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PATENT SPECIFICATION

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COMPLETE SPECIFICATION

Therapeutic Preparations containing Tetracycline

We, BRISTOL LABORATORIES LIMITED, formerly known as The Angier Chemical Company Limited, a British Company, of 211 Blackfriars Road, London, S.E.1, 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 compositions useful in antibacterial therapy and, more particularly, to compositions comprising tetracycline and at least one additional drug.

According to the present invention there is provided a therapeutic composition comprising tetracycline free base or a non-toxic metal or acid addition salt thereof, and at least one additional drug consisting of a sulpha drug, a vitamin, neomycin, streptomycin, dihydrostreptomycin, penicillin, chlorotetracycline, oxytetracycline or a non-toxic salt thereof or a hormone effective in increasing the resistance of the body to stress.

The additional drug may be a multiple combination of the above drugs.

The name tetracycline is used herein in a generic sense to include the free base including the anhydrous form and the tri-hydrate and non-toxic metal and acid addition salts of the free base.

More particularly, the present invention includes compositions comprising tetracycline and one or more of the following drugs: Sulpha drugs, (*e.g.* sulphadiazine, sulphamerazine, sulphamethazine, sulphabenzamide, sulphacetamide, sulphanilamide, sulphapyridine, sulphathiazole, sulphapyrazine, sulphaguanidine, sulphathalidine, sulphasuxidine, sulphisoxazole, sulphamylon, phthalylsulphacetamide, N^1-3,4-dimethylbenzoylsulphanilamide, benzylsulphanilamide and N^1-(2-quinoxalyl)-sulphanilamide), vitamins (*e.g.* Vitamins A_1, A_2, 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) and neomycin; in some cases such combinations attack a wider range of organisms or show synergistic efficacy or provide decreased toxicity with equal efficacy), or hormones (*e.g.* cortisone, adrenocotropic hormone).

The combination of tetracycline with hormones effective in increasing the resistance of the body to stress has also been found to be very useful in the treatment of certain infectious diseases. Hormones effective in increasing the resistance of the body to stress are ACTH, cortisone, hydrocortisone, prednisone and prednisolone. Cortisone and/or hydrocortisone are substances secreted by the adrenals and have a very important metabolic function. ACTH is a hormone secreted by the pituitary gland which controls the secretion of cortisone or hydrocortisone. Prednisone and prednisolone are chemical derivatives of cortisone and hydrocortisone with a more powerful action.

Multiple combinations of added agents are often useful, *e.g.* sulphadiazine and sulphamerazine to provide equal efficacy and reduced toxicity; substantially equal amounts of a non-toxic acid addition salt of streptomycin (sulphate; levo pimaric-6, 8a-cis-endosuccinate) and a non-toxic acid addition salt of dihydrostreptomycin (sulphate; sulphate iodide) to provide equal efficacy and reduced toxicity; multiple vitamins; highly water-soluble salts of penicillin (*e.g.* potassium) with moderately water-insoluble salts of penicillin (*e.g.* procaine).

The combination of tetracycline (or a salt thereof) with chlorotetracycline (or a salt thereof), preferably but not necessarily in a ratio in the range of 1:10 to 10:1 by weight, is found to be of particular value in providing increased activity and descreased toxicity. Such a combination of tetracycline with either chlorotetracycline or oxytetracycline may also be used to advantage to replace tetracycline alone in any of the combinations of the present invention.

The active ingredients of the present invention, are used as a simple powder, as tablets, as troches, as lozenges or in capsules. Aqueous suspensions are prepared in advance or *in situ*

[Price 3s. 6d.]

when the stability of other added agents (*e.g.* potassium benzyl-penicillin) so requires, and are a highly acceptable oral dosage form. A particularly useful oral dosage form is a suspension in a palatable, acceptable edible oil; coconut oil is preferred, particularly when liquid at room temperature or free of tristearin and gelled with an aluminium stearate. The active ingredients of the present invention are admixed with suitable buffers or pharmaceutical additives, preservatives, diluents, binders, lubricants, masticatory substances, colours, flavours, suspending agents, dispersing agents, resuspending agents, and stabilizing agents as desired.

