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PATENT SPECIFICATION

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COMPLETE SPECIFICATION

Improvements in or relating to Aqueous Solutions of Oxytetracycline

We, KONINKLIJKE NEDERLANDSCHE GISTEN SPIRITUSFABRIEK N.V., a Dutch limited liability company, having a place of business at Delft, the Netherlands, 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 invention relates to the preparation of stable solutions of oxytetracycline which are particularly suitable for parenteral administration of this therapeutically important antibiotic, but can also be made suitable for other therapeutic methods of administration.

Oxytetracycline is known to be poorly soluble in water. The salts of this compound with mineral acids indeed are much more soluble, but at the prevalent pH of such salt solutions (pH=2.0—3.0) these aqueous solutions are not sufficiently stable and thus not very suitable for the preparation of injection fluids with good keeping qualities. Moreover interamuscular injection of such solutions is very painful and is often attended by the occurrence of considerable necrotic reactions in the place of the injection. Attempts are made to mask the occurrence of painfulness to some extent by the addition of a local anaesthetic. Nevertheless these solutions are not used very much on account of the above-mentioned serious disadvantages.

It is further known that the solubility of tetracycline derivatives can be increased considerably by the additional presence of calcium or magnesium ions, as a result of which more readily soluble complexes are formed. Yet the solubility of these complexes is still altogether insufficient and it has not been possible to prepare water-soluble complexes with Mg- or Ca-salts of sufficiently high concentration and stability, and at a physiologically suitable pH, which may serve as injection fluids.

This can largely be achieved indeed if instead of water an organic solvent is used, for instance propylene glycol or a concentrated solution of certain carbonamides, such as dimethylacetamide or β-hydroxyethyllacetamide.

Injections with such high concentrations of organic solvent, however, in consequence of their marked hypertonic character also cause painfulness in the place of the injection, even apart from the rather undesirable fact of large quantities of such unphysiological organic compounds being injected as well.

Attempts have also been made to prepare water-soluble compounds satisfying the requirements of a good injection composition by reacting tetracycline (or its derivatives) with formaldehyde and certain amino compounds, such as dialkylamine, piperazine, morpholine, piperidine, and amino-acids, such as lysine. These so-called Mannich bases are indeed readily soluble in water, but frequently not very stable, so that in the case of prolonged storage the risk exists that the poorly soluble tetracycline (or its derivative) precipitates again. Moreover these compounds, which really must be regarded as new therapeutic products with properties which are not quite identical with those of their starting products, *viz.* the tetracycline antibiotics as such, must be specially prepared for this purpose.

The invention relates to the preparation of stable concentrated aqueous solutions of oxytetracycline, which are specially suitable for parenteral administration of this antiboitic. The invention relates in particular to oxytetracycline solutions suitable for intramuscular or intravenous use. The solutions obtained by the application of the invention are extremely stable and are substantially aqueous solutions as to their composition. Besides for the above-mentioned purposes they are also suitable, or can be made suitable, for other therapeutic methods of administration, such

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as a syrup for peroiral administration, *e.g.* in pediatrics, and a solution or jelly for intramammary administration in veterinary practice, for instance. This latter represents a mode of local administration.

Intramuscular injection of therapeutic doses of these solutions does not cause painfulness in the place of the injection, so that addition of a local anaesthetic is superfluoous. Moreover, a very high tetracycline level in the blood is attained shortly after the injection.

The solutions according to the invention are obtained by mixing together in an aqueous medium oxytetracycline, either as a base or as a salt, polyvinyl pyrrolidone and a magnesium compound ionizable in the medium to provide magnesium ions, and subsequently adjusting the pH of the mixture to a value in the range from 8.0 to 9.5. Preferably, the pH is adjusted to a value in the range from 8.5 to 9.0. The adjustment will of course be carried out with the aid of a physiologically harmless inorganic or organic base. Suitable bases are, for instance, sodium hydroxide, ammonia, ethanolamine, and ethylene diamine.

