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(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 JOHN ROBERT HAZLETT of 2632 El Goya, Modesto, California, U.S.A. and ELVIN ALBERT HOLSTIUS of 211 Steward Lane, Greenville, U.S.A. Both citizens of the United States of America.

(54) ANTIMICROBIAL 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, which was communicated from Burroughs Wellcome Co., of 3030 Cornwallis Road, Research Triangle Park, North Carolina 27709, being incorporated in the State of North Carolina, United States of America, 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 chemotherapeutic solutions containing a sulphonamide and a sulphonamide potentiator.

Sulphonamides having antimicrobial, and especially antibacterial activity have been described in the text of *Remington's Pharmaceutical Sciences*, Fourteenth Edition, Mack Publishing Company, Easton, Pennsylvania, copyrighted in 1970 by the Philadelphia College of Pharmacy and Science on pages 1195—1206. It has been found that the chemotherapeutic, especially the antibacterial, activities of the sulphonamides and of certain 2,4-diaminopyrimidines are mutually enhanced when these agents are acting together. Although the enhancement is mutual, these 2,4-diaminopyrimidines are herein referred to as sulphonamide potentiators.

Specific pyrimidines and methods of synthesis thereof are described, for example in British Patent Specification Nos. 715,813; 734,801; 875,562; 920,412; 957,797; 1,128,234; 1,133,766; 1,142,654; 1,223,881; 1,223,882; 1,261,455; 684,759; 774,094; 774,095; 913,710; 970,583; 1,084,103; 1,088,102; 1,129,084; United States Patent Specifications Nos. 2,926,166 and 3,021,332; South African Patent Specification No. 65/5618 and Belgian Patent Specifications Nos. 782,153; 782,154; 774,281 and 789,904.

Aqueous injectable preparations containing both a sulphonamide and a sulphonamide potentiator have previously been prepared using a pharmaceutically acceptable salt of the sulphonamide, either with the sulphonamide potentiator in solution in a water miscible organic solvent or with the sulphonamide potentiator in the form of particles as a dispersion. In both of these cases the pH of the formulation is highly basic.

It has been found that when the pH of the above solutions approaches the lower end of the basic scale, i.e. approaches neutral pH, insoluble complexes of the sulphonamide and the sulphonamide potentiator, e.g. insoluble complexes of sulfamethoxazole and trimethoprim may form. Formation of these complexes render the preparation unusable for injection purposes.

Although the above mentioned injectable preparations are useful they have certain limitations, i.e. their high pH may at times cause tissue damage at the injection site and at times haemolysis may occur which could cause formation of blood clots in the veins elsewhere. In addition, complexing may occur at a more rapid rate when the formulations are added to slightly acid or neutral intravenous solutions or drips, e.g. saline and dextrose.

It should be understood that the prior art dispersion is not suitable in any event for intravenous (hereinafter abbreviated to "I.V.") use because of its particulate nature.

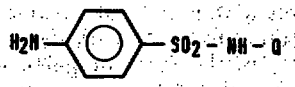
More particularly, common I.V. drips and infusions conventionally have a neutral to slightly acidic pH, e.g. saline, and accordingly if the injectable solution of the prior art is added to this type of infusion solution or drip, insoluble complexes tend to form prior to the complete infusion of the patient (conventionally it is desirable that the patients be infused for periods of 8 to 24 hours).

It has also been found that the sterilization of basic pH injectable preparations utilizing an autoclave at 121° C. for 20 minutes (a preferred sterilization technique because of its acceptability) usually causes the sulphonamide

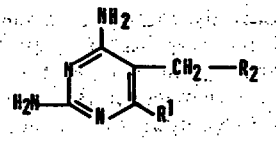
in the basic pH preparations, e.g. sulfamethoxazole, to oxidize and the preparation to take on a yellowish discolouration. This would make the injectable preparation unacceptable as a pharmaceutical product.

