PATENT SPECIFICATION

(11) 1 520 197

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(21) Application No. 52394/76 (22) Filed 15 Dec. 1976
(31) Convention Application No. 646295
(32) Filed 2 Jan. 1976 in
(33) United States of America (US)
(44) Complete Specification published 2 Aug. 1978
(51) INT CL² A61K 31/65 (A61K 31/40)
(52) Index at acceptance
A5B 215 21Y 503 50Y 541 54Y 565 56Y

(19)



(54) STABLE ANTIBIOTIC COMPOSITIONS

(71) We, PFIZER INC. a Corporation organized and existing under the laws of the State of Delaware, United States of America, of 235 East 42nd Street, New York, State of New York, United States of America, 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:—

This invention relates to antibiotic compositions suitable for pharmaceutical use. More particularly, it relates to aqueous oxytetracycline, doxycycline, tetracycline and chlortetracycline solutions containing 2-pyrrolidone.

Previous efforts made to prepare stable high concentration solutions of these tetacycline-type compounds have been unsuccessful. This is of particular importance in the case of veterinary parenteral compositions for administration to large animals.

Japanese Patent Publication No. Sho 47—303 discloses stable aqueous solutions of p-biphenylmethyl (dl-tropyl-α-tropinium) bromide, 2.5%, in which 2-pyrrolidone is present in a concentration of 20%. The use of polyvinylpyrrolidone at a concentration of 30% is also disclosed. The pH of these solutions is less than 7, the preferred range being 3—4.

Japanese Patent Publication No. Sho 43—1758 discloses insecticidal solutions containing hexachlorocyclohexane in alcohol and 2-pyrrolidone as solvents. The use of N-methylpyrrolidone as a co-solvent is also disclosed.

British Patent Specification No. 802,111 discloses pesticidal compositions containing 2-pyrrolidone or N-methylpyrrolidone as solvents for DDT, Dieldrin, aldrin and similar insecticides. The use of 67—82% of 2-pyrrolidone is exemplified.

British Patent Specification No. 805,026 discloses the use of N-methylpyrrolidone in concentrations of 40% as a solvent for various medicaments intended for parental administration, such as chloramphenicol, N,N-dibenzylethylenediamine-dipenicillin G and procaine penicillin.

United States Patent No. 2,987,437 discloses nematocidal compositions of 3,4-dichlorotetrahydrothiophene, 1,1-dioxide in 2-pyrrolidone.

German Patent No. 1,091,287 discloses stable aqueous solutions of tyrothricin 0.25% or subtilin 0.2% for nasal or otic use prepared with the aid of pyrrolidone and/or polyvinylpyrrolidone as solubilizers. Pyrrolidone is used in a concentration of 0.5% and polyvinylpyrrolidone can be used up to 10%.

United States Patent No. 3,957,980 discloses aqueous injectable solutions of doxycycline comprising a solution in water of from about 1% to 10% by weight of doxycycline, together with about 3 to 8 molar proportions of a phosphate salt selected from phosphoric acid, sodium or potassium orthophosphate, metaphosphate, pyrophosphate, tripolyphosphate or hexametaphosphate, and about 3 to 8 molar proportions of a pharmaceutically acceptable magnesium salt soluble in said aqueous pharmaceutical composition, said composition having a pH value in the range of from about 1 to 3.5.

United States Patent No. 3,674,859 discloses aqueous solutions of doxycycline containing from about 1% to 15% doxycycline and from about 5 per cent to 40 per cent by weight of polyvinylpyrrolidone having an average molecular weight that is in the range of from about 10,000 to about 60,000, said composition having a pH value in the range of from 5 to about 8.

J. Pharm. Sci. 46, p. 458 (1957) discloses that oxytetracycline forms soluble complexes with N-methyl-pyrrolidone in aqueous solution. The degree of interaction is limited by pH and solubility considerations.

United States Patent No. 2,980,584 discloses aqueous parenteral solutions of

oxytetracycline metal complexes containing 25—80% of an acetic or lactic acid carboxamide, such as N,N-dimethylacetamide and N-(β-hydroxyethyl) lactamide at a pH of 8.5—9.5. Concentrations of 10 to 100 mg./ml. are disclosed.

United State Patent No. 2,990,331 discloses parenteral solutions of oxytetracycline hydrochloride and tetracycline hydrochloride containing about 50 mg./ml. having a pH value between 5 and 7, containing magnesium ions, an alkali bisulfite and a carboxylic acid amide, such as lactic acid-hydroxyethyl amide.

United States Patent No. 3,062,717 discloses aqueous parenteral solutions of tetracycline calcium complexes containing 35—80% of an amide of acetic or lactic acid, such as N,N-dimethylacetamide or N-(β-hydroxyethyl) lactamide, at a pH of 7 to 9.5. Concentrations of 10 to 100 mg./ml. are disclosed.

United States Patent 3,557,280 discloses aqueous solutions of oxytetracycline containing 1 to 20% oxytetracycline, a magnesium compound and polyvinylpyrrolidone, 7.5 to 25%, at a pH of 8.0 to 9.5.

Belgian Patent No. 825,656 discloses aqueous solutions of oxytetracycline containing 4 to 11% oxytetracycline, 20 to 30% of a polyethylene glycol, such as polyethylene glycol 400, a magnesium compound and 0.10 to 0.35% of a buffer, such as tris-(hydroxymethyl)-aminomethane at a pH of 8 to 9.

French Patent Publication No. 2,258,187 discloses aqueous solutions of oxytetracycline containing 50 mg./ml. of oxytetracycline, 5 to 7.49% polyvinylpyrrolidone and up to 24.9% of an acid amide containing one to six carbon atoms, such as dimethylacetamide, at a pH of 8 to 9.5.