By choosing appropriately the concentrations of oxytetracycline, polyvinyl pyrrolidone, and magnesium compound, the solutions obtained are perfectly clear. Even dilutions of such solutions with water or serum remain clear, so that these solutions are also eminently suitable for intravenous administration of this antibiotic. It is readily possible, by applying the present invention, to prepare solutions of oxy tetracycline having an oxytetracycline concentrations of *e.g.* 7.5 to 15%, *i.e.* the concentration range which is particularly suitable for medical application.

Polyvinyl pyrrolidone, which is known to be used, *inter alia*, as a blood plasma expander and as such is medically acceptable, even when administered in large quantities, is a condensation product with an average molecular weight which may vary from about 10,000 to 1,000,000. High-molecular as well as low-molecular polyvinyl pyrrolidone exhibits the unexpectedly strong solubility-enhancing effect. In view of the higher viscosity of solutions of the high-molecular product, preference is given to the use of low-molecular polyvinyl pyrrolidones, *i.e.* with a molecular weight of 10,000 to 60,000. For the solutions according to the invention use is preferably made of polyvinyl pyrrolidone with an average molecular weight of 10,000 to 12,000 (K-value = 17). Solutions of 10 to 15% by weight of this product in water do not increase the viscosity appreciably, a property which must be considered particularly favourable for injection fluids.

On account of the still fairly high molecular weight, polyvinyl pyrrolidone also hardly affects the isotonicity of the injection fluid.

It is possible to prepare solutions according to the invention with 7.5 to 25% of polyvinyl pyrrolidone by weight; preferably 10 to 15% of polyvinyl pyrrolidone, by weight, is used.

For the production according to the present invention of aqueous oxytetracycline solutions a quantity of magnesium compound sufficient to form the more soluble magnesium complex previously mentioned has of course to be used, as will be clear to those skilled in the art. Preferably, there are 1 to 1.5 moles of magnesium compound to 1 mole of oxytetracycline. The magnesium compound can be a magnesium salt, preferably the chloride, or magnesium oxide, depending on whether the oxytetracycline is used in base or salt form. If prolonged stability of the solutions is to be ensured, it is further also favourable when, after small bottles or ampoules have been filled with the solutions according to the invention, the air above the fluid is replaced by an inert gas, preferably by nitrogen.

The stability is also favoured by the addition to the solutions of comparatively small quantities of a reducing substance, such as sodium metabisulfite, sodium sulfite, or sodium formaldehyde sulfoxylate.

In contrast to many other injection forms of oxytetracycline, intramuscular injection of a medically justified dose of this antibiotic in the new form for administration causes no appreciable pain reaction or necrosis in the place of the injection.

Solutions according to the invention can also be made suitable for peroral administration (*e.g.* in pediatrics) in a very effective way by the addition of taste and colour correctives.

Solutions according to the invention can also be made suitable for *e.g.* intramammary administration in veterinary practice by addition of a harmless thickening agent.

Example I.

In 82.5 ml of distilled, sterile, and pyrogen-free water are dissolved 0.5 g of sodium formaldehyde sulfoxylate and 15 g of polyvinyl pyrrolidone (K-value = 17). Subsequently 0.5 g of magnesium oxide is suspended in this solution. Then 5.5 g of oxytetracycline hydrochloride is added to the suspension thus obtained, and the pH is adjusted to 8.5 to 9.0 with the aid of ethanolamine, as a result of which a clear solution containing 50 mg of oxytetracycline per ml is obtained. This solution is sterilized by means of filtration through a sterilizing and pyrogen-adsorbing asbestos filter and subsequently distributed into suitable injection bottles or ampoules.

Example II.

In 84 ml of distilled, sterile, and pyrogen-free water are dissolved 0.5 g of sodium formaldehyde sulfoxylate and 7.5 g of polyvinyl pyrrolidone (K-value = 25). Subsequently 0.5

g of magnesium oxide is suspended in this solution. Then 5.5 g of oxytetracycline hydrochloride is added to the suspension thus obtained, and the pH is adjusted to 8.5 to 9.0 with the aid of 10% ammonia, as a result of which a clear solution is obtained, which contains 50 mg of oxytetracycline per ml. This solution is finally sterilized and distributed into bottles or ampoules as described in Example I.