Accordingly, a new and improved injectable solution was required to overcome the limitations of the prior art injectable preparations. The invention described hereinafter overcomes the limitations of the above mentioned injectable preparations in that it is injectable directly into the veins (slowly) without causing clotting or tissue damage. In addition, the solution of this invention is compatible with acidic I.V. infusions such as saline, dextrose or Ringer's solution in that no precipitation occurs over long periods of time when used with solutions of sufficient volume.

According to the present invention there is provided a clear solution for parental administration, comprising 1 to 40% (g/100 ml) of a sulphonamide of the formula (III):



wherein Q is a pyrimid-2-yl or -4-yl group or a pyrimid-2-yl or -4-yl group substituted by one or more methyl or methoxy groups or an isoxazolyl group substituted by one or more methyl groups or Q is an acetyl group; 30 to 90% (ml/ml) of a medicinally acceptable water-miscible organic solvent; 1 to 10% (g/100 ml) of a mono-acid addition salt of a compound of the formula (I):



wherein R_1 is hydrogen or lower alkyl, e.g. methyl or ethyl, and R_2 is a phenyl group substituted by one or more alkoxy, such as lower alkoxy, e.g. methoxy, ethoxy or isobutoxy, amino, nitro, halogen, preferably chlorine, alkyl, such as lower alkyl, e.g. methyl or ethyl, trifluoromethyl or hydroxy groups; and 10 to 70% (ml/ml) of water; said clear solution having a pH in the range 4 to 6.

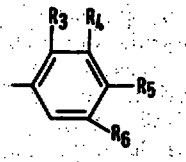
The above solution may be made by combining the sulphonamide of the formula (III), organic solvent, sulphonamide potentiator of the formula (I) in association with the appropriate amount of salt forming acid, and water and then adjusting, if necessary, the pH of the mixture so as to be in the range 4 to 6 either by altering the proportions of the various components or by adding pharmaceutically acceptable acid.

It is preferable that the injectable solution contains an amount of a pharmaceutically acceptable acid sufficient to prevent the formation of an insoluble sulphonamide-sulphonamide potentiator complex after or during formation of the solution. The water soluble pharmaceutically acceptable salts of the sulphonamide potentiator may be formed by the reaction of the sulphonamide potentiator with a pharmaceutically acceptable acid.

The sulphonamide potentiators included in the injectable solutions of the present invention have two free amino groups and are thus capable of forming mono- and di-acid addition salts. The preferential formation of one of the acid addition salts over the other or a mixture of the two will be dependent on the pH of the solution and the pKa's of the pharmaceutically acceptable acid and the sulphonamide potentiation. In the injectable solutions of the present invention the conditions favour the formation of the mono-acid addition salt.

When used herein the terms alkyl and alkoxy are defined as containing 1 to 20 carbon atoms and lower alkyl and lower alkoxy are defined as containing from 1 to 6 carbon atoms and most preferably 1 to 3 carbon atoms and may contain straight or branched alkyl or alkoxy groups.

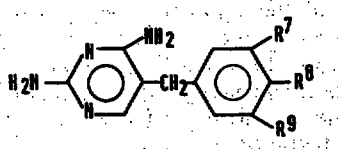
A preferred class of compounds of the formula (I) are those wherein R_2 is a group of the formula (II):



(II)

wherein one or both of R_3 and R_4 are hydrogen, halogen, preferably chlorine, lower alkyl and lower alkoxy and wherein one or both of R_5 and R_6 are halogen, preferably chlorine or bromine, lower alkyl and lower alkoxy.

A further preferred class of compounds of the formula (I) are those of the formula:



wherein R_7, R_8 and R_9 are the same or different and can each represent alkyl or alkoxy groups having from 1 to 4 carbon atoms.

