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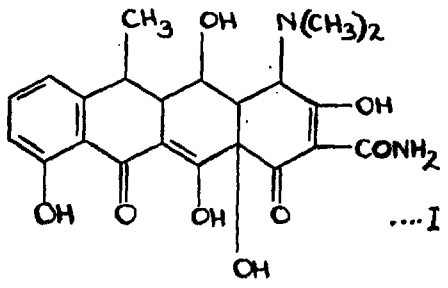
(54) DOXYCYCLINE SOLUTION FOR PARENTERAL, ORAL AND TOPICAL USE

(71) We, PFIZER CORPORATION, a Corporation organized under the laws of the Republic of Panama of Calle 15½, Avenida Santa Isabel, Colon, Republic of Panama, do hereby declare the invention, for which we pray that a Patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

The present invention relates to an aqueous doxycycline solution for parenteral, oral, and topical use, which is characterized in that it contains doxycycline in the form of the free base or of its pharmaceutically acceptable salts, polyvinylpyrrolidone, and water and exhibits a pH value of 5 to 8, as well as a process for the production of this solution.

"Doxycycline" is, as is known, the chemical abbreviation for alpha - 6 - deoxy - 5 - hydroxytetracycline, a bio-synthetic broad-spectrum antibiotic of the following formula:



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The activity spectrum of doxycycline comprises, as is known, the majority of the gram-positive and gram-negative bacteria (aerobics and anaerobics). The usefulness of this valuable antibiotic was, however, restricted until now by the fact that it has not been possible to produce solutions that are tolerated. Thus, doxycycline could not be administered in solution parenterally heretofore because, although solutions could be produced in the highly acid or alkaline range, these solutions were not physically stable nor were they tolerated topically.

The addition of polyvinylpyrrolidone to medicaments is known in several forms. Thus, polyvinylpyrrolidone has been used as depot substance for hormones, antibiotics, and alkaloids. Also, it has been added, as vehicle for the active substances, to a mixture of a penicillin derivative and of the circulatory hormone kallikrein. Further, there have been prepared easily soluble dry preparations of medicaments, such as vitamins or hormones, by means of polyvinylpyrrolidone.

In addition, polyvinylpyrrolidone has already been used as a solubilizer for polypeptide antibiotics, such as gramicidin, tyrocidine, and tyrothricin. Lastly, there is known a method for the production of aqueous oxytetracycline solutions, where the oxytetracycline is dissolved or suspended in water containing polyvinylpyrrolidone, a magnesium compound is added, and the solution is adjusted to a pH value of 8.0 to 9.5.

In the attempt to extend this known method to doxycycline, however, one does not obtain a solution.

Likewise, it had not been possible before to extend to doxycycline a method for the production of injectable oxytetracycline solutions by means of magnesium ions, sodium bisulfite, and a physiologically tolerated, water-soluble, substituted amide of a carboxylic acid, and this neither at a pH value of 8 to 9.5 adopted for oxytetracycline, but at which no solution is formed with doxycycline, nor at a pH value of 5 to 8, at which the doxycycline solution is topically not tolerated and is relatively unstable.

It was, therefore, highly surprising that the aqueous doxycycline solution according to the invention, which contains polyvinylpyrrolidone and water along with doxycycline and exhibits a pH value of 5 to 8, is relatively stable and topically well tolerated.

The process for the production of aqueous solutions for the parenteral, oral, and topical

use of doxycycline is characterized in that doxycycline in the form of the free base or of the pharmaceutically acceptable salts is dissolved in water together with polyvinylpyrrolidone at a pH value of 5 to 8.

Either the mixed substances in powder form can be dissolved shortly before the administration, or a stable solution ready for injection can be produced and kept in stock. In the latter case, it is advantageous to add a water-soluble magnesium compound, e.g., magnesium oxide, magnesium chloride, magnesium ascorbate, magnesium lactate, or magnesium gluconate.

If doxycycline is used in the form of its pharmaceutically acceptable salts, the pH value is advantageously adjusted with a base, in particular an organic base.

Examples of doxycycline salts are the hydrochloride, sulfate, nitrate, ascorbate, citrate, gluconate, lactate, isonicotinate, gentisinate, pantothenate, salicylate, glucuronate, formate, or glutamate. As used herein the term "base" refers to the organic bases tris-hydroxymethyl-aminomethane, amino-ethanol, dimethylamino-ethanol, diethylaminoethanol, dimethyl-amine, trimethylamine, diethylamine, triethylamine, or also ammonia or sodium hydroxide.

Tris-hydroxymethyl-aminomethane is suitable especially when the mixed pulverized substances are to be dissolved only shortly before application. The polyvinylpyrrolidone and possibly also the water-soluble magnesium compound may then be added to a special "solvent ampoule."

