

PATENT SPECIFICATION

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- (21) Application No. 59/10/72 (22) Filed 27 Dec. 1972
 (31) Convention Application No. 301 236 (32) Filed 26 Oct. 1972 in
 (33) United States of America (US)
 (44) Complete Specification published 18 April 1974
 (51) International Classification A61K 21/00
 (52) Index at acceptance
 A5B 20X 20Y 215 21Y 272 274 27Y 285 28Y 362 36Y
 385 38Y 390 401 402 40Y 501 50Y 541 54Y 566
 56Y 77Y



(54) DOXYCYCLINE PARENTERAL COMPOSITION

(71) We, PFIZER INC., a Corporation organized under the laws of the State of Delaware, United States of America, of 235 East 42nd Street, New York 17, 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 parenteral administration. More particularly it relates to doxycycline parenteral compositions.
 Because of the therapeutic importance of the tetracycline type antibiotics, efforts have been made to prepare compositions suitable for parenteral administration. Aqueous solutions of doxycycline can be prepared in the highly acid or alkaline pH range, but these solutions are found objectionable due to their low stability and poor local tolerance upon injection. With the exception of polyvinylpyrrolidone compositions and Mannich base derivatives very little pharmaceutical technology has been developed for a parenteral form of doxycycline.

It has now been found that a stable aqueous, injectable solution of doxycycline can be provided by means of an antibiotic composition comprising a solution in water of from 1% to 10% by weight of a pharmaceutically acceptable acid addition salt of doxycycline, together with at least 3 molar proportions of a water-soluble alkali metal phosphate salt and at least 3 molar proportions of a pharmaceutically acceptable water-soluble magnesium salt, said composition having a pH value in the range of from 1.0 to 3.5.

Doxycycline, the therapeutically-active component of the pharmaceutical compositions of this invention, is a tetracycline type antibiotic of high potency with excel-

lent oral absorption characteristics and a superior half-life. It is particularly described in United Kingdom Patent No. 995032 under the chemical name, α -6-deoxy-5-oxytetracycline. An effective concentration range for doxycycline in the aqueous solutions of this invention is generally from 1% to 10% by weight of the total in the form of a pharmaceutically acceptable acid addition salt.

Magnesium ions combine with doxycycline in solution to form magnesium-doxycycline chelates. Magnesium chloride is a convenient source of magnesium ions but other magnesium compounds useful for the purpose of this invention include magnesium oxide, magnesium ascorbate, magnesium lactate, and magnesium gluconate. The molar ratio of magnesium to doxycycline in these compositions is at least 3:1. The preferred ratio is from 3:1 to 8:1, with the especially preferred ratio being from 3:1 to 4:1.

The doxycycline antibiotic component is used in the form of one of its acid addition salts. Examples of suitable doxycycline acid addition salts which can be used for these purposes 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. The preferred acid addition salt is doxycycline hydrochloride, e.g., in the form of doxycycline hyclate, which is doxycycline hydrochloride hemiethanolate hemihydrate. If desired, the doxycycline may be introduced in the form of the free base, in which case the salt is formed *in situ* by the pH adjustment discussed below.

The pH value is adjusted to the preferred range of from 1.0 to 3.5 by means of a solid acid that is pharmaceutically acceptable, such as ascorbic acid, tartaric acid,

[Price 25p]

gluconic acid, glucuronic acid, citric acid, gentisic acid, isonicotinic acid, glutamic acid, and so forth. Of these compounds, ascorbic acid is preferred, since it also serves to act as an anti-oxidant for the mixture. When using higher doxycycline concentration, e.g. 80 mg/ml to 100 mg/ml, an acid buffer is not needed since the pH will be in the desired range from pH 1.0 to 3.5. The especially preferred range, however, is from pH 1.5 to 3.0.

A further component which may be utilized in the present composition with beneficial effect is a water-soluble local anaesthetic. The most useful of these compounds are procaine hydrochloride and lidocaine hydrochloride. Other dialkyl-amino alkanol esters of *p*-aminobenzoic acid as the water-soluble salts, e.g. hydrochloride, are also useful for this purpose.

