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STABILIZED BENZATHINE PENICILLIN COMPOSITIONS

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ABSTRACT OF THE DISCLOSURE

Benzathine penicillin compositions which include a minor amount of sodium formaldehyde sulfoxylate as storage-stabilizing component.

This invention relates generally to stabilized penicillin compositions, and more particularly to stabilized aqueous suspensions of N,N'-dibenzylethylenediamine di-penicillin, which suspensions are capable of being stored without refrigeration.

The compound N,N'-dibenzylethylenediamine di-penicillin, now known, and hereinafter referred to as benzathine penicillin G, is disclosed and claimed in Szabo and Bruce U.S.P. 2,627,491, and has been firmly established as a standard antibiotic of proven usefulness in the treatment of numerous infections in man, of the Gram positive type, including streptococcal and pneumococcal strains.

As described in said patent, benzathine penicillin G may be prepared by a process which generally comprises slowly adding a solution of N,N'-dibenzylethylenediamine diacetate in water to a solution of sodium penicillin G in water maintained in a lowered temperature (preferably about 0–4° C.), filtrating the slurry, washing the filtrate with cold water, and thereafter drying the filtrate to obtain the substantially water-insoluble product in the form of needle-like acicular crystals.

Among the problems found in preparing therapeutic compositions containing said crystals of benzathine penicillin G in a liquid medium was that the resulting compositions had excessive viscosities and a tendency to cause blockage of a hypodermic needle when parenteral administration was attempted. It was later discovered that, regardless of the then known methods for isolating the crystalline penicillin product, the latter was obtained as single needles or as rosettes or dendrites, but always acicular in crystal habit. In such form, the crystals provided therapeutic compositions which had a tendency to block hypodermic needles of 22 gauge (Stubbs), and even the larger diameter 20 gauge needle. On the other hand, when the crystals were comminuted to small particle sizes, a new problem of excessive viscosity made the resulting compositions exceedingly difficult to use.

As described and claimed in Bruce, Edwards and Apat U.S.P. 2,745,785, it was subsequently found that, when the penicillin salt is prepared in a formamide medium in which it is quite soluble, or when the needle-like crystals of the penicillin salt, obtained by the prior methods of preparation, are recrystallized from a formamide solution; the crystal habit is changed to a predominantly tabular or plate-shaped form of square or rectangular shape. These plates may be regulated in size depending on the precise conditions used. Regardless of whether they are large or small, or thick or thin, the platelet or

tabular form of crystal has been found superior to the needle form for parenteral compositions. Even in compositions containing both acicular and tabular forms, where the tabular form predominates in the parenteral compositions, excessive viscosities or blockage of a 22 gauge needle is satisfactorily avoided, as long as the compositions are not stored for any length of time and/or exposed to high temperature conditions, as referred to with greater particularity hereinafter.

A current typical commercial formulation for an aqueous suspension of a benzathine penicillin preparation in accordance with the teachings in U.S.P. 2,745,785 is given below:

Formula:	Per cc.
Benzathine penicillin G (micronized, lecithin coated) ----------μ--	300,000
Sodium citrate, anhydrous ----------mg--	10.0
Polyvinylpyrrolidone (K value 26–36) mg--	3.0
Carboxymethylcellulose (type 7 HP) -mg--	1.0
Sorbitan monopalmitate ----------mg--	0.5
Polyoxyethylene sorbitan monopalmitate mg--	0.5
Propylparaben, U.S.P. ----------mg--	0.14
Methylparaben, U.S.P. ----------mg--	1.2
Water for injection, U.S.P. qs. ad. ---cc.--	1.0

Compositions of the above type have shown stability of the penicillin potency when stored at temperatures as high as 35° C. for as long as two years, but as has since been found, not in a practical, usable manner. For example, the compositions, after only a few months at 35° C., became unusable because of discoloration and such pronounced gelling, that neither aspiration nor extrusion through conventional hypodermic needles may be effected.

Attempts have been made to obviate the aforesaid disadvantages of the otherwise highly useful benzathine penicillin G preparations of the prior art, which disadvantages are the more pronounced the higher the temperature conditions and/or the longer the period of time of the increased temperature conditions to which the compositions are subjected. As suggested in said U.S.P. 2,745,785, lecithin has been included in the previously known formulations for facilitating resuspension and free drainage from a silicone coated vial. Unfortunately, however, the lecithin, while increasing penicillin-potency stability somewhat, at the same time increases the gelling propensities of the compositions in an undesirable manner. Moreover, lecithin being oxidisable, causes early discoloration of the compositions. In an attempt to avoid these disadvantages in the use of lecithin, the latter has been omitted in the preparation of certain formulations for therapeutic preparations containing benzathine penicillin G. Although discoloration of the benzathine penicillin G compositions has been reduced to some degree by this expedient, the serious problem of gel thickening has not been obviated thereby.

