METHOD FOR SOLUBILIZING PYRIDONECARBOXYLIC ACIDS AND AQUEOUS SOLUTIONS CONTAINING PYRIDONECARBOXYLIC ACIDS

METHODE ZUR LÖSUNG VON PYRIDONECARBOXYLSÄUREN UND WÄSSRIGE LÖSUNGEN DIE PYRIDONECARBOXYLSÄUREN ENTHALTEN

PROCEDE DE SOLUBILISATION D'ACIDES PYRIDONECARBOXYLIQUES ET SOLUTIONS AQUEUSES CONTENANT DES ACIDES PYRIDONECARBOXYLIQUES

References cited:

- W. STEGLICH, B. FUGMANN AND S. LANG-FUGMANN, EDITORS: "Römpp Lexikon Naturstoffe" 1997 , GEORG THIEME VERLAG, STUTTGART, GERMANY XP002235042 See p.266-267 'Glycyrrhetinsäure' and literature cited therein
Description

Technical Field Of The Invention

[0001] The present invention relates to a method for solubilizing pyridonecarboxylic acid, which is an amphoteric compound and which has an antibacterial activity, and a pharmacologically acceptable salt thereof, an aqueous solution preparation containing solubilized pyridonecarboxylic acid, and a production method thereof.

Background Of The Invention

[0002] Pyridonecarboxylic acid and pharmacologically acceptable salts thereof are superior synthetic antibacterial agents. However, since pyridonecarboxylic acid has carboxylic acid and the dihydropyridine skeleton in a molecule, forming a zwitterion, it shows low solubility in water at a physiological pH, i.e., neutral range. This imposes a problem that an aqueous solution containing pyridonecarboxylic acid or a pharmacologically acceptable salt thereof cannot be formulated into a pharmaceutical preparation having a near neutral pH.

[0003] Hardly soluble pyridonecarboxylic acid and a pharmacologically acceptable salt thereof have been conventionally solubilized by, for example, adding an inorganic acid to pyridonecarboxylic lactate (JP-A-60-94910), or adding an excess base to pyridonecarboxylic acid (JP-A-61-180771), or adding a metal compound comprising aluminum, magnesium or zinc to pyridonecarboxylic acid or a salt thereof (JP-A-63-188626). The aqueous solutions thus obtained show changes in pH, which is caused by the solubilizer added, and the toxicity of the solubilizer itself which may cause a local irritation and the like. In addition, the absorption into the living body may decrease due to an interaction between the solubilizer and pyridonecarboxylic acid.

[0004] Thus, there has not been provided an aqueous solution containing solubilized pyridonecarboxylic acid, which is safe and useful at a physiological pH, i.e., about neutral pH (pH 6-8).

Disclosure Of The Invention

[0005] It is an object of the present invention to provide a method for solubilizing pyridonecarboxylic acid and a pharmacologically acceptable salt thereof.

[0006] Another object of the present invention is to provide an aqueous solution having an improved solubility of pyridonecarboxylic acid and a pharmacologically acceptable salt thereof.

[0007] A further object of the present invention is to provide a method for producing an aqueous solution comprising pyridonecarboxylic acid or a pharmacologically acceptable salt thereof.

[0008] The present inventors have conducted intensive studies in an attempt to achieve the above-mentioned objects, and found that glycyrrhizic acid and a salt thereof can solubilize pyridonecarboxylic acid and a pharmacologically acceptable salt thereof in water at a physiological pH, which resulted in the completion of the present invention.

[0009] Thus, the present invention provides the following.

