PATENT SPECIFICATION (11) 1399834

1399834

(21) Application No. 14529/71 (22) Filed 12 May 1971
(21) Application No. 57169/71 (22) Filed 9 Dec. 1971
(23) Complete Specification filed 21 April 1972
(44) Complete Specification published 2 July 1975
(51) INT CL[2] A61K 31/35
(52) Index at acceptance
A5B 232 23Y 27X 27Y 386 38Y 390 39X 401 402 40Y 411 41Y 422 42Y 481 482 483 48Y 503 50Y 542 54Y 550 55Y 565 56Y 576 57Y 616 61Y 644 64Y 650 65Y 66Y 77Y

(72) Inventors NEIL ARTHUR STEVENSON and GEORGE WARDELL

(54) PHARMACEUTICAL COMPOSITIONS

(71) We, FISONS LIMITED, a British Company, of Fison House, 9 Grosvenor Street, London, W.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:—

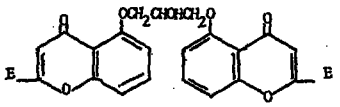
This invention relates to pharmaceutical compositions and methods for their preparation.

It is usually a simple matter to make clear solutions of water soluble pharmaceuticals, but our initial attempts to formulate 1,3 - bis (2 - carboxychromon - 5 - yloxy) - propan - 2 - ol, 5,5′ - [[5,5′ - (2 - hydroxytrimethylene)dioxy]bis[4 - oxo - 4H - 1 - benzopyran - 2 - yl]]tetrazole and their pharmaceutically acceptable salts as aqueous solutions produced compositions which rapidly became cloudy and were entirely unacceptable. A further difficulty was that the polar nature of the compounds and their high molecular weight indicated that they would combine with most of the known preservatives for aqueous pharmaceutical solutions to form insoluble precipitates thus simultaneously removing both active ingredient and preservative from the solution and further aggravating the problem of cloudiness mentioned above. Surprisingly we have found that in general, such precipitation as does occur is not detrimental to the properties of the solution.

We have now found that it is possible to formulate these highly polar compounds in such a way that clear solutions are formed.

According to our invention we provide a pharmaceutical composition comprising a clear, sterile aqueous solution containing as active ingredient a therapeutically useful proportion of 1,3 - bis(2 - carboxychromon - 5 - yloxy) - propan - 2 - ol, or a pharmaceutically acceptable (e.g. the di-sodium) salt thereof, or of 5,5′ - [[5,5′ - (2 - hydroxytrimethylene)dioxy]bis[4 - oxo - 4H - 1 - benzopyran - 2 - yl]]tetrazole, or a pharmaceutically acceptable (e.g. the di-sodium) salt thereof.

The active ingredients of this invention may be represented as compounds of formula,



in which each group E is a carboxy group or a pharmaceutically acceptable salt thereof; or is a tetrazole group or a pharmaceutically acceptable salt thereof.

The solution may contain from 0.1% to 10%, preferably from 0.5 to 5% and more preferably about 1 or 2% w/v of the active ingredient.

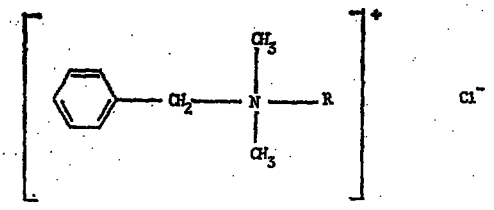
In addition to the active ingredient the composition may also contain an effective proportion of a pharmaceutically acceptable chelating or sequestering agent. Suitable sequestering or chelating agents include sodium carboxymethyl cellulose, citric, tartaric or phosphoric acid, and amino carboxylate compounds, preferably ethylenediamine tetraacetic acid or its salts, e.g. its calcium salt, its calcium-sodium salt, or more preferably its di-sodium salt. Further examples of amino carboxylate compounds are Perma Kleer 80 available from Refined Products Corporation of Lyndhurst N.J., U.S.A. and glycine derivatives, e.g. N,N-dihydroxy ethyl glycine and its salts, e.g. its sodium salt.

