaceutical ingredients, for example ibuprofen, encapsulated into a soft gelatin capsule. The solvent system of the present invention is useful in that it provides a clear aqueous solution of a poorly-soluble pharmaceutical ingredient, for example ibuprofen, in a volume that is small enough to permit easy swallowing.

One aspect is that clear solutions of ibuprofen can be prepared at a temperature not exceeding about 45 °C.

Background of the Invention

Ibuprofen is the most widely used analgesic and antipyretic and the most commonly used dosage form for the delivery of ibuprofen is a tablet. The absorption time of a tablet of ibuprofen is relatively long because of two significant factors. Ibuprofen being introduced as a solid needs to first dissolve before it can be absorbed by the body and further its absorption into the body is delayed because it is practically insoluble in water and in the acidic environment of the stomach.

Liquids and especially concentrated liquid pharmaceutical compositions offer many advantages over solid compositions. Liquids are easy to swallow and provide an excellent vehicle for the uniform delivery of pharmaceutical actives. These provide a rapid onset of pharmacological action, since the composition does not first have to disintegrate and dissolve in the gastrointestinal tract. Liquid compositions are ideally suited for encapsulation within a soft gelatin shell, to provide a portable and easy-to-swallow soft, flexible capsule.

Encapsulation permits accuracy and uniformity in delivering a unit dose of a pharmaceutical active. Additionally, soft gelatin capsules are aesthetically appealing (especially when filled with a transparent liquid) and can be manufactured in a wide variety of sizes, shapes, and colors. Furthermore, since the dosage form is generally swallowed, it is unnecessary to flavor or mask the unpleasant taste of the active pharmaceutical ingredients.

Finally unlike tablets, soft gelatin capsules do not chip or powder. A particularly good bioavailability of pharmaceutical active substance may be attained if the active is completely dissolved in a suitable solvent and the encapsulated solution is administered to the patient. Solutions provide the best liquid form to obtain optimal content uniformity. In addition a solution provides a faster and more uniform absorption. However, it is not always possible to prepare clear liquid compositions of the poorly soluble actives, to be filled into soft gelatin capsules due to constraints of solvent available.

Several processes and formulations have been developed in efforts to increase the solubility of ibuprofen. Such processes and formulations are discussed in , for example, U.S. Patent No. 4,690,823; U.S. Patent No. 6,387,400; U.S. Patent. No. 6,251,426; U.S. Patent No. 5,071,643; U.S. Patent 5,141,961; U.S. Patent No. 6,221,391; and PCT application No. WO 03/013481. The processes described involve significant heating to aid the mixing of all the ingredients that results in a clear solution.

Summary of the Invention

Herein are provided clear aqueous solutions comprising ibuprofen and a solvent system for filling into soft gelatin capsules.

In one aspect a process for obtaining clear aqueous solutions of ibuprofen wherein the process is carried out at a temperature not exceeding about 45°C is provided.

In another aspect, a capsule contains an alkalizing agent, preferably organic amines or bases, and more preferably N-emthylglucamine or potassium carbonate, to improve the solubility of ibuprofren.

In another aspect, clear aqueous solutions comprising ibuprofen and a solvent system are provided, wherein the solvent system comprises:

(a) greater than about 15% by weight, and preferably from about 15 to about 50% by weight of polyethylene glycol;

(b) greater than about 1% by weight, and preferably from about 1 to about 20% by weight of surfactant;

(c) from about 1 to about 10% by weight of alkalizing agent;

(d) from about 2 to about 10% of the solubilizer; and

(e) from about 2 to about 10% of water.

and wherein solubilization of ibuprofen is carried out at a temperature not exceeding about 45°C.

In yet another aspect, soft gelatin capsules filled with clear aqueous solutions comprising ibuprofen and a solvent system are provided, wherein the solvent system comprises:

(a) from about 15 to about 50% by weight of polyethylene glycol;

(b) from about 1 to about 20% by weight of surfactant;

(c) from about 1 to about 10% by weight of alkalizing agent;

(d) from about 2 to about 10% of the solubilizer; and

(e) from about 2 to about 10% of water.

and wherein solubilization of ibuprofen is carried out at a temperature not exceeding about 45°C.

