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(54) **Title:** PHARMACEUTICAL INCLUSION COMPLEXES CONTAINING A STEROID AND OPTIONALLY AN ANTIBACTERIAL AGENT

(57) **Abstract:** The present invention is concerned with pharmaceutical inclusion complexes for anti-inflammatory compounds, compositions including the same, and methods of treating employing the complexes and/or compositions.

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# PHARMACEUTICAL INCLUSION COMPLEXES CONTAINING A METHOD AND OPTIONALLZAN ANTIBACTERIAL AGENT

The present invention is concerned with pharmaceutical inclusion complexes for anti-inflammatory compounds, compositions including the same, and methods of treating employing the complexes and / or compositions.

Formulation of insoluble drugs has often proved to be problematic. Prior art techniques for solubilizing insoluble drugs have included formulating as a suspension, use of a surfactant or solubilizer, or by converting the drug into a soluble salt. Anti-inflammatory drugs, such as steroids, represent a class of insoluble drugs, and are thus difficult to formulate in aqueous solution. These agents may be used alone or in combination with an anti-infective agent, especially in inflammatory conditions associated with infections, for example infections which commonly occur in eye and ear infections caused by Gram negative and positive bacteria.

The glucocorticoids frequently used for ophthalmic and otic use include loteprednol, rimexonol, prednisolone, dexamethasone, flurometholone and hydrocortisone. Among the anti-bacterials, the quinolones and the aminoglycosides are the most preferred classes of compounds. The aminoglycosides include tobramycin, neomycin, gentamicin and framycetin and other members of this class. The quinolone anti-bacterials include ciprofloxacin, norfloxacin, ofloxacin and other members of this class.

Solubility of a drug is an important parameter in developing a formulation. This is particularly important, where the formulations are liquid in nature, that is solutions, suspensions and semi-solid formulations, such as gels and ointments, and even more important where the formulations contain an active ingredient that is poorly soluble in aqueous media.

Solubility of such poorly soluble drugs can be increased by various methods well known to a person skilled in the art, for example binding or complexing, or by use of a prodrug or a salt form of the insoluble drug. However, addition of a complexing agent such as cyclodextrin has in the past been found to be problematic, with the cyclodextrin binding preservatives in the ophthalmic solution and thus decreasing preservative ability, which can raise a serious threat to sensitive organs, such as the eyes and ears.

US Patent 5679336 discloses the use of ciprofloxacin in an ophthalmic preparation.

US Patent 6284804 describes the combination of ciprofloxacin, with insoluble dexamethasone, by formulating as a suspension. Suspensions are, however, pharmaceutically cumbersome and employ expensive technology.

WO 02/39993 describes the combination of an anti-inflammatory agent and an anti-infective agent, suitable for use as a solution or eye drops, an ointment or a gel. WO 02/39993 further describes aminoglycosides in combination with the glucocorticoids. WO 02/39993 also discloses a formulation comprising a steroid and an anti-bacterial agent, and a method of solubilizing dexamethasone by physically blending together with beta cyclodextrin for five minutes. However, such external addition of cyclodextrin, which is thus present in the formulation in free form, can bind with the preservatives in the ophthalmic solution and decreases the preservative ability, which can raise serious concerns as to the stability of an ophthalmic or otic preparation as described above.

It has now been found by the present invention that the formation of a cyclodextrin inclusion complex comprising an anti-inflammatory compound alleviates the problems of the prior art and in particular exhibits improved stability than is achieved by the prior art method of simply blending cyclodextrin and dexamethasone as referred to above for WO 02/39993. With the present invention, as an anti-inflammatory compound forms an inclusion complex with cyclodextrin, the compositions of the present invention are substantially free cyclodextrin in free form, which would otherwise interact with the preservatives of the compositions as was experienced in the prior art. The formation of an inclusion complex according to the present invention also serves to increase bioavailability of the anti-inflammatory compound.