The concentration of the chelating or sequestering agent may vary considerably, but in any case should be such as to ensure that no precipitate of metal salts of the active

ingredient occurs. A suitable concentration of chelating or sequestering agent may be from 0.01 to 0.1% w/v. When a very low concentration, i.e. less than 0.40, preferably less than 0.32 p.p.m., of 'metal ions' are present, for example when the solution contains less than 0.08 p.p.m. of ionic iron and less than 0.25 p.p.m. of ionic zinc, the chelating or sequestering agent may if desired be dispensed with. When a chelating or sequestering agent is used the concentration of 'metal ions' is preferably less than 20 p.p.m. and more preferably less than 10 p.p.m.

By the term 'metal ions' we mean ions of metals in groups IIa, Ib, IIb, and IVb of the periodic table and of the transition metals. Specific 'metal ions' which are detrimental, in excessive concentrations, i.e. above 20 p.p.m., to the compositions of the invention are Pb^{++}, Ca^{++}, Mg^{++} and in particular Fe^{++}, Fe^{+++} and Zn^{++} ions.

The composition may if desired contain an effective proportion, e.g. from 0.001 to 0.10% w/v, of a pharmaceutically acceptable preservative or sterilising agent. One example of a suitable preservative is sodium 2-(ethyl mercuriothio) benzoate known generically as 'Thiomersal', which may be present in the composition in from 0.001 to 0.05 and preferably from 0.005 to 0.02, e.g. about 0.01% w/v. Other suitable preservatives include pharmaceutically acceptable quaternary ammonium compounds, e.g. cetyl pyridinium chloride, tetradecyltrimethyl ammonium bromide known generically as "Cetrimide", benzyl dimethyl [2 - [2 - [p - (1,1,3,3 - tetramethyl butyl)]phenoxy]ethoxy] ammonium chloride, known generically as 'Benzethonium chloride', and myristyl - γ - picolinium chloride, any one of which may be used at a concentration of from 0.002 to 0.05, e.g. about 0.02% w/v. The preferred preservatives amongst the quaternary ammonium compounds are however the alkyl benzyl dimethyl ammonium chlorides and mixtures thereof, e.g. that known generically as 'Benzalkonium chloride'. This latter consists of a mixture of compounds of formula



in which R is an alkyl group C_8H_{17} to $C_{18}H_{37}$. We particularly prefer to use a mixture of such compounds in which R is $C_{10}H_{21}$ to $C_{14}H_{29}$ and especially that specific compound in which R is $C_{12}H_{25}$. 'Benzalkonium chloride', and the compounds of the formula given above, may be used at a concentration of from 0.005 to 0.10 preferably 0.005 to 0.05, e.g. about 0.01% w/v and may optionally be used in combination with 0.2 to 2.0, e.g. 0.4% w/v of 2-phenylethanol (B.P.C. 1963). 'Benzalkonium chloride' (and the compounds of the formula given above) and 2-phenylethanol have been found to have a synergistic effect, particularly against *Pseudomonas aeruginosa*, when used in combination with the di-sodium salt of ethylenediamine tetra acetic acid.

The composition may also contain conventional excipients, e.g. sodium chloride, and buffers, e.g. sodium dihydrogen orthophosphate (sodium acid phosphate B.P.) and disodium hydrogen phosphate (sodium phosphate B.P.). The production and concentration of excipients and buffers may be varied within fairly wide ranges, provided the resulting solution is stable and non-irritant when applied to the appropriate tissues. For maximum stability the preferred pH is from 5 to 7.5, preferably 5 to 6.5, with minimal buffering to avoid tissue irritation. The maximum total concentration of excipients and buffers is preferably less than 5% w/v and more preferably less than 2% w/v.

The composition, when it does not contain a preservative, may be made up using conventional techniques, by dissolving the components in water, filtering the solutions and sterilising the filtrate. More specifically the compositions may be made by dissolving the chelating or sequestering agent (if included) in freshly distilled water, adding the excipients, buffers etc. to the aqueous solution of chelating or sequestering agent, adding the active ingredient to the resulting solution, stirring, filtering and then sterilising the composition by autoclaving, for example at a temperature of about 115°C for about 30 minutes. The autoclaving of the product may, if desired, be omitted when the composition is produced by sterile filtration into a previously sterilised container under aseptic conditions.