We have now discovered that both discoloration and the gelling of the otherwise known aqueously suspended benzathine penicillin G preparations may be prevented and a product of surprisingly increased storage stability, as well as of excellent reconstituting characteristics, may be provided by a formulation wherein lecithin may be omitted from the vehicle in said preparations with advantage. Specifically, it has been found that the substitution of sodium formaldehyde sulfoxylate instead of lecithin in

the vehicle, and the inclusion of a surface-active agent combination as referred to hereinbefore, results in potency-stable, color-stable and gel-stable aqueous suspensions of benzathine penicillin G, which are resuspendible and fully usable for injection, even after storage for periods at least as long as 18 months at temperatures as high as 35° C. Preferably, the sodium formaldehyde sulfoxylate is included in the aqueous suspensions in amounts which provide from about 0.05% to about 0.5% of the total compositions on a weight to volume basis. Sodium formaldehyde sulfoxide, obtainable commercially as white crystals having a melting point of 65°, is soluble in water.

The following examples are illustrative of the invention but it is to be understood that they are not to be considered limitative.

Example 1

To 666 cc. of water for injection U.S.P. are added, with agitation, the following:

	Grams
Sodium citrate	10
Polyvinyl pyrrolidone (K value 26–36)	3
Sodium carboxymethylcellulose (high viscosity)	1
Sorbitan monopalmitate	0.5
Polyoxyethylene sorbitan monopalmitate	0.5

With constant agitation, this mixture is sterilized at 121° C. and 15 lbs. pressure for one hour, and cooled immediately to 60° C.; 0.13 gram of sterile propylparaben is then added with agitation until dissolved; followed by the addition of 1.2 grams of sterile methylparaben with agitation until dissolved.

After this mixture has cooled to 25° C., 25 cc. of a 4% weight by volume sterile solution of sodium formaldehyde sulfoxylate, followed by 300,000,000 Oxford units of sterile micronized benzathine penicillin G tabular crystals (1,170 units/mg.) (95% of the particles being less than 10 microns) are added with continuous agitation. Sufficient quantity of water for injection U.S.P. is then added to bring the volume of the suspension to one liter. Agitation is continued for one hour to ascertain a homogeneous suspension.

This therapeutic preparation is a uniform suspension of benzathine penicillin G which is stable and suitable for intramuscular injection into humans or animals. Injection of one ml. of this product furnishes 300,000 Oxford units of crystalline dibenzylethylenediamine dipenicillin G. After 18 months at 35° C., the potency diminishes less than 5%. More importantly, the easily resuspended compositions are still of suitable color and viscosity to permit injection with the use of hypodermic needles as thin as 23 gauge.

Example 2

Following the general procedure of Example 1, three separate therapeutic compositions containing benzathine penicillin G were prepared from the respective formulations given below:

Formula	Composition Designation		
	3A	3C	7A
Benzathine Penicillin G (Micronized, lecithin coated), μ	300,000	300,000	300,000
Sodium Citrate, Anhydrous, mg	10.0	10.0	10.0
Lecithin, R.G., mg	3.0		
Polyvinylpyrrolidone, K26-36 mg	3.0	3.0	3.0
Carboxymethylcellulose Type 7 HP, mg	1.0	1.0	1.0
Span 40, mg	0.5	0.5	0.5
Tween 40, mg	0.5	0.5	0.5
Sodium Formaldehyde Sulfoxylate, mg			1.0
Propylparaben, U.S.P., mg	0.14	0.14	0.14
Methylparaben, U.S.P., mg	1.2	1.2	1.2
Water for Injection, U.S.P. qs. ad., cc	1.0	1.0	1.0

Twenty 10 cc. samples of each of the foregoing compositions contained in separate vials, were subjected to stability tests based on storage for 18 months of 10 vials of each sample at 25° and the remaining 10 vials of each at 35° C. The averaged results of the various tests to which the stored samples were subjected are given below:

TABLE A

Determinations after 18 months	3A	3C	7A
Discoloration:			
25° C	Slight discoloration.	Slight discoloration.	None.
35° C	Discolored	Discolored	Slight discoloration.
Resuspension (No. of shakes):			
25° C	20	20	20.
35° C	20	15 [1]	20.
Injection (Thinnest needle gauge usable):			
25° C	25 ga.	25 ga.	25 ga.
35° C	20 ga.	22 ga.	23 ga.

[1] Resuspended previously.

As appears from the foregoing, the benzathine penicillin G compositions 7A containing sodium formaldehyde sulfoxylate as storage stabilizer in accordance with the invention, are only slightly discolored and still injectable through hypodermic needles as thin as 23 gauge, even after storage for 18 months at 35° C., whereas the prior art compositions 3A and 3C are discolored and not injectable through such thin gauge needles when subjected to the same severe storage conditions which simulate a southern climate.

In preparing the benzathine penicillin G for inclusion in the aqueous parenteral compositions of the invention, the particle size of the penicillin salt may range from about 5 to about 150 microns, but preferably 95% of the particles should be less than 10 microns in size with approximately 50% of the particles having a particle size from about 8 to 10 microns.