In still another aspect, a process of preparing soft gelatin capsules filled with a clear solution of ibuprofen is provided, comprising the steps of:

(a) preparing a solution of polyethylene glycol and a surfactant;

(b) mixing the solution with an aqueous solution of alkalizing agent;

(c) dispersing solubilizer in the mixture of step (b);

(d) adding ibuprofen to the dispersion of step (c) while stirring at a temperature not exceeding about 45°C to obtain a clear solution; and

(e) encapsulating the solution in a soft gelatin capsule.

In another general aspect, there are provided methods of treating an inflammatory conditions and for relieving pain in mammals in need of treatment, which include administering pharmaceutical compositions comprising soft gelatin capsules filled with clear ibuprofen solution, wherein solubilization of ibuprofen is carried out at a temperature not exceeding about 45°C.

The pharmaceutical composition may further include for example, one or more of glucosamine, pseudoephedrine, codeine, paracetamol, econazole, COX-2 inhibitor, alprazolam, dextromethorphan and chlorpheniramine.

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

Detailed Description of the Invention

The present invention is not limited to particular process steps and materials disclosed herein, but is extended to equivalents thereof as would be recognized by those ordinarily skilled in the relevant arts. It should also be understood that terminology employed herein is used for the purpose of describing particular embodiments only and is not intended to be limiting.

When used in the following description, "ibuprofen" will be understood to include ibuprofen in its free acid form. Ibuprofen constitutes from about 15% to about 40% of the solution by weight. In certain embodiments, the concentration of ibuprofen in the solution is less than about 30% by weight, exemplified by the concentration of less than about 27%, and more precisely, 26.67%, as illustrated in Examples 1 and 2, provided herein.

The term 'clear aqueous solutions', as used herein, describes liquid pharmaceutical compositions, which are substantially transparent and free from turbidity or cloudiness or foreign particulate matter.

The major constituent of the solvent system is a carrier in which the pharmaceutically active agent to be delivered is dissolved or dispersed. Polyethylene glycols (PEG) having an average molecular weight from about 200-800 Daltons, particularly from about 400-700 Daltons, and more particularly about 400 Daltons, are liquids at room temperature or have a melting point slightly above room temperature. Such materials can be employed. Mixtures of two or more polyethylene glycols of different average molecular weight range may be employed. Polyethylene glycols can be added in a concentration of about 15 to about 50% by weight of the formulation.

According to one of the embodiments, polyethylene glycols having an average molecular weight of about 400 Daltons are used as carrier.

Apart from polyethylene glycols, the solvent system comprises at least one surfactant to effectuate uniform dispersion of the drug in water or gastric juices without increasing the volume of the solvent system. Suitable surfactants may include hydrophilic surfactants, which may be anionic, cationic, zwitterionic or non-ionic, although non-ionic hydrophilic surfactants are particularly used. These non-ionic hydrophilic surfactants generally have HLB values greater than about 10. Mixtures of hydrophilic surfactants may also be employed.

Suitable non-ionic hydrophilic surfactants are selected from the group consisting of polyoxyethylene alkyl ethers; polyethylene glycol fatty acids esters; polyethylene glycol glycerol fatty acid esters; polyoxyethylene sorbitan fatty acid esters; polyoxyethylene-polyoxypropylene block copolymers; polyglycerol fatty acid esters; polyoxyethylene glycerides; polyoxyethylene vegetable oils; polyoxyethylene hydrogenated vegetable oils; reaction mixtures of polyols and at least one member of the group consisting of fatty acids, glycerides, vegetable oils, hydrogenated vegetable oils, and sterols; and mixtures thereof. Suitable examples of these are polyethylene glycol-20 laurate, polyethylene glycol-20 oleate, polyethylene glycol-35 castor oil, polyethylene glycol-40 palm kernel oil, polyethylene glycol-40 hydrogenated castor oil, polyethylene glycol-60 corn oil, polyethylene glycol-25 glyceryl trioleate, polyglyceryl-10 laurate, polyethylene glycol-6 caprate/caprylate glycerides, polyethylene glycol-8 caprate/caprylate glycerides, polyethylene glycol-30 cholesterol, polysorbate 20, polysorbate 80, polyoxyethylene-9 lauryl ether, polyoxyethylene-23 lauryl ether, polyoxyethylene-10 oleyl ether, polyethylene glycol-24 cholesterol, sucrose monostearate, sucrose monolaurate and poloxamers. The surfactants may constitute from about 1 to about 20%, by weight of the formulation. In certain embodiments, the concentration of surfactant in the solution is greater than about 10% by weight, such as the 12% concentration of the surfactant Polysorbate 80, as illustrated in Examples 1 and 2, provided herein.

