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(19)

(72) The inventors of this invention in the sense of being the actual devisers thereof within the meaning of Section 16 of the Patents Act, 1949, are ELVIN ALBERT HOLSTIUS of 211 Steward Lane, Greenville, North Carolina 27834, U.S.A. and GEORGE ERNEST ALVAN of 506 Westchester Drive, Greenville, North Carolina 27834, U.S.A. Both of U.S. Nationality.

(54) OPHTHALMIC AND OTIC PREPARATIONS

(71) We, THE WELLCOME FOUNDATION LIMITED, of 183—193 Euston Road, London, N.W.1., a company incorporated in England, 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 pharmaceutical formulations and in particular to otic and ophthalmic formulations which are suitable for use in treating microbial infections of, around and in the ears and eyes.

It has long been known that trimethoprim (2,4 - diamino - 5 - (3′,4′,5′ - trimethoxybenzyl)pyrimidine) potentiates the antimicrobial activity of sulphonamides (*vide* U.S. Patent No. 2,909,522) and that combinations of the two agents have been extensively used particularly in the treatment of bacterial infections. However, the treatment has generally been confined to those infections which require oral or parenteral administration of the drug and accordingly suitable formulations therefor have been marketed for some years.

It is also known that polymyxins are useful as antimicrobial agents particularly in the treatment of gram-negative infections and that certain polymyxins have been used in association with trimethoprim and sulphamethoxazole. For instance, *Chemotherapy*, 1972, *18*, 119—129 discloses that the oral administration of a combined dosage of trimethoprim and sulphamethoxazole followed by polymyxin B over a short period seems to be efficient in the treatment of particular types of salmonellosis. Also, a tripartite combination of trimethoprim, sulphamethoxazole and polymyxin E has been used for *in vitro* testing against gram-negative bacterial (*vide J. Clin. Path.* 1970, *23*, 757—764).

During the last few years, it became apparent that a new and improved broad spectrum ophthalmic and otic formulation was required for the treatment of the multitude of bacterial infections encountered in the eye and ear. Such a formulation in order to be useful as an antibacterial for ophthalmic and otic use would have to satisfy various stringent criteria. For example, the formulation would have to be stable for long periods of time, it should not lose its potency, it should not discolour, insoluble substances or complexes should not form, and also it should not be irritating to the eye or ear.

It has now been found that an ophthalmic and otic formulation meeting the above-mentioned criteria and having a broad spectrum antimicrobial, in particular antibacterial, activity can be provided using as active ingredients a combination of trimethoprim, sulphacetamide (N-acetylsulphanilamide) and a polymyxin. This is somewhat surprising in view of the known facts that polymyxins are known to lose their potency under certain conditions, that sulphacetamide base readily undergoes oxidation, especially in solution, giving rise to discolouration, and that trimethoprim and some sulphonamides form insoluble complexes. Indeed, after twenty-four months storage at 5°C and 25°C satisfactory potencies for all active ingredients have been observed.

In *in vitro* tests, such formulations have shown wide antibacterial activity at dilutions of at least 1:300 against those bacterial which are usually responsible for causing infections of, around and in the ears and eyes. For example, the formulations are active against

St. pyogenes, Staph. aureus, N. gonorrhoeae, Morax. phenylpyrovich, Morax. nonliquifaciens, St. pneumoniea I, Ps. aeruginosa and *H. influenzae.*

The formulations may be used in the treatment of acute and chronic conjunctivitis, pinkeye, infected sockets, corneal ulcers, keratitis, episcleritis and blepharitis. In particular, solutions containing the above three active ingredients have been found to be extremely useful in the treatment of severe cases of refractive chronic otitis media which had failed to respond to prior treatment with currently recommended drugs, e.g. gentamicin, chloramphenicol, neomycin and colymycin.

The formulations of the present invention are also useful as an adjunct to surgery in dacryocystitis; and prophylactically, before or after ophthalmic surgery and following serious eye injuries or removal of foreign bodies.