As specific compounds of high value there may be mentioned trimethoprim [2,4 - diamino - 5 - (3,4,5 - trimethoxybenzyl) pyrimidine], diaveridine [2,4 - diamino - 5 - (3,4 - dimethoxybenzyl) pyrimidine], 2,4-diamino - 5 - (3,4,6 - trimethoxybenzyl) pyrimidine, ormetoprim[2,4 - diamino - 5 - (2 - methyl - 4,5 - dimethoxybenzyl)pyrimidine] and 2,4 - diamino - 5 - (3,4 - dimethoxy - 5 - bromobenzyl) pyrimidine.

All these specific compounds are known to

have highly valuable chemotherapeutic activity and to be potentiators of sulphonamides in the sense referred to above.

It is believed that the mono acid addition salt which is formed is the salt in which the acid is combined with the 1-nitrogen atom of the pyrimidine moiety.

Substances which can be used as pharmaceutically acceptable acids to form water soluble pharmaceutically acceptable mono salts of the sulphonamide potentiator, are, for example, pharmaceutically acceptable mineral acids such as sulfuric, phosphoric, hydrochloric, hydrobromic, hydroiodic, as well as pharmaceutically acceptable organic acids such as pharmaceutically acceptable carboxylic acids preferably having between 1 to 20 carbon atoms and most preferably 1 to 10 carbon atoms; e.g., tartaric, citric, lactic, embonic, salicylic, glutamic, glutaric, naphthoic, acetic, and ethylenediamine-tetra acetic acid and other pharmaceutically acceptable organic acids such as methane sulphonic acid. The acids used herein to form the salts or the salts of the sulphonamide potentiator must be stronger acids, i.e., have a lower pKa than the sulphonamide. At present, the preferred acid is citric acid, being conveniently accessible and acceptable for the practice of the invention.

Examples of sulphonamides within the general formula (III) which have antimicrobial, e.g. antibacterial activity for use in this invention, the action of which is capable of being thus potentiated, are sulfadimethoxine [4 - (4 - aminobenzene - sulphonamido) - 2,6-dimethoxy - pyrimidine], sulphadiazine [2-(4 - aminobenzenesulphonamido) pyrimidine] sulfadoxine [4 - (4 - aminobenzenesulphonamido) - 5,6 - dimethoxypyrimidine], sulphamethoxazole [3 - (4 - aminobenzenesulphonamido) - 5 - methylisoxazole], sulphadimidine[2 - (4 - aminobenzenesulphonamido) - 4,6 - dimethylpyrimidine], sulfafurazole [5 - (4 - aminobenzenesulphonamido) - 3,4 - dimethylisoxazole], and sulfacetamide[N - sulfanilyacetamide].

The sulphonamides may be dissolved conveniently in a medicinally acceptable organic water miscible solvent preferably by stirring at room temperature. This may be accomplished readily either by adding the sulphonamide to the combination of the organic solvent and the water with or without the salt of the sulphonamide-potentiator present, or the sulphonamide may be mixed with the organic solvent and then both added to the water with or without the presence of the salt of the sulphonamide potentiator present. It is preferable to insure that the pH of the solution to which the sulphonamide or the salt of the sulphonamide potentiator is added in any order is maintained at a volume and pH sufficient to prevent formation of insoluble salts. In making the therapeutic solution of this invention the salt of the sulphonamide potentiator may be added for example, to the combination of the organic solvent, the water and the sulphonamide, or the salt of the sulphonamide potentiator may be formed by adding a pharmaceutically acceptable acid to the water with or without the presence of the organic solvent and with or without the presence of the sulphonamide by adding the sulphonamide-potentiator as base.

The end product formed, that is the solution of this invention, is precipitate free.

Suitable medicinally acceptable water miscible organic solvents for dissolving the sulphonamide include polar solvents such as polyethylene glycols having average molecular weights from about 190 to 7500 and containing 2 to 159 ethylene glycol monomer (CH_2CH_2O) units; 1,2-propylene glycol, glycerin, hexamethylene glycol, 1,3-butylene glycol, ethanol, diethylacetamide, dimethylacetamide, dimethylsulfoxide, dimethylformamide, di(1,2-propylene glycol, glycerin formal, polyethyleneglycoethers of tetrahydrofurfuryl alcohol and diethylene glycol.