In accordance with this invention there is provided a stable antibiotic composition comprising a solution of a chelated tetracycline in aqueous 2-pyrrolidone, said tetracycline being selected from oxytetracycline, doxycycline, tetracycline, chlortetracycline, and the pharmaceutically acceptable acid addition salts thereof. If desired, the composition also may contain polyvinylpyrrolidone.

2-Pyrrolidone is also known as 2-pyrrolidinone, 2-oxypyrrolidine, α-pyrrolidone and 2-ketopyrrolidine. It has an oral LD_{50} of 8 gm./kg. in rats and 3.8 gm./kg. by intraperitoneal injection in mice. Its use allows for minimum volume per dose and excellent syringeability due to low viscosity of the resultant composition.

As an optional ingredient polyvinylpyrrolidone having a molecular weight of between 5,000 and 100,000 (K-12 to 30) may also be present in the composition in a concentration of from 1 to 7% by weight. The polyvinylpyrrolidone preferred for this invention is one having an average molecular weight of about 10,000—17,000 (where K-value=17). It is present in part as a co-solubilizer and may improve tissue toleration.

The stability of these solutions for therapeutic administration may be still further enhanced by the inclusion of anti-oxidants such as sodium or magnesium formaldehyde sulfoxylate and monothioglycerol at levels of from about 0.01 to 1.0% by weight.

Previous efforts made to prepare oxytetracycline compositions suitable for topical or parenteral administration which contain more than 200 mg./ml. have been unsuccessful. This is of particular importance in the case of veterinary oxytetracycline parenteral compositions in which high doses are required.

Stable high potency solutions of oxytetracycline can be provided by means of a novel pharmaceutical composition according to the invention comprising a solution in water of from 1 to 40% by weight of an antibiotic compound selected from oxytetracycline and the pharmaceutically acceptable acid addition salts thereof, 0.8 to 1.3 molar proportions based on said antibiotic of a pharmaceutically acceptable magnesium compound soluble in said solution, and from 10 to 50% by weight of 2-pyrrolidone, said composition having a pH value in the range of from 7.5 to 9.5.

Oxytetracycline is a widely used tetracycline-type antibiotic. It is particularly described in United States Patent No. 2,516,080. An effective concentration range for oxytetracycline in the solutions of this invention is generally from 1 to 40% by weight of the total in the form of the free base or a pharmaceutically acceptable acid addition salt. The preferred form is the free base with the preferred concentration being from 10 to 40% by weight, with the especially preferred concentration being from 20 to 30% by weight.

Examples of suitable oxytetracycline acid addition salts which can be used include such pharmaceutically acceptable acid addition salts as the hydrochloride, hydrobromide, sulfate, nitrate, ascorbate citrate, gluconate, lactate, isonicotinate, gentisinate, pantothenate, salicylate, glucuronate, formate and glutamate. However, the preferred acid addition salt is oxytetracycline hydrochloride.

Magnesium ions combine with

oxytetracycline in solution to form magnesium-oxytetracycline chelates. Magnesium oxide is a convenient and preferred source of magnesium ions, but other magnesium compounds useful for this purpose include magnesium chloride, magnesium acetate, magnesium sulfate, magnesium ascorbate, magnesium lactate and magnesium gluconate. The molar ratio of magnesium to oxytetracycline in these compositions is from 0.8 to 1.3. This ratio is necessary to produce clear stable solutions. Suspended solids remain in the solvent when introduction of less than 0.8 or more than 1.3 moles of magnesium ion is used.

2-Pyrrolidone is present as a co-solvent for oxytetracycline in a concentration of from 10 to 50% based on the total weight of the composition.

The pH value is adjusted if necessary to pH 7.5 to 9.5. The preferred range is pH 8.5 to 9.0. The pH can be adjusted with organic bases such as aminoethanol, dimethylaminoethanol or dimethylamine. Of these compounds, aminoethanol is the preferred compound.

The compositions containing oxytetracycline are preferably prepared by mixing the magnesium compound with the 2-pyrrolidone and water at about 75°C. and slowly adding the oxytetracycline antibiotic with stirring until dissolved. The pH is then adjusted to the desired range. If polyvinyl pyrrolidone is to be included it is added to the 2-pyrrolidone and water before the addition of the magnesium compound as previously described.

Oxytetracycline is currently available for parenteral administration at a conecntration of 50 mg./ml. Therefore a 500 Kg steer would require 200 ml. of a 50 mg./ml. product injected into 5 to 10 different areas in order to receive an effective dose. The compositions of this invention obviate this difficulty in that easily syringeable high dosage compositions are now possible, e.g., 200 mg./ml.

These oxytetracycline compositions are also easy to syringe over a wide temperature range, have acceptable animal tissue toleration, give therapeutic blood levels and are satisfactory from a physical and chemical stability standpoint.

The primary application of these oxytetracycline compositions is as a parenteral composition but they can also be used for topical or oral application.

Stable high potency solutions of doxycycline can be provided by means of a novel pharmaceutical composition according to the invention comprising an aqueous solution of from 1 to 25% by weight of an antibiotic compound selected from doxycycline and the pharmaceutically acceptable acid addition salts thereof, 1.8 to 2.2 molar proportions based on said antibiotic of a pharmaceutically acceptable magnesium compound soluble in said solution, and from 10 to 70% by weight of 2-pyrrolidone, said composition having a pH value in the range of from 3 to 7.5.

Doxycycline is a widely used tetracycline-type antibiotic of high potency and having a superior half-life *in vivo*. It is particularly described in United States Patent No. 3,200,149 under the chemical name α-6-deoxy-5-oxytetracycline. An effective concentration range for doxycycline in the solutions of this invention is generally from 1 to 25% by weight of the total in the form of the free base or a pharmceutically acceptable acid addition salt. The preferred form is the free base with the preferred concentration being from 5% to 20% by weight, with the especially preferred concentration being from 10% to 20% by weight.