Even when doxycycline is used in the form of the free base and additionally contains magnesium chloride, for example, it may prove to be necessary to add a base for the adjustment of the pH value.

In most cases where doxycycline is used in the form of the free base, and in some cases where doxycycline salts and magnesium oxide are used, the pH value is advantageously adjusted by an acid, preferably an organic acid. As used herein the term "acid" refers to ascorbic acid, tartaric acid, lactic acid, formic acid, acetic acid, glucuronic acid, gluconic acid, gentistic acid, isonicotinic acid, glutamic acid, and also hydrochloric acid.

Ascorbic acid is especially preferred because it acts additionally as an anti-oxidant. Alternatively, anti-oxidants, such as formaldehyde sulfoxylates or sodium metabissulfite, may be added additionally in quantities of 0.1 to 1% with respect to the weight of the total composition of the solution.

As polyvinylpyrrolidone, there may be used commercial grades for parenteral pharmaceutical preparations of suitable purity having an average molecular weight of 10,000 to 60,000, preferably 10,000 to 17,000. Especially suited for parenteral use is a polyvinylpyrrolidone having an average molecular weight of 13,000. The concentration of the polyvinylpyrrolidone in the solution is 5 to 40%, preferably 10 to 25%, by weight of total composition.

The concentration of doxycycline in the solution may be 1 to 15%, by weight of total composition.

The molar ratio of magnesium to doxycycline may be 0.5 : 1 to 5 : 1. A ratio of 2 : 1 is preferred.

The "K-value" referred to in the Examples is a viscosity coefficient related to the average molecular weight of polymeric compositions.

The following Examples will illustrate the invention:

All percentages are by weight of total composition.

Example 1

(a) 0.200 Grams of doxycycline hydrochloride is intimately mixed with 0.120 g. of ascorbic acid and 1.400 g. of polyvinylpyrrolidone and 0.320 g. of tris-hydroxymethylaminomethane. The powder thus obtained is diluted with water to make 10 ml. of solution shortly before application. The solution has a pH value of 7.8.

(b) The polyvinylpyrrolidone (PVP) may alternatively be added to the "solvent ampoule."

Example 2

0.216 Grams of doxycycline hydrochloride is intimately mixed with 1.400 g. of polyvinylpyrrolidone and 0.120 g. of tris-hydroxymethyl - aminomethane. In a separate "solvent ampoule", 0.185 g. of magnesium chloride ($MgCl_2 . 6H_2O$) is dissolved in 8.5 ml. of water. Shortly before application, a solution is prepared by combining the two mixtures. The solution has a pH value of 5.5.

Example 3

In 5.0 g. of a 30% by weight aqueous polyvinylpyrrolidone solution (average molecular weight about 13,000), there is dissolved 0.185 g. of magnesium chloride ($MgCl_2 . 6H_2O$). In this solution, 0.200 g. of doxycycline base is suspended and adjusted to a pH value of 5 to 6, while stirring and slowly adding 2-aminoethanol. At this point, the doxycycline goes into solution. The product is diluted with water to make 10 ml. of solution. The solution has a pH value of 5.5.

Example 4

In 3.34 g. of a 30% by weight aqueous PVP solution (K value=17), there are suspended 0.0363 g. of magnesium oxide and 0.287 g. of doxycycline glucuronate. By slow addition of about 0.175 g. of glucuronic acid, the pH value of the solution is adjusted to 5.4 to 5.6. At this point the doxycycline goes into solution. One then dilutes with water to make 5.0 ml. of solution. The polyvinyl-

pyrrolidone content of the solution is then 20%.

EXAMPLE 5

In 3.34 g. of a 30% PVP solution (K value=17), there are suspended 0.0363 g. of magnesium oxide and 0.288 g. of doxycycline gluconate. By slow addition of about 3.6 g. of a 49% gluconic acid solution, the pH value is adjusted to 5.5 to 5.7, the doxycycline going into solution. Finally, one dilutes with water to make 10.0 ml. of solution.

EXAMPLE 6

0.279 Grams of doxycycline ascorbate and 0.0363 g. of magnesium oxide are suspended in 3.34 g. of a 30% by weight aqueous PVP solution (K value=17). By slow addition of about 0.158 g. of ascorbic acid, the pH value is adjusted to 5.4 to 5.6, the doxycycline going into solution. Subsequently, one dilutes with water to make 5.0 ml. of solution.