Usually the weight ratio of sulphonamide to sulphonamide potentiator as base useful to obtain a therapeutic effect is of the order of 5:1, though ratios lying between 10:1 to 0.1:1 are useful, and in certain cases it may be found desirable to have a ratio of as high as between 20:1 to 0.1:1.

In accordance with this invention the injectable solution contains from about 10 to 70 percent (all percentages in this application mean g/100 ml percentages unless otherwise specified) preferably 10 to 50 percent and most preferably 20 to 40 percent water (ml/ml) and 30 to 90 percent, preferably 40 to 80 percent and most preferably 50 to 70 percent (ml/ml) of the organic solvent.

The injectable solution also contains 1 to about 40 percent and preferably about 1 to 10 percent or 10 to 30 percent of the sulphonamide and from 1 to 10 percent and preferably 1 to 5 percent of the sulphonamide potentiator calculated as base.

The pH of the solution of this invention is from 4 to 6 and preferably from 4.5 to 5.5 especially for solutions of trimethoprim and sulfamethoxazole. The pH is preferably maintained within these pH limits by the addition of a sufficient amount of a pharmaceutically acceptable acid, the preferred amount being between 0.5 to 3.5%. Examples of suitable pharmaceutically acceptable acids as set forth earlier in the description are incorporated herein.

In order to add certain desirable properties to the injectable solution product, it may be advantageous to add preservatives, local anaesthesia components or other ingredients to enhance stability. Accordingly, it should be understood that other ingredients may be

added so long as these additional ingredients do not detract from the desirable properties of the injectable solution.

The quantity of the injectable solution of this invention which can be injected into a host mammal or animal for the treatment of bacterial infections or even protozoan infections (if the sulphonamide selected also possesses this activity) varies according to the species of the host, its size, its age, general condition of health and severity and type of infection. Conveniently from about 1 ml. to about 1000 ml. of a solution containing about 5 percent g/100 ml of the sulphonamide potentiator and about 25 percent g/100 ml of the sulphonamide can be employed in the treatment of bacterial infections such as those caused by *Proteus mirabilis* or *Haemophilus influenzae*.

The frequency at which the injectable solution of this invention will be administered to a host will vary depending upon the quality of the active medicaments present therein and the needs and requirements of the host.

Under ordinary circumstances, however, up to about 200 mg/kg of the sulphonamide and up to about 150 mg/kg of the sulphonamide potentiator (calculated as base) in combinations can be administered daily in several dosages. It is to be understood, however, that the mentioned ranges are in no sense critical and the dosages can be adjusted in accordance with the needs of the host.

The following examples further illustrate this invention. It is to be noted that all temperatures are in degrees centigrade, unless otherwise specified and where no temperature is given for the mixing of the ingredients or to prepare the salt, room temperature is the temperature at which the ingredients were mixed or at which temperature the salt was formed. Obviously higher or lower temperatures may be used depending on how quickly it is desired for the mixing or the formation of the salt to take place as is well known by those skilled in the art. All percentages in this application mean grams per 100 ml percentages, unless otherwise specified.

Example 1.

The following ingredients were used:

Citric Acid (anhydrous)	1.2 g.
Sulfamethoxazole (SMX)	8.0 g.
Trimethoprim (TMP)	1.6 g.
Polyethylene Glycol 400	30.0 ml.
Propylene Glycol	40.0 ml.
USP Alcohol (95% ethanol)	13.0 ml.
Water	17.0 ml.