Examples of suitable doxycycline acid addition salts which can be used include such pharmaceutically acceptable acid addition salts as hydrochloride, hydrobromide and sulfate. However, the preferred acid addition salt is doxycycline hydrochloride, e.g., in the form of doxycycline hyclate, which is doxycycline hydrochloride hemiethanolate hemihydrate.

Magnesium ions combine with doxy cycline in solution to form magnesium-doxycycline chelates. Magnesium oxide is a convenient and preferred source of magnesium ions, but other magnesium compounds useful for the purpose of this invention include magnesium chloride, magnesium acetate and magnesium sulfate. The molar ratio of magnesium to doxycycline in these compositions is about from 1.8 to 2.2. This ratio is advisable to produce clear stable solutions.

2-Pyrrolidone is present as a co-solvent for the doxycycline in a concentration of from 10 to 70% and preferably from 30 to 50%, based on the total weight of the composition.

The pH value is adjusted if necessary to pH 3 to 7.5. The preferred range is pH 5 to 7. The pH can be adjusted by means of an acid that is pharmaceutically acceptable, such as hydrochloric acid or by means of an organic base, such as monoethanolamine.

The doxycycline compositions of this invention are preferably prepared by mixing the magnesium compound with the 2-pyrrolidone and water at about 50°C. and slowly adding the doxycycline antibiotic with stirring and adjusting the pH to the desired range. If polyvinyl pyrrolidone is to be included it is added to the 2-pyrrolidone and water before the addition of the

magnesium compound as previously described.

These doxycycline compositions are also easy to syringe over a wide temperature range and are satisfactory from a physical and chemical stability standpoint.

The use of these high potency doxycycline compositions enables a reduction of the number of injections that must be administered to large animals, such as steers, in order to receive an effective dose.

The primary application is as a parenteral composition but the new doxycycline compositions can also be used for topical or oral application.

Stable high potency solutions of tetacycline can be provided by means of a novel pharmaceutical composition according to the invention comprising an aqueous solution of from 1 to 15% by weight of an antibiotic compound selected from tetracycline and the pharmaceutically acceptable acid addition salts thereof, 0.8 to 1.3 molar proportions based on said antibiotic of a pharmaceutically acceptable magnesium compound soluble in said solution, and from 10 to 70% by weight of 2-pyrrolidone, said composition having a pH value in the range of from 7.5 to 9.5.

Tetracycline is a widely used tetracycline-type antibiotic. It is particularly described in United States Patent No. 2,699,054. An effective concentration range for tetracycline in the solutions of this invention is generally from 1 to 15% by weight of the total in the form of the free base or a pharmaceutically acceptable acid addition salt. The preferred form is the free base with the preferred concentration being from 5 to 15% by weight, with the especially preferred concentration being from 5 to 10% by weight.

Examples of suitable tetracycline acid addition salts which can be used include such pharmaceutically acceptable acid addition salts as hydrochloride, hydrobromide and sulfate, however, the preferred acid addition salt is tetracycline hydrochloride.

Magnesium ions combine with tetracycline in solution to form magnesium-tetracycline chelates. Magnesium oxide is a convenient and preferred source of magnesium ions, but other magnesium compounds useful for the purpose of this invention include magnesium chloride, magnesium acetate and magnesium sulfate. The molar ratio of magnesium to tetracycline in these compositions is from 0.8 to 1.3. This ratio is advisable to produce clear stable solutions.

2-Pyrrolidone is present as a co-solvent for the tetracycline in a concentration of from 10 to 70%, and preferably from about 60 to 70%, based on the total weight of the composition.

The pH value is adjusted if necessary to pH 7.5 to 9.5. The preferred range is pH 8 to 9. The pH can be adjusted with an organic base such as monoethanolamine or with an acid that is pharmaceutically acceptable, such as hydrochloric acid.

The tetracycline compositions of this invention are prepared by mixing the magnesium compound with the 2-pyrrolidone and water at about 50°C. and slowly adding the tetracycline antibiotic with stirring until dissolved. The pH is then adjusted to the desired range. If polyvinylpyrrolidone is to be included it is added to the 2-pyrrolidone and water before the addition of the magnesium compound as previously described.

These tetracycline compositions are also easy to syringe over a wide temperature range and are satisfactory from a physical and chemical stability standpoint.

The use of these high potency tetracycline compositions enables a reduction of the number of injections that must be administered to large animals, such as steers, in order to receive an effective dose.

The primary application of these tetracycline compositions is as a parenteral composition but the new compositions can also be used for topical or oral application.

It has now been found that stable high potency solutions of chlortetracycline can be provided by means of a novel pharmaceutical composition according to the invention comprising an aqueous solution of from 5 to 20% by weight of an antibiotic compound selected from chlortetracycline and the pharmaceutically acceptable acid addition salts thereof, 2 to 4 molar proportions based on said antibiotic of a pharmaceutically acceptable calcium compound soluble in said solution, and from 50 to 70% by weight of 2-pyrrolidone, said composition having a pH value in the range of from 8 to 10.

Chlortetracycline is a widely used tetracycline-type antibiotic. It is particularly described in United States Patent No. 2,482,055. An effective concentration range for chlortetracycline in the solutions of this invention is generally from 5 to 20% by weight of the total in the form of the free base or a pharmaceutically acceptable acid addition salt. The preferred form is the acid addition salt with the preferred concentration being from 10 to 20% by weight, with the especially preferred concentration being from 10 to 15% by weight.

Examples of suitable chlortetracycline acid addition salts which can be used

include such pharmaceutically acceptable acid addition salts as hydrochloride, hydrobromide and sulfate. However, the preferred acid addition salt is chlortetracycline hydrochloride.

