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PATENT SPECIFICATION

DRAWINGS ATTACHED

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COMPLETE SPECIFICATION

Antibiotic Compositions and the manufacture thereof

We, PIERREL S.P.A., an Italian Body Corporate, existing under the laws of the Italian Republic of Via Turati 30, Milan, Italy 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 a process for the preparation of parenteral and peroral stable solutions of oxytetracycline.

It is generally known that the antibiotics of the tetracycline series, of which oxytetracycline is a member, are broad spectrum antibiotics, which are effective against a large number of infective microorganisms when administered orally, topically and parenterally.

The chemical forms of oxytetracycline which are commonly employed for oral and parenteral administration are the amphoteric base and the hydrochloride. The basic form is insoluble in water and therefore can be utilised only in pharmaceutical compositions such as coated tablets, capsules and suspension for oral administration.

The blood levels which are achieved by means of these pharmaceutical forms based on amphoteric oxytetracycline are irregular and depend on each individual and particularly on the pH of the gastric juice, at the moment of administration; in fact the insoluble base must be transformed into the soluble hydrochloride form by the HCl present in the gastric juice. In that form, the active principle is rapidly absorbed by the gastric walls.

It is evident that significant disadvantages are connected with such administrable pharmaceutical forms and the results obtained in different individuals are not always the same.

Furthermore the orally administrable suspensions prepared with the amphoteric form of oxytetracycline have the disadvantage of all suspensions; the active principle is not homogeneously distributed and the individual dosages result in irregular absorption of the medicine.

The hydrochloride form of oxytetracycline which is soluble can be employed for the preparation of coated tablets and injectable solutions.

It cannot be utilised for the preparation of syrup pharmaceutical forms, because of the instability of such forms.

The hydrochloride form of oxytetracycline has an acid pH value (ranging from 2.2—2.5) and it needs, for the preparation of injectable solutions, considerable quantities of buffers. The administration is always very painful.

The solutions of oxytetracycline hydrochloride, even when buffered, are not stable and when they come into contact with the tissue fluid or with the blood serum, they are rapidly hydrolysed giving the insoluble base. For that reason the dosages for intramuscular administration are limited to 100 mg. only. In consequence, the blood levels are low and the therapeutically valuable concentration of oxytetracycline in the blood disappears rapidly as shown in the accompanying drawing. It is therefore necessary to repeat the administration every 4—6 hours.

The graphs refer to injection of conventional preparations of the antibiotic tetracycline and not to the ready made solutions of the present invention.

Graph 1 refers to the administration of a conventional oxytetracycline preparation at a dosage of 100 mg. (1.5 mg. of oxytetracycline per kg. of body weight). Graph 2 refers to administration of a dosage of 250 mg. and Graph 3 to a dosage of 500 mg.

Thus, the drawing shows the blood concentration of the administered antibiotic in mcg/ml of blood at various time intervals after administration in a quantity of 1.5 mg/kg of body weight (human intramuscular administration) corresponding to 100 mg. of antibiotic for Graph 1 and 4 mg./kg of body

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weight corresponding to 250 mg. of antibiotic for Graph 2 and 8 mg./kg. corresponding to 500 mg. of graph 3.

The three Graphs show that, after a small blood concentration of antibiotic at 1 hour after administration, the blood concentration of antibiotic reaches a maximum after 4 hours then decreases very rapidly after about 6 to 10 hours. After 6 hours practically no therapeutically valuable concentration of antibiotic is present in the blood.

The disadvantages of the injectable pharmaceutical forms prepared by the addition of the solvent to the antibiotic powder prior to administration, are mainly characteristic of the hydrochloride form. In addition, the practical preparation of the injections, using the sterile powder and the solvent is laborious for the physician, and gives rise to serious doubts as to the sterility conditions during the preparation of the injection.

Consequently, it is evident that the pharmaceutical forms of oxytetracycline normally administered orally and parenterally, are not successful and desired forms because of the various disadvantages which are connected with their administration and with their absorption by the human body.

