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"PHARMACEUTICAL PREPARATIONS"

The present invention is concerned with pharmaceutical preparations based on sulphonamide-potentiator combinations.

Combinations of sulphonamides and sulphonamide potentiators (the latter being referred to hereinafter as potentiators for the sake of simplicity) are used extensively for the treatment of bacterial infections in human and veterinary medicine. Because of the different solubility characteristics of the sulphonamides and of the potentiators and because of weak base (potentiator) must be combined with a weak acid (sulphonamide) in non-stoichiometric amounts, the manufacture of pharmaceutically usable solutions (e.g. injection solutions) of combinations of these substances causes difficulties. The hitherto proposed solutions have not been entirely satisfactory having regard to the compatibility of the solvent (especially large amounts of organic solvent), having regard to the liberation of the active substances or the stability of the preparations, or also having regard to their manufacturing costs. The object of the present invention is to remedy these deficiencies by providing pharmaceutical preparations in aqueous form or preparations convertible in a simple manner

into an aqueous form, which possess a satisfactory compatibility and activity, have a high active substance concentration and a physiologically favourable pH-value, are sufficiently stable and contain no expensive adjuvants.

The invention is accordingly concerned with aqueous solutions made from a water-soluble sulphonamide salt, a potentiator and an aldehyde; and dry residues of such solutions.

The preparations in accordance with the invention are not simple solutions of the three components in water. Physico-chemical investigations as well as the fact that the dry residues can again be reconstituted to aqueous solutions point to the formation of a chemical compound in which the aldehyde participates. For example, a preparation obtained from formaldehyde, trimethoprim and sulphadoxine shows in the ^{13}C nuclear resonance spectrum two signals at 67.51 and 52.74 ppm which are characteristic for methylene groups and in the IR spectrum no carbonyl band which is characteristic for formaldehyde.

The expression potentiator denotes compounds which increase the antibacterial activity of sulphonamides more than additively. Such sulphonamide potentiators are

especially compounds which inhibit dihydrofolate reductase such as preferably 2,4-diaminopyrimidine derivatives. Examples of such 2,4-diaminopyrimidine derivatives are 2,4--diamino-5-benzylpyrimidines which are substituted in the phenyl ring such as 2,4-diamino-5-(3,4,5-trimethoxybenzyl)--pyrimidine (trimethoprim), 2,4-diamino-5-(3,5-dimethoxy-4--methoxy-ethoxybenzyl)-pyrimidine (tetroxoprim) and 2,4--diamino-5-(3,5-dimethoxy-4-methylthiobenzyl)-pyrimidine (metioprim). Other examples of dihydrofolate reductase inhibitors are 2,4-diamino-5-(4-bromo-3,5-dimethoxybenzyl)--pyrimidine, 2,4-diamino-5-[3,5-diethoxy-4-(pyrrol-1-yl)-benzyl]-pyrimidine, 2,4-diamino-5-(3,4-dimethoxybenzyl)--pyrimidine (diaveridine), 2,4-diamino-4-(p-chlorophenyl)--6-ethylpyrimidine (pyrimethamine) and 2,4-diamino-5-(2--methyl-4,5-dimethoxybenzyl)-pyrimidine.

Examples of sulphonamides which can be present in the preparations in accordance with the invention are especially N^1-heterocyclic substituted sulphonamides such as those having a 5- or 6-membered heterocycle (e.g. a pyrimidine, pyrazine, pyridazine, oxazole, isoxazole, thiazole or thiadiazole ring). Specific examples of sulphonamides are sulphadiazine, sulphamethoxazole, sulphatroxazole, sulphamerazine, sulphadioxine, sulphadimethoxine, sulphamethazine, sulphapyrazole, sulphaquinoxaline, sulphachloropyridazine,

sulphaguanidine, sulphalene, sulphametin, sulphamethoxine, sulphamethoxy-pyridazine, sulphamethylphenazole, sulphaphenazole, sulphamoxole, sulphapyrazine, sulphapyridazine, sulphapyridine, sulphasymazine, sulphathiozole and sulphametrole.

Of particular interest as ingredients of the preparations in accordance with the invention are the combinations

sulphamethoxazole/trimethoprim;
sulphadiazine/trimethoprim;
sulphadoxine/trimethoprim;
sulphametrole/trimethoprim;
sulphadiazine/tetroxoprim;
sulphadoxine/pyrimethamine.

The aldehyde used for the manufacture of the preparations in accordance with the invention is preferably a lower aliphatic aldehyde, especially formaldehyde. Examples of other aldehydes which can be used are glycol aldehyde and glycerine aldehyde.

The molar ratio of potentiator: aldehyde is conveniently $\leq$ 1:1, i.e., one mol of aldehyde or more is present per mol of potentiator. A preferred molar ratio

potentiator: aldehyde is 1:1 to 1:4, especially 1:1.5 to 1:2.5.