Calcium ions combine with chlortetracycline in solution to form calcium-tetracycline chelates. Calcium chloride is a convenient and preferred source of calcium ions, but other compounds useful for the purpose of this invention include calcium oxide, calcium acetate and calcium sulfate. The molar ratio of calcium to chlortetracycline in these compositions is from 2 to 4. This ratio is advisable to produce clear stable solutions.

2-Pyrrolidone is present as a co-solvent in a concentration of from 50 to 70% and preferably from 60 to 70% based on the total weight of the composition.

The pH value is adjusted if necessary to pH 8 to 10. The preferred range is pH 8.5 to 9.5. The pH can be adjusted with an organic base such as monoethanolamine or with a pharmaceutically acceptable acid, such as hydrochloric acid.

The chlortetracycline compositions of this invention are preferably prepared by mixing the calcium compound with the 2-pyrrolidone and water at about 50°C, and slowly adding the chlortetracycline antibiotic with stirring and adjusting the pH to the desired range until dissolved. The pH is then adjusted to the desired range. If polyvinylpyrrolidone is to be included it is added to the 2-pyrrolidone and water before the addition of the calcium compound as previously described.

These chlortetracycline compositions are also easy to syringe over a wide temperature range and are satisfactory from a physical and chemical stability standpoint.

The use of these high potency chlortetracycline compositions enables a reduction of the number of injections that must be administered to large animals, such as steers, in order to receive an effective dose.

The primary application of these chlortetracycline compositions is as a parenteral composition but the new compositions can also be used for topical or oral application.

EXAMPLE 1

	gm./100 ml.
Oxytetracycline (based on a potency of 927 γ/mg. plus a 5% overage)	22.65
Magnesium oxide	1.921
2-Pyrrolidone	40.00
Magnesium formaldehyde sulfoxylate	0.44
2-Aminoethanol	0.10
Water q.s. to	100 ml.

The 2-pyrrolidone was mixed with the water. The solution was heated to about 75°C. and the magnesium formaldehyde sulfoxylate was added and dissolved with stirring. The magnesium oxide was then slurried with the solution. The oxytetracycline was slowly added with stirring until a clear solution resulted. The solution was allowed to cool to room temperature and the pH adjusted to 8.5 with 2-aminoethanol. The solution was then brought up to volume with water.

The above solution containing 200 mg./ml. of oxytetracycline activity had a viscosity of 13.0 cts. at 25°C.

Tissue toleration was acceptable and blood levels were satisfactory after subcutaneous injection in cattle.

The substitution of 1.0 gm. of sodium formaldehyde sulfoxylate for the magnesium formaldehyde sulfoxylate produced a product similar to the above.

EXAMPLE 2

	gm./100 ml.
Oxytetracycline (based on a potency of 927 γ/mg. plus a 5% overage)	22.65
Magnesium oxide	1.921
2-Pyrrolidone	40.00
Polyvinylpyrrolidone, K-17	5.00
Magnesium formaldehyde sulfoxylate	0.44
2-Aminoethanol	0.17
Water q.s. to	100 ml.

The 2-pyrrolidone was mixed with water. Polyvinylpyrrolidone was then added and stirred until dissolved. The procedure as described in Example 1 was then followed.

The resulting product, containing 200 mg./ml. of oxytetracycline activity, had a viscosity of 23 cts. at 25°C.

Tissue toleration was acceptable and blood levels satisfactory after subcutaneous and intramuscular injection in cattle.

The substitution of 1.0 gm. of sodium formaldehyde sulfoxylate for the magnesium formaldehyde sulfoxylate produced a product similar to the above.

EXAMPLE 3

The following solution containing 25 mg./ml. of oxytetracycline activity was prepared using the procedure described in Example 1.

	gm./100 ml.
Oxytetracycline (based on a potency of 927 γ/mg. plus a 5% overage)	2.831
Magnesium oxide	0.245
2-Pyrrolidone	10.00
Sodium formaldehyde sulfoxylate	1.00
2-Aminoethanol	0.012
Water q.s. to	100 ml.

The viscosity was 2 cts. at 25°C.

EXAMPLE 4

The following solution containing 50 mg./ml. of oxytetracycline activity was prepared using the procedure described in Example 1.

	gm./100 ml.
Oxytetracycline (based on a potency of 927 γ/mg. plus a 5% overage)	5.662
Magnesium oxide	0.490
2-Pyrrolidone	20.00
Sodium formaldehyde sulfoxylate	1.00
2-Aminoethanol	0.065
Water q.s. to	100 ml.

The viscosity was 2.5 cts. at 25°C.

EXAMPLE 5

A solution containing 100 mg./ml. of oxytetracycline activity was prepared using the procedure described in Example 1.

	gm./100 ml.
Oxytetracycline (based on a potency of 927 γ/mg. plus a 5% overage)	11.325
Magnesium oxide	0.480
2-Pyrrolidone	35.00
Sodium formaldehyde sulfoxylate	1.00
Water q.s. to	100 ml.

The viscosity was 3.0 cts. at 25°C.

EXAMPLE 6

The following solution containing 200 mg./ml. of oxytetracycline activity was prepared using the procedure described in Example 2.

	gm./100 ml.
Oxytetracycline (based on a potency of 927 γ/mg. plus a 5% overage)	22.65
Magnesium oxide	1.421
2-Pyrrolidone	40.00
Polyvinylpyrrolidone, K-30	5.00
Magnesium formaldehyde sulfoxylate	0.44
2-Aminoethanol	0.50
Water q.s. to	100 ml.

The viscosity was 5.0 cts. at 25°C.

EXAMPLE 7

A solution containing 200 mg./ml. of oxytetracycline activity was prepared using the procedure described in Example 2.

	gm./100 ml.
Oxytetracycline hydrochloride (based on a potency of 905 γ/mg. plus a 5% overage)	23.20
Magnesium oxide	1.921
2-Pyrrolidone	40.00
Polyvinylpyrrolidone, K-17	5.00
Magnesium formaldehyde sulfoxylate	0.44
2-Aminoethanol	3.84
Water q.s. to	100 ml.