Moreover the fact that the maximum amount of antibiotic cannot exceed the range of 100 mg. for the intramuscular formulation constitutes a remarkable hindrance.

It has been always desirable, therefore, to succeed in obtaining a suitable stable pharmaceutical solution of oxytetracycline which could be administrable both parenterally and orally.

It is obvious that there are great advantages which could be achieved in the provision of a ready made peroral stable solution of oxytetracycline, which could be administered orally or parenterally, assuring rapid and regular absorption of the antibiotic and maintenance of useful therapeutic blood levels thereof.

The object of the present invention is to provide a stable solution of oxytetracycline for parenteral and peroral administration, which is ready for use and which allows a regular, rapid absorption of the antibiotic, either by the gastro-enteric walls, of capillary walls of tissue.

The blood levels attained by means of the administration of these parenteral ready-made solutions of oxytetracycline are maintained at high therapeutical concentrations for more than 8—10 hours.

After this period, the antibiotic concentration in the blood decreases slowly and therapeutically useful values are maintained for a period of 24 hours after the administration.

Such a clinical action allows the effect obtained with the stable solutions of oxytetracycline to be considered as being "a long acting one".

After the oral administration of the oxytetracycline composition, the clinical picture is slightly different. The oxytetracycline from the orally administered solution is rapidly absorbed by the gastric walls, giving immediate high therapeutic levels of the antibiotic.

This rapid absorption is followed also by a rapid excretion of the antibiotic, so that after 6 hours the administration should be repeated, if the dosage has been 250 mg. The advantage of the oral administration of this antibiotic solution lies in the fact that the high blood oxytetracycline concentration can be obtained in a short time after the oral administration; that no variations from individual to individual should result because the dosage is very precise, and the absorption does not depend on the momentary pH value of the gastric juice.

Furthermore the soluble compositions prepared with the present procedure of the invention, are characterised by the fact that they contain the antibiotic substance in the form of an aqueous solution at a slightly alkaline pH, of being ready for use and possessing the maximum of stability, wherein the antibiotic is also stable and therefore such compositions can be advantageously administered orally and parenterally.

In a more precise form, the solutions ready for use contain the antibiotic oxytetracycline, in the form of the base, solubilised and maintained in stable form with N - N' - bis-(beta - hydroxyethyl) - piperazine or N-(beta - hydroxyethyl) - piperazine, propylene glycol, water, magnesium chloride and a suitable antioxidant substance in the case of the injectable preparations.

During the studies for the preparation of the desired compositions, we have found that N-(beta-hydroxyethyl)piperazine may be used as the solvent for the oral preparations, but cannot be used for the injectable solutions because it has a pronounced hypotensive action which enhances the same type of action of tetracycline. For that reason we have tried various other piperazine derivatives and have found that N,N - bis(beta - hydroxyethyl)-piperazine has no hypotensive activity, and is suitable for the preparation of injectable solutions.

Another characteristic of the pharmaceutical composition herein described is constituted by the fact that the preparation for injectable administration is quite painless and easily tolerated; and so no local anaesthetic need be added to the solution for intramuscular injections. This fact represents a considerable

advantage, enabling the use of the injectable formulation for procaine sensitive patients.

The pharmaceutical formulations of this invention are composed of:

Oxytetracycline base amphoteric pure	25 to 80	mg/ml;
Propylene glycol	300 to 1000	mg/ml;
Magnesium chloride hexahydrate	12.5 to 50	mg/ml;
N - N'bis - (beta - hydroxyethyl) - piperazine or N - (beta - hydroxyethyl) - piperazine	25 to 100	mg/ml;
Rhodite A (formaldehyde sodium sulphoxylate)—as antioxidant in injectable preparations but optional in oral preparations.	0.1 to 5	mg/ml;
Bidistilled water q.s.		