The citric acid was dissolved in the water. The USP alcohol and propylene glycol were added with stirring to the water. With continuous stirring, the TMP was added to the above. The Polyethylene Glycol 400 and SMX were added and the mixture stirred until clear. The pH was 4.6. The solution was vacuum filtered through Whatman (Registered Trade Mark) No. 2 filter paper. The solution was sparged with nitrogen for 30 seconds and filled into 5 ml. ampuls. The area above the solution was purged with nitrogen for 10 seconds. The ampuls were heat sealed and autoclaved at 121° C. for 20 minutes.

Example 2.

Example 1 was repeated except that 0.1 g. of potassium metabisulfite was added to the water after the citric acid. Also, nitrogen was not used. The solution was autoclaved at 121° C. for 20 minutes.

Example 3.

The following ingredients were used:

Citric Acid (anhydrous)	1.2 g.
Sulfamethoxazole	8.0 g.
Trimethoprim	1.6 g.
N,N-Dimethylacetamide (DMA)	50.0 ml.
Water	50.0 ml.

The citric acid was dissolved in the water. The TMP was added to the solution and stirred until clear. The DMA and SMX were added and the mixture stirred until clear. The pH of the solution was 4.6. The solution was vacuum filtered through Whatman No. 2 filter paper. The solution was sparged with nitrogen for 30 minutes and filled in 5 ml. ampuls. The area above the solution was purged with nitrogen for 10 seconds. The ampuls were heat sealed and autoclaved at 121°C. for 20 minutes.

Example 4.

Example 3 was repeated except that 0.6 g. of citric acid was used giving a solution with pH 5.6.

Example 5.

The contents of one ampul (5 ml.) of the product of Example 3 were drawn into a syringe and injected into 1 litre of 0.9% sodium chloride with agitation. No precipitate appeared within 16 hours.

Example 6.

The procedure used in Example 5 was followed except a solution of 8.60 g. sodium chloride and 0.33 g. calcium chloride with sufficient water to make 1 litre, commonly referred to as Ringers Solution, was used instead of 0.9% sodium chloride. No precipitate was observed within 16 hours.

Example 7.

The following ingredients were used:

Citric Acid (anhydrous)	1.0 g.
Polyethylene Glycol 400	50.0 ml.
USP Alcohol (95% ethanol)	10.0 ml.
Propylene Glycol	10.0 ml.
Sulfamethoxazole	8.0 g.
Trimethoprim	1.6 g.
Water	30.0 ml.

The citric acid was dissolved in the water. The TMP was then added with continuous stirring until solution was affected. The Polyethylene Glycol 400, USP alcohol (95% ethanol), propylene glycol, and SMX were added to the above and the mixture stirred till the solids dissolved. The pH was 4.6. The solution was vacuum filtered through Whatman No. 2 filter paper. The solution was nitrogen sparged, filled into 5 ml. ampuls, nitrogen purged, heat sealed, and autoclaved at 121° C. for 20 minutes.

The same amount of ingredients and procedure were followed except 0.1 g. of potassium metabisulfite was added and the mixture stirred until a clear solution was obtained. It was filled into 5 ml. ampuls, heat sealed, autoclaved at 121° C. for 20 minutes. Discoloration was noted with the nitrogen purged batch but not with the batch with bisulfite.

Example 8.

The following ingredients were used:

Water	40.0 ml.
Citric Acid (anhydrous)	0.9 g.
Trimethoprim	1.6 g.
Polyethylene Glycol 4000	48.0 g.
Propylene Glycol	10.0 ml.
USP Alcohol (95% ethanol)	10.0 ml.
Sulfamethoxazole	8.0 g.

The citric acid was dissolved in the water. The TMP was added with continuous stirring until a clear solution was obtained. The polyethylene glycol was dissolved in the solution. The propylene glycol, USP alcohol (95% ethanol), and SMX were then added and stirred to give a clear solution. The pH was 5.1. The solution was vacuum filtered through Whatman No. 2 filter paper. Half the batch was nitrogen sparged, filled into 5 ml. ampuls, nitrogen purged, heat sealed, and autoclaved at 121° C. for 20 minutes.