Accordingly, there is provided a pharmaceutical formulation, which comprises a polymyxin in the form of a pharmaceutically acceptable water soluble salt, trimethoprim, sulphacetamide, and a pharmaceutical carrier acceptable for ophthalmic and/or otic purposes.

In a preferred aspect the formulation comprises from 0.05 to 0.66 g/100 ml of sulphacetamide, from 0.005 to 1.0 g/100 ml of trimethoprim, and from 0.01 to 0.3 g/100 ml of polymyxin, whilst the most preferred formulation comprises from 0.1 to 0.5 g/100 ml of sulphacetamide, from 0.1 to 0.5 g/100 ml of trimethoprim, and from 0.05 to 0.15 g/100 ml of polymyxin. (N.B. the above proportions of active ingredients are with reference to the base in every case). The remaining proportion is taken up by the carrier and optional excipients.

In order to obtain a therapeutic effect, such as to treat bacterial infections, the ratio of sulphacetamide to trimethoprim as base or polymyxin as base is from about 20:1 to 0.1:1 (w/w), preferably from 10:1 to 0.1:1 (w/w) and most preferably is 5:1 (w/w).

While the present invention is not limited to a particular polymyxin, and accordingly all of the polymyxins disclosed in The Merck Index, 1968, 8th Ed. pages 848, 278 and 279 are included within the scope of the invention, it is preferred that polymyxin B is used.

Suitable pharmaceutically acceptable, water soluble salts of polymyxin which may be employed in the present invention include the sulphate and the hydrochloride salts.

It is particularly desired that the formulation utilises trimethoprim in the form of a pharmaceutically acceptable, water soluble, mono acid addition salt consisting of monoprotonated trimethoprim and an anion of a pharmaceutically acceptable acid. Substances which may be used as pharmaceutically acceptable acids in this connection must be acids which have a lower pKa value than that for sulphacetamide and include such mineral acids as sulphuric, phosphoric, hydrochloric, hydrobromic and hydriodic as well as such organic acids as methane sulphonic acid and carboxylic acids having from 1 to 20 carbon atoms, preferably from 1 to 10 carbon atoms, for example tartaric, citric, lactic, embonic, salicylic, glutamic, glutaric, naphthoic and ethylenediamine tetra-acetic acid. At present, the particularly preferred acids are lactic acid and sulphuric acid. All such recommended salts of trimethoprim may be prepared simply by the reaction of trimethoprim and a pharmaceutically acceptable acid.

In a preferred aspect of the invention, the active ingredients are presented as either an aqueous solution or an ointment formulation.

The amount of polymyxin per 100 ml of solution or per 100 mg of ointment which may be used is from 500,000 to 2,000,000 units, preferably from 1,000,000 to 1,200,000 units, 1,200,000 units of polymyxin represents 0.15 g of polymyxin B in terms of base.

Aqueous solution formulations preferably have a pH from 4 to 6.5, more preferably from 4.5 to 5.5 and most preferably 5.0 ± 0.3.

Suitable pH adjusting agents which may be employed in the solution formulations include the pharmaceutically acceptable acids mentioned above, such as hydrochloric, acid and under certain conditions pharmaceutically acceptable bases, such as sodium hydroxide and potassium hydroxide. The amount of pH adjusting agent which is normally used if needed is from 0.02 to 1.0 g/100 ml with 0.03 to 0.07 g/100 ml being preferred.

In addition, the solution may contain tonicity adjusting agents, such as sodium chloride which may be used in an amount from 0.3 to 1.2 g/100 ml of solution, desirably from 0.6 to 1.0 g/100 ml of solution.

Viscosity increasing and film forming agents such as Methocel 65 HG, 4000 cps (Hydroxypropylmethylcellulose) may also be incorporated into an aqueous solution formulation of the invention in order to prolong contact of the solution with the mucous membrane

Other optional excipients, such as preservatives, e.g. thiomersal (made by Eli Lilly and Co.), benzalkonium chloride and 2-phenylethanol, may also be included.