The amount of sulphonamide in the preparations in accordance with the invention is governed by the therapeutic activity of the sulphonamide-potentiator combinations. In the commercial combinations the molar ratio sulphonamide: potentiator is $\geq$ 1:1, in the case of the commercial combinations sulphamethoxazole: trimethoprim it is, for example, about 5.7:1 (corresponding to a weight ratio of 5:1). A preferred preparation in accordance with the invention contains sulphamethoxazole, trimethoprim and formaldehyde in the molar ratio of about 5.7:1:2.

The preparations in accordance with the invention can be manufactured, as a general rule, by mixing the ingredients and warming the mixture, conveniently at about 80°, for example by adding a potentiator and aqueous aldehyde solution to an aqueous solution of a sulphonamide salt and warming the mixture until complete solution has occurred. The sulphonamide is conveniently dissolved in water which contains the requisite amount of base for the salt formation. In a particular embodiment, the aqueous aldehyde solution is added to the solution of the sulphonamide salt and then the potentiator is added. As bases for the salt formation there come into consideration especially alkali hydroxides

such as sodium hydroxide or potassium hydroxide or pharmaceutically usable organic bases such as N-methylglucamine or basic amino acids such as lysine, arginine or ornithine.

The concentration of the solutions in accordance with the invention (i.e. the content of dissolved substances) can amount to 40 weight percent or more, 10-20 percent solutions preferably being manufactured. In the case of certain sulphonamide-potentiator combinations it can be convenient during the manufacture to add to the solution a suitable organic solvent which is miscible with water such as glycofurol or polyethyleneglycol 400.

The aqueous solutions in accordance with the invention can be brought to dryness by means of galenical techniques which are known per se; for example, by freeze-drying or spray-drying. The thus-obtained dry preparations, which are likewise an object of the invention, can be re-converted, if desired after prior sterilization, into solutions (e.g. injection solutions) by the addition of water.

Furthermore, the preparations can be sterilized by means of galenical techniques which are usual in the manufacture of parenteral administration forms; for example, by heat sterilization or sterile filtration.

The applicability of the preparations in accordance with the invention is not limited to injection solutions; the preparations can also be used for other purposes in which a sulphonamide-potentiator combination in dissolved form should be employed.

The preparations in accordance with the invention exhibit in vitro and in vivo the known antibacterial activity of the corresponding sulphonamide-potentiator combinations and can accordingly be used for the same indications.

The following Examples illustrate the present invention:

Example 1

800 mg of sulphamethoxazole are dissolved under nitrogen at 40°C in 3.15 ml of 1N sodium hydroxide. The solution is diluted with ca 5 ml of water and thereafter there are added 160 mg of trimethoprim and 0.08 ml of ca 35% formaldehyde solution or an equivalent amount of paraformaldehyde. The suspension is immersed in a bath (warmed at 80°C) while stirring for 5-7 minutes, a clear solution resulting. After cooling to room temperature, the total volume is made up to 10 ml with water, a solution of pH 8.8 being obtained.

Example 2

In analogy to Example 1, from 800 mg of sulphamethoxazole, 3.15 ml of 1N sodium hydroxide, 160 mg of trimethoprim, 132 mg of glycol aldehyde and water ad 10 ml there is obtained a solution of pH 8.6.

Example 3

In analogy to Example 1, from 1.5 g of trimethoprim,

4.5 g of sulphadiazine, 18.0 ml of 1N sodium hydroxide, 0.9 ml of ca 35% formaldehyde solution and water ad 100 ml there is obtained a solution of pH 9.1.

Example 4

In analogy to Example 1, from 2.0 g of tetroxoprim, 5.0 g of sulphadiazine, 20.0 ml of 1N sodium hydroxide, 0.85 ml of ca 35% formaldehyde solution and water ad 100 ml there is obtained a solution of pH 9.5.

Example 5

In analogy to Example 1, from 4.0 g of trimethoprin, 20.0 g of sulphadoxine, 64.5 ml of 1N sodium hydroxide, 1.8 ml of ca 35% formaldehyde solution and water ad 100 ml there is obtained a solution of pH 9.1.

Example 6

In analogy to Example 1, from 4.0 g of trimethoprim, 20.0 g of sulphatroxazole, 74.8 ml of 1N sodium hydroxide, 1.5 ml of ca 35% formaldehyde solution and water ad 100 ml there is obtained a solution of pH 9.2.

Example 7

In analogy to Example 1, from 4.0 g of 2,4-diamino--5-(4-bromo-3,5-dimethoxybenzyl)-pyrimidine, 20.0 g of sulphadimethoxine, 32.0 ml of 2N sodium hydroxide, 40.0 ml of glycofurol 75, 2.2 ml of ca 35% formaldehyde solution and water ad 100 ml there is obtained a solution of pH 9.6.