The compositions of this invention may be prepared by merely mixing the doxycycline acid addition salt with the desired proportions of the other ingredients. It is usually preferable to introduce all solid ingredients in finely divided form and to blend the mixture to obtain a uniform product. Standard pharmaceutical equipment may be used for this purpose. The mixture may also be milled if desired. However, prolonged high temperature should be avoided.

An essential component of this invention is a water-soluble alkali metal/phosphate salt, such as sodium or potassium orthophosphate, metaphosphate, pyrophosphate, tripolyphosphate or hexametaphosphate. The preferred salt, however, is sodium orthophosphate, also known as sodium dihydrogen phosphate. The inclusion of a water-soluble alkali metal phosphate salt in the compositions of this invention provides effective blood levels of doxycycline, prevents gelling of the compositions when water is added and prevents precipitation of doxycycline in blood serum. The molar ratio of water-soluble alkali metal phosphate salt to doxycycline in these compositions is one that is in the range of at least 3:1. The preferred ratio is from 3:1 to 8:1, with the especially preferred ratio being from 3:1 to 4:1.

In the following illustrative examples the doxycycline hydrochloride is employed in the form of the hemiethanolate hemihydrate (hyclate).

EXAMPLE I

A dry solid pharmaceutical composition was prepared by intimately blending 635.0 mg. of doxycycline hydrochloride with 641.77 mg. of magnesium chloride tetrahydrate, 529.7 mg. of sodium dihydrogen phosphate and 675.99 mg. of ascorbic acid.

The blended powder thus obtained was then dissolved in 8.4 ml. of sterile water which brought the total volume to 10 ml. The resulting solution was found to have a pH value of 2.0. The solution remained fluid and clear for over 24 hours at room temperature.

Animal protection tests were carried out in mice against *Staphylococcus aureus* 01A005 by intramuscular and intravenous administration. Results indicated that satisfactory protection was achieved by the use of this composition.

EXAMPLE II

Dry solid compositions may be prepared by substituting an equivalent molar amount of sodium metaphosphate, sodium pyrophosphate, sodium tripolyphosphate or sodium hexametaphosphate for the sodium dihydrogen phosphate contained in Example I.

EXAMPLE III

A mixture of the following materials was prepared:

	Mgs.	
Doxycycline hydrochloride	635.00	
Magnesium chloride.4H ₂ O	641.77	
sodium dihydrogen phosphate	529.70	
Ascorbic acid	675.99	95
Lidocaine hydrochloride	200.00	

This composition when dissolved in 8.1 ml. of water provided a clear product with a pH of 2.0.

EXAMPLE IV

A mixture of the following materials was prepared:

	Mgs.	
Doxycycline hydrochloride	635.00	
Magnesium gluconate	308.66	
Sodium dihydrogen phosphate	529.70	
Ascorbic acid	675.99	110

When this mixture was diluted with 8.0 ml. of water, a clear solution with pH 2.0 resulted.

EXAMPLE V

A mixture of the following materials was prepared:

	Mgs.	
Doxycycline hydrochloride	635.00	
Magnesium chloride.4H ₂ O	855.69	120
Sodium dihydrogen phosphate	529.70	
Ascorbic acid	655.8	

This composition when dissolved in 8.0 ml. of water produced a clear solution with a pH of 2.0.

EXAMPLE VI

A mixture of the following materials was prepared:

- 5 Doxycycline hydrochloride 1,265.0
Magnesium chloride.4H₂O 1,755.9
Sodium dihydrogen phosphate 1,190.0
- When this composition is dissolved in 8.2 ml. of water, a clear solution containing 100 mg/ml. of doxycycline activity results having a pH of 2.0.

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EXAMPLE VII

A mixture of the following materials was prepared:

- 15 Doxycycline hydrochloride 127.55
Magnesium chloride.4H₂O 128.39
Sodium dihydrogen phosphate 105.94
Ascorbic acid 131.10

- 20 When this composition is dissolved in 8.3 ml. of water, a clear solution, having a pH of 2.0, and containing 10 mg/ml of doxycycline activity is produced.