Suitable carriers for the ointment formulation are white soft paraffin and polyethylene glycol.

Again, other optional excipients, such as preservatives, may be included in the ointment formulation.

In both formulations, it may be desirable to add local anaesthetic agents to enhance stability.

The present invention further provides a method for the preparation of a pharmaceutical formulation, as herein defined, which comprises the admixture of trimethoprim, sulphacetamide, a polymyxin in the form of a

pharmaceutically acceptable, water soluble salt, and a pharmaceutical carrier for ophthalmic and/or otic purposes.

In the preparation of ophthalmic and/or otic aqueous solutions of this invention, the sulphacetamide and trimethoprim as the salt are conveniently dissolved in the solution at elevated temperatures of 85 to 90°C although lower temperatures may also be used, in which case the sulphacetamide may be added to the water with or without the salt of trimethoprim being present. However, it is preferable to ensure that in all cases the pH and volume of the solution are sufficient to prevent formation of an insoluble salt.

The polymyxin may be readily dissolved in the solution at room temperature with or without stirring.

In the preparation of ophthalmic and/or otic ointments of the present invention, the polymyxin as the salt, the sulphacetamide and the trimethoprim either as the free base or as the salt may be mixed with the ointment base, conveniently Methocell, glycerin, propylene glycol or a soft petroleum base, and milled, e.g. in a ball mill, to a desired consistency. Methocell is a Registered Trade Mark.

It should be understood that the ophthalmic and otic aqueous solutions and ointments of this invention are sterile and that the water used in their preparation is preferably distilled water.

The present invention even further provides a method of treating or preventing microbial infections of, around and in the ears or eyes of mammals, which comprises administering to the mammal an effective antibacterial treatment amount of the formulation, as herein defined.

The aqueous solution formulations of this invention would normally be administered in or around the eye or ear in an amount from 0.02 to 0.1 ml drops containing the active ingredients in the concentrations set forth above. Usually one or two drops of the solution would be administered from 1 to 4 times daily. For example, in the treatment of bacterial infections of, around and in the eye (e.g. conjunctivitis), two 0.07 ml drops from a solution containing 1 mg/ml of trimethoprim, 5 mg/ml of sulphacetamide and 10,000 units/ml of polymyxin B may be administered 2 to 4 times daily.

Ophthalmic ointments are usually administered in the conjunctival sac wall of the eye in amounts of about 0.02 to 0.1 ml, which amounts are applied from 1 to 4 times daily.

The present invention will now be described in detail with reference to specific embodiments which should not be construed as restricting the scope of the invention in any way.

Example 1

Ophthalmic or Otic Solution

Sulphacetamide	0.50 g
Trimethoprim hemisulphate monohydrate equivalent to	
Trimethoprim base	0.10 g
Polymyxin B sulphate (including 20% overage)	1,200,000 units (0.15 g)
Thiomersal	0.001 g
Sodium Chloride	0.83 g
Water for injection, q.s.	
	100.00 ml

The polymyxin B sulphate was added to water (10 ml) and allowed to dissolve without stirring.

In a separate container, the trimethoprim hemisulphate monohydrate and sulphacetamide was dissolved in water (35 ml) and heated to 85—90°C. Cold water (35 ml) was then added and the solution mixed continuously to ensure complete dissolution of the ingredients, after which the sodium chloride was added.

The solution of polymyxin B sulphate was then added to the solution of the trimethoprim salt and sulphacetamide together with water (10 ml) which was used for rinsing the container of the first-mentioned solution. Thiomersal was added and the volume of the solution increased with water to just under 100 ml. The solution was cooled to room temperature (25°C) and the pH adjusted with 2N sodium hydroxide solution to 5.0 ± 0.3.

Water was then added to make the solution up to 100 ml, the solution mixed for ten minutes and the pH rechecked.

Finally, the solution was passed through a filter and 10 ml aliquots were dispensed into amber bottles with subsequent sealing and autoclaving at 121°C for 20 minutes to sterilise the solutions.