Compositions which contain preservatives may be made up by mixing two aqueous solutions of equal volumes one containing twice the desired final concentration of the active ingredient, chelating or sequestering agent, and other additives, and the other containing twice the desired final concentration of the preservative. The resulting mixture may then be filtered under sterile conditions. Surprisingly we find that mixture of a solution of the anionic active ingredients with a solution of a cationic quaternary ammonium preservative does not precipitate all the preservative from the mixed solution.

The components of the composition should be as free as possible from 'metal ions' and contact with materials yielding such ions

should be avoided during manufacture. If desired 'metal ions' may be removed from the components of the composition by conventional means, e.g. by ion exchange.

The compositions of the invention are indicated for use as eye drops in the treatment of vernal kerato conjunctivitis, the occular symptoms of hay fever and/or marginal corneal infiltration. The compositions and in particular the preserved compositions may be used in the treatment of hay fever by administration to the nose, e.g. as a nasal spray. For nasal application we prefer a composition containing about 2% w/v of active ingredient. The dosage given will vary with the particular compositions used and the condition to be treated. In general however a dosage of 1 or 2 drops (i.e. from 0.66 to 1.32 mg of active ingredient) into the affected eye from 2 to 4 times a day is indicated when the composition is used as eye drops and a dosage of about 0.16 ml (i.e. about 3.2 mg of active ingredient) is indicated when the composition is used for administration to the nose (0.08 ml per nostril).

The unpreserved compositions may be put up in single application containers containing from 0.3 to 0.7 ml of solution and the preserved compositions may be put up in multi-dose (plastics, e.g. polyethylene, or glass) packs containing 10 to 20, preferably 14—15, ml of solution.

The invention is illustrated but in no way limited by the following Examples:—

Example 1

Unpreserved eye drop solution

Di-sodium salt of 1,3 - bis (2 - carboxy - chromon - 5 - yloxy) - propan - 2 - ol	1.0% w/v
Sodium chloride B.P.	0.56% w/v
Sodium acid phosphate B.P.	0.26% w/v
Sodium phosphate B.P.	0.59% w/v
Di-sodium edetate B.P.	to 100%
Distilled water	0.01% w/v

Example 2

Preserved Nasal Spray Solution

Di-sodium salt of 1 - 3 - bis (2 - carboxy - chromon - 5 - yloxy) - propan - 2 - ol (Sodium cromoglycate B.P.)	2.0% w/v
Di-sodium edetate B.P.	0.01% w/v
Thiomersal B.P.	0.01% w/v
Sterile distilled water	to 100%

Thiomersal B.P. may be replaced by the following preservatives

Benzalkonium chloride U.S.P	0.01% w/v
Benzalkonium chloride solution B.P.	0.02% w/v
Benzethonium chloride	0.02% w/v
Cetrimide B.P.	0.02% w/v
Myristyl - γ - picolinium chloride	0.02% w/v
Chlorocresol B.P.	0.1% w/v
Chlorbutol B.P.	0.5% w/v
Chlorhexidine salts (e.g. acetate, glyconate	0.005—0.01% w/v
Phenyl mercuric salts (e.g. nitrate, acetate)	0.1% w/v
p-hydroxy benzoates	0.4—0.8% w/v
Phenylethyl alcohol B.P.C. 1963	0.3—0.6% w/v
Cetyl pyridinium chloride B.P.	0.02% w/v
Domiphen bromide B.P.	0.01% w/v
or Phenoxyethanol B.P.C.	0.5—1.0%

Pharmaceutically acceptable combinations of the above preservatives may also be used

e.g. Benzalkonium chloride B.P.	0.02% w/v
+ Phenylethylalcohol	0.4% w/v
p-hydroxybenzoates + phenoxyethanol B.P.C.	0.4% ("Phenonip", "Phenonip" is a Registered Trade Mark)

The sodium cromoglycate B.P. may be replaced by

5,5′ - [[5,5′ - (2 - hydroxytrimethylene)dioxy]bis[4 - oxo - 4H - 1 - benzopyran - 2 - yl]]tetrazole di-sodium salt	2.0 w/v

Example 3

Preserved Buffered isotonic eye-drop solution

Sodium cromoglycate B.P.	1.0% w/v
Di-sodium edetate B.P.	0.01% w/v
Sodium chloride B.P.	0.42% w/v
Sodium phosphate B.P. ($Na_2HPO_4 . 12H_2O$)	0.12% w/v
Sodium acid phosphate B.P. ($NaH_2PO_4 . 2H_2O$)	0.47% w/v
Thiomersal B.P.	0.01% w/v
Sterile distilled water	to 100%

Thiomersal B.P. may be replaced by any of the preservatives listed in Example 2. In some cases, the quantity of sodium chloride in the formulation may have to be adjusted to maintain isotonicity.