(1) A method for solubilizing (a) a pyridonecarboxylic acid of the formula (I)

\[
\begin{align*}
\text{R}^1 & \quad \text{R}^2 \\
\text{R}^3 & \quad \text{R}^4 \\
\text{R}^5 & \quad \text{CO}_2\text{H}
\end{align*}
\]

wherein X, Y and Z may be the same or different and each is nitrogen atom or optionally substituted CH, and R1, R2, R3, R4 and R5 may be the same or different and each is hydrogen atom, halogen, carboxyl group, optionally substituted lower alkyl, optionally substituted cycloalkyl, optionally substituted acyl, optionally substituted aryl or optionally substituted heterocyclic group, or at least two members selected from R1, R2, R3, R4 and R5 in combination form an optionally substituted 4- to 7-membered ring via or not via a hetero atom or (b) sparflouxacin or a pharmacologically acceptable salt thereof, comprising incorporating glycyrrhizic acid or a salt thereof and the (a) pyridonecarboxylic acid or (b) sparflouxacin or a pharmacologically acceptable salt thereof.
(2) The method according to item (1), which comprises adding the (a) pyridonecarboxylic acid of the formula (I) or (b) sparfloxacin or a pharmacologically acceptable salt thereof to water, adjusting pH to not more than 3, adding glycyrrhizic acid or a salt thereof and adjusting pH of the aqueous solution to 3.5 - 8.5.

(3) The method according to item (1), wherein the (a) pyridonecarboxylic acid of the formula (I) is a compound selected from the group consisting of lomefloxacin, norfloxacin, enoxacin, ofloxacin, ciprofloxacin, tosufloxacin, fleroxacin, cinoxacin and levofloxacin.

(4) An aqueous solution comprising (a) a pyridonecarboxylic acid of the formula (I)

\[
\text{(I)}
\]

wherein \(X, Y\) and \(Z\) may be the same or different and each is nitrogen atom or optionally substituted CH, and \(R^1, R^2, R^3, R^4, R^5\) may be the same or different and each is hydrogen atom, halogen, carboxyl group, optionally substituted lower alkyl, optionally substituted cycloalkyl, optionally substituted acyl, optionally substituted aryl or optionally substituted heterocyclic group, or at least two members selected from \(R^1, R^2, R^3, R^4, R^5\) in combination form an optionally substituted 4- to 7-membered ring via or not via a hetero atoms or (b) sparfloxacin or a pharmacologically acceptable salt thereof, and glycyrrhizic acid or a salt thereof.

(5) The aqueous solution of item (4), which is in the form of an eye drop, nasal drop or ear drop.

**Detailed Description of the Invention**

[0010] The pyridonecarboxylic acid and a pharmacologically acceptable salt thereof, which are amphoteric compounds and which have an antibacterial activity, are solubilized by incorporating these compounds and a solubilizing agent containing glycyrrhizic acid or a salt thereof as an active ingredient.

[0011] For example, pyridonecarboxylic acid or a pharmacologically acceptable salt thereof is added to water, the mixture is adjusted to pH 3 or below with an acid such as hydrochloric acid, phosphoric acid, and acetic acid, glycyrrhizic acid or a salt thereof is added thereto, and this aqueous solution is adjusted to pH 3.5 - 8.5, preferably 6 - 8, with an alkali such as sodium hydroxide, potassium hydroxide, monoethanolamine and tromethamine. The pyridonecarboxylic acid and a pharmacologically acceptable salt thereof are generally subjected to the above-mentioned solubilization in water at around room temperature.

[0012] The pyridonecarboxylic acid is free of any particular limitation as long as it is a compound having a carboxyl group at the 3-position of the pyridine skeleton or pyridazine skeleton and an oxo group at the 4-position thereof.

[0013] The pyridonecarboxylic acid capable of exerting a significant effect as a solubilization target in the present invention has a solubility in water, which corresponds to the solubility of from "somewhat insoluble" to "sparingly soluble" in the solubility test as defined in Japan Pharmacopoeia, 13th Edition, Explanation (1996), Hirokawashoten, Tokyo, p. A-51, General Notices 23, Description, or from "sparingly soluble to "practically insoluble" as defined in International Pharmacopoeia III.

[0014] The pyridonecarboxylic acid to be used has the following formula (I):
wherein X, Y and Z may be the same or different and each is nitrogen atom or optionally substituted CH, R1, R2, R3, R4 and R5 may be the same or different and each is hydrogen atom, halogen, carboxylic group, optionally substituted lower alkyl, optionally substituted cycloalkyl, optionally substituted acyl, optionally substituted acryl or optionally substituted heterocyclic group, or at least two members selected from R1, R2, R3, R4 and R5 in combination form an optionally substituted 4- to 7-membered ring via or not via a hetero atom.