Alternatively, the solution may be sterilized by filtration through a suitable sterile filter and aseptically subdividing the resulting solution into sterile bottles.

Example 2

Ophthalmic or Otic Solution

Sulphacetamide	0.50 g
Trimethoprim hemisulphate monohydrate equivalent to	
Trimethoprim base	0.10 g
Polymyxin B sulphate (including 20% overage)	1,200,000 units (0.15 g)
Thiomersal	0.001 g
Hydroxypropylmethyl cellulose	0.25 g
Sodium chloride	0.83 g
Water for injection, q.s.	
	100.00 ml

The polymyxin B sulphate was added to water (10 ml) and allowed to dissolve without stirring.

In a separate container, the trimethoprim hemisulphate monohydrate and the sulphacetamide were dissolved in water (70 ml) previously heated to 70°C, after which the sodium chloride was added. After the sodium chloride had dissolved, the hydroxypropylmethylcellulose was added and dispersed. The solution was cooled with constant stirring to 5°C whereupon the solution was allowed to stand until clear.

The solution of polymyxin B sulphate was added to the solution of the trimethoprim salt and sulphacetamide together with water (10 ml) which was used for rinsing the container of the first-mentioned solution. Then the thiomersal was added and the volume of the solution increased with water to just under 100 ml.

The pH was adjusted to 5.0 ± 0.3 with $2N$ sodium hydroxide and the solution made up to 100 ml with water. After the solution had been mixed for ten minutes, the pH was rechecked.

Finally, the solution was passed through a filter and 10 ml aliquots were dispensed into amber bottles with subsequent sealing and sterilized by autoclaving at 121°C for 20 minutes.

Example 3

Ophthalmic or Otic Solution

Sulphacetamide	0.05 g
Trimethoprim Lactate equivalent to Trimethoprim base	0.01 g
Polymyxin B sulphate (including 20% overage)	1,200,000 units (0.15 g)
Water for injection, q.s.	
	100.00 ml

The above formulation was prepared using the relevant general procedure of Example 1.

Example 4

Ophthalmic or Otic Solution

Sulphacetamide	0.50 g
Trimethoprim lactate equivalent to Trimethoprim base	0.10 g
Polymyxin B sulphate (including 20% overage)	1,200,000 units (0.15 g)
Water for injection, q.s.	
	100.00 ml

The above formulation was prepared using the relevant general procedure of Example 1.

Example 5

Ophthalmic or Otic Solution

Sulphacetamide	0,50 g
Trimethoprim hemisulphate monohydrate equivalent to	
Trimethoprim base	0.1 g
Polymyxin B sulphate (including 20% overage)	1,200,000 units (0.15 g)
Thiomersal	0.001 g
Sodium chloride	0.83 g
Purified water, q.w.	
	100.00 ml

This formulation was prepared using the relevant general procedure of Example 1. The resulting solution was clear, bright and colourless and the pH was in the range from 5.0 to 5.5.

Example 6

Ophthalmic Ointment

Sulphacetamide	0.5 g
Trimethoprim base	0.1 g
Polymyxin B sulphate (including 20% overage)	1,100,000 units
White soft paraffin, q.s.	
	100.0 g

The White Soft Paraffin was sterilized by heating it at 160°C for 1 hour. The temperature was allowed to cool to around 40°C and under aseptic conditions the active ingredients were incorporated, previously sterilized by gamma-irradiation. The resulting formulation was mixed thoroughly to achieve good dispersion and homogeneity and then filled into sterilized collapsible metal tubes.