Micronization of the platelets of benzathine penicillin G may be carried out by comminuting the salt with an air blast under pressure, causing fragmentation to particle sizes, in general, ranging from about 5 to 20 microns, but usually less than about 10 microns.

As suspending agent, there may be included in the compositions either salts of carboxymethylcellulose, methyl cellulose, polyvinylpyrrolidone, gelatin, pectin, agar, dextrin, sodium alginate, or various gums, such as gum arabic, gum tragacanth, gum karaya, etc., or mixtures of these agents. Other suspending agents which are assimilable in the body and which are relatively nontoxic in the amounts used may be used in place of those mentioned. A preferred suspending agent system has been found to be a combination of sodium carboxymethylcellulose and polyvinylpyrrolidone.

In preparing the storage-stabilized aqueous parenteral compositions of the invention, in addition to the penicillin salt and suspending agent or agents, it has been found useful to have a buffering agent present in order to extend the shelf-life, and a preservative to inhibit bacterial or fungal action. Methyl paraben, propyl paraben, sodium benzoate, as well as the alkyl-p-hydroxy-benzoates are useful preservatives, while suitable buffers for the penicillin are sodium citrate, $CaCO_3$, various mixed phosphate buffers or any of the buffers described in Alburn et al. U.S.P. 2,438,106. Preferably, the penicillin particles are coated with a wetting agent such as lecithin to increase the wetting characteristics of the penicillin salt. Similarly, there are advantageously added to the compositions, emulsifiers, surface-active and defoaming agents, such as various partial higher fatty acid esters of sorbitan or polyoxyalkylene derivatives thereof known as Spans or Tweens, aryl alkyl polyether alcohols or salts thereof known as Tritons, the dialkyl esters of sodium sulfosuccinic acid known as Aerosols, and the like.

The carboxymethylcellulose may be varied in the formulations from about 0.1% to 0.4% by weight, while the polyvinylpyrrolidone may be varied from about 0.1% to 0.8% by weight; or, if desired, either one or the other suspending agent may be used alone to provide the total suspending agent employed.

The buffer content may vary in the formulations from 0.5% to 5.0% by weight, while the preservative content may also be varied within the range of about 0.12% to 0.25% for the methyl derivative and about 0.013% to 0.05% for the propyl derivative.

While sorbitan monopalmitate and its polyoxyalkylene derivative were used in the above examples, there may be used in place thereof, the monolaurate, monostearate or monooleate sorbitans, and/or the corresponding polyoxyethylene derivatives thereof. These wetting agents may be used to the extent of about 0.05% to 0.3% by weight. All of these percentages are on a weight basis, in grams per 100 cc. of liquid volume.

As will appear to those skilled in the art from the foregoing, various modifications of the formulations employing the invention are possible within the scope thereof as defined by the appended claims as long as the advantages of the invention with respect to potency stability, color stability and gel stability are attained.

We claim:

1. A stabilized therapeutic composition consisting of comminuted crystals of benzathine penicillin G in an aqueous suspending medium which includes a minor storage-stabilizing amount of sodium formaldehyde sulfoxylate.

2. A stabilized therapeutic composition consisting of micronized, lecithin-coated crystals of benzathine penicillin G in an aqueous suspending medium which includes a minor amount of a suspending agent, a minor amount of a buffering agent, a minor amount of a surface-active agent, a minor amount of a preservative agent, and a minor storage-stabilizing amount of sodium formaldehyde sulfoxylate.

3. A stabilized therapeutic composition consisting of micronized, lecithin-coated crystals of benzathine penicillin G in an aqueous suspending medium in concentration affording approximately 300,000 units potency per 1 cc. of total composition, from about 0.2% to about 1.2% by weight to volume of a suspending agent, from about 0.5% to about 5.0% by weight to volume of a buffering agent, from about 0.05% to about 0.3% by weight to volume of a surface-active agent, from about 0.12% to about 0.30% by weight to volume of a preservative agent, from about 0.05% to about 0.5% by weight to volume of sodium formaldehyde sulfoxylate as storage-stabilizer for the composition.

4. A stabilized therapeutic composition consisting of the following formulation:

Component:	Approx. conc. per cc.
Benzathine penicillin G (micronized, lecithin coated) ____μ__	300,000
Sodium citrate, anhydrous ____mg__	10.0
Polyvinylpyrrolidone ____mg__	3.0
Carboxymethylcellulose ____mg__	1.0
Sorbitan monopalmitate ____mg__	0.5
Polyoxyethylene sorbitan monopalmitate ____mg__	0.5
Sodium formaldehyde sulfoxylate ___mg__	1.0
Propylparaben, U.S.P. ____mg__	0.14
Methylparaben, U.S.P. ____mg__	1.2
Water for injection, U.S.P., qs. ad. ___cc__	1.0

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