[0015] "Halogen" is exemplified by fluorine, chlorine, bromine, and iodine.

[0016] The lower alkyl moiety of the "optionally substituted lower alkyl" preferably has 1 to 6 carbon atoms, and is exemplified by a linear or branched one, such as methyl, ethyl, propyl, isopropyl, isobutyl, tert-butyl, pentyl, isopentyl, neopentyl, tert-pentyl, hexyl, isohexyl, and neoheptyl.

[0017] Examples of the substituent of lower alkyl include halogen (e.g., fluorine, chlorine, bromine and iodine), with preference given to fluorine, chlorine and bromine.

[0018] The cycloalkyl moiety of the "optionally substituted cycloalkyl" preferably has 3 to 9 carbon atoms, and is exemplified by cyclopentyl, cyclohexyl, cycloheptyl, and cyclohepteryl.

[0019] The substituents of cycloalkyl include lower alkyl (e.g., those having 1 to 4 carbon atoms such as methyl, ethyl, propyl, and isopropyl), halogen (e.g., fluorine, chlorine, bromine and iodine).

[0020] The acyl moiety of the "optionally substituted acyl" may be, for example, alkanoyl such as formyl, acetyl, propionyl, butyryl, isobutyryl, and valeryl, and aromatic acyl such as benzoyl, naphthoyl, toluoyl, and salicyloyl.

[0021] The above-mentioned acyl may be substituted by substituents which may be the same or different, such as lower alkyl (e.g., those having 1 to 4 carbon atoms, such as methyl, ethyl, propyl); lower alkoxy (e.g., those having 1 to 4 carbon atoms, such as methoxy, ethoxy, propoxy); lower alkylthio (e.g., those having 1 to 4 carbon atoms, such as methylthio, ethylthio); lower alkylamino (e.g., those having 1 to 4 carbon atoms, such as methylamino, ethylamino, and propylamino); cyclo(lower)alkyl such as cyclo(C1-C5)alkyl (e.g., cyclopentyl, cyclohexyl); cyclo(lower)alkenyl such as cyclo(C1-C6)alkenyl (e.g., cyclohexenyl, cyclohexadienyl); halogen (e.g., fluorine, chlorine, bromine, and iodine); amino; protected amino; hydroxy; protected hydroxy; cyano; nitro; carboxy; protected carboxy; sulfo; sulfamoyl; imino; oxo; amino(lower)alkyl (e.g., those having 4 to 6 carbon atoms, such as aminomethyl, aminoethyl); carbamoyloxy; hydroxy(lower)alkyl (e.g., those having 1 to 4 carbon atoms, such as hydroxymethyl, 1- or 2-hydroxyethyl, 1- or 2-or 3-hydroxypropyl).

[0022] The aryl moiety of the "optionally substituted aryl" preferably has not more than 14 carbon atoms. Examples thereof include phenyl, and napthyl, with particular preference given to naphthyl.

[0023] The heterocyclic moiety of the "optionally substituted heterocyclic group" preferably has not more than 14 carbon atoms. In addition, it has at least one hetero atom besides carbon atom, which is selected from nitrogen atom, sulfur atom and oxygen atom, as an atom constituting the ring. The heterocyclic group encompasses saturated or unsaturated heterocyclic and heteropolycyclic groups.

[0024] Preferable heterocyclic groups are the following:

3- to 6-membered unsaturated heterocyclic group having 1 to 4 nitrogen atoms, such as pyrrolyl, pyrrolinyl, imidazolyl, pyrazolyl, pyridyl, pyrimidinyl, pyrazinyl, pyridazinyl, triazolyl (e.g., 4H-1,2,4-triazolyl, 1H-1,2,3-triazolyl, 2H-1,2,3-triazolyl, tetrazolyl (e.g., 1H-tetrazolyl, 2H-tetrazolyl), triazinyl (e.g., 1,2,4-triazinyl); 3- to 7-membered saturated heterocyclic group having 1 to 4 nitrogen atoms, such as pyrrolidinyl, imidazolidinyl, piperidinyl, piperazinyl, and homopiperazinyl; saturated heteropolycyclic group having 1 to 4 nitrogen atoms, such as quinuclidinyl; unsaturated heteropolycyclic group having 1 to 5 nitrogen atoms, such as indolyl, isoindolyl, 3H-indolyl, indolizinyl, benzimidazolyl, quinolyl, isoquinolyl, indazolyl, phthalazinyl, naphthyridinyl, quinoxalinyl, quinazolinyl, cinnolinyl, benzotriazolyl, tetrazolopyridazinyl (e.g., tetrazolyl[1,5-bipyridazinyl]), pteridinyl, carbazolyl, phenanthridinyl, acridinyl, and perimidinyl; 3- to 6-membered unsaturated heterocyclic group having 1 to 3 nitrogen atoms and 1 or 2 oxygen atoms, such as oxazolyl, isoxazolyl, oxadiazolyl (e.g., 1,2,4-oxadiazolyl, 1,3,4-oxadiazolyl, 1,2,5-oxadiazolyl); 3- to 6-membered saturated heterocyclic group having 1 to 3 nitrogen atoms and 1 or 2 oxygen atoms, such as morpholinyl, and sydnonyl; unsaturated condensed heterocyclic group having 1 to 3 nitrogen atoms and 1 or 2 oxygen atoms, such as benzofurazanyl, benzoxazolyl, benzoxazinyl, benzoxadiazolyl; 3- to 6-membered unsaturated condensed heterocyclic group having 1 to 3 nitrogen atoms and 1 or 2 sulfur atoms, such as thiazolyl, isothiazolyl, thiadiazolyl (e.g., 1,2,4-thiadiazolyl, 1,3,4-thiadiazolyl, 1,2,5-thiadiazolyl); 3- to 6-membered saturated heterocyclic group having 1 to 3 nitrogen atoms and 1 or 2 sulfur atoms, such as thiadizolidinyl;
unsaturated condensed heterocyclic group having 1 to 3 nitrogen atoms and 1 or 2 sulfur atoms, such as benzothiazolyl, and benzothiadiazolyl;
3- to 6-membered unsaturated heteromonocyclic group having 1 oxygen atom, such as furyl, and pyranyl;
3- to 6-membered unsaturated heteromonocyclic group having 1 or 2 sulfur atoms, such as thieryl, and dihydrothienyl;
unsaturated condensed heterocyclic group having 1 or 2 sulfur atoms, such as benzothienyl.

[0025] The above-mentioned "heterocyclic group" and "aryl" are optionally substituted by one or more substituents. Examples of the substituent include hydroxyl, halogen, alkyl optionally substituted by halogen, aralkyl, aliphatic carboxylic acid residue, aromatic carboxylic acid residue, acyloxy, arroyloxy, alkoxy, aryloxy, aliphatic alcohol residue, aromatic alcohol residue, aliphatic aldehyde, aromatic aldehyde, amino, aliphatic amino, and aromatic amino. The substituent of heterocyclic group may be aryl.

[0026] The "hetero atom" is exemplified by nitrogen, oxygen and sulfur. The number of hetero atom is preferably 2.

[0027] The 4- to 7-membered ring moiety of the "optionally substituted 4- to 7-membered ring" is cycloalkyl and heterocyclic group, preferably heterocyclic group.

[0028] Preferable heterocyclic group includes thieryl, furyl, pyrrolyl, imidazolyl, pyrazolyl, thiazolyl, isothiazolyl, oxazolyl, isoxazolyl, oxadiazolyl, thiadiazolyl, triazolyl, pyridyl, pyrazinyl, pyrimidinyl, triazinyl, dithiazolyl, dioxolanyl, dithiolanyl, pyrrolidinyl, thiazolinyl, dithiadiazinyl, morpholinyl, oxazinyl, thiazinyl, piperezinyl, piperdinyl, pyranyl, and thiopyranyl.

[0029] The substituent for the 4- to 7-membered ring is exemplified by lower alkyl (e.g., those having 1 to 4 carbon atoms, such as methyl, ethyl, propyl, isopropyl, etc.).

[0030] R1, R2, R3, R4 and R5 can be a substituent of any ring of any of the condensed ring in the formula (I).