Example 7

Ophthalmic or Otic Ointment

Sulphacetamide	0.5 g
Trimethoprim base	0.1 g
Polymyxin B sulphate (including 20% overage)	1,200,000 units (0.15 g)
Propylene glycol	20.0 g
Polyethyleneglycol 300	25.0 g
Polyethylene glycol 1500	54.25 g
	100.0 g

Propylene glycol and the polyethylene glycols were melted together at a temperature not exceeding 60°C. The hot liquid was then cooled to 40°C and the active ingredients were dispersed in a small fraction of the base and mixed until a smooth paste was produced. This paste was then incorporated with the bulk and mixed well until homogeneous. The resulting ointment was filled into sterilized collapsible metal tubes.

Example 8

Otic Solution

Sulphacetamide	0.50 g
Trimethoprim hemisulphate monohydrate equivalent to Trimethoprim base	0.1 g
Polymyxin B sulphate (including 20% overage)	1,200,000 units
Polysorbate 80	0.5 g
2-phenylethanol	0.5 ml
Sodium chloride	0.5 g
Water for injection, q.s.	
	100.0 ml

The above formulation was prepared using the general procedure of Example 1 but adding the 2-phenylethanol in place of Thiomersal and the polysorbate 80.

Example 9

Otic or Ophthalmic Paraffin Gauze Dressing

An ointment according to Example 6 was prepared as described.

Under aseptic conditions this ointment was used to impregnate cotton or cotton/rayon gauzes 10 cm square at a temperature not exceeding 55°C. After cooling, the gauzes were packed individually or in multiple packs into sealed foil or metal containers.

Example 10

Treatment of Refractive Chronic Otitis Media

Ears infected with refractive chronic otitis media were treated by cleaning them with cotton wool and applying 8 drops of the aqueous solution described and prepared in Example 1. The ears were then occluded with cotton wool.

This procedure was repeated twice daily for 21 days.

In 21 out of 26 cases the result was a dry, non-infected ear.

Example 11

Ophthalmic or Otic Ointment

Polymyxin B Sulphate (including 20% overage)	12,000 units
Trimethoprim Hemisulphate monohydrate equivalent to Trimethoprim base	1 mg
Sulphacetamide	5 mg
Special White Petrolatum, q.s.	1 g

The above formulation was prepared using the relevant general procedure of Example 7 except that the special white petrolatum replaced the glycols and also that heating is optional.

Example 12

Ophthalmic or Otic Ointment

Polymyxin B sulphate (including 20% overage)	12,000 units
Trimethoprim hemisulphate monohydrate equivalent to Trimethoprim base	3 mg
Sulphacetamide	15 mg
Special White Petrolatum, q.s.	1 g

The above formulation was prepared using the relevant general procedure of Example 7 except that the special white petrolatum replaced the glycols and also that heating is optional.

Example 13

Ophthalmic or Otic Ointment

Polymyxin B sulphate (including 20% overage)	12,000 units
Trimethoprim hemisulphate monohydrate equivalent to Trimethoprim base	10 mg
Sulphacetamide	50 mg
Special White Petrolatum, q.s.	1 g

The above formulation was prepared using

the relevant general procedure of Example 7 except that the special white petrolatum replaced the glycols and also that heating was optional.

WHAT WE CLAIM IS:—

1. A pharmaceutical formulation, which comprises a polymyxin in the form of a pharmaceutically acceptable water soluble salt, trimethoprim, sulphacetamide and a pharmaceutical carrier acceptable for ophthalmic and/or otic purposes.

2. A formulation according to claim 1, wherein the pharmaceutical carrier is acceptable for ophthalmic purposes.

3. A formulation according to claim 2, wherein the sulphacetamide comprises from 0.05 to 0.66 g/100 ml, the trimethoprim comprises from 0.005 to 1.0 g/100 ml, and the polymyxin comprises from 0.01 to 0.3 g/100 ml.

4. A formulation according to claim 3, wherein the sulphacetamide comprises from 0.1 to 0.5 g/100 ml, the trimethoprim comprises from 0.01 to 0.5 g/100 ml, and the polymyxin comprises from 0.05 to 0.15 g/100 ml.