EXAMPLE III.

In 83 ml of distilled, sterile, and pyrogen-free water are dissolved 0.5 g of sodium formaldehyde sulfoxylate and 15 g of polyvinyl pyrrolidone (K-value=17). Subsequently 0.83 g of magnesium oxide is suspended in this solution, after which 9.2 g of oxytetracycline hydrochloride is added and the pH is adjusted to 8.5 to 9.0 with the aid of ethylene diamine. The solution thus obtained then contains approximately 83 mg of oxytetracycline per ml. The solution is sterilized and distributed into bottles or ampoules as described in Example I.

EXAMPLE IV

In 80 ml of distilled, sterile, and pyrogen-free water are successively dissolved 0.5 g of sodium formaldehyde sulfoxylate, 15 g of polyvinyl pyrrolidone (K-value=17), 2.5 g of magnesium chloride 6 aq., and 5.5 g of oxytetracycline hydrochloride, Subsequently the pH of this solution is adjusted to 8.5 to 9.0 with the aid of ethanolamine, as a result of which a clear solution containing 50 mg of oxytetracycline per ml is formed. This solution is sterilized and distributed into bottles or ampoules as described in Example I.

EXAMPLE V

In 80 ml of distilled, sterile, and pyrogen-free water are disolved 0.5 g of sodium formaldehyde sulfoxylate, 15 g of polyvinyl pyrrolidone (K-value=17), and 2.5 g of magnesium chloride 6 aq. To this solution is added 5.5 g of oxytetracycline dihydrate, and the pH is adjusted to 8.5 to 9.0 with the aid of ethanolamine, as a result of which a clear solution containing 50 mg of oxytetracycline per ml is obtained. This solution can finally be sterilized and distributed into bottles or ampoules as described in Example I.

EXAMPLE VI.

In 78 ml of distilled, sterile, and pyrogen-free water are dissolved 0.5 g of sodium formaldehyde sulfoxylate and 15 g of polyvinyl pyrrolidone (K-value=17), after which 0.5 g of magnesium oxide is suspended in this solution. In the suspension thus obtained 5.5 g of oxytetracycline hydrochloride is subsequently dissolved, and the pH is adjusted to 8.5 to 9.0 with the aid of 10% ammonia. The clear solution thus obtained, which contains 50 mg of oxytetracycline per ml, is finally sterilized and distributed into bottles or ampoules as described in Example I.

EXAMPLE VII.

In 86 ml of distilled, sterile, and pyrogen-free water are dissolved 0.5 g of sodium formaldehyde sulfoxylate and 10 g of polyvinyl pyrrolidone (K-value=17). In this solution 0.5 g of magnesium oxide is subsequently suspended, after which 6.0 g of oxytetracycline citrate is added. Finally the pH is adjusted to 8.5 to 9.0 with the aid of ethanolamine, as a result of which a clear solution containing 50 mg of oxytetracycline per ml is formed. This solution is sterilized and distributed into bottles or ampoules as described in Example I.

EXAMPLE VIII.

In 55 ml of water the following substances are dissolved successively:

0.09	g of methyl p-hydroxybenzoate
0.01	g of propyl p-hydroxybenzoate
0.5	g of sodium sulfite 7 aq.
1.6	g of magnesium sulfate 7 aq.
10	g of polyvinyl pyrrolidone (K-value =30)
1	g of sodium cyclamate
40	g of crystallized sugar
2.75	g of oxytetracycline hydrochloride

Subsequently the pH of the liquid is adjusted to 8.5 to 9.0 with the aid of ammonia, and the volume is supplemented with water to 100 ml, if necessary.

In this way a solution with a good taste is obtained, which contains 25 mg of oxytetracycline per ml and is suitable for peroral administration.