Example 4

Sodium cromoglycate B.P.	2.0% w/v
Disodium edetate B.P.	0.01% w/v
Thiomersal B.P.	0.002% w/v
Sterile distilled water	to 100% w/v

200 g of sodium cromoglycate, 1 g of sodium edetate and 0.20 g of Thiomersal are dissolved with stirring in 10 litres of sterile distilled water. The resulting solution is then sterile filtered and bottled in 10 or 15 ml bottles.

Example 5

Sodium cromoglycate B.P.	2.0% w/v
Disodium edetate B.P.	0.01% w/v
Benzalkonium chloride solution B.P.	0.04% w/v
Phenylethyl alcohol BPC 1963	0.4% w/v
Sterile distilled water	to 100% w/v

1 g of sodium edetate and 200 g of sodium cromoglycate are dissolved, in that order, with stirring in 4 litres of sterile filtered distilled water to yield a solution A. 40 g of phenylethyl alcohol and 4 ml of Benzalkonium chloride are dissolved, in that order, in 4 litres of sterile filtered distilled water with gentle stirring to yield a solution B. Solution B is then added gradually over a period of 5 minutes to solution A with stirring. The resulting solution is then made up to 10 litres with sterile filtered distilled water, stirred for 20 minutes, allowed to settle and filtered under pressure through a Whatman (Whatman is a Registered Trade Mark) gamma 12 filter. The filtered solution is then bottled in 10 or 15 ml bottles.

WHAT WE CLAIM IS:—

1. A pharmaceutical composition comprising a clear, sterile aqueous solution containing as active ingredient a therapeutically useful proportion of 1,3 - bis(2 - carboxy - chromon - 5 - yloxy) - propan - 2 - ol, or a pharmaceutically acceptable salt thereof, or of 5,5′ - [[5,5′ - (2 - hydroxytrimethylene) dioxy]bis[4 - oxo - 4H - 1 - benzopyran - 2 - yl]]tetrazole, or a pharmaceutically acceptable salt thereof.

2. A composition according to Claim 1 containing from 0.1 to 10% w/v of the active ingredient.

3. A composition according to Claim 1 or Claim 2 containing from 0.5 to 5% w/v of active ingredient.

4. A composition according to any one of the preceding claims containing an effective proportion of a pharmaceutically acceptable chelating or sequestering agent.

5. A composition according to Claim 4, wherein the chelating or sequestering agent is sodium carboxymethyl cellulose, citric, tartaric or phosphoric acid or an amino carboxylate compound.

6. A composition according to Claim 5, wherein the amino carboxylate compound is ethylene diamine tetraacetic acid or a salt thereof.

7. A composition according to Claim 5, wherein the amino carboxylate compound is ethylene diamine tetraacetic acid di-sodium salt.

8. A composition according to any one of Claims 4 to 7, wherein the concentration of chelating or sequestering agent is from 0.01 to 0.1% w/v.

9. A composition according to any one of Claim 4 to 8, wherein the concentration of 'metal ions', as hereinbefore defined, is less than 20 p.p.m.

10. A composition according to claim 9, wherein the concentration of 'metal ions', as hereinbefore defined, is less than 10 p.p.m.

11. A composition according to any one of the preceding claims, wherein the concentration of 'metal ions', as hereinbefore defined, is less than 0.40 p.p.m.

12. A composition according to any one of the preceding claims containing less than 0.08 p.p.m. of ionic iron and less than 0.25 p.p.m. of ionic zinc.

13. A composition according to any one of the preceding claims containing less than 20 p.p.m. of Pb^{++}, Ca^{++}, Mg^{++}, Fe^{++}, Fe^{+++} and Zn^{++} ions.

14. A composition according to any one of the preceding claims containing an effective proportion of a pharmaceutically acceptable preservative.