According to the present invention, therefore, there is provided an inclusion complex comprising an anti-inflammatory compound and cyclodextrin, or derivatives or analogs thereof.

An inclusion complex according to the present invention is such as to provide an anti-inflammatory compound employed therein in substantially stable form, therefore facilitating formulation thereof into final dosage form and obviating the need to employ special precautions to stabilise the anti-inflammatory compound during formulation. Typically, the anti-inflammatory compound may be selected from a class of steroids recognized as having poor aqueous solubility and preferred steroids for use in an inclusion complex as provided by

the present invention can be selected from the group consisting of loteprednol, rimexonol, prednisolone, dexamethasone, flurometholone and hydrocortisone, or a pharmaceutically acceptable salt, solvate or physiologically functional derivative thereof. A particularly preferred anti-inflammatory compound for use in an inclusion complex according to the present invention is dexamethasone

The term "physiologically functional derivative" as used herein denotes a chemical derivative of any of the specific therapeutic agents described herein having the same or similar physiological function as the free base therapeutic agent and, for example, being convertible in the body thereto. According to the present invention, examples of physiologically functional derivatives include esters.

The term "cyclodextrin" as used herein denotes without limitation any cyclodextrin suitable for use in an inclusion complex and compositions as provided by the present invention. Also encompassed within the definition of cyclodextrins as used herein are derivatives or analogs thereof as referred to above. Such derivatives can include methyl-, ethyl-, hydroxyethyl-, hydroxymethyl- and hydroxypropyl- substituted cyclodextrins, and also sulphonated cyclodextrin. Specific examples of cyclodextrins suitable for use according to the present invention include beta cyclodextrin, gamma cyclodextrin, dimethyl beta cyclodextrin, trimethyl beta cyclodextrin, 2-hydroxypropyl beta cyclodextrin, 3-hydroxypropyl beta cyclodextrin and sulphonated cyclodextrin, with the use of 3-hydroxypropyl beta cyclodextrin being preferred. It is also possible that a combination of more than one of the above mentioned cyclodextrins can be employed in a composition according to the present invention.

Although the use of cyclodextrins as solubilizing agents is known in the pharmaceutical field, it cannot be predicted what affect cyclodextrins will have on bioavailability or other biological characteristics of an active ingredient. It is advantageous that according to the present invention the use of a cyclodextrin inclusion complex for an anti-inflammatory compound, otherwise known to have poor aqueous solubility, can solubilize the anti-inflammatory compound and as such improve bioavailability thereof. A cyclodextrin inclusion complex further provides the anti-inflammatory compound in a substantially stable form, alleviating many of the associated formulation problems encountered in the prior art.

The present invention further comprises a pharmaceutical composition comprising an

inclusion complex substantially as hereinbefore described, together with one or more pharmaceutically acceptable carriers or excipients therefor. The composition can comprise any suitable dosage form, such as a tablet, capsule or the like, or a solution, gel or ointment, particularly a composition suitable for ophthalmic or otic treatment.

The present invention further provides use of an inclusion complex substantially as hereinbefore described in the manufacture of a medicament for the treatment of an inflammatory condition which is susceptible to treatment by one or more steroids.

The present invention also provides a method for the treatment or prophylaxis of an inflammatory condition, which method comprises administration to a patient suffering from, or susceptible to, an inflammatory condition, a therapeutically effective amount of an inclusion complex, or a composition comprising the same, substantially as hereinbefore described.

Typically an anti-inflammatory condition to be treated according to the present invention is an ophthalmic, otic or related disorder.

There is also provided by the present invention a method of improving the bioavailability in a patient of an anti-inflammatory compound substantially as hereinbefore described, which method comprises administering a therapeutically effective amount of an inclusion complex, or a composition, according to the present invention, to a patient in need of treatment by such an anti-inflammatory compound. Such treatment according to the present invention achieves an improvement in bioavailability of an anti-inflammatory compound administered by way of an inclusion complex, or a pharmaceutical composition containing the same, when compared to the administration of such an anti-inflammatory compound as present in a composition according to the prior art.