To the other half, 0.05 g. of potassium metabisulfite was added and the mixture stirred until clear. The solution was filled into 5 ml. ampuls, heat sealed, and autoclaved at 121° C. for 20 minutes.

In Examples 9 and 10 following the method of Example 1, the listed ingredients were mixed and 8 g. of sulfamethoxazole and 1.6 g. of trimethoprim were dissolved therein. In Example 11 and 12 following the method of Example 3, the listed ingredients were mixed and 8 g. of sulfamethoxazole and 1.6 g. of trimethoprim were dissolved therein. In Examples 13 and 14 following the method of Example 8, the listed ingredients were mixed and 8 g. of sulfamethoxazole and 1.6 g. of trimethoprim were dissolved therein.

Example	Water*	Citric Acid (anhydrous)	Polyethylene Glycol**	N,N-dimethylacetamide	USP Alcohol	Propylene Glycol	pH	Notes
9	15	1.2	400/30	–	10	45	4.7	
10	40	1.2	400/50	–	10	–	4.9	
11	50	1.2	400/10	40	–	–	4.6	
12	50	0.9	6000***/12	40	–	–	4.6	
13	50	0.9	400/10	38	–	–	4.6	2 ml. Benzyl Alcohol was also added
14	50	0.9	4000***/24	30	–	–	5.0	

* Liquids are by volume in ml., solids by weight in grams
** The first number indicates the polyethylene glycol used, the second the volume in ml. (or the weight in grams for example, 13 and 14).

Example 15.

The following ingredients were used:

DMA	7.5	ml.
Sulfacetamide	2.0	g.
Citric Acid (anhydrous)	0.15	g.
Trimethoprim	0.40	g.
Water	17.5	m.

The citric acid was dissolved in the water. The TMP was added and the mixture was stirred until a clear solution was obtained. The DMA and sulfacetamide were added and the mixture stirred till clear. The pH of the solution was 4.7.

Example 16.

The following ingredients were used:

Sulfamethoxazole	2.0	g.
Trimethoprim	0.4	g.
Water	12.5	ml.
DMA	12.5	ml.
Glacial Acetic Acid	0.1	ml.

The glacial acetic acid and DMA were added to the water and mixed. The TMP was added and the mixture stirred until clear. The SMX was added and the mixture stirred to give a clear solution. The pH of the solution was 5.8.

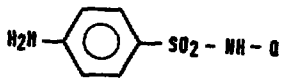
(17)

Examples 17—19.

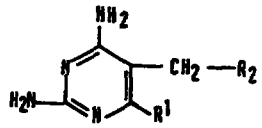
Example 1 was repeated with the exception that instead of trimethoprim there was used as the sulfonamide potentiator the following pyrimidines: 2,4 - diamino - 5 - (3,5-diethyl - 4 - methoxybenzyl)pyrimidine; 2,4-diamino - 5 - (3,5 - dimethoxy - 4 - methylbenzyl)pyrimidine and 2,4 - diamino - 5-(3,4,5 - triethylbenzyl)pyrimidine.

WHAT WE CLAIM IS:—

1. A clear solution for parental administration comprising 1 to 40% (g/100 ml) of a sulphonamide of the formula (III)



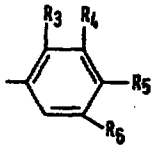
wherein Q is a pyrimid-2-yl or -4-yl group or a pyrimid-2-yl or -4-yl group substituted by one or more methyl or methoxy groups or an isoxazolyl group substituted by one or more methyl groups, or Q is an acetyl group, 30—90% (ml/ml) of a medicinally acceptable water-miscible organic solvent, 10 to 70% (v/v) of water and 1 to 10% (g/100 ml) of the mono acid addition salt of a compound of the formula (I):



wherein R_1 is hydrogen or lower alkyl and R_2 is a phenyl group substituted by one or more alkoxy, amino, nitro, halogen, alkyl, trifluoromethyl or hydroxy groups, said clear solution having a pH in the range 4 to 6.