15. A composition according to Claim 14 containing from 0.001 to 0.10% w/v of a pharmaceutically acceptable preservative.

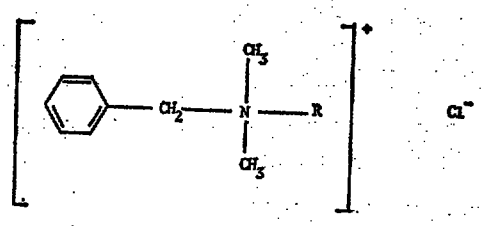
16. A composition according to Claim 14 containing from 0.001 to 0.05% w/v of sodium 2-(ethyl mercuriothio) benzoate.

17. A composition according to Claim 14 or Claim 15, wherein the preservative is a quaternary ammonium compound.

18. A composition according to Claim 17 containing from 0.02 to 0.05% w/v of cetyl pyridinium chloride, tetradecyltrimethyl ammonium bromide, benzyl dimethyl [2 - [2 - [p - (1,1,3,3 - tetramethyl butyl)] phenoxy]ethoxy] ammonium chloride or myristyl - γ - picolinium chloride.

19. A composition according to Claim 17, wherein the preservative is an alkyl benzyl dimethyl ammonium chloride or a mixture thereof.

20. A composition according to Claim 19, wherein preservative is a mixture of compounds of formula,



in which R is an alkyl group C_8H_{17} to $C_{18}H_{37}$.

200 g of sodium cromoglycate, 1 g of sodium edetate and 0.20 g of Thiomersal are dissolved with stirring in 10 litres of sterile distilled water. The resulting solution is then sterile filtered and bottled in 10 or 15 ml bottles.

Example 5

Sodium cromoglycate B.P.	2.0% w/v
Disodium edetate B.P.	0.01% w/v
Benzalkonium chloride solution B.P.	0.04% w/v
Phenylethyl alcohol BPC 1963	0.4% w/v
Sterile distilled water	to 100% w/v

1 g of sodium edetate and 200 g of sodium cromoglycate are dissolved, in that order, with stirring in 4 litres of sterile filtered distilled water to yield a solution A. 40 g of phenylethyl alcohol and 4 ml of Benzalkonium chloride are dissolved, in that order, in 4 litres of sterile filtered distilled water with gentle stirring to yield a solution B. Solution B is then added gradually over a period of 5 minutes to solution A with stirring. The resulting solution is then made up to 10 litres with sterile filtered distilled water, stirred for 20 minutes, allowed to settle and filtered under pressure through a Whatman (Whatman is a Registered Trade Mark) gamma 12 filter. The filtered solution is then bottled in 10 or 15 ml bottles.

WHAT WE CLAIM IS:—

1. A pharmaceutical composition comprising a clear, sterile aqueous solution containing as active ingredient a therapeutically useful proportion of 1,3 - bis(2 - carboxy - chromon - 5 - yloxy) - propan - 2 - ol, or a pharmaceutically acceptable salt thereof, or of 5,5′ - [[5,5′ - (2 - hydroxytrimethylene) dioxy]bis[4 - oxo - 4H - 1 - benzopyran - 2 - yl]]tetrazole, or a pharmaceutically acceptable salt thereof.

2. A composition according to Claim 1 containing from 0.1 to 10% w/v of the active ingredient.

3. A composition according to Claim 1 or Claim 2 containing from 0.5 to 5% w/v of active ingredient.

4. A composition according to any one of the preceding claims containing an effective proportion of a pharmaceutically acceptable chelating or sequestering agent.

5. A composition according to Claim 4, wherein the chelating or sequestering agent is sodium carboxymethyl cellulose, citric, tartaric or phosphoric acid or an amino carboxylate compound.

6. A composition according to Claim 5, wherein the amino carboxylate compound is ethylene diamine tetraacetic acid or a salt thereof.

7. A composition according to Claim 5, wherein the amino carboxylate compound is ethylene diamine tetraacetic acid di-sodium salt.

8. A composition according to any one of Claims 4 to 7, wherein the concentration of chelating or sequestering agent is from 0.01 to 0.1% w/v.