There is also provided by the present invention a process of preparing an inclusion complex substantially as hereinbefore described, which process comprises providing a solution of cyclodextrin, or derivatives or analogs thereof, substantially as hereinbefore described, in a substantially non-aqueous solvent; adding an anti-inflammatory compound substantially as hereinbefore described to the so formed solution; and removing the solvent so as to yield an inclusion complex comprising said cyclodextrin and said anti-inflammatory compound. An inclusion complex formed in this way exhibits enhanced stability of the anti-inflammatory compound compared to the prior art blends comprising cyclodextrin and an anti-inflammatory compound.

Suitably, the molar ratio of the anti-inflammatory compound to the cyclodextrin is in the range of from 1:1 to 1:20, with the ratio of 1:5 to 1:15 being preferred.

A preferred solvent is absolute ethanol, and the temperature of a reaction mass comprising a solution of the cyclodextrin and the solvent is maintained in the range of 40-45°C. The anti-inflammatory compound is subsequently added to the above reaction mass.

Typically, the solvent is then removed by distillation under reduced pressure, and the subsequently obtained slurry is typically cooled (suitably to 5 - 15°C) to achieve precipitation or crystallization of an inclusion complex. The precipitated or crystallized complex is then filtered and dried, followed by milling to obtain substantially uniform particle size so as to achieve an inclusion complex according to the present invention, which is suitable for pharmaceutical handling. Alternatively, the distillation can be carried out to remove the solvent and the residue scratched out, followed by milling as referred to above so as to achieve an inclusion complex according to the present invention, which is suitable for pharmaceutical handling. An inclusion complex according to the present invention thus obtained by a process as described above can be formulated easily into a final dosage form such as solutions, gels, ointments, tablets, capsules and the like, with excipients known in the art similarly being employed in such dosage forms, without the need to take special precautions to stabilise the anti-inflammatory compound during processing.

There is also provided by the present invention an inclusion complex obtained by a process substantially as hereinbefore described.

An inclusion complex according to the present invention substantially as hereinbefore described can advantageously be employed in combination with one or more antibacterial agents. It will be appreciated, therefore, that the present invention further provides a pharmaceutical product comprising (i) an inclusion complex substantially as hereinbefore described, and (ii) at least one antibacterial agent, as a combined preparation for simultaneous, separate or sequential use in the treatment of an inflammatory condition associated with infection.

It will also be appreciated from the above, that the respective therapeutic agents of the combined preparation can be administered simultaneously, either in the same or different pharmaceutical compositions, or separately or sequentially. If there is separate or sequential administration, it will also be appreciated that the subsequently administered therapeutic agents should be administered to a patient within a time scale so as to achieve, or more

particularly optimise, an advantageous synergistic therapeutic effect of a combined preparation as present in a pharmaceutical product according to the present invention.

It is preferred according to the present invention, however, that the inclusion complex and the anti-bacterial agent are employed in a single dosage form and there is further provided by the present invention a pharmaceutical composition comprising a therapeutically effective amount of an inclusion complex substantially as hereinbefore described, a therapeutically effective amount of one or more antibacterial agents, and one or more pharmaceutically acceptable carriers or excipients therefor.

A composition according to the present invention further comprises at least one further solubilizing agent, or co-solubilizer, which can suitably be selected from the group consisting of polyvinyl pyrrolidone, polyvinyl alcohol, hydroxy propylmethyl cellulose, methylcellulose and the like. Such co-solubilizers can also serve as thickeners in a composition as provided by the present invention.

A composition according to the present invention can also further comprise at least one chelating agent. Suitably a chelating agent for use in a composition according to the present invention can be selected from the group consisting of disodium edetate, sodium citrate, citric acid and the like.