EXAMPLE IX

In 40 ml of water the following substances are dissolved successively:

0.09	g of methyl p-hydroxybenzoate
0.01	g of propyl p-hydroxybenzoate
0.2	g of sodium bisulfite
1	g sodium cyclamate
25	g of polyvinyl pyrrolidone (K-value =17)
40	g of crystallized sugar
10	g of glycerine
2.8	g of oxytetracycline phosphate

The liquid is subsequently mixed with 0.25 g of magnesium oxide, and the pH is adjusted to 8.5 to 9.0 with the aid of 4N sodium hydroxide, after which, if necessary, the volume is brought to 100 ml with water.

In this way a solution with a good taste is obtained, which contains 25 mg of oxytetracycline per ml and is suitable for peroral administration.

EXAMPLE X.

In 73 ml of distilled, sterile, and pyrogen-free water are dissolved 0.5 g of sodium formaldehyde sulfoxylate and 15 g of polyvinyl pyrrolidone (K-value=17). In this solution 1.5 g of magnesium oxide is then suspended, after which 16.5 g of oxytetracycline hydrochloride is added. The pH of the liquid is subsequently adjusted to 8.5 to 9.0 with the aid of ethanolamine, as a result of which a clear viscous liquid is obtained, which contains approximately 150 mg of oxytetracycline per ml and is suitable, for instance, for intramammary administration with a view to combating mastitis.

WHAT WE CLAIM IS:—

1. A process for the preparation of aqueous solutions of oxytetracycline suitable for parenteral, peroral, and local administration, characterized in that oxytetracycline, either as a salt or as a base, polyvinyl pyrrolidone and a magnesium compound ionizable in the medium to provide magnesium ions, are mixed together in an aqueous medium and the pH of the mixture is then adjusted to a value in the range from 8.0 to 9.5.

2. A process according to claim 1, characterized in that polyvinyl pyrrolidone with an average molecular weight from 10,000 to 60,000 is used.

3. A process according to claim 1 or 2, characterized in the polyvinyl pyrrolidone concentration in the final solution is from 7.5 to 25% by weight.

4. A process according to any one of claims 1 to 3, characterized in that the magnesium compound is a magnesium salt or magnesium oxide.

5. A process according to any one of claims 1 to 4, characterized in that the solutions obtained are sterilized by filtration and introduced into injection bottles or ampoules.

6. An injection bottle or ampoule obtained according to the process of claim 5.

7. A process according to claim 1 for the preparation of aqueous solutions of oxytetracycline suitable for parenteral, peroral and local administration, substantially as hereindescribed with especial reference to the Examples.

8. Aqueous solutions of oxytetracycline whenever prepared by processes according to claims 1 to 4.

For the Applicants:
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Gillett House,
55 Basinghall Street,
London, E.C.2.

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ERRATA

SPECIFICATION No. 1,131,007

Page 1, line 24, *for* "interamuscular" *read* "intramuscular"
Page 1, line 77, *for* "antiboitic" *read* "antibiotic"
Page 2, line 1, *for* "peroiral" *read* "peroral"
Page 2, line 9, *for* "superfluoous" *read* "superfluous"
Page 3, line 105, *after* "g" *insert* "of"

THE PATENT OFFICE
5th May 1969

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EXAMPLE X.

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WHAT WE CLAIM IS:—

1. A process for the preparation of aqueous solutions of oxytetracycline suitable for parenteral, peroral, and local administration, characterized in that oxytetracycline, either as a salt or as a base, polyvinyl pyrrolidone and a magnesium compound ionizable in the medium to provide magnesium ions, are mixed together in an aqueous medium and the pH of the mixture is then adjusted to a value in the range from 8.0 to 9.5.

2. A process according to claim 1, characterized in that polyvinyl pyrrolidone with an average molecular weight from 10,000 to 60,000 is used.

3. A process according to claim 1 or 2, characterized in the polyvinyl pyrrolidone concentration in the final solution is from 7.5 to 25% by weight.

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5th May 1969

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