The active ingredients of the present invention are presented for parenteral use as a suspension in an injectable oil (*e.g.* peanut oil), as a suspension in a gelled injectable oil (*e.g.* peanut oil gelled with 2% aluminium monostearate), as an aqueous suspension or as a powder to which a sterile, aqueous diluent is added before use to generate an injectable suspension. These aqueous suspensions often advantageously contain non-toxic suspending or dispersing agents, such as sodium carboxymethylcellulose, methylcellulose, polyvinyl alcohol, polyvinylpyrrolidone, gum tragacanth, gelatin, pectin, alginates, dextrans, gum karaya, lecithin, "Spans," "Tweens," Amerchols, inositolphosphoric acids and their non-toxic salts (*e.g.* sodium phytate), glyceryl monostearate, Kreelon CD, polyoxyalkylenesorbitols, not more than 2.0 per cent of an injectable oil such as peanut oil and condensation products, having molecular weights greater than 1500, of ethylene oxide with a condensation product of propylene oxide with propylene glycol (*e.g.* Pluronic F 68). On occasion, it is advantageous to actually coat the particles of active ingredients, at least in part, with one of these agents, *e.g.* lecithin.

The combination of the present invention is presented for topical use in a large variety of pharmaceutical forms. These include aqueous or oil solutions or suspensions for use on dressings or by instillation or by direct application. The product may be applied directly in dry solid form, using suitable solid diluents as is convenient. The combination is useful in ointment form in oils, which may be gelled, in emulsions of oil and water and in aqueous gels prepared for example, from sodium carboxymethylcellulose or propylene glycol and carbowax. Anhydrous oils are preferred when the combination is found to be unstable to water under the expected conditions and duration of storage in commercial use. The product may be administered in suppositories, in dental cones, or in bougies. Non-aqueous ointments may have as their base wool fat, petrolatum, cottonseed oil, peanut oil or oxycholesterin derivatives from wool fat.

If desired, buffering agents may be added such as sodium citrate or sodium phosphates, as when one of the active ingredients of this invention is an alkali metal salt of penicillin. When appropriate, the suspensions may be buffered by the addition of free acids, *e.g.* citric acid or phosphoric acid. If appropriate, a stabilizing agent for penicillin is added, such as hexamethylenetetramine or sodium phytate. Small amounts of preservative are often used, *e.g.* phenol, cresol, or alkyl esters of *p*-hydroxybenzoic acid. Useful variations in the properties of the active ingredients of the present invention are obtained by altering particle size or shape, as by varying procedures of crystallization or, more easily, by mechanical means such as grinding, hammer-milling, pulverizing, or micronizing. When using tetracycline free base, either the anhydrous form or the trihydrate is used; the trihydrate is not used where its water of hydration will make the product unstable as determined by simple test.

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

EXAMPLE I.

Magnesium stearate (5.7 g.), oil of peppermint U.S.P. (1.5 cc), 60 mesh potassium penicillin G (35 g.), 60 mesh $CaCO_3$,- starch (178.2 g.) and 60 mesh tetracycline hydrochloride (50 g.) are mixed, slugged, ground to pass through a #26 mesh screen and tabletted to make 500 tablets.

EXAMPLE II.

Magnesium stearate (5.7 g.), oil of peppermint U.S.P. (1,5 cc), 60 mesh chlorotetracycline hydrochloride (50 g.), 60 mesh $CaCO_3$,- starch (178.2 g.) and 60 mesh tetracycline hydrochloride (50 g.) are mixed, slugged, ground to pass through a #26 mesh screen and tabletted to make 500 tablets.

EXAMPLE III.

Lecithin-coated pulverized tetracycline trihydrate and Vitamin B_{12} are weighed into blenders under sterile conditions, blended for six days, filled under sterile conditions into a vial and reconstituted before use by the addition of sterile water to give approximately one therapeutic dose of each ingredient per cc.

EXAMPLE IV.

Lecithin-coated pulverized tetracycline trihydrate and procaine penicillin G are weighed into blenders under sterile conditions, blended for six days, filled under sterile conditions into a vial and reconstituted before use by the addition of sterile water to give approximately one therapeutic dose of each ingredient per cc.

EXAMPLE V.

Lecithin-coated pulverized tetracycline trihydrate and A.C.T.H. are weighed into blenders, under sterile conditions, blended for six days, filled under sterile conditions into a vial and reconstituted before use by the addition of sterile water to give approximately one

therapeutic dose of each ingredient per cc.

EXAMPLE VI.

Lecithin-coated pulverized tetracycline trihydrate and streptomycin sulphate are weighed into blenders under sterile conditions, blended for six days, filled under sterile conditions into a vial and reconstituted before use by the addition of sterile water to give approximately one therapeutic dose of each ingredient per cc.