In one of the embodiments, the surfactant comprises polyoxyethylene sorbitan fatty acid esters. Particularly, it comprises polysorbate 80.

To prevent the repreciptation or recrystallization of ibuprofen from the solution and to stabilize the preparation, suitable solubilizers are added. Suitable solubilizers may be selected from amongst triacetin, triethylcitrate, ethyl oleate, ethyl caprylate, dimethylacetamide, N-methylpyrrolidone, polyvinylpyrrolidone, hydroxypropyl methylcellulose, hydroxypropyl cyclodextrins, ethanol, glycofurol, transcutol, propylene glycol, and dimethyl isosorbide. Particularly polyvinyl pyrrolidone is added. Polyvinyl pyrrolidone is a polymeric compound formulated to specific molecular weights, which can range from approximately 2000 to about 1,500,000 Daltons. Polyvinyl pyrrolidone has the capacity or property of forming water-soluble complexes with water insoluble drug substances such as ibuprofen. Typically, higher molecular weight polyvinyl pyrrolidones are used as thickeners while low molecular weight polyvinyl pyrrolidones are typically used as solubilizers or crystallization inhibitors. Polyvinyl pyrrolidone K-12 (molecular weight approximately 2000-3000 Daltons), Polyvinyl pyrrolidone K-17 (molecular weight approximately 7000-11,000 Daltons), and Polyvinyl pyrrolidone K-30 molecular weight approximately 30,000 Daltons) are utilized as solubilizers. The solubilizers constitute about 2 to about 10% by weight of the formulation. In certain embodiments, the concentration of such a solubilizer in the solution is apprixmately 4% by weight, such as the concentration of the solubilizer polyvinylpyrrolidone, as illustrated in Examples 1 and 2, provided herein.

An alkalizing agent may also be added to the composition to improve the solubility of the ibuprofen during the formulation of the composition. The alkalizing agents may be selected from amongst organic amines and bases. Suitable organic amines include colamine (ethanolamine), lysine, triethanolamine, N- methylglucamine (meglumine), ethylene diamine, trimethylamine, and triisopantolamine. Suitable bases, which are salts of pharmaceutically acceptable acids include ammonium bicarbonate, sodium bicarbonate, calcium bicarbonate, potassium bicarbonate, potassium carbonate, sodium carbonate, calcium carbonate, ammonium hydroxide, sodium hydroxide, calcium hydroxide, ammonium hydroxide or mixtures thereof. The alkalizing agent constitutes from about 1 to about 10 % by weight of the formulation.

In order to prepare a solution of alkalizing agent, water may be added in approximately about 2 to 10% by weight of the solution.

The solution may further contain other pharmaceutically acceptable additives, such as antioxidants, buffering agents, antifoaming agents, detackifiers, preservatives, chelating agents, viscosity modifiers, tonicifiers, flavorants, colorants, odorants, opacifiers, stabilizing agents, fillers, plasticizing agents, or mixtures thereof.

Soft gelatin capsules containing clear aqueous solutions can be prepared using conventional and known encapsulation techniques. For example, the solution can be deposited between two opposing ribbons of a gel composition. The composition of the ribbons may include gelatin, modified starches, gums, carrageenans and mixtures thereof. The opposing ribbons are then run between two die rollers having die pockets thereon the surface of which corresponds to the configuration of the desired soft capsule. The composition is sealed within the fused casing.