The viscosity was 45 cts. at 25°C.

EXAMPLE 8

A solution containing 200 mg./ml. of oxytetracycline activity was prepared using the procedure described in Example 2.

	gm./100 ml.
Oxytetracycline (based on a potency of 927 γ/mg. plus a 5% overage)	22.65
Magnesium chloride, hexahydrate	9.668
2-Pyrrolidone	40.00
Polyvinylpyrrolidone, K-17	5.00
Magnesium formaldehyde sulfoxylate	0.44
2-Aminoethanol	0.88
Water q.s. to	100 ml.

The viscosity was 35 cts. at 25°C.

EXAMPLE 9

The following solution containing 200 mg./ml. of oxytetracycline activity was prepared using the procedure described in Example 1.

	gm./100 ml.
Oxytetracycline (based on a potency of 927 γ/mg. plus a 5% overage)	22.65
Magnesium acetate, tetrahydrate	10.021
2-Pyrrolidone	40.00

Sodium formaldehyde sulfoxylate	1.00
2-Aminoethanol	0.76
Water q.s. to	100 ml.

The viscosity was 33 cts. at 25°C.

EXAMPLE 10

A solution containing 300 mg./ml. of oxytetracycline activity was prepared using the procedure described in Example 1.

	gm./100 ml.
Oxytetracycline (based on a potency of 927 γ/mg. plus a 5% overage)	33.975
Magnesium oxide	2.94
2-Pyrrolidone	50.00
Sodium formaldehyde sulfoxylate	1.00
Water q.s. to	100 ml.

The viscosity was 70 cts. at 25°C.

EXAMPLE 11

A solution containing 350 mg./ml. of oxytetracycline activity was prepared using the procedure described in Example 1.

	gm./100 ml.
Oxytetracycline (based on a potency of 927 γ/mg. plus a 5% overage)	39.597
Magnesium oxide	3.43
2-Pyrrolidone	50.00
Sodium formaldehyde sulfoxylate	1.00
Water q.s. to	100 ml.

The viscosity was 200 cts. at 25°C.

EXAMPLE 12

A solution containing 400 mg./ml. of oxytetracycline activity was prepared using the procedure described in Example 1.

	gm./100 ml.
Oxytetracycline (based on a potency of 927 γ/mg. plus a 5% overage)	45.30
Magnesium oxide	3.92
2-Pyrrolidone	50.00
Sodium formaldehyde sulfoxylate	1.00
Water q.s. to	100 ml.

The viscosity was 785 cts. at 25°C.

EXAMPLE 13

The following solution containing 100 mg./ml. of doxycycline activity was prepared.

	gm./100 ml.
Doxycycline (based on a potency of 930 γmg. plus a 5% overage)	11.29
Magnesium oxide	1.921
2-Pyrrolidone	50.00
Sodium formaldehyde sulfoxylate	1.00
Concentrated hydrochloric acid, to adjust pH to 7.3	
Water q.s. to	100 ml.

The 2-pyrrolidone was mixed with water. The solution was heated to about 50°C. and the sodium formaldehyde sulfoxylate was added and dissolved with stirring. The magnesium oxide was then slurried with the solution. The doxycycline was slowly added with stirring and the pH adjusted with concentrated hydrochloric acid. The resultant solution was allowed to cool to room temperature and the pH further adjusted to 7.3 with concentrated hydrochloric acid. The solution was then brought up to volume with water.

Solutions comparable to the above were also made by adjusting the pH to 5.0 and 6.5, respectively.

EXAMPLE 14

The following solution containing 100 mg./ml. of doxycycline activity was prepared using the procedure described in Example 13.

	gm./100 ml.
Doxycycline (based on a potency of 930 γ/mg. plus a 5% overage)	11.29
Magnesium oxide	1.921
2-Pyrrolidone	40.00
Sodium formaldehyde sulfoxylate	1.00
Concentrated hydrochloric acid, adjust to pH 7.2	
Water q.s. to	100 ml.

A solution comparable to the above was also made by adjusting the pH to 5.2.

EXAMPLE 15

The following solution containing 200 mg./ml. doxycycline activity was prepared using the procedure described in Example 13.

	gm./100 ml.
Doxycycline (based on a potency of 930 γ/mg. plus a 5% overage)	22.58
Magnesium oxide	3.828
2-Pyrrolidone	50.00

Sodium formaldehyde sulfoxylate	1.00
Concentrated hydrochloric acid, adjust to pH 7.2	
Water q.s. to	100 ml.

A solution comparable to the above was also made by adjusting the pH to 5.2.

EXAMPLE 16

The following solution containing 200 mg./ml. of doxycycline activity was prepared using the procedure described in Example 13.

	gm./100 ml.
Doxycycline (based on a potency of 930 γ/mg. plus a 5% overage)	22.58
Magnesium oxide	3.828
2-Pyrrolidone	40.00
Sodium formaldehyde sulfoxylate	1.00
Concentrated hydrochloric acid, adjust to pH 7.0	
Water q.s. to	100 ml.

EXAMPLE 17

The following solution containing 200 mg./ml. of doxycycline activity was prepared using the procedure described in Example 13.

	gm./100 ml.
Doxycycline (based on a potency of 930 γ/mg. plus a 5% overage)	22.58
Magnesium oxide	3.828
2-Pyrrolidone	30.00
Sodium formaldehyde sulfoxylate	1.00
Concentrated hydrochloric acid, adjust to pH 5.8	
Water q.s. to	100 ml.