2. A clear solution according to claim 1 wherein R_2 is a phenyl group substituted by one or more lower alkoxy, amino, nitro, halogen, lower alkyl, trifluoromethyl or hydroxy groups.

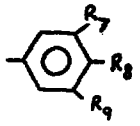
3. A clear solution according to either claim 1 or 2 wherein R_2 is a group of the formula (II):



(II)

wherein one or both of R_3 and R_4 are hydrogen, halogen, lower alkyl and lower alkoxy and wherein one or both of R_5 and R_6 are halogen, lower alkyl and lower alkoxy.

4. A clear solution according to claim 1 wherein R_1 is hydrogen and R_2 is a group:



wherein R_7, R_8 and R_9 are the same or different and can each represent C_{1-4} alkoxy groups.

5. A clear solution according to claim 1 wherein the compound of the formula (I) is trimethoprim[2,4 - diamino - 5 - (3,4,5 - trimethoxybenzyl)pyrimidine].

6. A clear solution according to claim 1 wherein the compound of the formula (I) is diaveridine[2,4 - diamino - 5 - (3,4 - dimethoxybenzyl)pyrimidine].

7. A clear solution according to any one of claims 1—6 wherein the mono acid addition salt of a compound of the formula (I) is formed from a pharmaceutically acceptable carboxylic acid having between 1 to 10 carbon atoms.

8. A clear solution according to any one of claims 1 to 6 wherein the sulphonamide is sulphamethoxazole, sulfadimethoxine or sulphadiazine.

9. A clear solution according to any one of claims 1 to 8 wherein there is 1 to 10% (g/100 ml) of sulphonamide present.

10. A clear solution according to any one of claims 1 to 9 having a pH in the range 4.5 to 5.5.

11. A clear solution according to any one of claims 1 to 10 wherein the clear solution also contains a pharmaceutically acceptable acid.

12. A clear solution according to claim 11 wherein the pharmaceutically acceptable acid is present in an amount of from 0.5 to 3.5 per cent by weight of the solution.

13. A clear solution according to any one of claims 1 to 12 wherein the water-miscible organic solvent is selected from a polyethylene glycol having an average molecular weight from about 190 to 7500 and containing 2 to 159 ethylene glycol monomer (CH_2CH_2O) units, 1,2-propylene glycol, glycerin, hexamethylene glucol, 1,3-butylene glycol, ethanol, diethylacetamide, dimethylacetamide, dimethylsulphoxide, dimethylformamide, di(1,2-propylene)glycol, glycerin formal, polyethyleneglycoethers of tetrahydrofurfuryl alcohol and diethylene glycol.

14. A clear solution according to claim 13 wherein the water-miscible organic solvent is dimethylacetamide, a polyethylene glycol, propylene glycol, ethanol or glycerin formal.

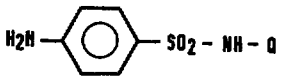
15. A clear solution according to any one of claims 1 to 14 wherein the ratio of sulphonamide of the formula (III) present to a compound of the formula (I) present is approximately 5:1.

Examples 17—19.

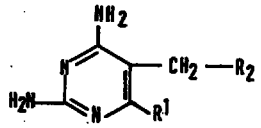
Example 1 was repeated with the exception that instead of trimethoprim there was used as the sulfonamide potentiator the following pyrimidines: 2,4 - diamino - 5 - (3,5-diethyl - 4 - methoxybenzyl)pyrimidine; 2,4-diamino - 5 - (3,5 - dimethoxy - 4 - methylbenzyl)pyrimidine and 2,4 - diamino - 5-(3,4,5 - triethylbenzyl)pyrimidine.