According to one of the embodiments, a clear aqueous solutions of ibuprofen can be prepared by following steps: preparing a solution of polyethylene glycol and the surfactant, mixing the solution with an aqueous solution of alkalizing agent, dispersing solubilizer in it, adding ibuprofen to the dispersion and stirring at a temperature not exceeding about 45°C to obtain a clear solution.

In another embodiment, a clear aqueous solutions of ibuprofen can be prepared by following steps: preparing a solution of polyethylene glycol 400 and polysorbate 80, mixing the solution with an aqueous solution of N-methylglucamine, dispersing polyvinyl pyrrolidone in it, adding ibuprofen to the dispersion and stirring the solution at a temperature not exceeding about 45°C to obtain a clear solution.

According to yet another embodiment, soft gelatin capsules of ibuprofen may comprise clear aqueous solutions comprising from about 15 to about 40% by weight of ibuprofen, from about 15 to about 50% by weight of polyethylene glycol, from about 1 to about 20% by weight of surfactant, from about 1 to about 10% by weight of alkalizing agent, from about 2 to about 10% of the solubilizer, from about 2 to about 10% of water.

According to yet another embodiment, soft gelatin capsules of ibuprofen may comprise from about 15 to about 40% by weight of ibuprofen, from about 15 to about 50% by weight of polyethylene glycol 400, from about 1 to about 20% by weight of polysorbate-80,

from about 1 to about 10% by weight of N-methylglucamine, from about 2 to 10% of the polyvinyl pyrrolidone, from about 2 to 10% of water.

The invention can be illustrated in more detail by means of the following Examples. This is for illustration only and does not limit the scope of the invention.

Example 1: Preparation of soft gelatin capsules of ibuprofen:

	Ingredients	**Quantity per Capsule (%w/w)**
1.	Ibuprofen	26.67
2.	N-methylglucamine	03.60
3.	Water	05.33
4.	Polysorbate 80	12.00
5.	Polyvinyl pyrrolidone	04.00
6.	Polyethylene Glycol (PEG 400)	48.40

Process:

1. N-methylglucamine was dissolved in purified water.
2. Polyethylene glycol and Polysorbate 80 were mixed separately, to obtain a clear solution.
3. The solution of Step 1 was mixed with that of Step 2 and polyvinyl pyrrolidone was dispersed in it.
4. Ibuprofen was added slowly to the dispersion and stirred continuously till clear solution was obtained.
5. The solution of Step 4 was allowed to deaerate.
6. The deareated solution was finally encapsulated in a soft gelatin shell.

While several particular forms of the invention have been illustrated and described, it will be apparent that various modifications and combinations of the invention detailed in the text can be made without departing from the spirit and scope of the invention. For example, the alkalizing agent used in the pharmaceutical compositions does not necessarily need to include only N-methyl glucamine but instead can be made up of any other alkalizing agent or

mixture of different alkalizing agents, e.g., potassium carbonate. Further aspects of this invention, together with additional features contributing thereto and advantages accruing therefrom will be apparent from the following hypothetical example.

Example 2: Preparation of soft gelatin capsules of ibuprofen:

	Ingredients	**Quantity per Capsule (%w/w)**
1.	Ibuprofen	26.67
2.	Potassium carbonate	03.60
3.	Water	05.33
4.	Polysorbate 80	12.00
5.	Polyvinyl pyrrolidone	04.00
6.	Polyethylene Glycol (PEG 400)	48.40

Process:

1. Dissolve potassium carbonate in purified water.
2. Separately mix polyethylene glycol and Polysorbate 80, to obtain a clear solution.
3. Mix the solution of Step 1 with that of Step 2 and disperse polyvinyl pyrrolidone in it.
4. Add ibuprofen slowly to the dispersion and stir continuously to obtain clear solution.
5. Allow the solution of step 4 to deaerate.
6. Encapsulate the deareated solution in a soft gelatin shell.