5. A formulation according to any one of the preceding claims, wherein the polymyxin is polymyxin B.

6. A formulation according to any one of the preceding claims, wherein trimethoprim is in the form of a pharmaceutically acceptable, water soluble, mono acid addition salt consisting of mono-protonated trimethoprim and an anion of a pharmaceutically acceptable acid.

7. A formulation according to any one of the preceding claims, wherein the formulation constitutes an ointment.

8. A formulation according to claim 6, wherein the formulation constitutes an aqueous solution.

9. A formulation according to claim 8, wherein the pH of the aqueous solution is from 4.0 to 6.5.

10. A formulation according to claim 9, wherein the pH is from 4.5 to 5.5.

11. A formulation according to claim 10, wherein the pH is 5.0 ± 0.3.

12. A method for the preparation of a pharmaceutical formulation, as defined in any one of claims 1 to 11, which comprises the admixture of trimethoprim, sulphacetamide, a polymyxin in the form of a pharmaceutically acceptable, water soluble salt, and a pharmaceutical carrier for ophthalmic and/or otic purposes.

13. A method of treating or preventing microbial infections of, around and in the ears or eyes of non-human mammals, which comprises administering to the mammal an effective antibacterial amount of the formulation, as defined in any one of claims 1 to 12.

14. A pharmaceutical formulation substantially as described herein and with reference to any one of Examples 1 to 10 and 12 to 14.

15. A method for the preparation of a pharmaceutical formulation substantially as described herein and with reference to any one of Examples 1 to 10 and 12 to 14.

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the relevant general procedure of Example 7 except that the special white petrolatum replaced the glycols and also that heating was optional.

WHAT WE CLAIM IS:—

1. A pharmaceutical formulation, which comprises a polymyxin in the form of a pharmaceutically acceptable water soluble salt, trimethoprim, sulphacetamide and a pharmaceutical carrier acceptable for ophthalmic and/or otic purposes.

2. A formulation according to claim 1, wherein the pharmaceutical carrier is acceptable for ophthalmic purposes.

3. A formulation according to claim 2, wherein the sulphacetamide comprises from 0.05 to 0.66 g/100 ml, the trimethoprim comprises from 0.005 to 1.0 g/100 ml, and the polymyxin comprises from 0.01 to 0.3 g/100 ml.

4. A formulation according to claim 3, wherein the sulphacetamide comprises from 0.1 to 0.5 g/100 ml, the trimethoprim comprises from 0.01 to 0.5 g/100 ml, and the polymyxin comprises from 0.05 to 0.15 g/100 ml.

5. A formulation according to any one of the preceding claims, wherein the polymyxin is polymyxin B.

6. A formulation according to any one of the preceding claims, wherein trimethoprim is in the form of a pharmaceutically acceptable, water soluble, mono acid addition salt consisting of mono-protonated trimethoprim and an anion of a pharmaceutically acceptable acid.

7. A formulation according to any one of the preceding claims, wherein the formulation constitutes an ointment.

8. A formulation according to claim 6, wherein the formulation constitutes an aqueous solution.

9. A formulation according to claim 8, wherein the pH of the aqueous solution is from 4.0 to 6.5.

10. A formulation according to claim 9, wherein the pH is from 4.5 to 5.5.

11. A formulation according to claim 10, wherein the pH is 5.0 ± 0.3.

12. A method for the preparation of a pharmaceutical formulation, as defined in any one of claims 1 to 11, which comprises the admixture of trimethoprim, sulphacetamide, a polymyxin in the form of a pharmaceutically acceptable, water soluble salt, and a pharmaceutical carrier for ophthalmic and/or otic purposes.

13. A method of treating or preventing microbial infections of, around and in the ears or eyes of non-human mammals, which comprises administering to the mammal an effective antibacterial amount of the formulation, as defined in any one of claims 1 to 12.

14. A pharmaceutical formulation substantially as described herein and with reference to any one of Examples 1 to 10 and 12 to 14.

15. A method for the preparation of a pharmaceutical formulation substantially as described herein and with reference to any one of Examples 1 to 10 and 12 to 14.

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