EXAMPLE 18

The following solution containing 200 mg./ml. of doxycycline activity was prepared.

	gm./100 ml.
Doxycycline (based on a potency of 930 γ/mg. plus a 5% overage)	22.58
Magnesium oxide	3.828
2-Pyrrolidone	40.00
Sodium formaldehyde sulfoxylate	1.00
Polyvinylpyrrolidone, K-17	5.00
Concentrated hydrochloric acid, adjust to pH 6.6	
Water q.s. to	100 ml.

The 2-pyrrolidone was mixed with water. Polyvinylpyrrolidone was then added and stirred until dissolved. The procedure as described in Example 13 was then followed.

A comparable solution was prepared using 30 gm. of 2-pyrrolidone instead of 40 gm.

EXAMPLE 19

The following solution containing 100 mg./ml. of doxycycline activity was prepared using the procedure described in Example 13.

	gm./100 ml.
Doxycycline hydrochloride (based on potency of 850 γ/mg. plus a 5% overage)	12.353
Magnesium oxide	2.02
2-Pyrrolidone	60.00
Sodium formaldehyde sulfoxylate	1.00
Concentrated hydrochloric acid, to adjust to pH 7.2	
Water q.s. to	100 ml.

Solutions comparable to the above were also made by adjusting the pH to 6.5 and 5.0, respectively.

EXAMPLE 20

The following solution containing 100 mg./ml. of doxycycline activity was prepared using the procedure described in Example 13.

	gm./100 ml.
Doxycycline (based on a potency of 930 γ/mg. plus a 5% overage)	11.29
Magnesium oxide	0.059
Sodium formaldehyde sulfoxylate	1.00
2-Pyrrolidone	70.00
Concentrated hydrochloric acid, to adjust pH to 7.2	
Water q.s. to	100 ml.

Solutions comparable to the above were also made by adjusting the pH to 6.5 and 5.2, respectively.

EXAMPLE 21

The following solution containing 10 mg./ml. of doxycycline activity was prepared using the procedure described in Example 13.

	gm./100 ml.
Doxycycline (based on a potency of 930 γ/mg. plus a 5% overage)	1.129
Magnesium oxide	0.206

2-Pyrrolidone	10.00
Sodium formaldehyde sulfoxylate	1.00
Concentrated hydrochloric acid, to adjust pH to 6.7	
Water q.s. to	100 ml.

A solution comparable to the above was also made by adjusting the pH to 5.

EXAMPLE 22

The following solution containing 100 mg./ml. of tetracycline hydrochloride activity was prepared.

	gm./100 ml.
Tetracycline (based on a tetracycline hydrochloride potency of 955 γ/mg. plus a 5% overage)	10.995
Magnesium oxide	0.958
2-Pyrrolidone	70.00
Sodium formaldehyde sulfoxylate	1.00
Polyvinylpyrrolidone K-17	5.00
Monoethanolamine, to adjust pH to 8.5	
Water q.s. to	100 ml.

The 2-pyrrolidone was mixed with water. Polyvinylpyrrolidone was then added and stirred until dissolved. The solution was heated to about 50°C. and the sodium formaldehyde sulfoxylate was added and dissolved with stirring. The magnesium oxide was then slurried with the solution. The tetracycline was slowly added with stirring until a clear solution resulted. The solution was allowed to cool to room temperature and the pH adjusted to 8.5 with monoethanolamine. The solution was then brought up to volume with water.

A comparable solution was made by using 60.00 gm./100 ml. of 2-pyrrolidone instead of 70.00 gm./100 ml.

EXAMPLE 23

The following solution containing 50 mg./ml. of tetracycline hydrochloride activity was prepared using the procedure described in Example 22.

	gm./100 ml.
Tetracycline (based on a tetracycline hydrochloride potency of 955 γ/mg. plus a 5% overage)	5.496
Magnesium oxide	0.479
2-Pyrrolidone	70.00
Sodium formaldehyde sulfoxylate	1.00
Polyvinylpyrrolidone K-17	5.00
Monoethanolamine, to adjust pH to 8.5	
Water q.s. to	100 ml.

A solution comparable to the above was also made by using 50.00 g./100 ml. of 2-pyrrolidone instead of 70.00 g./100 ml.

EXAMPLE 24

The following solution containing 50 mg./ml. tetracycline hydrochloride activity was prepared using the procedure described in Example 22.

	gm./100 ml.
Tetracyline (based on a tetracycline hydrochloride potency of 955 γ/mg. plus a 5% overage)	5.496
Magnesium oxide	0.479
2-Pyrrolidone	60.00
Magnesium formaldehyde sulfoxylate	0.44
Polyvinylpyrrolidone K-17	5.00
Monoethanolamine, to adjust pH to 8.5	
Water q.s. to	100 ml.

EXAMPLE 25

The following solution containing 100 mg./ml. of tetracycline hydrochloride activity was prepared using the procedure described in Example 22, except the polyvinylpyrrolidone is not present.

	gm./100 ml.
Tetracycline (based on a tetracycline hydrochloride potency of 955 γ/mg. plus a 5% overage)	10.995
Magnesium oxide	0.958
2-Pyrrolidone	60.00
Magnesium formaldehyde sulfoxylate	0.44
Monoethanolamine, to adjust pH to 8.9	
Water q.s. to	100 ml.

A comparable solution containing 70.00 g./ml. of 2-pyrrolidone with the pH adjusted to 8.8 was also prepared.

EXAMPLE 26

The following solution containing 50 mg./ml. of tetracycline hydrochloride activity was prepared using the procedure described in Example 25.

	gm./100 ml.
Tetracycline (based on a tetracycline hydrochloride potency of 955 γ/mg. plus a 5% overage)	5.496

Magnesium oxide	0.479
2-Pyrrolidone	60.00
Magnesium formaldehyde sulfoxylate	0.44
Monoethanolamine, to adjust pH to 8.8	
Water q.s. to	100 ml.