We Claim:

1. A clear aqueous solution comprising ibuprofen and a solvent system, wherein the solvent system comprises:

(a) from about 15 to about 50% by weight of polyethylene glycol,

(b) from about 1 to about 20% by weight of surfactant,

(c) from about 1 to about 10% by weight of alkalizing agent,

(d) from about 2 to about 10% of the solubilizer,

(e) from about 2 to about 10% of water.

wherein, the solubilization of ibuprofen is carried out at a temperature not exceeding about 45°C.

2. The solution according to claim 1, wherein ibuprofen constitutes from about 15 to about 40% of the solution by weight.

3. The solution according to claim 1, wherein polyethylene glycol is has an average molecular weight of about 200-800 Daltons.

4. The solution according to claim 1, wherein the surfactant is selected from hydrophilic non-ionic surfactants having an HLB value equal to or greater than about 10.

5. The solution according to claim 4, wherein the hydrophilic non-ionic surfactant is selected from polyoxyethylene alkyl ethers; polyethylene glycol fatty acids esters; polyethylene glycol glycerol fatty acid esters; polyoxyethylene sorbitan fatty acid esters; polyoxyethylene-polyoxypropylene block copolymers; polyglycerol fatty acid esters; polyoxyethylene glycerides; polyoxyethylene vegetable oils; polyoxyethylene hydrogenated vegetable oils; reaction mixtures of polyols and at least one member of the group consisting of fatty acids, glycerides, vegetable oils, hydrogenated vegetable oils, and sterols; and mixtures thereof.

6. The solution according to claim 5, wherein the hydrophilic non- ionic surfactant is polyoxyetheylene sorbitan fatty acid ester.

7. The solution according to claim 1, wherein the alkalizing agent is selected from organic amines and bases.

8. The solution according to claim 7, wherein the organic amine is selected from ethanolamine, lysine, triethanolamine, and N-methylglucamine.

9. The solution according to claim 7, wherein the bases are selected from ammonium bicarbonate, sodium bicarbonate, calcium bicarbonate, potassium bicarbonate, potassium carbonate, sodium carbonate, calcium carbonate, ammonium hydroxide, sodium hydroxide, calcium hydroxide, ammonium hydroxide or mixture thereof.

10. The solution according to claim 1, wherein the solubilizer is polyvinyl pyrrolidone.

11. The solution according to claim 1, further comprising pharmaceutically acceptable additives selected from the group comprising antioxidants, buffering agents, antifoaming agents, detackifiers, preservatives, chelating agents, viscosity modifiers, tonicifiers, flavorants, colorants, odorants, opacifiers, stabilizing agents, fillers, plasticizing agents, or mixtures thereof.

12. A process for preparing a clear aqueous solution of ibuprofen, comprising the steps of:

(a) preparing a solution of polyethylene glycol and the surfactant;
(b) mixing the solution with an aqueous solution of alkalizing agent;
(c) dispersing ibuprofen in solubilizer;
(d) mixing the dispersion with the mixture of step (b);
(e) stirring the solution at a temperature not exceeding about 45 °C to obtain a clear solution; and
(f) encapsulating the solution in a soft gelatin capsule.

13. A soft gelatin capsule filled with clear aqueous solution, comprising ibuprofen and a solvent system, wherein the solvent system comprises:

(a) from about 15 to about 50% by weight of polyethylene glycol,
(b) from about 1 to about 20% by weight of surfactant,
(c) from about 1 to about 10% by weight of alkalizing agent,
(d) from about 2 to about 10% of the solubilizer; and
(e) from about 2 to about 10% of water.

(f) wherein, solubilization of ibuprofen is carried out at a temperature not exceeding about 45°C.

14. A method of treating an inflammatory condition in mammals in need of such treatment comprising administering to said mammal a clear aqueous solution comprising ibuprofen and a solvent system, wherein the solvent system comprises:

(a) from about 15 to about 50% by weight of polyethylene glycol;

(b) from about 1 to about 20% by weight of surfactant;

(c) from about 1 to about 10% by weight of alkalizing agent;

(d) from about 2 to about 10% of the solubilizer; and

(e) from about 2 to about 10% of water.

wherein, solubilization of ibuprofen is carried out at a temperature not exceeding about 45°C.