[0031] With regard to the "optionally substituted CH", by optionally substituted is meant that the group may be substituted by any of R1 to R5.

[0032] When two or more of X, Y and Z are nitrogen atoms at the same time, the total number of the substituents may be 4 or less.

[0033] Examples of the pyridonecarboxylic acid include enoxacin: [1-ethyl-6-fluoro-1,4-dihydro-4-oxo-7-(1-piperazinyl)-1,8-naphthyridine-3-carboxylic acid], ofloxacin: [5-amino-1-cyclopropyl-7-(cis-3,5-dimethyl-1-piperazinyl)-6,8-difluoro-1,4-dihydro-4-oxo-3-quinolinecarboxylic acid], sparflloxacin: [5-amino-1-cyclopropyl-7-(cis-3,5-dimethyl-1-piperazinyl)-6,8-difluoro-1,4-dihydro-4-oxo-3-quinolinecarboxylic acid], tosflloxacin: [(±)-7-(3-amino-1-pyrrolidinyl)-1-(2,4-difluorophenyl)-6-fluoro-1,4-dihydro-4-oxo-1,8-naphthyridine-3-carboxylic acid], levofloxacin: [6,8-difluoro-1-[2-fluoroethyl]-1,4-dihydro-7-(4-methyl-1-piperazinyl)-4-oxo-3-quinolinecarboxylic acid], flocloxacin: [6,8-difluoro-1-[2-fluoroethyl]-1,4-dihydro-7-(4-methyl-1-piperazinyl)-4-oxo-3-quinolinecarboxylic acid], floxacin: [6,8-difluoro-1-[2-fluoroethyl]-1,4-dihydro-7-(4-methyl-1-piperazinyl)-4-oxo-3-quinolinecarboxylic acid], norfloxacin: [1-ethyl-6-fluoro-1,4-dihydro-4-oxo-7-(1-piperazinyl)-3-quinolinecarboxylic acid], ciprofloxacin: [1-cyclopropyl-6-fluoro-1,4-dihydro-4-oxo-7-(1-piperazinyl)-3-quinolinecarboxylic acid], piperacillin: [1-ethyl-6-fluoro-1,4-dihydro-4-oxo-7-(1-piperazinyl)-3-quinolinecarboxylic acid], lomefloxacin: [1-ethyl-6-fluoro-1,4-dihydro-4-oxo-7-(1-piperazinyl)-3-quinolinecarboxylic acid], and drugs such as amoxicillin, penicillin, oxytetracycline, erythromycin, and the like.

[0034] The pharmacologically acceptable salts of pyridonecarboxylic acid are, for example, acid addition salts with inorganic acids such as hydrochloric acid, sulfuric acid, phosphoric acid, with organic acids such as acetic acid, lactic acid, succinic acid, methanesulfonic acid, maleic acid, malonic acid, gluconic acid, p-toluenesulfonic acid, or with amino acids such as aspartic acid, glutamic acid; alkali metal salts such as sodium salt, potassium salt. The above-mentioned "heterocyclic group" and "aryl" may be substituted by any of R1 to R5.

[0035] The pharmacologically acceptable salts of pyridonecarboxylic acid include, for example, acid addition salts with inorganic acids such as hydrochloric acid, sulfuric acid, phosphoric acid, with organic acids such as acetic acid, lactic acid, succinic acid, methanesulfonic acid, maleic acid, malonic acid, gluconic acid, p-toluenesulfonic acid, or with amino acids such as aspartic acid, glutamic acid; alkali metal salts such as sodium salt, potassium salt.

[0036] The salt of glycyrrhizic acid may be alkali metal salt, such as sodium salt, potassium salt, alkaline earth metal salt, such as magnesium salt, calcium salt.

[0037] The amount of glycyrrhizic acid to be added to pyridonecarboxylic acid or a pharmacologically acceptable salt thereof is preferably about 0.001 - 100 parts by weight, more preferably about 0.001 - 10 parts by weight, per part by weight of pyridonecarboxylic acid or a pharmacologically acceptable salt thereof.

[0038] The solubilizer for pyridonecarboxylic acid and a pharmacologically acceptable salt thereof contains glycyrrhizic acid or a salt thereof as a active ingredient.

