PATENT SPECIFICATION

817,181

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COMPLETE SPECIFICATION

Therapeutic Products containing Tetracycline

We, BRISTOL LABORATORIES INC., a Corporation organised and existing under the laws of the State of New York, United States of America, of Thompson Road, East Syracuse, 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 a formulation of the antibiotic tetracycline which produces unusually high blood levels upon oral or parenteral administration.

Most unsuccessful work has been done in an attempt to increase the speed and efficiency of absorption of antibiotics on both oral and parenteral administration. Very little is known by way of general principles and, indeed, in the case of oral administration, it may be said that there are no methods known at all for increasing speed or efficiency of absorption other than the use of highly water-soluble salts, e.g. potassium penicillin. It is the object of the present invention to so formulate the antibiotic tetracycline that upon oral or parenteral administration there will be produced immediate absorption into the blood stream of amounts of this antibiotic which are substantially greater than those obtained by the use of such present formulations as capsules, aqueous suspensions or aqueous solutions of tetracycline hydrochloride, tetracycline base or calcium tetracycline.

The object of the present invention has been achieved by providing a mixture of a form of tetracycline and a non-toxic phosphate compound, the phosphate compound having when in the form of its sodium salt a $Na_2O:P_2O_5$ ratio from 1.0 to 2.0 inclusive and the non-toxic compound being present in an amount by weight equal to at least one-fifth of the weight of said form of tetracycline.

As might be expected, various phosphate compounds do not always provide precisely the same increase in the blood levels upon administration. Some combinations are more effective by parenteral administration and others are preferred for oral use.

Throughout the present description and claims, the phrase "a form of tetracycline" denotes organic and inorganic acid addition salts of tetracycline, the hydrated or anhydrous amphoteric form of tetracycline, metal salts of tetracycline, and chelates, complexes and simple esters of tetracycline which are rapidly hydrolyzed in the body.

With respect to the tetracycline antibiotic, use may be made of any acidic tetracycline salt or the physiological equivalent thereof. The preferred forms of tetracycline are tetracycline hydrochloride, tetracycline base, and the tetracycline sodium hexametaphosphate complex described below. Other forms which are effective but not to the extent of the preferred embodiments include normal organic and inorganic acid addition salts such as are used in therapy in general, e.g. bromide, sulphate, nitrates, orthophosphate, acetate, tartrate and citrate. By the term "physiological equivalent" is meant tetracycline base or one of its hydrated forms which when used orally are likely to be converted *in situ* in the stomach to the hydrochloride. Such forms are not physiologically equivalent when administered parenterally because they are not then exposed to concentrated hydrochloric acid and thus are not converted to the hydrochloride. Use may be made in the present invention of rapidly hydrolyzed esters, chelates and complexes of tetracycline.

With regard to the phosphate compounds which have been found to accelerate the absorption and utilization of the tetracycline antibiotic, it is again found that some are far more effective than others and that the utility of a given phosphate compound will vary with the route of administration. As exemplified below, the preferred embodiment relies on the use in combination with tetracycline base, an acid addition salt of tetracycline, or the tetracycline sodium hexametaphosphate complex of

[Price 3s. 6d.]

a weight of a hexametaphosphate, e.g., sodium hexametaphosphate, which is in the range of 0.2 to 2.0 times the weight of the tetracycline salt.

While the preferred embodiment gives the greatest improvement in the blood level picture, both on oral and on parenteral administration, some useful improvement is obtained by the use of phosphate compounds other than orthophosphates, such as metaphosphate, tripolyphosphate, tetrametaphosphate, trimetaphosphate, polymetaphosphate, pyrophosphate or any of the other available nontoxic phosphates which have when in the form of their sodium salts a $Na_2O:P_2O_5$ ratio from 1.0 to 2.0 inclusive. These phosphates must of course be supplied in combination with a cation and use is made of any non-toxic cation. Naturally the most satisfactory compounds and the most readily available are the sodium and potassium salts of these phosphates, such as sodium metaphosphate, sodium tripolyphosphate, potassium metaphosphate and mixtures thereof in amounts equal to one-fifth to twice the weight of tetracycline antibiotic in each dosage unit. Soluble salts are preferred but not essential for the parenteral products. When desired, these products may be prepared *in situ* or altered by the adjustment of the pH of an aqueous solution or suspension by the addition of a base such as sodium hydroxide or ammonium hydroxide or of an acid such as hydrochloric acid, sulfuric acid, ascorbic acid or citric acid.