A composition according to the present invention can advantageously also further comprise an anti-microbial agent, or preservative, selected from the group consisting of benzalkonium chloride, chlorobutanol, phenyl mercuric nitrate, chloro-m-cresol, phenyl ethyl alcohol and the like. Advantageously, according to the present invention, interaction of such anti-microbial agents, or preservatives, with cyclodextrin in free form is obviated due to the cyclodextrin being present in complexed form as provided by an inclusion complex according to the present invention. More particularly, it is preferred that a composition as provided according to the present invention is substantially free from cyclodextrin in free form and as such interaction between cyclodextrin in free form and anti-microbial agents, or preservatives, present in the composition is substantially obviated.

Suitably, a composition according to the present invention may further comprise buffering agents, such as sodium chloride, boric acid, monobasic and dibasic sodium phosphate and the like. Furthermore, the composition may further comprise tonicity adjusting agents, such as sodium chloride, boric acid and the like. Typically, the composition can also comprise pH adjusting agents to maintain the pH of the composition to suit the

stability of the antibacterial agent.

Preferably, the antibacterial agent is selected from aminoglycosides and quinolone antibacterial agents. In the case where the antibacterial agent is selected from aminoglycosides, it is preferred that the antibacterial agent is selected from the group consisting of neomycin, tobramycin, gentamicin, framycetin, and the like, or a pharmaceutically acceptable salt, solvate or physiologically functional derivative thereof. A preferred aminoglycoside for use according to the present invention is tobramycin sulphate. In the case where the antibacterial agent is selected from quinolone antibacterial agents, it is preferred that the antibacterial agent is selected from the group consisting of ciprofloxacin, norfloxacin, ofloxacin, pefloxacin, and the like, or a pharmaceutically acceptable salt, solvate or physiologically functional derivative thereof. A preferred quinolone antibacterial agent for use according to the present invention is ciprofloxacin hydrochloride.

The present invention further provides use of an inclusion complex substantially as hereinbefore described, together with one or more antibacterial agents substantially as hereinbefore described, in the manufacture of a medicament for the treatment of an inflammatory condition associated with infection.

The present invention also provides a method for the treatment or prophylaxis of an inflammatory condition associated with infection, which method comprises administration to a patient suffering from, or susceptible to, an inflammatory condition associated with infection, a therapeutically effective amount of a pharmaceutical product, or a composition, which comprise an inclusion complex according to the present invention and one or more bacterial agents substantially as hereinbefore described.

There is further provided by the present invention a process of preparing a pharmaceutical product substantially as hereinbefore described, which process comprises providing as a combined preparation for simultaneous, separate or sequential use in the treatment of an inflammatory condition associated with infection: (i) an inclusion complex substantially as hereinbefore described, and (ii) at least one antibacterial agent, or a pharmaceutically acceptable salt, solvate or physiologically functional derivative thereof.

There is further provided by the present invention a process of preparing a pharmaceutical composition substantially as hereinbefore described, which process comprises admixing an inclusion complex substantially as hereinbefore described, and one or more antibacterial agents substantially as hereinbefore described, in the presence of one or more

pharmaceutically acceptable carriers, excipients or ingredients as described herein, so as to provide a pharmaceutical composition according to the present invention.

There is still further provided by the present invention a pharmaceutical composition prepared by a process as described above.

The present invention will now be further illustrated by the following Examples, which do not limit the scope of the invention in any way.

Examples

Example 1

3kgs of hydroxypropyl beta cyclodextrin was added to 25 litres of absolute alcohol and stirred. The temperature of the solution was maintained at 40-45°C. 105gms of dexamethasone was added to the above solution and stirred for 30 minutes. The alcohol was then distilled off under reduced pressure and a thick slurry was obtained. The slurry was then cooled to about 10°C and filtered. The filter cake was then dried in the oven. The content of dexamethasone was calculated by an assay method using HPLC.