[0039] The solvent to be used for the aqueous solution of the present invention is purified water, and distilled water for injection is particularly preferable. The concentration of pyridonecarboxylic acid in the aqueous solution is strikingly increased to generally not less than 0.5 (w/w)%, preferably not less than 5.0 (w/w)%, particularly preferably 10 (w/w)%, by the addition of glycyrrhizic acid or a salt thereof.

[0040] This aqueous solution may contain various additives as appropriate, such as buffer, isotonication agent, sol-
Examples of the buffer include phosphate buffer, borate buffer, citrate buffer, tartrate buffer, acetate buffer, and amino acid.

Examples of the isotonication agent include sugars such as sorbitol, glucose, mannitol etc., polyhydric alcohols such as glycerol, propylene glycol, salts such as sodium chloride.

Examples of the solubilizer include nonionic surfactants such as polyoxyethylenesorbitan monooleate, polyoxyethyleneoxystearic acid triglyceride, polyethyleneglycol, polyoxyethylene hydrogenated castor oil.

Examples of the antiseptic include quaternary ammonium salts such as benzalkonium chloride, benzethonium chloride, cetylpyridinium chloride, p-hydroxybenzoates such as methyl p-hydroxybenzoate, ethyl p-hydroxybenzoate, propyl p-hydroxybenzoate, butyl p-hydroxybenzoate etc., benzyl alcohol, phenylethyl alcohol, sorbic acid, salts thereof, thimerosal, chlorobutanol, and sodium dehydroacetate.

Examples of the thickener include polyvinylpyrrolidone, hydroxyethylcellulose, hydroxypropylcellulose, methylcellulose, hydroxypropylmethylcellulose, carboxymethylcellulose, salts thereof.

Examples of the chelating agent include sodium edetate, and citric acid.

Examples of the aromatic include 1-menthol, borneol, camphor, and eucalyptus oil.

The aqueous solution of the present invention is preferably used as an eye drop, nasal drop or ear drop. When it is used as an eye drop, its pH is generally adjusted to about 3.5-8.5, preferably about 6-8; when it is used as a nasal drop, its pH is generally adjusted to about 3.5-8.5, preferably about 6-8; and when it is used as an ear drop, its pH is generally adjusted to about 3.5-8.5, preferably about 6-8.

The method for producing the aqueous solution of the present invention is similar to the solubilization of pyridonecarboxylic acid and a pharmacologically acceptable salt thereof mentioned earlier. The above-mentioned various additives can be added during a suitable step.

When the aqueous solution of the present invention is used as an eye drop, for example, the dose thereof need only be sufficient to effectively suppress inflammation in the eye, and may vary according to symptoms, the kind of inflammation, the patients in need of the liquid preparation, the kind of animal, and the like. Atypical dose is 20-200 µg/dose, preferably 50-100 µg/dose, which may be administered 1 to 12 times a day.

The present invention is described in more detail by way of Experimental Example and Example.

**Experimental Example**

Effect of glycyrrhizic acid and a salt thereof on the solubility of pyridonecarboxylic acid

To a 1.6% aqueous boric acid solution (100 ml) containing 0.1% dipotassium glycyrrhizinate was added an excess lomefloxacin hydrochloride, and the pH was adjusted to 7 with sodium hydroxide. To an aqueous phosphoric acid solution (isotonized with sodium chloride) containing 0.1% dipotassium glycyrrhizinate was added an excess ofloxacin, and the pH was adjusted to 7 with sodium hydroxide. These solutions were shaken at 25°C for about one week and filtered through a 0.45 µm membrane filter. The contents of lomefloxacin hydrochloride and ofloxacin were measured by high performance liquid chromatography. The results are shown in Table 1.