The preferred acid tetracycline salt is either tetracycline hydrochloride or tetracycline sodium hexametaphosphate complex. This latter complex, which forms the subject matter of our co-pending application No. 24094/57, (Serial No. 817,180), is prepared by mixing aqueous, acid solutions of tetracycline, e.g. tetracycline hydrochloride, and sodium hexametaphosphate and collecting by filtration under acid conditions the precipitated crystalline salt. The ratios by weight of tetracycline hydrochloride to sodium hexametaphosphate to be used can vary widely; ratios of 1:2 to 1:0.05 are effective and about 1:0.25 or 1:0.33 is preferred. The acidity must be sufficient to maintain the tetracycline reagent in solution, e.g. less than about pH 2.0. The insolubility of the product makes the concentration used of little importance; reasonably concentrated solutions are, of course, more practical.

The preferred phosphate compound according to this invention other than orthophosphates is one of the commercially available hexametaphosphates, e.g. sodium hexametaphosphate, potassium hexametaphosphate, or mixtures thereof. When administered orally, as in the form of capsules, nothing else needs to be added although use may be made, if desired, of additional filling agents, lubricating agents and the like. In the case of aqueous suspensions for oral use, there may be added customary ingredients such as suspending agents, sweetening agents, preservatives, flavours and colours. For parenteral products most of these ingredients are normally omitted but there may be added the agents previously used in parenteral tetracycline products such as ascorbic acid, sources of metal ions such as magnesium chloride, and local anesthetics such as procaine hydrochloride and lidocaine hydrochloride (α-diethylamino-2,6-aceto-xylidide hydrochloride).

The combinations of the present invention can be used for oral application in powdered form, as tablets or in capsules, but may also be used in suspensions in aqueous liquids or in anhydrous, edible oils, such as peanut oil, sesame oil, or a modified coconut oil with a setting point below 60° F. or in aqueous emulsions of such oils. Parenteral use may be made of certain of these products which, upon reconstitution with water, give solutions at least temporarily.

When desired for specific purposes and rendered pharmaceutically compatible, there may be admixed with the combinations of the present invention various other additional medicaments, such as antihistamines, sulphur drugs (e.g. sulphadiazine, sulphabenzamide, sulphacetamide, sulphanilamide, sulphapyridine, sulphathiazole, sulphapyrazine, sulphguanidine, sulphathalidine, sulphasuxidine, sulphisoxazole, sulphamylon, phthalylsulphacetamide, N^1-3,4-dimethylbenzoylsulphanilamide, benzylsulphanilamide and N^1-2-(2-quinoxalyl)-sulphanilamide), lipotropic agents (particularly methionine, choline, inositol and beta-sitosterol and mixtures thereof), stimulants of the central nervous system (e.g. caffeine, amphetamines), local anesthetics, analgesics (e.g. aspirin, salicylamide, sodium gentisate, p-acetylaminophenol, phenacetin, codeine), laxatives (e.g. phenolphthalein), sedatives (e.g. barbiturates, bromides), salts of penicillin (e.g. potassium penicillin G, procaine penicillin G, 1-ephenamine penicillin G, dibenzylamine penicillin G; these combinations are particularly useful to enable variations of the pattern of blood levels obtained), phenoxymethylpenicillin and salts thereof, other antibiotic agents (e.g. streptomycin, dihydrostreptomycin, bacitracin, polymixin, tyrothricin, erythromycin, Aureomycin, "Terramycin" (Registered Trade Mark), oleandomycin, chloramphenicol, "Magnamycin" (Registered Trade Mark), novobiocin cycloserine; in some cases such combinations attack a wider range of organisms or show synergistic efficacy or provide decreased toxicity with equal efficacy), vitamins (e.g. Vitamins A, A_1, B_1, B_2, B_6, B_{12} and members of that family, folic acid and members of that family, Vitamins C, D_2, D_3 and E), hormones (e.g. cortisone, hydrocortisone, 9α-fluorocortisone, 9α-fluorohydrocortisone, prednisone and prednisolone), anabolic agents (e.g. 11,17-dihydroxy-9α-fluoro-17α-methyl-4-androsten-

3-one; 17α-ethyl-19-nortestosterone) and antifungal agents (e.g. mycostatin).

Following is a description by way of example of methods of carrying the invention into effect.

EXAMPLE I.