The oxytetracycline base is suspended in a mixture of propylene glycol and water; magnesium chloride and N- or N,N'-bis-(beta-hydroxyethyl)piperazine are added and the mixture is stirred for a few hours, until the oxytetracycline is completely dissolved. Rhodite A is added in the case of the injectable preparation and optionally in the case of the oral preparation the volume adjusted to the required volume and the solution filtered until sparkling clear.

The following non-limitative Examples illustrate the compositions of the present invention.

EXAMPLE 1.

To a 2 lt. glass flask, equipped with stirrer and sintered glass bottom sparger, 750 gm. of propylene glycol, 1.0 gm. of Rhodite A, 80 gm. of oxytetracycline base, 40 gm. of magnesium chloride hexahydrate and 80 gm. of N - N'bis - (beta - hydroxyethyl)piperazine are added. The mixture is then stirred and nitrogen is bubbled through the sparger, for about 10 hours, at room temperature. When the solubilisation of the components is complete, the total volume is brought to 1 lt. by the addition of distilled water. The solution so obtained, is sterilised by filtration, through the membrane filter (porosity: 0.25μ). The solution is bright yellow in colour, sparkling clear and contains 80 mg/ml. of oxytetracycline activity. This solution may be distributed into vials for intramuscular or intravenous injections; as follows: 3.2 ml. per vial for 250 mg. intramuscular injection; 6.5 ml. per vial for 500 mg. intravenous infusion only.

EXAMPLE 2.

To a 2 lt. glass flask, equipped with stirrer and sintered glass bottom sparger, 585 gm. of propylene glycol, 0.5 gm. of Rhodite A, 25 gm. of Oxytetracycline base, 12.5 gm. of Magnesium Chloride hexahydrate and 31.0 gm. of N - N'bis(beta - hydroxyethyl)-piperazine are added.

The mixture is stirred and nitrogen is is bubbled through the sparger, for about 10 hours, at room temperature. When the solution is complete, the volume is brought to 1 lt. with distilled water. The solution is sterilised by filtration through a membrane filter (porosity 0.25μ).

This solution is bright yellow in colour, sparkling clear and contains 25 mg/ml. of oxytetracycline activity. This solution may be distributed in vials for intramuscular and intravenous injections as follows:

4.0 ml. per vial for 100 mg. intramuscular injection.

10 ml. per vial for 250 mg. intravenous injection.

The solutions of Examples 1 and 2 have a slightly alkaline reaction (pH between 7.5—8.5), are non-pyrogenic, non-toxic, sterile and do not contain histamine like substances. They are well tolerated and are painless when administered.

EXAMPLE 3.

Two solutions are prepared as follows:

Solution A—Sodium saccharinate gm. 1.0, Glycamil (Ammonium salt of glycyrrhizinic acid) gm. 5.0, and 30 per cent by weight saccharose syrup are made up to a volume of 500 ml.

Solution B—50 gm. oxytetracycline base, 40 gm. N - (beta - hydroxyethyl)piperazine, 20.0 gm. Magnesium Chloride hexahydrate, 230 gm. of propylene glycol; Solution B is stirred under nitrogen until the solution is complete. Solution A and solution B are mixed by slowly pouring solution B into solution A, with gentle stirring and bubbling nitrogen into the reaction vessel. The final solution is given a banana or raspberry flavour. The final volume is brought to 1 lt. with 30 per cent by weight saccharose syrup. The solution is filtered sparkling clear through clarifying membrane filters and is ready for use.

This solution is bright yellow in colour, and sparkling clear; it is slightly alkaline (pH is between 7.5—8.5), its density is 1.14 and the oxytetracycline activity is 45—50 mg/ml. The solution may be administered orally, one teaspoonful (5 ml.) as a single adult dosage.

The pharmacological studies have demonstrated that the oxytetracycline ready-made solution is less toxic than the oxytetracycline itself, and that the blood levels for the injectable form are maintained above the useful

therapeutic concentrations for longer periods than after the administration of oxytetracycline alone.