Example 2

| | |
|---|---|
| Ciprofloxacin Hydrochloride | 0.35% w/v |
| Dexamethasone –cyclodextrin complex | quantity equivalent to 0.35% w/v |
| Disodium edetate | 0.05%w/v |
| Benzalkonium chloride | 0.01%w/v |
| Sodium chloride | 0.75%w/v |
| Polyvinylpyrrolidone | 0.3%w/v |
| Purified water | q.s. |

Example 3

| | |
|---|---|
| Tobramycin sulphate | 0.35% w/v |
| Dexamethasone –cyclodextrin complex | quantity equivalent to 0.35% w/v |
| Disodium edetate | 0.05%w/v |

| | |
|---|---|
| Benzalkonium chloride | 0.01%w/v |
| Sodium chloride | 0.75%w/v |
| Polyvinylpyrrolidone | 0.3%w/v |
| Purified water | q.s. |

Example 4

| | |
|---|---|
| Dexamethasone –cyclodextrin complex | quantity equivalent to 0.35% w/v |
| Disodium edetate | 0.05%w/v |
| Benzalkonium chloride | 0.01%w/v |
| Sodium chloride | 0.75%w/v |
| Polyvinylpyrrolidone | 0.3%w/v |
| Purified water | q.s. |

Process for Examples 2, 3 and 4:

Povidone was added to purified water, heated to 70°C and dissolved by stirring. Beta hydroxypropyl cyclodextrin-dexamethasone complex was added. The required quantity of disodium edetate was added, and stirred to dissolve. Sodium chloride and ciprofloxacin hydrochloride / tobramycin sulphate solution were added as appropriate. The mixture was stirred to dissolve. Benzalkonium chloride solution was added slowly with constant stirring. The pH was adjusted to 3.5 to 5.5 with 0.1N HCl and the volume made up as required.

Example 5

1.5 kgs of hydroxypropyl beta cyclodextrin was added to 12 litres of absolute alcohol and stirred. The temperature of the solution was maintained at 40-45°C. 52 gms of Prednisolone was added to the above solution and stirred for 30 minutes. The alcohol was then distilled off under reduced pressure and thick slurry was obtained. The slurry was then cooled to about 10°C and filtered. The filter cake was then dried in the oven. The content of Prednisolone was calculated by an assay method using HPLC.

Example 6

| | |
|---|---|
| Ciprofloxacin Hydrochloride | 0.35 %w/v |
| Prednisolone –cyclodextrin complex | quantity equivalent to 0.175 % w/v |
| Disodium edetate | 0.05%w/v |
| Benzalkonium chloride | 0.01%w/v |
| Sodium chloride | 0.75%w/v |
| Polyvinylpyrrolidone | 0.3%w/v |
| Purified water | q.s. |

Process for Example 6 as Examples 2 - 4 above.

CLAIMS

1. An inclusion complex comprising an anti-inflammatory compound and cyclodextrin, or derivatives or analogs thereof.

2. An inclusion complex according to claim 1, wherein said anti-inflammatory compound is a steroid having poor aqueous solubility.

3. An inclusion complex according to claim 2, wherein said steroid is selected from the group consisting of loteprednol, rimexonol, prednisolone, dexamethasone, flurometholone and hydrocortisone, or a pharmaceutically acceptable salt, solvate or physiologically functional derivative thereof.

4. An inclusion complex according to claim 3, wherein the steroid is dexamethasone.

5. An inclusion complex according to any of claims 1 to 4, wherein said cyclodextrin, or one or more derivatives or analogs thereof, is selected from the group consisting of beta cyclodextrin, gamma cyclodextrin, dimethyl beta cyclodextrin, trimethyl beta cyclodextrin, 2-hydroxypropyl beta cyclodextrin, 3-hydroxypropyl beta cyclodextrin and sulphonated cyclodextrin.

6. An inclusion complex according to claim 5, wherein said cyclodextrin derivative is 3-hydroxypropyl beta cyclodextrin.

7. A process of preparing an inclusion complex according to any of claims 1 to 6, which process comprises providing a solution of cyclodextrin, or derivatives or analogs thereof, in a substantially non-aqueous solvent; adding an anti-inflammatory compound to the so formed solution; and removing the solvent so as to yield an inclusion complex comprising said cyclodextrin and said anti-inflammatory compound.