A comparable solution containing 70.00 g./ml. of 2-pyrrolidone with the pH adjusted to 8.7 was also prepared.

EXAMPLE 27

The following solution containing 100 mg./ml. of tetracycline hydrochloride activity was prepared using the procedure described in Example 25.

	gm./ 100 ml.
Tetracycline hydrochloride (based on a tetracycline hydrochloride potency of 980 γ/mg. plus a 5% overage)	10.714
Magnesium oxide	0.939
2-Pyrrolidone	60.00
Sodium formaldehyde sulfoxylate	1.00
Monoethanolamine, to adjust pH to 8.5	
Water q.s. to	100 ml.

EXAMPLE 28

The following solution containing 10 mg./ml. of tetracycline hydrochloride activity was prepared following the procedure described in Example 25, except that the pH is adjusted with concentrated hydrochloric acid.

	gm./ 100 ml.
Tetracycline (based on a tetracycline hydrochloride potency of 955 γ/mg. plus a 5% overage)	1.099
Magnesium oxide	0.096
2-Pyrrolidone	30.00
Sodium formaldehyde sulfoxylate	1.00
Concentrated hydrochloric acid, to adjust pH to 7.5	
Water q.s. to	100 ml.

Solutions comparable to the above were also made by adjusting the pH to 6.5 and 5.2, respectively.

EXAMPLE 29

The following solution containing 100 mg./ml. of chlortetracycline hydrochloride activity was prepared.

	gm./ 100 ml.
Chlortetracycline hydrochloride (based on a chlortetracycline hydrochloride potency of 950 γ/mg plus a 5% overage)	11.053
Calcium chloride	4.96
2-Pyrrolidone	60.00
Monothioglycerol	1.00
Monoethanolamine, to adjust pH to 8.8	
Water q.s. to	100 ml.

The 2-pyrrolidone was mixed with water. The solution was heated to about 50°C. and the monothioglycerol was added and dissolved with stirring. The calcium chloride was then slurried with the solution. The chlortetracycline hydrochloride was slowly added with stirring and the pH raised with monoethanolamine until solution resulted. The solution was allowed to cool to room temperature and the pH adjusted to 8.8 with monoethanolamine. The solution was then brought up to volume with water.

Solutions comparable to the above were also made by adjusting the pH to 8.0 and 9.5, respectively.

EXAMPLE 30

The following solution containing 100 mg./ml. of chlortetracycline hydrochloride activity was prepared using the procedure described in Example 29.

	gm./ 100 ml.
Chlortetracycline hydrochloride (based on a chlortetracycline hydrochloride potency of 950 γ/mg. plus a 5% overage)	11.053
Calcium chloride	9.92
2-Pyrrolidone	60.00
Monothioglycerol	1.00
Monoethanolamine, to adjust pH to 8.8	
Water q.s. to	100 ml.

Solutions comparable to the above were also made by adjusting the pH to 8.0 and 9.5, respectively.

EXAMPLE 31

The following solution containing 50 mg./ml. of chlortetracycline hydrochloride activity was prepared.

	gm./100 ml.
Chlortetracycline hydrochloride (based on a chlortetracycline hydrochloride potency of 950 γ/mg. plus a 5% overage)	5.527
Calcium chloride	2.48
2-Pyrrolidone	50.00
Polyvinylpyrrolidone	5.00
Monothioglycerol	1.00
Monoethanolamine, to adjust pH to 8.8	
Water q.s. to	100 ml.

The 2-pyrrolidone was mixed with water. Polyvinylpyrrolidone was then added with stirring until dissolved. The procedure described in Example 29 was then followed.

Solutions comparable to the above were also made by adjusting the pH to 8.0 and 9.5, respectively.

EXAMPLE 32

The following solution containing 200 mg./ml. of chlortetracycline hydrochloride activity was prepared using the procedure described in Example 29.

	gm./100 ml.
Chlortetracycline hydrochloride (based on a chlortetracycline hydrochloride potency of 950 γ/mg. plus a 5% overage)	22.106
Calcium chloride	9.92
2-Pyrrolidone	60.00
Monothioglycerol	1.00
Monoethanolamine, to adjust pH to 8.8	
Water q.s. to	100.00

Solutions comparable to the above were also made by adjusting the pH to 8.0 and 9.5, respectively.

EXAMPLE 33

The following solution containing 100 mg./ml. of chlortetracycline hydrochloride activity was prepared using the procedure described in Example 29.

	gm./100 ml.
Chlortetracycline hydrochloride (based on a chlortetracycline hydrochloride potency of 950 γ/mg. plus a 5% overage)	11.053
Calcium chloride	4.96
2-Pyrrolidone	70.00
Monothioglycerol	1.00
Monoethanolamine, to adjust pH to 8.8	
Water q.s. to	100 ml.

Solutions comparable to the above were also made by adjusting the pH to 8.0 and 9.5, respectively.

EXAMPLE 34

The following solution containing 100 mg./ml. of chlortetracycline hydrochloride activity was prepared using the procedure described in Example 31.

	gm./100 ml.
Chlortetracycline hydrochloride (based on a chlortetracycline hydrochloride potency of 950 γ/mg. plus a 5% overage)	11.053
Calcium chloride	4.96
2-Pyrrolidone	60.00
Polyvinylpyrrolidone	5.00
Monothioglycerol	1.00
Monoethanolamine, to adjust pH to 8.8	
Water q.s. to	100 ml.

Solutions comparable to the above were also made by adjusting the pH to 8.0 and 9.5, respectively.