EXAMPLE 7

In 3.34 g. of a 30% by weight aqueous PVP solution (K value=17), there are suspended 0.269 mg. of doxycycline gentisinate and 0.0363 g. of magnesium oxide. Subsequently, the pH value is adjusted to 5.2 to 5.4 with about 0.138 g. of gentisic acid, the doxycycline going into solution. One then dilutes with water to make 5.0 ml. of solution

EXAMPLE 8

0.216 Grams of doxycycline hydrochloride and 0.183 g. of magnesium chloride-hexahydrate are suspended in 2.17 g. of a 20% by weight aqueous PVP solution (K value=17). With about 0.06 g. of monoetholamine, the pH value is gradually brought to 5.4 to 5.6, the doxycycline going into solution. Subsequently, 0.02 g. of sodium formaldehyde sulfoxylate are dissolved in the mixture as antioxidant. Lastly, one dilutes with water to make 3.0 ml. of solution.

If the solution is intended for intramuscular application, there may be incorporated into the solution additionally 2% of a suitable local anaesthetic (e.g., N,N - diethylamino-2,6-dimethylacetanilide).

EXAMPLE 9

In 3.34 g. of a 30% by weight aqueous PVP solution (K value=17), there are suspended 0.240 g. of doxycycline lactate and 0.363 g. of magnesium oxide. With about 0.137 g. of a 90% lactic acid, the pH value is slowly adjusted to 5.0, the doxycycline going into solution. Then one dilutes with water to make 5.0 ml. of solution

EXAMPLE 10

0.200 Grams of doxycycline base and 0.389 g. of magnesium gluconate are suspended in 3.34 g. of a 30% by weight aqueous PVP solution (K value=17). With monoethanolamine the pH value is slowly adjusted to 5.6 to 5.8, the doxycycline going into solution. As antioxidant, 0.020 g. of sodium metabisulfite is dissolved in the mixture. Then one dilutes with water to make 5.0 ml. of solution.

EXAMPLE 11

0.217 Grams of doxycycline hydrochloride is intimately mixed with 0.389 g. of magnesium gluconate, 0.123 g. of tris-hydroxymethyl - aminomethane, 1.40 g. of polyvinylpyrrolidone (K value=17) and 0.020 g. of sodium metabisulfite. The powder mixture is filled up to 10 ml. shortly before the injection with sterile, pyrogen-free water, and dissolved. The pH value of the solution is 5.5 to 5.6.

The polyvinylpyrrolidone and the sodium metabisulfite may alternatively be contained in the "solvent ampoule" separately.

EXAMPLE 12

0.220 Grams of doxycycline formate and 0.0363 g. of magnesium oxide are suspended in 3.34 g. of a 30% by weight aqueous PVP solution (K value=17). With about 0.042 g. of formic acid, the pH value is brought to 5.1 to 5.2, the doxycycline going into solution. Subsequently, one dilutes with water to make 5.0 ml. of solution.

EXAMPLE 13

In 3.34 g. of a 30% by weight aqueous PVP solution (K value=17), there are suspended 0.255 g. of doxycycline isonicotinate and 0.0363 g. of magnesium oxide. With about 0.111 g. of isonicotinic acid, the pH value of the solution is adjusted to 5.7 to 5.9, the doxycycline gradually going into solution. Water is then added to make 5.0 ml. of solution.

EXAMPLE 14

0.266 Grams of doxycycline glutamate are suspended with 0.0363 g. of magnesium oxide in 3.34 g. of a 30% by weight aqueous PVP solution (K value=17). Then the pH value is brought to 5.6 to 5.8 with about 0.133 g. of glutamic acid. At this point, the doxycycline dissolves. Lastly, water is added to make 5.0 ml. of solution.

EXAMPLE 15

0.183 Grams of magnesium chloride-hexahydrate is dissolved in 3.34 g. of a 30% by weight aqueous PVP solution (K value=17). Subsequently, 0.200 g. of doxycycline base is suspended and the pH value is adjusted to 5 to 6 by addition of monoethanolamine. At this point, the doxycycline dissolves. The volume is then brought to 5.0 ml. with water.

EXAMPLE 16

0.200 Grams of doxycycline base and 0.0363 of magnesium oxide are suspended in a 30% by weight aqueous PVP solution (mean molecular weight, about 13,000), whereupon the pH value is adjusted with a suitable acid (see Examples 4 to 7, 9, 12, 13, 14) to 5 to 7. The resulting solution of the doxycycline - magnesium compound is subsequently diluted with water to make 5.0 ml. of solution.

EXAMPLE 17

In 5 g. of a 30% by weight aqueous PVP solution (K value=17), there are suspended 0.0458 g. of magnesium chloride-hexahydrate and 0.054 g. of doxycycline hydrochloride. Then the pH value is adjusted to 5.5 to 5.7 with about 0.020 g. of monoethanolamine. At this point, the doxcycline goes into solution. The solution is then diluted with water to make 10.0 ml. of solution.

The solution contains 5 mg. of doxycycline per ml. and serves for topical application on the eye and in the ear.