8. A process according to claim 7, wherein the molar ratio of said anti-inflammatory

compound to said cyclodextrin is in the range of from 1:1 to 1:20.

9. A process according to claim 8, wherein said ratio is in the range of from 1:5 to 1:15.

10. A process according to any of claims 7 to 9, wherein said substantially non-aqueous solvent is absolute ethanol.

11. A process according to any of claims 7 to 10, wherein the temperature of a reaction mass comprising said solution of said cyclodextrin and said solvent is maintained in the range of 40-45°C.

12. A process according to any of claims 7 to 11, wherein said solvent is removed by distillation under reduced pressure.

13. An inclusion complex obtained by a process according to any of claims 7 to 12.

14. A pharmaceutical composition comprising an inclusion complex according to any of claims 1 to 6, or 13, together with one or more pharmaceutically acceptable carriers or excipients therefor.

15. Use of an inclusion complex according to any of claims 1 to 6, or 13, in the manufacture of a medicament for the treatment of an inflammatory condition which is susceptible to treatment by one or more steroids.

16. A method for the treatment or prophylaxis of an inflammatory condition, which method comprises administration to a patient suffering from, or susceptible to, an inflammatory condition, a therapeutically effective amount of an inclusion complex according to any of claims 1 to 6, or 13, or a composition according to claim 14.

17. A method of improving the bioavailability in a patient of an anti-inflammatory compound, which method comprises administering a therapeutically effective amount of an inclusion complex according to any of claims 1 to 6, or 13, or a composition, according to

claim 14, to a patient in need of anti-inflammatory treatment.

18. A pharmaceutical product comprising (i) an inclusion complex according to any of claims 1 to 6, or 13, and (ii) at least one antibacterial agent, as a combined preparation for simultaneous, separate or sequential use in the treatment of an inflammatory condition associated with infection.

19. A pharmaceutical composition comprising a therapeutically effective amount of an inclusion complex according to any of claims 1 to 6, or 13, a therapeutically effective amount of one or more antibacterial agents, and one or more pharmaceutically acceptable carriers or excipients therefor.

20. A composition according to claim 19, which further comprises at least one further solubilizing agent, or co-solubilizer, selected from the group consisting of polyvinyl pyrrolidone, polyvinyl alcohol, hydroxy propylmethyl cellulose, and methylcellulose.

21. A composition according to claim 19 or 20, which further comprises at least one chelating agent.

22. A composition according to claim 21, wherein said chelating agent is selected from the group consisting of disodium edetate, sodium citrate and citric acid.

23. A composition according to any of claims 19 to 22, which further comprises an anti-microbial agent, or preservative, selected from the group consisting of benzalkonium chloride, chlorobutanol, phenyl mercuric nitrate, chloro-m-cresol and phenyl ethyl alcohol.

24. A composition according to any of claims 19 to 23, substantially free from cyclodextrin in free form.

25. A composition according to claim 23 and 24, wherein interaction of said anti-microbial agent, or preservative, with cyclodextrin in free form, is obviated due to cyclodextrin being present in complexed form as provided by an inclusion complex according

to any of claims 1 to 6, or 13.

26. A composition according to any of claims 19 to 25, which further comprises at least one buffering agent selected from the group consisting of sodium chloride, boric acid, monobasic and dibasic sodium phosphate.

27. A composition according to any of claims 19 to 26, which further comprises a tonicity adjusting agent which is either sodium chloride or boric acid.

28. A product according to claim 18, or a composition according to any of claims 19 to 27, wherein said antibacterial agent is selected from aminoglycosides and quinolone antibacterial agents.

29. A product or composition according to claim 28, wherein in the case where said antibacterial agent is selected from aminoglycosides, said antibacterial agent is selected from the group consisting of neomycin, tobramycin, gentamicin and framycetin, or a pharmaceutically acceptable salt, solvate or physiologically functional derivative thereof.