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EXAMPLE VIII

A mixture of the following materials was prepared:

- 30 Doxycycline hydrochloride 255.10
Magnesium chloride.4H₂O 256.78
Sodium dihydrogen phosphate 211.88
Ascorbic acid 400.00

- 35 When this composition is dissolved in 9.4 ml. of water, a clear solution containing 20 mg/ml. of doxycycline activity is produced. The pH is 1.9.

EXAMPLE IX

- 40 A mixture of the following materials was prepared:

- 45 Doxycycline hydrochloride 1,020.40
Magnesium chloride.4H₂O 1,164.7
Sodium dihydrogen phosphate 960.7

- 50 When this composition is dissolved in 8.3 ml. of water, a clear solution containing 80 mg/ml. of doxycycline activity and having a pH of 1.66 is produced.

EXAMPLE X

A mixture of the following materials was prepared:

- 55 Doxycycline hydrochloride 635.00
Magnesium chloride.4H₂O 641.77
Potassium dihydrogen phosphate 522.3
60 Ascorbic acid 675.99

When this mixture was diluted with 8.5 ml. of water, a clear solution with pH 2.0 resulted.

EXAMPLE XI

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A mixture of the following materials was prepared:

- Doxycycline hydrochloride 635.00
Magnesium chloride.4H₂O 642.00 70
Potassium dihydrogen phosphate 522.00
Citric acid 3,570.00

When this composition is dissolved in 6.5 ml. of water, a clear solution containing 10 ml. of doxycycline activity and having a pH of 1.1 is produced.

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EXAMPLE XII

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A mixture of the following materials was prepared:

- Doxycycline hydrochloride 635.00
Magnesium chloride.4H₂O 725.00 85
Sodium dihydrogen phosphate 598.00
Sodium citrate hydrous 300.00

This composition when dissolved in 9.1 ml. of water produced a clear solution with a pH of 3.5.

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EXAMPLE XIII

A mixture of the following materials was prepared:

- Doxycycline hydrochloride 635.00
Magnesium chloride.4H₂O 1,506.00
Sodium dihydrogen phosphate 1,367.00 100

This composition when dissolved in 8.1 ml. of water produced a clear solution having a pH of 2.0.

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WHAT WE CLAIM IS:—

1. An aqueous pharmaceutical composition comprising a solution in water of from 1% to 10% by weight of a pharmaceutically acceptable acid addition salt of doxycycline, together with at least 3 molar proportions of a water-soluble alkali metal phosphate salt, and at least 3 molar proportions of a pharmaceutically acceptable water-soluble magnesium salt, said composition having a pH value in the range of from 1.0 to 3.5.

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2. A composition as claimed in claim 1, wherein said doxycycline acid addition salt is doxycycline hydrochloride.

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3. A composition as claimed in claim 1 or 2, wherein said alkali metal phosphate salt is sodium or potassium orthophosphate, metaphosphate, pyrophosphate, tripolyphosphate or hexametaphosphate.

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4. A composition as claimed in claim 3, wherein said water-soluble alkali metal

- 5
10
- | | <i>Mgs.</i> |
|--------------------------------------|-------------|
| Doxycycline hydrochloride | 1,265.0 |
| Magnesium chloride.4H ₂ O | 1,755.9 |
| Sodium dihydrogen phosphate | 1,190.0 |
- When this composition is dissolved in 8.2 ml. of water, a clear solution containing 100 mg/ml. of doxycycline activity results having a pH of 2.0.

EXAMPLE VII

A mixture of the following materials was prepared:

- 15
20
- | | <i>Mgs.</i> |
|--------------------------------------|-------------|
| Doxycycline hydrochloride | 127.55 |
| Magnesium chloride.4H ₂ O | 128.39 |
| Sodium dihydrogen phosphate | 105.94 |
| Ascorbic acid | 131.10 |
- When this composition is dissolved in 8.3 ml. of water, a clear solution, having a pH of 2.0, and containing 10 mg/ml of doxycycline activity is produced.

EXAMPLE VIII

A mixture of the following materials was prepared:

- 30
- | | <i>Mgs.</i> |
|--------------------------------------|-------------|
| Doxycycline hydrochloride | 255.10 |
| Magnesium chloride.4H ₂ O | 256.78 |
| Sodium dihydrogen phosphate | 211.88 |
| Ascorbic acid | 400.00 |

- 35
- When this composition is dissolved in 9.4 ml. of water, a clear solution containing 20 mg/ml. of doxycycline activity is produced. The pH is 1.9.