WHAT WE CLAIM IS:—

1. A stable antibiotic composition comprising a solution of a chelated tetracycline in aqueous 2-pyrrolidone, said tetracycline being selected from oxytetracycline, doxycycline, tetracycline, chlortetracycline, and the pharmaceutically acceptable acid addition salts thereof,

2. A composition according to claim 1, comprising an aqueous solution of from 1 to 40% by weight of oxytetracycline or a pharmaceutically acceptable acid addition salt thereof, from 0.8 to 1.3 molar proportions based on said oxytetracycline of a pharmaceutically acceptable magnesium compound soluble in said solution and from 10 to 50% by weight of 2-pyrrolidone, said composition having a pH from 7.5 to 9.5.

3. A composition according to claim 1, comprising an aqueous solution of from 1 to 25% by weight of doxycycline or a pharmaceutically acceptable acid addition salt thereof, from 1.8 to 2.2 molar proportions based on said doxycycline of a pharmaceutically acceptable magnesium compound soluble in said solution and from 10 to 70% by weight of 2-pyrrolidone, said composition having a pH value from 3 to 7.5.

	gm./100 ml.
Chlortetracycline hydrochloride (based on a chlortetracycline hydrochloride potency of 950 γ/mg. plus a 5% overage)	5.527
Calcium chloride	2.48
2-Pyrrolidone	50.00
Polyvinylpyrrolidone	5.00
Monothioglycerol	1.00
Monoethanolamine, to adjust pH to 8.8	
Water q.s. to	100 ml.

The 2-pyrrolidone was mixed with water. Polyvinylpyrrolidone was then added with stirring until dissolved. The procedure described in Example 29 was then followed.

Solutions comparable to the above were also made by adjusting the pH to 8.0 and 9.5, respectively.

EXAMPLE 32

The following solution containing 200 mg./ml. of chlortetracycline hydrochloride activity was prepared using the procedure described in Example 29.

	gm./100 ml.
Chlortetracycline hydrochloride (based on a chlortetracycline hydrochloride potency of 950 γ/mg. plus a 5% overage)	22.106
Calcium chloride	9.92
2-Pyrrolidone	60.00
Monothioglycerol	1.00
Monoethanolamine, to adjust pH to 8.8	
Water q.s. to	100.00

Solutions comparable to the above were also made by adjusting the pH to 8.0 and 9.5, respectively.

EXAMPLE 33

The following solution containing 100 mg./ml. of chlortetracycline hydrochloride activity was prepared using the procedure described in Example 29.

	gm./100 ml.
Chlortetracycline hydrochloride (based on a chlortetracycline hydrochloride potency of 950 γ/mg. plus a 5% overage)	11.053
Calcium chloride	4.96
2-Pyrrolidone	70.00
Monothioglycerol	1.00
Monoethanolamine, to adjust pH to 8.8	
Water q.s. to	100 ml.

Solutions comparable to the above were also made by adjusting the pH to 8.0 and 9.5, respectively.

EXAMPLE 34

The following solution containing 100 mg./ml. of chlortetracycline hydrochloride activity was prepared using the procedure described in Example 31.

	gm./100 ml.
Chlortetracycline hydrochloride (based on a chlortetracycline hydrochloride potency of 950 γ/mg. plus a 5% overage)	11.053
Calcium chloride	4.96
2-Pyrrolidone	60.00
Polyvinylpyrrolidone	5.00
Monothioglycerol	1.00
Monoethanolamine, to adjust pH to 8.8	
Water q.s. to	100 ml.

Solutions comparable to the above were also made by adjusting the pH to 8.0 and 9.5, respectively.

WHAT WE CLAIM IS:—

1. A stable antibiotic composition comprising a solution of a chelated tetracycline in aqueous 2-pyrrolidone, said tetracycline being selected from oxytetracycline, doxycycline, tetracycline, chlortetracycline, and the pharmaceutically acceptable acid addition salts thereof,

2. A composition according to claim 1, comprising an aqueous solution of from 1 to 40% by weight of oxytetracycline or a pharmaceutically acceptable acid addition salt thereof, from 0.8 to 1.3 molar proportions based on said oxytetracycline of a pharmaceutically acceptable magnesium compound soluble in said solution and from 10 to 50% by weight of 2-pyrrolidone, said composition having a pH from 7.5 to 9.5.

3. A composition according to claim 1, comprising an aqueous solution of from 1 to 25% by weight of doxycycline or a pharmaceutically acceptable acid addition salt thereof, from 1.8 to 2.2 molar proportions based on said doxycycline of a pharmaceutically acceptable magnesium compound soluble in said solution and from 10 to 70% by weight of 2-pyrrolidone, said composition having a pH value from 3 to 7.5.

4. A composition according to claim 1, comprising an aqueous solution of from 1 to 15% by weight of tetracycline or a pharmaceutically acceptable acid addition salt thereof, from 0.8 to 1.3 molar proportions based on said tetracycline of a pharmaceutically acceptable magnesium compound soluble in said solution, and from 10 to 70% by weight of 2-pyrrolidone, said composition having a pH value of from 7.5 to 9.5.

5. A composition according to claims 2, 3 or 4, wherein said magnesium compound is magnesium oxide.

6. A composition according to claim 1, comprising an aqueous solution of from 5 to 20% by weight of chlortetracycline or a pharmaceutically acceptable acid addition salt thereof, from 2 to 4 molar proportions based on said chlortetracycline of a pharmaceutically acceptable calcium compound soluble in said solution and from 50 to 70% by weight of 2-pyrrolidone, said composition having a pH value of 8 to 10.

7. A composition according to claim 6, wherein said calcium compound is calcium chloride.

8. A composition according to any of the preceding claims, wherein polyvinylpyrrolidone having an average molecular weight of about 5,000 and 100,000 is also present in a concentration of from 1 to 7% by weight of the total.

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Printed for Her Majesty's Stationery Office, by the Courier Press, Leamington Spa, 1978
Published by The Patent Office, 25 Southampton Buildings, London, WC2A 1AY, from which copies may be obtained.