30. A product or composition according to claim 29, wherein said antibacterial agent is tobramycin sulphate

31. A product or composition according to claim 28, wherein in the case where said antibacterial agent is selected from quinolone antibacterial agents, said antibacterial agent is selected from the group consisting of ciprofloxacin, norfloxacin, ofloxacin and pefloxacin, or a pharmaceutically acceptable salt, solvate or physiologically functional derivative thereof.

32. A product or composition according to claim 31, wherein said antibacterial agent is ciprofloxacin hydrochloride.

33. A process of preparing a pharmaceutical product according to any of claims 18, or 28 to 32, which process comprises providing as a combined preparation for simultaneous, separate or sequential use in the treatment of an inflammatory condition associated with

infection: (i) an inclusion complex according to any of claims 1 to 6, or 13, and (ii) at least one antibacterial agent, or a pharmaceutically acceptable salt, solvate or physiologically functional derivative thereof.

34. A process of preparing a pharmaceutical composition according to any of claims 19 to 32, which process comprises admixing an inclusion complex according to any of claims 1 to 6, or 13, and one or more antibacterial agents, in the presence of one or more pharmaceutically acceptable carriers, excipients or ingredients, so as to provide said pharmaceutical composition.

35. A pharmaceutical composition prepared by a process according to claim 34.

36. Use of an inclusion complex according to any of claims 1 to 6, or 13, together with one or more antibacterial agents, in the manufacture of a medicament for the treatment of an inflammatory condition associated with infection.

37. Use according to claim 36, wherein said antibacterial agent is selected from aminoglycosides and quinolone antibacterial agents.

38. Use according to claim 37, wherein in the case where said antibacterial agent is selected from aminoglycosides, said antibacterial agent is selected from the group consisting of neomycin, tobramycin, gentamicin and framycetin, or a pharmaceutically acceptable salt, solvate or physiologically functional derivative thereof.

39. Use according to claim 38, wherein said antibacterial agent is tobramycin sulphate

40. Use according to claim 37, wherein in the case where said antibacterial agent is selected from quinolone antibacterial agents, said antibacterial agent is selected from the group consisting of ciprofloxacin, norfloxacin, ofloxacin and pefloxacin, or a pharmaceutically acceptable salt, solvate or physiologically functional derivative thereof.

41. Use according to claim 40, wherein said antibacterial agent is ciprofloxacin

hydrochloride.

42. A method for the treatment or prophylaxis of an inflammatory condition associated with infection, which method comprises administration to a patient suffering from, or susceptible to, an inflammatory condition associated with infection, a therapeutically effective amount of a pharmaceutical product according to any of claims 18, or 28 to 32, or a composition according to any of claims 19 to 32, or 35.

# INTERNATIONAL SEARCH REPORT

ational Application No
PCT/GB2004/000422

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K47/48 A61K31/00 A61K31/573 A61K31/7036 A61K31/495
A61P29/00 A61P31/00

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 A61P

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, BIOSIS, CHEM ABS Data, EMBASE, PAJ

C. DOCUMENTS CONSIDERED TO BE RELEVANT

| Category ° | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|---|---|---|
| X | WO 02/39993 A (CHANDAVARKAR NANDAN MOHAN ; CHANDRASHEKHAR MAINDE (IN); CHANDAVARKAR M) 23 May 2002 (2002-05-23) cited in the application page 4, line 12; claims 1-24; examples 1-9 page 3, paragraph 3 | 1-42 |
| Y | DATABASE WPI Section Ch, Week 200111 Derwent Publications Ltd., London, GB; Class B01, AN 2001-101077 XP002279092 & RU 2 157 214 C2 (MEDICINAL COMPOUNDS RES CENTRE) 10 October 2000 (2000-10-10) abstract | 1-42 |

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

[X] Patent family members are listed in annex.

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