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(54) COMPLEXES OF TETRACYCLINES

(71) We, MEDIMPEX GYOGYSZERKUL-
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ter, Budapest V., Hungary, a body corpor-
ate, duly organised under the laws of Hun-
gary, 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 complexes of
tetracyclines.

Consequent to the low solubility of tetra-
cyclines in the pH range suitable to paren-
teral administration their derivatives are
generally used, inter alia their metal-acid
complexes e.g. their aluminium gluconates
(Remmers E. G., Barringer W. C., Sieger
G. M., Doerschuk A. P.: "Metal-Acid
Complexes with Members of the Tetra-
cycline Family", J. Pharm. Scie. 53, 1452,
1534 (1964); 54, 49 (1965); U.S.P. 2,736,725;
U.S.P. 3,053,892; American Cyanamid
U.S.P. 3,068,264); their magnesiumoxyethyl
ammonium salts (Neumann H., Viehmann:
Arzneim. Forsch. 9, 711 (1959)); their pyr-
rolidinomethyl derivatives (Siedel W., Söder
A., Lindner, F.: "Die Aminomethylierung
der Tetracycline", Münch. med. Wschr. 100,
661 (1958); German Auslegeschriften Nos.
1,044,806 (1958) and 1,063,598 (1959)); or
those obtained by the Mannich-base reaction
(Blackwood, R. K.: "Water-soluble α -6-
Deoxy-5-hydroxy-tetracycline Derivatives",
Pfizer German Patentschrift 1,914,194
(1968)).

The present invention provides a new type
of derivative of tetracyclines, namely the
complexes thereof formed with tris-(hy-
droxymethyl)-aminomethane (in the follow-
ing: Tris). Their preparation and proper-
ties are described, and some suggested but
however not the sole possible examples of
formulations for pharmaceutical use are
given.

[Price 33p]

The complexes may be obtained in a
crystalline form by simply dissolving both
the respective tetracycline and Tris (molar
ratio 1:3 to 1:6) in an appropriate organic
solvent (e.g. methanol) or water, and evapor-
ating the solvent in vacuo or lyophilizing, re-
spectively.

The products prove to be true complexes
of the tetracyclines and Tris, as can be
shown by comparing the infra-red spectra
of potassium bromide discs of the starting
antibiotics with those of the products:

(a) Starting from *Oxytetracycline* hydro-
chloride its band at 678 cm⁻¹ of medium
intensity disappeared or changed into a low
shoulder; its weak band at 818 cm⁻¹ dis-
appeared; its band at 1540 cm⁻¹ shifted to
1520 cm⁻¹; the bands at 1590 and 1625 cm⁻¹
changed into a shoulder at 1600 cm⁻¹ and
a very intense band at 1636 cm⁻¹; and the
band at 1671 cm⁻¹ present in the starting
material was lacking from the product.

(b) Starting from *Doxycycline* (α -6-
deoxy-5-hydroxytetracycline) a band of
medium intensity at 660 cm⁻¹ and a shoulder
678 cm⁻¹ appeared instead of the double
band of the starting material at 662 and 670
cm⁻¹; a weak band at 823 cm⁻¹ appeared
replacing those of doxycycline at 818 cm⁻¹
and 828 cm⁻¹; another weak band at 855
cm⁻¹ appeared instead of the band of the
starting material at 849 cm⁻¹; and a new
band of more than medium intensity ap-
peared at 1513 cm⁻¹.

(c) In the case of *Methacycline* (6-
methylene-5-hydroxy-tetracycline hydro-
chloride) its band at 653 and 677 cm⁻¹ were
replaced by a shoulder at 645 cm⁻¹; the
intensities of the bands at 820 and 840 cm⁻¹
decreased; and instead of the band of meth-
acycline at 873 cm⁻¹ a weak band appeared
at 860 cm⁻¹; further a new band of medium
intensity appeared at 1512 cm⁻¹.

(d) In the product obtained from *Chlor-*

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tetracycline hydrochloride a new weak band at 595 cm^{-1} was discernible.