A mixture of equal parts by weight of tetracycline hydrochloride and sodium hexametaphosphate was prepared, filled into capsules and administered orally in single dosage to dogs to provide a dose of 12.5 mg. tetracycline hydrochloride per kg. Determination of the blood levels at various times after the administration of this single dose gave the following results:

Dog	Blood Levels in mcg./ml. Hours after Administration			
	0	1	4	24
365	NR	6.25	3.71	.26
380	NR	2.00	1.37	NR
385	NR	NR	.66	NR
412	NR	NR	.67	NR
		2.06	1.60	.065

(NR means no activity)

Administration of 12.5 mg. tetracycline hydrochloride per kg. without the added sodium hexametaphosphate to nine dogs gave average blood levels in mcg./ml. of 0.77—0.92 after one hour and about 0.75 after four hours.

A mixture of tetracycline hydrochloride and sodium hexametaphosphate in a ratio of 2:1 administered to dogs in the same manner and at the same dosage level provided average blood levels of 1.52 and 2.23 after one and four hours respectively.

A ratio of 4:1 provided average blood levels of 1.23 and 1.48 respectively.

Other ratios are 3:2, 2:3, 1:4, and 1:3, giving average blood levels one hour after administration of 0.91, 2.90, 1.14 and 1.45 mcg./ml. respectively, and after four hours average blood levels of 1.77, 2.24, 4.13, and 1.78 mcg./ml. respectively.

EXAMPLE II.

Tetracycline base and sodium hexametaphosphate were mixed, the mixture filled into capsules and administered orally in single dosage to dogs, to provide a dose of 12.5 mg. tetracycline hydrochloride activity per kg. body weight. Determination of the blood levels at various times after the administration of single doses with varying ratios of tetracycline base and sodium hexametaphosphate gave the following results:

Weight Ratio of Tetracycline Base to Sodium Hexametaphosphate	No. of Dogs	Average Blood Levels in mcg./ml. Hours after Administration	
		1	4
2:3	4	2.70	2.50
1:2	4	2.32	2.57
2:1	4	1.45	0.88
1:3	4	3.15	3.00

EXAMPLE III.

Tetracycline hydrochloride and sodium tetrametaphosphate were mixed in a ratio of 1:0.8, filled into capsules, and administered orally in single dosage to dogs to provide a dose of 12.5 mg. tetracycline hydrochloride activity per kg. Determination of the blood levels after one and four hours following the administration of this single dose gave blood levels of 1.41 and 1.61 mcg./ml. respectively.

EXAMPLE IV.

Tetracycline hydrochloride and sodium tetrapolyphosphate, $Na_6P_4O_{13}$ were mixed in ratios of 1:0.5 and 1:0.8, filled into capsules, and administered orally in single dosage to dogs to provide a dose of 12.5 mg. tetracycline hydrochloride activity per kg. body weight. The results of the determination of the blood levels are shown below:

Weight Ratio of Tetracycline Hydrochloride to Sodium Tetraphosphate	No. of Dogs	Average Blood Levels in mcg./ml. Hours after Administration	
		1	4
1:0.5	4	1.65	1.74
1:0.8	4	2.13	1.91

EXAMPLE V.

Tetracycline hydrochloride and sodium tripolyphosphate were mixed in a ratio of 1:0.8. The mixture was filled into capsules and administered orally in single dosage to dogs to provide a dose of 12.5 mg. tetracycline hydrochloride activity per kg. body weight. Average blood levels of 0.51 and 1.70 mcg./ml. were assayed after one and four hours following administration respectively.

EXAMPLE VI.

Tetracycline hydrochloride was mixed with potassium metaphosphate in a ratio of 2:3, the mixture filled into capsules and administered orally in single dosage to dogs to provide a dose of 12.5 mg. tetracycline hydrochloride activity per kg. body weight. Determination of the average blood levels after one and four hours following administration showed 1.65 and 1.85 mcg./ml. respectively.

EXAMPLE VII.

Tetracycline hydrochloride and potassium polymetaphosphate were mixed in a ratio of 1:0.8, the mixture filled into capsules and administered orally in single dosage to dogs to provide a dose of 12.5 mg. tetracycline hydrochloride activity per kg. of body weight. Determination of the average blood levels at one and four hours following administration showed 1.53 and 1.86 mcg./ml. respectively.

EXAMPLE VIII.

Tetracycline base and potassium pyrophosphate were mixed in a ratio of 2:3, the mixture filled into capsules and administered orally in single dosage to dogs to provide a dose of 12.5 mg. tetracycline hydrochloride activity per kg. body weight. Determination of the average blood levels at one and four hours following the administration gave 1.35 and 1.35 mcg./ml. respectively.