WHAT WE CLAIM IS:—

1. A clear solution for parental administration comprising 1 to 40% (g/100 ml) of a sulphonamide of the formula (III)



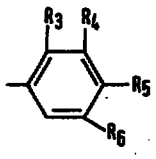
wherein Q is a pyrimid-2-yl or -4-yl group or a pyrimid-2-yl or -4-yl group substituted by one or more methyl or methoxy groups or an isoxazolyl group substituted by one or more methyl groups, or Q is an acetyl group, 30—90% (ml/ml) of a medicinally acceptable water-miscible organic solvent, 10 to 70% (v/v) of water and 1 to 10% (g/100 ml) of the mono acid addition salt of a compound of the formula (I):



wherein R_1 is hydrogen or lower alkyl and R_2 is a phenyl group substituted by one or more alkoxy, amino, nitro, halogen, alkyl, trifluoromethyl or hydroxy groups, said clear solution having a pH in the range 4 to 6.

2. A clear solution according to claim 1 wherein R_2 is a phenyl group substituted by one or more lower alkoxy, amino, nitro, halogen, lower alkyl, trifluoromethyl or hydroxy groups.

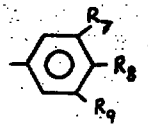
3. A clear solution according to either claim 1 or 2 wherein R_2 is a group of the formula (II):



(II)

wherein one or both of R_3 and R_4 are hydrogen, halogen, lower alkyl and lower alkoxy and wherein one or both of R_5 and R_6 are halogen, lower alkyl and lower alkoxy.

4. A clear solution according to claim 1 wherein R_1 is hydrogen and R_2 is a group:



wherein R_7, R_8 and R_9 are the same or different and can each represent C_{1-4} alkoxy groups.

5. A clear solution according to claim 1 wherein the compound of the formula (I) is trimethoprim[2,4 - diamino - 5 - (3,4,5 - trimethoxybenzyl)pyrimidine].

6. A clear solution according to claim 1 wherein the compound of the formula (I) is diaveridine[2,4 - diamino - 5 - (3,4 - dimethoxybenzyl)pyrimidine].

7. A clear solution according to any one of claims 1—6 wherein the mono acid addition salt of a compound of the formula (I) is formed from a pharmaceutically acceptable carboxylic acid having between 1 to 10 carbon atoms.

8. A clear solution according to any one of claims 1 to 6 wherein the sulphonamide is sulphamethoxazole, sulfadimethoxine or sulphadiazine.

9. A clear solution according to any one of claims 1 to 8 wherein there is 1 to 10% (g/100 ml) of sulphonamide present.

10. A clear solution according to any one of claims 1 to 9 having a pH in the range 4.5 to 5.5.

11. A clear solution according to any one of claims 1 to 10 wherein the clear solution also contains a pharmaceutically acceptable acid.

12. A clear solution according to claim 11 wherein the pharmaceutically acceptable acid is present in an amount of from 0.5 to 3.5 per cent by weight of the solution.

13. A clear solution according to any one of claims 1 to 12 wherein the water-miscible organic solvent is selected from a polyethylene glycol having an average molecular weight from about 190 to 7500 and containing 2 to 159 ethylene glycol monomer (CH_2CH_2O) units, 1,2-propylene glycol, glycerin, hexamethylene glucol, 1,3-butylene glycol, ethanol, diethylacetamide, dimethylacetamide, dimethylsulphoxide, dimethylformamide, di(1,2-propylene)glycol, glycerin formal, polyethyleneglycoethers of tetrahydrofurfuryl alcohol and diethylene glycol.

14. A clear solution according to claim 13 wherein the water-miscible organic solvent is dimethylacetamide, a polyethylene glycol, propylene glycol, ethanol or glycerin formal.

15. A clear solution according to any one of claims 1 to 14 wherein the ratio of sulphonamide of the formula (III) present to a compound of the formula (I) present is approximately 5:1.

16. A clear solution according to claim 1 as hereinbefore described with reference to any one of the foregoing Examples.

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