Different optical rotations of the tetracyclines and of their Tris-complexes further indicate that true complexes form: $[\alpha_D]$ of oxytetracycline equals -120° , that of its Tris-complex -145° .

The above complexes of tetracyclines and Tris are watersoluble, yielding solutions up to 10 per cent concentration in the pH range 7.3—8.0. However, identical solutions of the complexes may be obtained by merely dissolving the tetracyclines in Tris-buffer.

Stable preconstituted parenteral formulations include an antioxidant.

After storage of these solutions at 58°C for 30 days, less than 10 per cent decrease of light-absorption at the maxima of the latter (e.g. at 353 $\text{m}\mu$ in the case of oxytetracycline) was found to have occurred. However there was no decrease of antibiotic activity.

Antibiotic activities of the Tris-tetracyclines proved to be 0—40 per cent higher but never less than those of corresponding starting materials of the same concentration. Intravenous or intramuscular administration of Tris-oxytetracycline into rabbits yielded higher and longer-lasting plasma values than other derivatives. Both in tissue cultures and in vivo the absence of any local damaging effect of the Tris-tetracyclines was striking. In the injected rabbits no signs of toxicity or side-effects were observed.

The application of the present invention to different tetracyclines and modes of administration is exemplified but not limited to the following formulations:

EXAMPLE 1

Dry fill: 100 mg. tetracycline hydrochloride is dissolved in 8 ml. methanol in a nitrogen atmosphere, 144 mg. Tris is added, the pH is set to 7.9 with hydrochloric acid, and the obtained solution is evaporated in vacuo to dryness.

Dissolving ampoule: 2 ml. distilled water. Administration: not only intravenous, but also by subcutaneous and intramuscular injection (being non-irritant). The material has been injected also, with good results, into the anterior chamber and vitreous humour of patients's eyes; suggested also for drip infusion, intrathecal, intracystic and intraarticular use and for sprays to be inhaled. Both for human and veterinary use.

EXAMPLE 2

Dry fill: 100 mg. oxytetracycline hydrochloride is dissolved in 4 ml. distilled water containing 144 mg. Tris and 200 mg. sucrose, the pH is set to 7.9 with hydrochloric acid and the material is lyophilized in a nitrogen atmosphere.

Dissolving ampoule: 2 ml. distilled water. Administration: same as Example 1.

EXAMPLE 3

5 g. oxytetracycline hydrochloride is dissolved in 100 ml. 50 per cent N,N-dimethylacetamide, containing 9.0 g. Tris, 2.0 g. crystalline magnesium chloride, 2 ml. lactic acid, 0.5 g. sodium formaldehyde sulphoxylate, and 0.1 g. nordihydroguaiaric acid. The solution is sealed in ampoules under a nitrogen atmosphere (pH=7.94).

Administration: intravenous injection only.

EXAMPLE 4

5 g. doxycycline hydrochloride is dissolved in 100 ml. 50 per cent N,N-dimethylacetamide, containing 3.6 g. Tris, 5.3 g. ascorbic acid, 0.5 g. sodium formaldehyde sulphoxylate, 0.1 g. nordihydroquaric acid, and sealed in ampoules under a nitrogen atmosphere (pH=7.50).

Administration: intravenous injection only.

EXAMPLE 5

Dry fill: 100 mg. tetracycline hydrochloride.

Dissolving ampoule: 72 mg. Tris in 2 ml. distilled water, the pH set to 8.8 with hydrochloric acid. After having dissolved the dry fill in the solvent, the final pH is 7.5.

Administration: same as Example 1.

EXAMPLE 6

Dry fill: 100 mg. chlortetracycline hydrochloride.

Dissolving ampoule: same as Example 5.

Administration: same as Example 1.

EXAMPLE 7

Dry fill: 100 mg. methacycline hydrochloride.

Dissolving ampoule: same as Example 5.

Administration: same as Example 1.

Up to now, the only injectable solution in water of methacycline hydrochloride.

EXAMPLE 8

Dry fill: 100 mg. doxycycline hydrochloride.