EXAMPLE IX.

A mixture of tetracycline base and potassium tripolyphosphate was prepared in a ratio of 2:3 filled into capsules and administered orally in single dosage to dogs to provide a dose of 12.5 mg. tetracycline hydrochloride activity per kg. of body weight. Determination of the average blood levels at one and four hours following the administration showed 1.45 and 1.00 mcg./ml. respectively.

From the Examples I—IX it is apparent that all these compositions of the present invention give results far superior to those obtained with the ordinary tetracycline hydrochloride capsules. In particular good results are obtained with the mixture of tetracycline base or tetracycline hydrochloride with sodium hexametaphosphate.

EXAMPLE X.

A formulation containing per cc. 50 mg. tetracycline hydrochloride, 150 mg. ascorbic acid and 25 mg. sodium hexametaphosphate when administered intramuscularly to groups of five rabbits in single doses of 2.5 mg. of tetracycline hydrochloride per kg. gave average blood levels of tetracycline of 1.72 mcg./ml. one hour after administration and of 0.85 mcg./ml. four hours after administration.

EXAMPLE XI.

Three dry mixtures suitable for oral use upon reconstitution with water (q.s. ad 100 cc.) were prepared by mixing 0.375 g. potassium alginate (Kelmar), 40 g. granulated sugar, 0.080 g. 200 mesh U.S.P. Methyl Paraben, 0.020 g. 200 mesh U.S.P. Propyl Paraben, 0.14 g. reagent grade sodium bisulphite, 0.20 g. U.S.P. sodium citrate, 0.067 g. 200 mesh U.S.P. sodium saccharin, 0.167 g. 200 mesh Sodium Sucaryl, tetracycline base equivalent to 2.50 g. tetracycline hydrochloride and either 0.50 g., 2.50 g. or 5.00 g. sodium hexametaphosphate.

WHAT WE CLAIM IS:—

1. A therapeutic composition for the treat-

EXAMPLE III.

Tetracycline hydrochloride and sodium tetrametaphosphate were mixed in a ratio of 1:0.8, filled into capsules, and administered orally in single dosage to dogs to provide a dose of 12.5 mg. tetracycline hydrochloride activity per kg. Determination of the blood levels after one and four hours following the administration of this single dose gave blood levels of 1.41 and 1.61 mcg./ml. respectively.

EXAMPLE IV.

Tetracycline hydrochloride and sodium tetrapolyphosphate, $Na_6P_4O_{13}$ were mixed in ratios of 1:0.5 and 1:0.8, filled into capsules, and administered orally in single dosage to dogs to provide a dose of 12.5 mg. tetracycline hydrochloride activity per kg. body weight. The results of the determination of the blood levels are shown below:

Weight Ratio of Tetracycline Hydrochloride to Sodium Tetraphosphate	No. of Dogs	Average Blood Levels in mcg./ml. Hours after Administration	
		1	4
1:0.5	4	1.65	1.74
1:0.8	4	2.13	1.91

EXAMPLE V.

Tetracycline hydrochloride and sodium tripolyphosphate were mixed in a ratio of 1:0.8. The mixture was filled into capsules and administered orally in single dosage to dogs to provide a dose of 12.5 mg. tetracycline hydrochloride activity per kg. body weight. Average blood levels of 0.51 and 1.70 mcg./ml. were assayed after one and four hours following administration respectively.

EXAMPLE VI.

Tetracycline hydrochloride was mixed with potassium metaphosphate in a ratio of 2:3, the mixture filled into capsules and administered orally in single dosage to dogs to provide a dose of 12.5 mg. tetracycline hydrochloride activity per kg. body weight. Determination of the average blood levels after one and four hours following administration showed 1.65 and 1.85 mcg./ml. respectively.

EXAMPLE VII.

Tetracycline hydrochloride and potassium polymetaphosphate were mixed in a ratio of 1:0.8, the mixture filled into capsules and administered orally in single dosage to dogs to provide a dose of 12.5 mg. tetracycline hydrochloride activity per kg. of body weight. Determination of the average blood levels at one and four hours following administration showed 1.53 and 1.86 mcg./ml. respectively.

EXAMPLE VIII.

