

PATENT SPECIFICATION

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 AND INVENTION

(54) IMPROVED WATER-SOLUBLE TETRACYCLINE COMPLEX

(71) I, ISRAEL MARCUS of 7 Narkis Street, Jerusalem, Israel, an Israeli Citizen, do hereby declare the invention, for which I pray that a patent may be granted to me, 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 water-soluble complex of a tetracycline antibiotic. Tetracycline itself is almost insoluble in water and, consequently, when it is administered to a patient, not only is it not properly dispersed throughout the patient's system, but it also may cause local disorders, e.g. malfunction of the intestines and the renal system and destruction or damage to other sensitive tissues. Consequently, a number of attempts have been made to produce a tetracycline derivative which is not only water-soluble, but also retains the activity of tetracycline.

These attempts have not met with unqualified success. Although it is now possible to manufacture a water-soluble derivative of tetracycline, the compounds prepared suffer from certain disadvantages, e.g. a solubility which is not so great as desired and which, consequently, leads to some of the disadvantages of tetracycline itself, an increased toxicity, an activity lower than that of tetracycline, and expense of manufacture.

Thus, the present invention consists in a water-soluble complex of a tetracycline antibiotic with a methylene-amino-salicylate or methyleneamino-salicylic acid.

The complex may be simply prepared by reacting together the tetracycline and the methyleneamino-salicylate or methyleneamino-salicylic acid in a suitable solvent and then separating the complex so formed. However, it is preferred that the complex should be prepared as follows:

A tetracycline hereinafter referred to solely as tetracycline, although it will, of course, be understood that the tetracycline antibiotics in general are included) and the methyleneamino-salicylate or methyleneamino-salicylic acid are dissolved in a common solvent

or in two different but miscible solvents, either together, or as two separate solutions which are then mixed. The solvent or solvents should be such that the complex is insoluble in it or them. The reaction is suitably carried out in an inert atmosphere, such as nitrogen and in the absence of light. A suitable common solvent is methyl alcohol. Separation of the tetracycline-methyleneamino-salicylate complex takes place immediately. The deposit is then filtered off, washed with a liquid in which it is not soluble, e.g. methanol, and is dried, suitably in a vacuum. The dried product will be without water of crystallization and in order to regain this, it may be left in the air for a suitable period of time.

The complex may be administered in association with any pharmaceutically acceptable diluent or excipient and may be supplied to the patient in any conventional form and by any conventional route, e.g. the parenteral route, the oral route, or the anal route. The complex may be formulated as, e.g. an injection solution in a suitable solvent, especially a solvent comprising water, or with a solid carrier in tablet form, or as a suppository. In general, the complex is administered in tablet form in association with a suitable solid carrier.

The addition complexes have been found not to be stable. This may be shown, by inter alia, the fact that they react very easily with other substances. A solution of the complex will react with, for example, streptomycin, dihydrostreptomycin or neomycin, to cause a rearrangement, a complex being formed between the methyleneamino-salicylate and the streptomycin, dihydrostreptomycin or neomycin, and the tetracycline being liberated. We therefore believe that the new complex is a loosely bound addition complex.

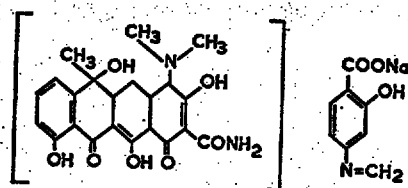
The invention is further illustrated with reference to the following Example which is, of course, not to be taken in any limiting sense.

[Price 5s. 0d. (25p)]

EXAMPLE

Preparation of a tetracycline-sodium methyleneamino-salicylate complex.

- 5 One gram of amphoteric tetracycline, protected from the light, was dissolved, with stirring and with the introduction of nitrogen, in 10 ml of methyl alcohol. A second solution was prepared by dissolving 0.5 g of sodium methylene-amino-salicylate in 2 ml of methyl alcohol (approximately equivalent quantities). The solutions were then mixed. The tetracycline-sodium methyleneamino-salicylate separated immediately. It may be generally represented by the following formula:



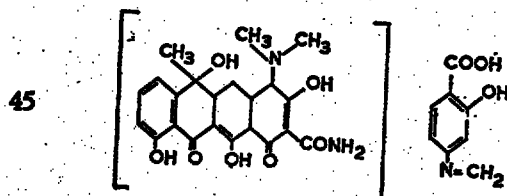
The deposit was filtered off, washed three times with methanol and dried in a vacuum.

- 20 The dry product was allowed to stand for twelve hours in air, in order to regain its water of crystallization. The complex was a bright yellow colour, soluble in water and in a physiological saline solution. Its stability was found to be dependent upon its concentration in the solution. A highly concentrated solution is stable for 6-8 hours. Increasing the concentration of the complex increases its stability.

- 30 5 Grams of this tetracycline-sodium methyleneaminosalicylate complex was dissolved in 100 ml. of a mixture containing 50% water and 50% ethanol, with stirring and slight heating. A solution of 9.6 g of dihydrostreptomycin in ethanol was added. A deposit formed which was filtered off. It is believed that there was formed an unstable addition compound of dihydrostreptomycin with sodium methyleneamino-salicylate.

WHAT I CLAIM IS:—

- 40 1. A water-soluble complex of a tetracycline antibiotic with a methyleneamino-salicylate or methyleneamino-salicylic acid.
2. A water-soluble complex of tetracycline having the following formula:



or a physiologically acceptable salt thereof.

3. A complex according to claim 1 or claim 2, in the form of the sodium salt.

4. A complex according to claim 1, substantially as hereinbefore described.

5. A pharmaceutical composition comprising a complex according to any one of claims 1 to 4 in association with a pharmaceutically acceptable diluent or excipient.

6. A pharmaceutical composition according to claim 5 in the form of a solution in a suitable solvent.

7. A pharmaceutical composition according to claim 6, in which said solvent comprises water.

8. A pharmaceutical composition according to claim 5, in which said diluent or excipient is a solid carrier.

9. A pharmaceutical composition according to claim 8, in tablet form.

10. A pharmaceutical composition according to claim 5, in the form of a suppository.

11. A pharmaceutical composition according to claim 5, substantially as hereinbefore described.

12. A method of making a complex according to any one of claims 1 to 4, which comprises reacting a tetracycline with a methyleneamino-salicylate or methyleneamino-salicylic acid in a suitable solvent.

13. A method according to claim 12, in which said tetracycline and said methyleneamino-salicylate or salicylic acid are reacted in the presence of a suitable solvent, in which said complex is substantially insoluble, and in an atmosphere of nitrogen to produce a precipitate of said complex, said complex is then filtered, washed with a liquid in which it is substantially insoluble and dried.

14. A method according to claim 12 or claim 13, in which said solvent is methyl alcohol.

15. A method according to claim 13 in which said liquid with which said complex is washed is methyl alcohol.

16. A method according to any one of claims 12 to 15, effected in the absence of light.

17. A method according to any one of claims 12 to 16, in which said complex is dried in a vacuum.

18. A method according to any one of claims 12 to 17, in which, after drying, said complex is allowed to stand in air to take up water of crystallization.

19. A method according to any one of claims 12 to 18, in which said methyleneamino-salicylate is sodium methyleneamino-salicylate.

20. A method according to claim 12, substantially as hereinbefore described with reference to the foregoing Example.

21. A water-soluble complex when prepared by a method according to any one of claims 12 to 20.

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