Dissolving ampoule: same as Example 5.

Administration: same as Example 1.

Up to now, the only injectable solution in water of doxycycline hydrochloride.

EXAMPLE 9

Dry fill: 100 mg. oxytetracycline hydrochloride is dissolved in 8 ml. methanol containing 144 mg. Tris, the pH is set to 7.9 with hydrochloric acid and the material evaporated in a nitrogen atmosphere.

Dissolving ampoule: 2 ml. 13 per cent

polyethyleneglycol 400, containing 1 mg. sodium pyrosulphite per ml.

Administration: intravenous injection and drip infusion.

EXAMPLE 10

100 mg. chlortetracycline hydrochloride is dissolved in 8 ml. methanol in a nitrogen atmosphere, 144 mg. Tris is added the pH set to 7.9 and the solvent is evaporated in vacuo. The crystalline compound obtained is filled into capsules.

Administration: per os.

EXAMPLE 11

A mixture containing Tris together with a tetracycline compound is filled into dry capsules: 100 mg. oxytetracycline hydrochloride, 72 mg. Tris, 30 mg. boric acid, 30 mg. sodium chloride, 10 mg. citric acid. The content of one capsule dissolved in 10 ml. distilled water gives an isotonic solution; the pH is 7.3.

Administration: for external use (e.g. eye-drops) only.

By the term "a tetracycline" when used herein is meant tetracycline and derivatives of tetracycline and acid addition salts thereof. Both the basic compounds and their acid addition salts form the complexes.

WHAT WE CLAIM IS:—

1. A complex of tetracycline and tris-(hydroxymethyl) aminomethane.

2. A complex according to claim 1 wherein the tetracycline is tetracycline, oxytetracycline, doxycycline, methacycline, or chlortetracycline.

3. A process for preparing a complex of a tetracycline and tris(hydroxymethyl) aminomethane which comprises reacting, in a solvent, the tetracycline with tris(hydroxymethyl) aminomethane.

4. A process according to claim 3 wherein the tetracycline is tetracycline, oxytetracycline, doxycycline, methacycline, or chlortetracycline.

5. A process according to claim 3 or 4 wherein there are used 3 to 6 mols of tris-(hydroxymethyl) aminomethane per mol of the tetracycline.

6. A process according to claim 3 substantially as described in any one of the Examples.

7. A complex of a tetracycline and tris-(hydroxymethyl)aminomethane prepared by the process claimed in any one of claims 3 to 6.

8. A pharmaceutical composition comprising a complex as claimed in claims 1, 2 or 7 and a pharmaceutically acceptable carrier or diluent.

9. A composition according to claim 8 substantially as described in any one of the Examples.

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polyethyleneglycol 400, containing 1 mg. sodium pyrosulphite per ml.

Administration: intravenous injection and drip infusion.

EXAMPLE 10

100 mg. chlortetracycline hydrochloride is dissolved in 8 ml. methanol in a nitrogen atmosphere, 144 mg. Tris is added the pH set to 7.9 and the solvent is evaporated in vacuo. The crystalline compound obtained is filled into capsules.

Administration: per os.

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3. A process for preparing a complex of a tetracycline and tris(hydroxymethyl) aminomethane which comprises reacting, in a solvent, the tetracycline with tris(hydroxymethyl) aminomethane.

4. A process according to claim 3 wherein the tetracycline is tetracycline, oxytetracycline, doxycycline, methacycline, or chlortetracycline.

5. A process according to claim 3 or 4 wherein there are used 3 to 6 mols of tris-(hydroxymethyl) aminomethane per mol of the tetracycline.

6. A process according to claim 3 substantially as described in any one of the Examples.

7. A complex of a tetracycline and tris-(hydroxymethyl)aminomethane prepared by the process claimed in any one of claims 3 to 6.

8. A pharmaceutical composition comprising a complex as claimed in claims 1, 2 or 7 and a pharmaceutically acceptable carrier or diluent.

9. A composition according to claim 8 substantially as described in any one of the Examples.

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