Tetracycline base and potassium pyrophosphate were mixed in a ratio of 2:3, the mixture filled into capsules and administered orally in single dosage to dogs to provide a dose of 12.5 mg. tetracycline hydrochloride activity per kg. body weight. Determination of the average blood levels at one and four hours following the administration gave 1.35 and 1.35 mcg./ml. respectively.

EXAMPLE IX.

A mixture of tetracycline base and potassium tripolyphosphate was prepared in a ratio of 2:3 filled into capsules and administered orally in single dosage to dogs to provide a dose of 12.5 mg. tetracycline hydrochloride activity per kg. of body weight. Determination of the average blood levels at one and four hours following the administration showed 1.45 and 1.00 mcg./ml. respectively.

From the Examples I—IX it is apparent that all these compositions of the present invention give results far superior to those obtained with the ordinary tetracycline hydrochloride capsules. In particular good results are obtained with the mixture of tetracycline base or tetracycline hydrochloride with sodium hexametaphosphate.

EXAMPLE X.

A formulation containing per cc. 50 mg. tetracycline hydrochloride, 150 mg. ascorbic acid and 25 mg. sodium hexametaphosphate when administered intramuscularly to groups of five rabbits in single doses of 2.5 mg. of tetracycline hydrochloride per kg. gave average blood levels of tetracycline of 1.72 mcg./ml. one hour after administration and of 0.85 mcg./ml. four hours after administration.

EXAMPLE XI.

Three dry mixtures suitable for oral use upon reconstitution with water (q.s. ad 100 cc.) were prepared by mixing 0.375 g. potassium alginate (Kelmar), 40 g. granulated sugar, 0.080 g. 200 mesh U.S.P. Methyl Paraben, 0.020 g. 200 mesh U.S.P. Propyl Paraben, 0.14 g. reagent grade sodium bisulphite, 0.20 g. U.S.P. sodium citrate, 0.067 g. 200 mesh U.S.P. sodium saccharin, 0.167 g. 200 mesh Sodium Sucaryl, tetracycline base equivalent to 2.50 g. tetracycline hydrochloride and either 0.50 g., 2.50 g. or 5.00 g. sodium hexametaphosphate.

WHAT WE CLAIM IS:—

1. A therapeutic composition for the treat-

ment of bacterial infection comprising in admixture a form of tetracycline and a non-toxic phosphate compound, the phosphate compound having when in the form of its sodium salt a $Na_2O:P_2O_5$ ratio from 1.0 to 2.0 inclusive, and the non-toxic phosphate compound being present in an amount by weight equal to at least one-fifth of the weight of the form of tetracycline.

2. A therapeutic composition as claimed in claim 1 wherein the phosphate compound is present in an amount by weight in the range of one-fifth to twice the weight of the form of tetracycline.

3. A therapeutic composition as claimed in claim 1 or claim 2 wherein the tetracycline is in the form of an acid addition salt or tetracycline base.

4. A composition as claimed in claim 3 wherein the acid addition salt of tetracycline is tetracycline hydrochloride.

5. A therapeutic composition as claimed in any one of the preceding claims wherein the non-toxic phosphate compound is a hexametaphosphate, a metaphosphate or a polyphosphate.

6. A therapeutic composition as claimed in claim 5 wherein the non-toxic phosphate compound is sodium hexametaphosphate, sodium metaphosphate or sodium polyphosphate.

7. A therapeutic composition as claimed in claim 5 wherein the non-toxic hexametaphosphate and said form of tetracycline are present in substantially equal parts by weight.

8. A therapeutic composition for the treatment of bacterial infection comprising tetracycline sodium hexametaphosphate complex and sodium hexametaphosphate, said sodium hexametaphosphate being present in an amount by weight in the range of one-fifth to twice the weight of said tetracycline sodium hexametaphosphate complex.

9. A method for the preparation of a therapeutic composition for the treatment of bacterial infection substantially as described with reference to any one of the specific examples hereinbefore set forth.

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ERRATA

SPECIFICATION NO. 817,181

Page 1, line 15, *for* "Most" *read* "much".

Page 1, line 32, *after* "solutions" *delete* ",".

Page 1, line 69, *for* "nitrates" *read* "nitrate".

Page 2, line 33, *for* "sulfuric" *read* "sulphuric".

Page 2, line 38, *after* "complex" *insert* ",".

Page 2, line 39, *for* "24094/57" *read* "24090/57".

Page 2, line 40, *after* "817,180)" *delete* ",".

Page 2, line 92, *for* "sulph" *read* "sulpha".

THE PATENT OFFICE,
26th January, 1960

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