EXAMPLE IX

- 40
- A mixture of the following materials was prepared:

- 45
- | | <i>Mgs.</i> |
|--------------------------------------|-------------|
| Doxycycline hydrochloride | 1,020.40 |
| Magnesium chloride.4H ₂ O | 1,164.7 |
| Sodium dihydrogen phosphate | 960.7 |

- 50
- When this composition is dissolved in 8.3 ml. of water, a clear solution containing 80 mg/ml. of doxycycline activity and having a pH of 1.66 is produced.

EXAMPLE X

A mixture of the following materials was prepared:

- 55
60
- | | <i>Mgs.</i> |
|--------------------------------------|-------------|
| Doxycycline hydrochloride | 635.00 |
| Magnesium chloride.4H ₂ O | 641.77 |
| Potassium dihydrogen phosphate | 522.3 |
| Ascorbic acid | 675.99 |

When this mixture was diluted with 8.5 ml. of water, a clear solution with pH 2.0 resulted.

EXAMPLE XI

A mixture of the following materials was prepared:

- | | <i>Mgs.</i> | |
|--------------------------------------|-------------|----|
| Doxycycline hydrochloride | 635.00 | |
| Magnesium chloride.4H ₂ O | 642.00 | 70 |
| Potassium dihydrogen phosphate | 522.00 | |
| Citric acid | 3,570.00 | |

When this composition is dissolved in 6.5 ml. of water, a clear solution containing 10 ml. of doxycycline activity and having a pH of 1.1 is produced.

EXAMPLE XII

A mixture of the following materials was prepared:

- | | <i>Mgs.</i> | |
|--------------------------------------|-------------|----|
| Doxycycline hydrochloride | 635.00 | |
| Magnesium chloride.4H ₂ O | 725.00 | 85 |
| Sodium dihydrogen phosphate | 598.00 | |
| Sodium citrate hydrous | 300.00 | |

This composition when dissolved in 9.1 ml. of water produced a clear solution with a pH of 3.5.

EXAMPLE XIII

A mixture of the following materials was prepared:

- | | <i>Mgs.</i> | |
|--------------------------------------|-------------|-----|
| Doxycycline hydrochloride | 635.00 | |
| Magnesium chloride.4H ₂ O | 1,506.00 | |
| Sodium dihydrogen phosphate | 1,367.00 | 100 |

This composition when dissolved in 8.1 ml. of water produced a clear solution having a pH of 2.0.

WHAT WE CLAIM IS:—

1. An aqueous pharmaceutical composition comprising a solution in water of from 1% to 10% by weight of a pharmaceutically acceptable acid addition salt of doxycycline, together with at least 3 molar proportions of a water-soluble alkali metal phosphate salt, and at least 3 molar proportions of a pharmaceutically acceptable water-soluble magnesium salt, said composition having a pH value in the range of from 1.0 to 3.5.
2. A composition as claimed in claim 1, wherein said doxycycline acid addition salt is doxycycline hydrochloride.
3. A composition as claimed in claim 1 or 2, wherein said alkali metal phosphate salt is sodium or potassium orthophosphate, metaphosphate, pyrophosphate, tripolyphosphate or hexametaphosphate.
4. A composition as claimed in claim 3, wherein said water-soluble alkali metal



phosphate salt is sodium orthophosphate.

5. A composition as claimed in any one of claims 1 to 4, also containing a water-soluble local anaesthetic.

5 6. A composition as claimed in any one of the preceding claims, wherein said water-soluble magnesium salt is magnesium chloride or magnesium gluconate.

10 7. A composition as claimed in claim 6, wherein said water-soluble magnesium salt is magnesium chloride.

STEVENS, HEWLETT & PERKINS,

Chartered Patent Agents,

5, Quality Court,

Chancery Lane,

London W.C.2.

Tel. 01-405 8393.

Printed for Her Majesty's Stationery Office by The Tweeddale Press Ltd., Berwick-upon-Tweed, 1974.
Published at the Patent Office, 25 Southampton Buildings, London, WC2A 1AY, from which copies
may be obtained.