Example 8

In analogy to Example 1, from 1.6 g of trimethoprim, 8.0 g of sulphametrole, 28.0 ml of 1N sodium hydroxide, 0.8 ml of ca 35% formaldehyde solution and water ad 100 ml there is obtained a solution of pH 9.6.

Example 9

In analogy to Example 1, from 4.08 g of trimethoprim, 20.4 g of sulphadimethoxine, 66 ml of 1N sodium hydroxide and 2.5 ml of ca 35% formaldehyde solution and water ad 100 ml there is obtained a solution of pH 9.6.

Example 10

In analogy to Example 1, from 10.86 g of a molecular compound trimethoprin-sulphamethoxazole (1:1) [F.Giordano,

G.P. Bettinetti, A. La Manca, P. Ferloni, Il Pharmaco Ed Sci., 32, 889 (1977)], 20 ml of 1N sodium hydroxide, 1.3 g of paraformaldehyde (95-97%) and water ad 100 ml there is obtained a solution of pH 9.75. This solution was evaporated to dryness at 25° under reduced pressure (0.1 Torr) and the residue was dried at room temperature for 48 hours.

Analysis of the residue (2 analyses).

Found:	C 50.18%	H 5.29%	N 15.49%	S 4.98%
	50.19%	5.16%	15.69%	5.09%

H_2O: 3.86%

This residue can be dissolved in 100 ml of water in order to reconstitute an injection solution.

Example 11

In analogy to Example 1, from 5 g of sulphadioxine 16.1 ml of 1N sodium hydroxide, 0.25 g of pyrimethamine and 0.80 ml of ca 35% formaldehyde solution with the addition of 7.5 ml of polyethyleneglycol 400 and water ad 50 ml there is obtained a solution of pH 9.1.

Example 12

320 g of sulphamethoxazole are suspended under nitrogen in ca 1 l of water and dissolved by the addition of 20% sodium hydroxide solution (ad pH 8.8). To this solution there are added 32 ml of ca 35% formaldehyde solution and the mixture is warmed to 90°. Thereafter, 64 g of trimethoprim are added and dissolved while stirring. The solution is cooled to room temperature, the pH of the solution is adjusted to 9.0 and the total volume is made up to 2 l with water. This solution can be lyophilised at -32° (freezing temperature -35°).

CLAIMS:

1. Aqueous solutions made from a water-soluble sulphonamide salt, a sulphonamide potentiator and an aldehyde; and dry residues of such solutions.

2. Solutions in accordance with claim 1, in which the aldehyde is a lower aliphatic aldehyde; and dry residues of such solutions.

3. Solutions in accordance with claim 2, in which the lower aliphatic aldehyde is formaldehyde; and dry residues of such solutions.

4. Solutions in accordance with claims 1-3, in which the potentiator is a dihydrofolate reductase inhibitor; and dry residues of such solutions.

5. Solutions in accordance with claim 4, in which the dihydrofolate reductase inhibitor is a 2,4-diamino-pyrimidine derivative; and dry residues of such solutions.

6. Solutions in accordance with claim 5, in which the 2,4-diamino-pyrimidine derivative is a 2,4-diamino-5-benzyl-pyrimidine derivative; and dry residues of such solutions.

7. Solutions in accordance with claim 6, in which the 2,4-diaminopyrimidine derivative is trimethoprim, tetroxoprim or metioprim; and dry residues of such solutions.

8. Solutions in accordance with claims 1-7, in which the sulphonamide is sulphamethoxazole, sulphadiazine, sulphadioxine or sulphametrole; and dry residues of such solutions.

9. Solutions in accordance with claims 1-8, in which the molar ratio potentiator: aldehyde is $\leq$ 1:1; and dry residues of such solutions.

10. Solutions in accordance with claim 9, in which the molar ration potentiator: aldehyde is 1:1 to 1:4, especially 1:1.5 to 1:2.5; and dry residues of such solutions.

11. Solutions in accordance with claims 1-10, in which the molar ratio sulphonamide: potentiator is $\geq$ 1:1; and dry residues of such solutions.

12. Solutions in accordance with claims 1-11, containing a water-soluble sulphamethoxazole salt, trimethoprim and formaldehyde; and dry residues of such solutions.

13. Solutions in accordance with claim 12, in which the molar ratio sulphamethoxazole: trimethoprim: formaldehyde is about 5.7:1:2; and dry residues of such solutions.

14. Sterile injection solutions made from a solution in accordance with claims 1-13.

15. A process for the manufacture of the solutions in accordance with claims 1-13 and of dry residues of such solutions, which process comprises mixing an aqueous solution of a sulphonamide salt, a sulphonamide potentiator and aqueous aldehyde solution, warming the mixture until complete solution has occurred and, if desired, sterilizing the resulting solution and/or bringing said solution to dryness and, if desired, sterilizing the dry residue.

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