<table>
<thead>
<tr>
<th>Drug name</th>
<th>Solubility (mg/ml)</th>
<th>without addition</th>
<th>Incorporating 0.1% dipotassium glycyrrhizinate</th>
</tr>
</thead>
<tbody>
<tr>
<td>lomefloxacin hydrochloride</td>
<td>1.10 (n=2)</td>
<td>2.98 (n=2)</td>
<td></td>
</tr>
<tr>
<td>ofloxacin</td>
<td>5.16 (n=1)</td>
<td>9.42 (n=1)</td>
<td></td>
</tr>
</tbody>
</table>

n: number of sample

As is evident from Table 1, the incorporation of 0.1% dipotassium glycyrrhizinate resulted in about 3 times higher solubility of lomefloxacin hydrochloride and about 2 times higher solubility of ofloxacin, demonstrating a striking solubilizing effect afforded by 0.1% dipotassium glycyrrhizinate.

**Example**

An eye drop was prepared according to the following recipe

Lomefloxacin hydrochloride (0.3 g) was added to water (100 ml) and the mixture was adjusted to pH 3 with hydrochloric acid to dissolve lomefloxacin hydrochloride. Thereto was added dipotassium glycyrrhizinate (0.1 g) and the mixture was adjusted to pH 7 with sodium hydroxide.
This solution was free of precipitation of crystals after storage at room temperature for 3 days. When dipotassium glycyrrhizinate was not added, crystals precipitated after storage at room temperature for about 1 hr to 1 day.

<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>lomefloxacin hydrochloride</td>
<td>0.3 g</td>
</tr>
<tr>
<td>dipotassium glycyrrhizinate</td>
<td>0.1 g</td>
</tr>
<tr>
<td>boric acid</td>
<td>1.6 g</td>
</tr>
<tr>
<td>sodium hydroxide</td>
<td>appropriate amount</td>
</tr>
<tr>
<td>hydrochloric acid</td>
<td>appropriate amount</td>
</tr>
<tr>
<td>sterile purified water</td>
<td>appropriate amount</td>
</tr>
<tr>
<td>total amount</td>
<td>100 ml</td>
</tr>
<tr>
<td>pH</td>
<td>7.0</td>
</tr>
</tbody>
</table>

Industrial Applicability

According to the solubilizing method of the present invention, the solubility of pyridonecarboxylic acid compound and salts thereof at near physiological pH can be increased. Therefore, these compounds can be prepared into an aqueous solution to be applied as an eye drop, a nasal drop and an ear drop.

This application is based on application No. 265523/1998 filed in Japan, the contents of which are incorporated hereinto by reference.

Claims

1. A method for solubilizing (a) a pyridonecarboxylic acid of the formula (I)

\[
\begin{align*}
\text{O} & \quad \text{CO}_2\text{H} \\
\text{R}_1 & \quad \text{X} \\
\text{R}_2 & \quad \text{Z} \\
\text{R}_3 & \quad \text{Y} \\
\text{R}_4 & \quad \text{N} \\
\text{R}_5 & \\
\end{align*}
\]

wherein \(X, Y \) and \(Z\) may be the same or different and each is nitrogen atom or optionally substituted CH, and \(R_1, R_2, R_3, R_4, R_5\) may be the same or different and each is hydrogen atom, halogen, carboxyl group, optionally substituted lower alkyl, optionally substituted cycloalkyl, optionally substituted acyl, optionally substituted aryl or optionally substituted heterocyclic group, or at least two members selected from \(R_1, R_2, R_3, R_4, R_5\) in combination form an optionally substituted 4- to 7-membered ring via or not via a hetero atom or (b) sparfloxacin or a pharmacologically acceptable salt thereof, comprising incorporating glycyrrhizic acid or a salt thereof and the (a) pyridonecarboxylic acid or (b) sparfloxacin or a pharmacologically acceptable salt thereof.

2. The method according to claim 1, which comprises adding the (a) pyridonecarboxylic acid of the formula (I) or (b) sparfloxacin or a pharmacologically acceptable salt thereof to water, adjusting pH to not more than 3, adding glycyrrhizic acid or a salt thereof and adjusting pH of the aqueous solution to 3.5 - 8.5.

3. The method according to claim 1, wherein the (a) pyridonecarboxylic acid of the formula (I) is a compound selected from the group consisting of lomefloxacin, norfloxacin, enoxacin, ofloxacin, ciprofloxacin, tosufloxacin, fleroxacin, cinoxacin and levofloxacin.