EXAMPLE VII.

The following ingredients are mixed under sterile conditions and filled into 2-ounce bottles:

Ingredients		Formulation Number 1	2	3	4
Pulverized Sugar	g.	24.0	24.0	24.0	24.0
Soluble saccharin	g.	0.3	0.3	0.3	0.3
Sodium benzoate	g.	0.06	0.06	0.06	0.06
Anhydrous sodium citrate, U.S.P.	g.	0.12	0.12	0.12	0.12
"Sucaryl"	g.	1.20	1.20	1.20	1.20
Potassium alginate	g.	0.20	0.20	0.20	0.20
Tetracycline trihydrate	g.	1.20	1.20	1.20	1.20
Sulphadiazine	g.	12.0	—	—	4.0
Sulphamerazine	g.	—	12.0	—	4.0
Sulphamethazine	g.	—	—	12.0	4.0
Anethole	ml.	0.02	.02	0.02	0.02

These mixtures are reconstituted by the addition of sterile water (q.s. ad 2 oz.) and administered orally.

EXAMPLE VIII.

Soluble saccharin (0.60 g.), "Sucaryl" (4 g.), powdered sugar (20 g.), d-sorbitol (8 g.), potassium alginate (6 g.), tetracycline hydrochloride (4 g.), and chlorotetracycline hydrochloride (4 g.) are well mixed (q.s. ad 200 cc.) into one of the following bases.

Base #1 is composed of 100% coconut oil.

Base #2 is composed of 100% coconut oil sufficiently free of tristearin, to be liquid at 60°F.

Base #3 is composed of 80% coconut oil and 20% peanut oil.

Base #4 is composed of 95% coconut oil and 5% peanut oil.

Base #5 is composed of 95% coconut oil and 5% peanut oil.

Base #6 is composed of 90% coconut oil and 10% peanut oil, gelled with 1% aluminium monostearate.

Base #7 is composed of 90% coconut oil and 10% peanut oil gelled with 2% aluminium monostearate.

Base #8 is composed of 90% coconut oil and 10% mineral oil gelled with 2% aluminium monostearate.

Base #9 is composed of 90% coconut oil and 10% mineral oil gelled with 1% aluminium monostearate.

Base #10 is composed of 90% coconut oil and 10% mineral oil.

Base #11 is composed of 100% coconut oil gelled with 2% aluminium monostearate. "Spans", "Tweens" and "Sucaryl" are Registered Trade Marks.

What we claim is:—

1. A therapeutic composition comprising tetracycline free base or a non-toxic metal or acid addition salt thereof, and at least one additional drug consisting of a sulpha drug, a vitamin, neomycin, streptomycin, dihydrostreptomycin, penicillin, chlorotetracycline, oxytetracycline or a non-toxic salt thereof or a hormone effective in increasing the resistance of the body to stress.

2. A composition as claimed in claim 1 wherein the additional drug is a multiple combination of sulpha drugs.

3. A composition as claimed in claim 1

therapeutic dose of each ingredient per cc.

EXAMPLE VI.

Lecithin-coated pulverized tetracycline trihydrate and streptomycin sulphate are weighed into blenders under sterile conditions, blended for six days, filled under sterile conditions into a vial and reconstituted before use by the addition of sterile water to give approximately one therapeutic dose of each ingredient per cc.

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Sodium benzoate	g.	0.06	0.06	0.06	0.06
Anhydrous sodium citrate, U.S.P.	g.	0.12	0.12	0.12	0.12
"Sucaryl"	g.	1.20	1.20	1.20	1.20
Potassium alginate	g.	0.20	0.20	0.20	0.20
Tetracycline trihydrate	g.	1.20	1.20	1.20	1.20
Sulphadiazine	g.	12.0	—	—	4.0
Sulphamerazine	g.	—	12.0	—	4.0
Sulphamethazine	g.	—	—	12.0	4.0
Anethole	ml.	0.02	.02	0.02	0.02

These mixtures are reconstituted by the addition of sterile water (q.s. ad 2 oz.) and administered orally.

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2. A composition as claimed in claim 1 wherein the additional drug is a multiple combination of sulpha drugs.

3. A composition as claimed in claim 1

* C L M S *

wherein the additional drug is a cortisone.

4. A method for the preparation of a therapeutic composition as claimed in claim 1 substantially as herein described.

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