9. A composition according to any one of Claim 4 to 8, wherein the concentration of 'metal ions', as hereinbefore defined, is less than 20 p.p.m.

10. A composition according to claim 9, wherein the concentration of 'metal ions', as hereinbefore defined, is less than 10 p.p.m.

11. A composition according to any one of the preceding claims, wherein the concentration of 'metal ions', as hereinbefore defined, is less than 0.40 p.p.m.

12. A composition according to any one of the preceding claims containing less than 0.08 p.p.m. of ionic iron and less than 0.25 p.p.m. of ionic zinc.

13. A composition according to any one of the preceding claims containing less than 20 p.p.m. of Pb^{++}, Ca^{++}, Mg^{++}, Fe^{++}, Fe^{+++} and Zn^{++} ions.

14. A composition according to any one of the preceding claims containing an effective proportion of a pharmaceutically acceptable preservative.

15. A composition according to Claim 14 containing from 0.001 to 0.10% w/v of a pharmaceutically acceptable preservative.

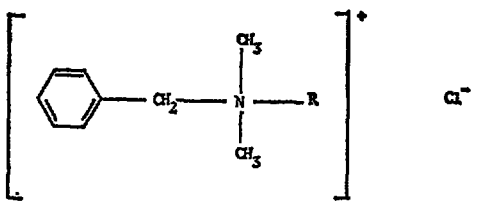
16. A composition according to Claim 14 containing from 0.001 to 0.05% w/v of sodium 2-(ethyl mercuriothio) benzoate.

17. A composition according to Claim 14 or Claim 15, wherein the preservative is a quaternary ammonium compound.

18. A composition according to Claim 17 containing from 0.02 to 0.05% w/v of cetyl pyridinium chloride, tetradecyltrimethyl ammonium bromide, benzyl dimethyl [2 - [2 - [p - (1,1,3,3 - tetramethyl butyl)] phenoxy]ethoxy] ammonium chloride or myristyl - γ - picolinium chloride.

19. A composition according to Claim 17, wherein the preservative is an alkyl benzyl dimethyl ammonium chloride or a mixture thereof.

20. A composition according to Claim 19, wherein preservative is a mixture of compounds of formula,



in which R is an alkyl group C_8H_{17} to $C_{18}H_{37}$.

* C L M S *

21. A composition according to Claim 20, wherein R is $C_{10}H_{21}$ to $C_{14}H_{29}$.

22. A composition according to Claim 19, wherein the preservative is a compound of the formula defined in Claim 20 in which R is $C_{12}H_{25}$.

23. A composition according to any one of Claims 19 to 22 containing from 0.005 to 0.10% w/v of the preservative.

24. A composition according to any one of Claims 19 to 23 also containing from 0.2 to 2.0% w/v of 2-phenylethanol.

25. A composition according to any one of the preceding claims having a pH of from 5 to 7.5.

26. A composition according to Claim 25 having a pH of from 5 to 6.5.

27. A composition according to any one of the preceding claims containing less than 5% w/v of excipients and buffers.

28. A composition according to any of the preceding claims in a pack containing from 10 to 20 ml of solution.

29. A pharmaceutical composition according to Claim 1 and substantially as hereinbefore described in any one of Examples 1 to 5.

30. A method of making a composition according to Claim 1 which comprises dissolving the component or components of the composition in water, filtering the solution and sterilising the filtrate.

31. A method of making a composition according to any one of Claims 14 to 28, which comprises mixing two aqueous solutions of equal volumes one containing twice the desired final concentration of the active ingredient, chelating or sequestering agent, and other additives, and the other containing twice the desired final concentration of the preservative.

32. A method of making a composition according to Claim 1 substantially as hereinbefore described.

33. A method of making a composition according to Claim 1 substantially as hereinbefore described in Example 4 or Example 5.

C. B. CRAIG,
Chartered Patent Agent,
Agent for the Applicants,
Fisons Limited,
Fison House,
Princes Street,
Ipswich,
Suffolk.

Reference has been directed in pursuance of section 9, subsection (1) of the Patents Act 1949, to patent No. 1,144,905.

Printed for Her Majesty's Stationery Office, by the Courier Press, Leamington Spa, 1975.
Published by The Patent Office, 25 Southampton Buildings, London, WC2A 1AY, from which copies may be obtained.