In the following Table the comparison between the toxicity in mice and rats of oxytetracycline and the oxytetracycline in ready-made solution, is shown.

LD 50 in mg/Kg. intravenous

	Mice	Rates
Oxytetracycline	178	260
Oxytetracycline in ready made solution	202	328.4

LD 50 in mg/Kg intramuscular

Oxytetracycline in ready made solution	>450

The blood levels obtained in rats, dogs and humans after the administration of various dosages, are demonstrated in the following Table.

Dosage		Blood concentrations in mcg/ml. of blood			
			10 min.	30 min.	1 hr.
Rat	5 mg/Kg.	intravenous intramuscular	3.10 2.00	2.40 2.90	1.75 2.08
Dog	5 mg/Kg.	intravenous	—	5.97	4.36
		intramuscular	—	2.76	4.88
Man	100 mg.	intramuscular	—	—	0.82
	200 mg.	intramuscular	—	—	1.00
	250 mg.	intramuscular	—	—	1.40
	250 mg.	intravenous	—	—	3.70
	250 mg.	oral	—	—	1.10

Continued

Dosage		Blood concentrations in mcg/ml. of blood				
			3 hr.	6 hr.	12 hr.	24 hr.
Rat	5 mg/Kg.	intravenous	1.0	0.60	<0.30	—
		intramuscular	1.50	0.50	<0.30	—
Dog	5 mg/Kg.	intravenous	2.53	1.77	1.0	0.60
		intramuscular	2.68	2.64	1.20	0.65
Man	100 mg.	intramuscular	0.70	0.60	0.50	—
	200 mg.	intramuscular	2.00	1.70	0.85	0.30
	250 mg.	intramuscular	3.80	2.86	2.20	0.80
	250 mg.	intravenous	2.10	1.60	1.05	0.35
	250 mg.	oral	0.74	0.45	—	—

Considering the data of blood concentration in mcg/ml of blood set forth in the above Tables for the ready made solution, it appears evident that the 'long acting action' exerted by this solution, as a therapeutically valuable concentration of the antibiotic in the blood, can be detected after 10 hours and that useful values are maintained up to a period of 24 hours after administration.

WHAT WE CLAIM IS:—

1. A stable orally administerable therapeutic oxytetracycline solution comprising oxytetracycline in the form of the base and an aqueous mixture of N-(β-hydroxyethyl)-piperazine, propylene glycol and magnesium chloride.

2. A composition as claimed in claim 1 and comprising also an antioxidant.

3. A stable parenterally administerable therapeutic oxytetracycline solution comprising oxytetracycline in the form of the base and an aqueous mixture of N,N′ - bis-(β - hydroxyethyl)piperazine, propylene glycol, magnesium chloride and an antioxidant.

4. A therapeutic composition as claimed in claim 2 or 3 wherein the antioxidant is formaldehyde sodium sulphoxylate.

5. A process for the preparation of a stable parenterally administerable therapeutic composition as claimed in claim 3 or 4 which comprises suspending the oxytetracycline base in a mixture of propylene glycol and water, adding magnesium chloride and N - N′-bis - (β - hydroxyethyl)piperazine stirring the mixture for a few hours until the oxytetracycline is completely dissolved, adding the antioxidant, adjusting the volume to the required volume and filtering the solution until clear.

6. A process for the preparation of a stable orally administerable therapeutic composition as claimed in claim 1 or 2 which comprises suspending the oxytetracycline base in a mixture of propylene glycol in water, adding magnesium chloride and N-(β-hydroxyethyl)-piperazine stirring the mixture for a few hours until the oxytetracycline is completely dissolved, if desired adding an antioxidant, adjusting the volume to the required volume and filtering the solution until clear and then adding if desired a sweetening composition.