EXAMPLE 18

In 3.34 g. of a 30% by weight aqueous PVP solution (K value=17), dissolve 0.183 g. of magnesium chloridehexahydrate and suspend 0.216 g. of doxycycline hydrochloride. By adjusting the pH value to 5.5 to 5.7 with about 0.055 g. of monoethanolamine, the doxycycline goes into solution. Then water is added to make 5 ml. of solution.

WHAT WE CLAIM IS:—

1. An aqueous doxycycline (alpha - 6 - deoxy - 5 - hydroxytetracycline) solution for parenteral, oral, and topical use, containing doxycycline in the form of the free base or of its pharmaceutically acceptable acid addition salts, polyvinylpyrrolidone, and water, and having a pH of 5 to 8.

2. An aqueous doxycycline solution according to claim 1, containing doxycycline in the form of a pharmaceutically acceptable acid addition salt and additionally a base, preferably an organic base, as herein defined.

3. An aqueous doxycycline solution according to claim 1, containing doxycycline in the form of the free base and additionally an acid as herein defined, preferably ascorbic acid.

4. An aqueous doxycycline solution according to claims 1 to 3, containing additionally a water-soluble magnesium compound.

5. An aqueous doxycycline solution according to claims 1 to 4, containing a polyvinylpyrrolidone having an average molecular weight of from 10,000 to 60,000, preferably from 10,000 to 17,000.

6. Process for the production of aqueous solutions for parenteral, oral, and opical use of doxycycline according to claim 1, wherein doxycycline in the form of the free base or of its pharmaceutically acceptable acid addition salts, together with polyvinylpyrrolidone, is dissolved in water at a pH of 5 to 8.

7. Process according to claim 6, wherein the pharmaceutically acceptable acid addition salts of doxycycline is dissolved in the presence of a base, preferably an organic base, as herein defined.

8. Process according to claim 6, wherein when using the free base, the pH is adjusted by means of an acid as herein defined, preferably ascorbic acid.

9. A process for preparing aqueous solutions of doxycycline according to claim 6, substantially as described.

10. Aqueous solutions of doxycycline according to claim 1, whenever prepared by the process substantially as described.

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EXAMPLE 16

0.200 Grams of doxycycline base and 0.0363 of magnesium oxide are suspended in a 30% by weight aqueous PVP solution (mean molecular weight, about 13,000), whereupon the pH value is adjusted with a suitable acid (see Examples 4 to 7, 9, 12, 13, 14) to 5 to 7. The resulting solution of the doxycycline - magnesium compound is subsequently diluted with water to make 5.0 ml. of solution.

EXAMPLE 17

In 5 g. of a 30% by weight aqueous PVP solution (K value=17), there are suspended 0.0458 g. of magnesium chloride-hexahydrate and 0.054 g. of doxycycline hydrochloride. Then the pH value is adjusted to 5.5 to 5.7 with about 0.020 g. of monoethanolamine. At this point, the doxcycline goes into solution. The solution is then diluted with water to make 10.0 ml. of solution.

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EXAMPLE 18

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WHAT WE CLAIM IS:—

1. An aqueous doxycycline (alpha - 6 - deoxy - 5 - hydroxytetracycline) solution for parenteral, oral, and topical use, containing doxycycline in the form of the free base or of its pharmaceutically acceptable acid addition salts, polyvinylpyrrolidone, and water, and having a pH of 5 to 8.

2. An aqueous doxycycline solution according to claim 1, containing doxycycline in the form of a pharmaceutically acceptable acid addition salt and additionally a base, preferably an organic base, as herein defined.

3. An aqueous doxycycline solution according to claim 1, containing doxycycline in the form of the free base and additionally an acid as herein defined, preferably ascorbic acid.

4. An aqueous doxycycline solution according to claims 1 to 3, containing additionally a water-soluble magnesium compound.

5. An aqueous doxycycline solution according to claims 1 to 4, containing a polyvinylpyrrolidone having an average molecular weight of from 10,000 to 60,000, preferably from 10,000 to 17,000.

6. Process for the production of aqueous solutions for parenteral, oral, and opical use of doxycycline according to claim 1, wherein doxycycline in the form of the free base or of its pharmaceutically acceptable acid addition salts, together with polyvinylpyrrolidone, is dissolved in water at a pH of 5 to 8.

7. Process according to claim 6, wherein the pharmaceutically acceptable acid addition salts of doxycycline is dissolved in the presence of a base, preferably an organic base, as herein defined.

8. Process according to claim 6, wherein when using the free base, the pH is adjusted by means of an acid as herein defined, preferably ascorbic acid.

9. A process for preparing aqueous solutions of doxycycline according to claim 6, substantially as described.

10. Aqueous solutions of doxycycline according to claim 1, whenever prepared by the process substantially as described.

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