4. An aqueous solution comprising (a) a pyridonecarboxylic acid of the formula (I)
wherein X, Y and Z may be the same or different and each is nitrogen atom or optionally substituted CH, and R₁, R₂, R₃, R₄ and R₅ may be the same or different and each is hydrogen atom, halogen, carboxyl group, optionally substituted lower alkyl, optionally substituted cycloalkyl, optionally substituted acyl, optionally substituted aryl or optionally substituted heterocyclic group, or at least two members selected from R₁, R₂, R₃, R₄ and R₅ in combination form an optionally substituted 4- to 7-membered ring via or not via a hetero atom or (b) sparfloxacin or a pharmacologically acceptable salt thereof, and glycyrrhizic acid or a salt thereof.

5. The aqueous solution of claim 4, which is in the form of an eye drop, nasal drop or ear drop.

**Patentansprüche**

1. Verfahren zum Löslichmachen (a) einer Pyridoncarbonsäure der Formel (I)

2. Verfahren gemäß Anspruch 1, das das Zufügen der (a) Pyridoncarbonsäure der Formel (I) oder (b) von Sparfloxacin oder eines pharmakologisch annehmbaren Salzes davon zu Wasser, Einstellen des pH auf nicht mehr als 3, Zufügen von Glyzyrrhizinsäure oder eines Salzes davon und Einstellen des pH der wäßrigen Lösung auf 3,5-8,5 umfaßt.

3. Verfahren gemäß Anspruch 1, wobei die Pyridoncarbonsäure der Formel (I) (a) eine Verbindung ist, die aus der aus Lomefloxacin, Norfloxacin, Enoxacin, Ofloxacin, Ciprofloxacin, Tosufloxacin, Fleroxacin, Cinoxacin und Levofoxacin bestehenden Gruppe ausgewählt ist.

4. Wäßrige Lösung umfassend (a) eine Pyridoncarbonsäure der Formel (I)
worin X, Y und Z gleich oder verschieden sein können und jeweils ein Stickstoffatom oder gegebenenfalls substituiertes CH sein können und R<sub>1</sub>, R<sub>2</sub>, R<sub>3</sub>, R<sub>4</sub> und R<sub>5</sub> gleich oder verschieden sein können und jeweils ein Wasserstoffatom, Halogen, eine Carboxygruppe, eine gegebenenfalls substituierte Niederalkyl-, gegebenenfalls substituierte Cycloalkyl-, gegebenenfalls substituierte Acyl-, gegebenenfalls substituierte Aryl- oder gegebenenfalls substituierte heterocyclische Gruppe sind oder wenigstens zwei von R<sub>1</sub>, R<sub>2</sub>, R<sub>3</sub>, R<sub>4</sub> und R<sub>5</sub> in Kombination einen gegebenenfalls substituierten 4- bis 7gliedrigen Ring über ein oder über kein Heteroatom bilden oder (b) Sparfloxacain oder ein pharmakologisch annehmables Salz davon umfaßt.

5. Wäßrige Lösung des Anspruchs 4, die in Form von Augentropfen, Nasentropfen oder Ohrentropfen vorliegt.
dans laquelle X, Y et Z peuvent être identiques ou différents et chacun est un atome dazote ou un groupe CH éventuellement substitué, et R₁, R², R³ et R⁵ peuvent être identiques ou différents et chacun est un atome dhydrogène, un halogène, un groupe carboxyle, un groupe alkyle inférieur éventuellement substitué, un groupe cycloalkyle éventuellement substitué, un groupe acyle éventuellement substitué, un groupe aryle éventuellement substitué ou un groupe hétérocyclique éventuellement substitué, ou au moins deux éléments choisis parmi R₁, R², R³, R⁴ et R⁵ en combinaison forment un cycle de 4 à 7 chaînons éventuellement substitué par l'intermédiaire ou non d'un hétéroatome ou (b) de la sparfloxacine ou un sel pharmaceutiquement acceptable de celle-ci, et de l'acide glycyrrhizique ou un sel de celui-ci.

5. Solution aqueuse selon la revendication 4, qui est sous la forme de gouttes oculaires, de gouttes nasales ou de gouttes auriculaires.