7. A process as claimed in claim 5 or 6 wherein the antioxidant used is formaldehyde sodium sulphoxylate.

8. An aqueous pharmaceutical composition conntaining 25 to 80 mg/ml. of amphoteric pure, oxytetracycline base, from 300 to 1,000 mg/ml. of propylene glycol, from 12.5 to 50 mg/ml. of magnesium chloride hexahydrate, from 25 to 100 mg/ml. of N-(β-hydroxyethyl)piperazine or N,N′-bis-(β-hydroxyethyl)piperazine and from 0.1 to 5 mg/ml. of antioxidant.

9. A therapeutic solution of oxytetracycline substantially as herein described with reference to the Examples.

Continued

Dosage		Blood concentrations in mcg/ml. of blood				
			3 hr.	6 hr.	12 hr.	24 hr.
Rat	5 mg/Kg.	intravenous	1.0	0.60	<0.30	—
		intramuscular	1.50	0.50	<0.30	—
Dog	5 mg/Kg.	intravenous	2.53	1.77	1.0	0.60
		intramuscular	2.68	2.64	1.20	0.65
Man	100 mg.	intramuscular	0.70	0.60	0.50	—
	200 mg.	intramuscular	2.00	1.70	0.85	0.30
	250 mg.	intramuscular	3.80	2.86	2.20	0.80
	250 mg.	intravenous	2.10	1.60	1.05	0.35
	250 mg.	oral	0.74	0.45	—	—

Considering the data of blood concentration in mcg/ml of blood set forth in the above Tables for the ready made solution, it appears evident that the 'long acting action' exerted by this solution, as a therapeutically valuable concentration of the antibiotic in the blood, can be detected after 10 hours and that useful values are maintained up to a period of 24 hours after administration.

WHAT WE CLAIM IS:—

1. A stable orally administerable therapeutic oxytetracycline solution comprising oxytetracycline in the form of the base and an aqueous mixture of N-(β-hydroxyethyl)-piperazine, propylene glycol and magnesium chloride.

2. A composition as claimed in claim 1 and comprising also an antioxidant.

3. A stable parenterally administerable therapeutic oxytetracycline solution comprising oxytetracycline in the form of the base and an aqueous mixture of N,N′ - bis-(β - hydroxyethyl)piperazine, propylene glycol, magnesium chloride and an antioxidant.

4. A therapeutic composition as claimed in claim 2 or 3 wherein the antioxidant is formaldehyde sodium sulphoxylate.

5. A process for the preparation of a stable parenterally administerable therapeutic composition as claimed in claim 3 or 4 which comprises suspending the oxytetracycline base in a mixture of propylene glycol and water, adding magnesium chloride and N - N′-bis - (β - hydroxyethyl)piperazine stirring the mixture for a few hours until the oxytetracycline is completely dissolved, adding the antioxidant, adjusting the volume to the required volume and filtering the solution until clear.

6. A process for the preparation of a stable orally administerable therapeutic composition as claimed in claim 1 or 2 which comprises suspending the oxytetracycline base in a mixture of propylene glycol in water, adding magnesium chloride and N-(β-hydroxyethyl)-piperazine stirring the mixture for a few hours until the oxytetracycline is completely dissolved, if desired adding an antioxidant, adjusting the volume to the required volume and filtering the solution until clear and then adding if desired a sweetening composition.

7. A process as claimed in claim 5 or 6 wherein the antioxidant used is formaldehyde sodium sulphoxylate.

8. An aqueous pharmaceutical composition conntaining 25 to 80 mg/ml. of amphoteric pure, oxytetracycline base, from 300 to 1,000 mg/ml. of propylene glycol, from 12.5 to 50 mg/ml. of magnesium chloride hexahydrate, from 25 to 100 mg/ml. of N-(β-hydroxyethyl)piperazine or N,N′-bis-(β-hydroxyethyl)piperazine and from 0.1 to 5 mg/ml. of antioxidant.

9. A therapeutic solution of oxytetracycline substantially as herein described with reference to the Examples.

* C L M S *

10. A therapeutic solution of oxytetracycline when prepared by a process as claimed in any of claims 5 to 8.

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