15. The method according to claim 15 further comprising concurrently or sequentially administering one or more of glucosamine, pseudoephedrine, codeine, paracetamol, econazole, cyclooxygenase-2 inhibitor, alprazolam, dextromethorphan, chlorpheniramine or mixtures thereof.

16. The method according to claim 15 wherein the clear aqueous solution of ibuprofen further comprises one or more of glucosamine, pseudoephedrine, codeine, paracetamol, econazole, cyclooxygenase-2 inhibitor, alprazolam, dextromethorphan, chlorpheniramine or mixtures thereof.

INTERNATIONAL SEARCH REPORT

ational Application No
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A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K47/00 A61K9/48 A61K31/192 A61P29/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61K

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

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, WPI Data, PAJ, MEDLINE, BIOSIS, EMBASE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,X	WO 2005/046727 A (RANBAXY LABORATORIES LIMITED; BHATIA, INDERDEEP, SINGH; SINGLA, AJAY,) 26 May 2005 (2005-05-26) example 6	1-16
X	US 5 468 502 A (ARGIRIADI ET AL) 21 November 1995 (1995-11-21) examples 1,2	1-16
X	US 5 376 688 A (MORTON ET AL) 27 December 1994 (1994-12-27) column 4, lines 36-43 column 4, line 56 - column 5, line 5 examples 5,6 column 3, lines 14-18	1-16

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[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° 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

"T" 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.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
27 October 2005	08/11/2005

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

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INTERNATIONAL SEARCH REPORT

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/IB2005/001697

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 6 387 400 B1 (TINDAL STEPHEN CHARLES ET AL) 14 May 2002 (2002-05-14) cited in the application column 5, lines 12-18 column 5, lines 26-46 example 1	1-16
X	US 4 690 823 A (LOHNER ET AL) 1 September 1987 (1987-09-01) cited in the application column 1, line 63 - column 3, line 5	1-16

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INTERNATIONAL SEARCH REPORT

ernational application No.
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Box 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.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claims 14-16 are 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.

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 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 fee, this Authority did not invite payment of any additional fee.

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.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

ational Application No
/IB2005/001697

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 2005046727 A	26-05-2005	NONE	
US 5468502 A	21-11-1995	AU 4607496 A	10-07-1996
		WO 9619202 A1	27-06-1996
US 5376688 A	27-12-1994	AU 692431 B2	11-06-1998
		AU 5851894 A	19-07-1994
		CA 2152062 A1	07-07-1994
		DE 69330353 D1	19-07-2001
		DE 69330353 T2	02-05-2002
		EP 0678019 A1	25-10-1995
		ES 2157975 T3	01-09-2001
		JP 8507494 T	13-08-1996
		WO 9414423 A1	07-07-1994
US 6387400 B1	14-05-2002	AU 2431702 A	13-03-2002
		BR 0113539 A	15-07-2003
		CA 2419993 A1	07-03-2002
		CN 1477953 A	25-02-2004
		DE 01984557 T1	22-04-2004
		EP 1365749 A2	03-12-2003
		ES 2206081 T1	16-05-2004
		HU 0401224 A2	29-11-2004
		JP 2004526664 T	02-09-2004
		MX PA03001762 A	04-06-2003
		NO 20030897 A	26-02-2003
		PL 365752 A1	10-01-2005
		TW 589199 B	01-06-2004
		WO 0217855 A2	07-03-2002
		ZA 200301007 A	13-02-2004
US 4690823 A	01-09-1987	CA 1248876 A1	17-01-1989
		DE 3437599 A1	17-04-1986
		EP 0178436 A1	23-04-1986
		ES 8608868 A1	16-12-1986
		JP 1941563 C	23-06-1995
		JP 6067829 B	31-08-1994
		JP 61158921 A	18-07-1986
		NO 853497 A	14-04-1986
		ZA 8506841 A	28-05-1986