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THERAPEUTIC COMPOSITION COMPRISING TABULAR N,N'-DIBENZYLETHYLENEDI- AMINE DI-PENICILLIN, AND PROCESS FOR PREPARING SAME

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This invention relates to penicillin compositions and, more particularly, to therapeutic compositions containing N,N'-dibenzylethylenediamine-penicillin.

The di-penicillin salt of N,N'-dibenzylethylenediamine is disclosed in the patent application of Szabo and Bruce, Serial No. 174,115, filed July 15, 1950, and also has been described and its properties discussed in the publication "Antibiotics and Chemotherapy," vol. 1, No. 8, November 1951, pages 499-508. This penicillin salt has been found to be both therapeutically active and relatively water-insoluble. Comparison with procaine penicillin indicates the diamine salt to be substantially more insoluble than the procaine salt and, as a consequence, a longer lasting effect is achieved when compositions containing this diamine penicillin salt are administered either orally or parenterally. It has been found that regardless of the type of compositions used, whether oral or parenteral, comparisons under similar conditions with procaine penicillin indicate the compositions of the invention to have a prolonged action, from at least 2 to 4 times as long as procaine penicillin compositions.

Among the problems found in preparing compositions containing the diamine salt was the preparation of a suitable crystalline salt that could successfully be suspended in a liquid vehicle, particularly avoiding excessive viscosities, and the development of a composition that would not have a tendency to cause blockage of a hypodermic needle.

It was discovered that, regardless of the method of preparation known heretofore, the diamine penicillin salt was always obtained largely as needle-like crystals, either as single needles or as rosettes or dendrites, but always acicular in crystal habit. Attempts to use such crystalline material in parenteral compositions invariably resulted in a tendency toward blockage of the hypodermic needle of 22 gauge (Stubbs), or even of the larger 20 gauge needle. The problem of blockage with acicular crystals was invariably encountered when using the naturally formed crystals, regardless of earlier methods of manufacture or treatment, and when these crystals were comminuted to small particle sizes a new problem of excessive viscosity made the compositions exceedingly difficult to use.

Attempts to obtain a non-acicular crystalline structure which would not block the standard hypodermic needle normally used for penicillin injection and which would not pack excessively led to trials with various recrystallization procedures when different methods of reaction failed to produce an acceptable product. Many well-known, commercially available solvents were tried without success, either because of substantial insolubility of the salt therein or, where appreciable solubility was found, the acicular type of crystal predominated in the product obtained.

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It has been found, most unexpectedly, that when the penicillin salt is prepared in a formamide medium in which it is quite soluble, or when the needle-like penicillin salt is recrystallized from a formamide solution, the crystal habit is changed to a predominantly tabular or plate-like form of square or rectangular shape. These plates may be regulated in size depending on the precise conditions used. However, 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 composition, excessive viscosities or blockage of a 22 gauge needle is satisfactorily avoided. No other solvent has proved as capable as formamide in producing the diamine salt in substantially tabular form.

The following example is illustrative of the formation of the acicular type of penicillin salt described above.

Example 1

About 63 grams of potassium penicillin G was dissolved in 160 cc. of water.

N,N'-dibenzylethylenediamine di-acetate was also dissolved in water, approximately 30 grams being dissolved in 160 cc. of water.

The two solutions were mixed together drop-wise and simultaneously to about 280 cc. of water which was agitated during addition and for about 2 hours after the addition was complete. The crystalline product was obtained by filtration and was washed with water and acetone and then dried. The crystals were acicular, forming into rosettes and single needles.

The following examples illustrate procedures for obtaining the new tabular form of N,N'-dibenzylethylenediamine di-penicillin G.

Example 2

100 grams of potassium penicillin G were dissolved in 300 ml. of 50% aqueous formamide.

37.0 grams of N,N'-dibenzylethylenediamine were added to 2 liters of formamide and neutralized by the addition of 18.5 grams of glacial acetic acid. To this solution, warmed to 55° C., was added with stirring the solution of potassium penicillin. 650 ml. of water was added slowly to cause crystallization. The mixture was cooled to 5° C. and the crystals filtered off, washed with water, acetone and ether and dried in a vacuum desiccator. The crystals were in the form of regular plates, with a bulk density 2.5 cc./gram. The material was satisfactory for injectable aqueous suspension type dosage forms.

Example 3

100 grams of potassium penicillin G were dissolved in 250 ml. of 50% aqueous formamide, filtered and then added to 2 liters of formamide heated to 55° C.

59.5 grams of N,N'-dibenzylethylenediamine diacetate (120% of theoretical) were dissolved in 100 ml. of water at 50° C. and dropped slowly into the stirred solution of potassium penicillin. The mixture of crystals was cooled in an ice bath to 20° C. and then placed in a refrigerator at 5° C. overnight.

The crystals of N,N'-dibenzylethylenediamine penicillin were filtered off, washed with water, acetone and ether and dried in a vacuum desiccator. The crystals were in the form of square or rectangular plates. The yield was 121.5 grams, 1200 u./mg.

Example 4

100 grams of potassium penicillin G were dissolved in 2 liters of formamide at 55° C.

53.5 grams of N,N'-dibenzylethylenediamine diacetate (110% of theoretical) in 1100 ml. of water at 50° C. were added slowly to the stirred solution of potassium penicillin. Crystallization occurred before all the N,N'-dibenzylethylenediamine diacetate solution was added. The mixture was cooled in an ice bath before filtering. The crystals were washed with water, acetone and ether.

The crystals were in the form of fairly uniform, square plates.

In the preceding examples, a small amount of acetone (about 1/10 the formamide volume) may be added to the penicillin-formamide solution to reduce the viscosity and help in the filtering step.

While the above examples demonstrate crystallization from a formamide and water medium, the latter acting to reduce the solubility of the diamine salt in the solution, hasten the crystallization, and increase the yield, one may also obtain the tabular crystals from substantially pure formamide by reducing the temperature of a relatively hot solution of the penicillin salt in formamide. Conversely, while the examples show crystallization where the formamide is in excess, one may still obtain the desired platelets even when enough water is present to reduce the formamide content to as low as about 15% by volume.

The stirring or agitation of the solution when forming the crystals should not be too rapid if large crystals and thicker plates are desired. An anchor type of stirrer is desirable. A homogenizer type of agitation produces excessive shear, causing undesirably small particle sizes. Relatively low temperatures during crystallization will also produce small crystal plates. While temperatures as high as about 60° C. may be used in forming the penicillin salt, a temperature ranging from about 20° C. to about 45° C. is preferred. During the crystallization period, the solutions may be cooled to a temperature ranging from about 0° to 20° C.

Examples 2-4 illustrate crystallization of the penicillin salt from formamide to which water was added to reduce the solubility of the penicillin salt and it has already been pointed out that another solvent may be present in minor amount for purposes of mechanically improving the filtration procedure. However, it is also possible to crystallize from a mixture of solvents and obtain the desired tabular crystals as long as a substantial amount of formamide is present. Thus, using a mixture of formamide and dimethyl formamide, one may obtain the penicillin crystals in substantial tabular habit as long as there is at least about 50% of formamide present in the solvent mixture.

The following examples illustrate the feasibility of recrystallization to the tabular type of crystal from an original acicular crystal.

Example 5

25 grams of acicular N,N'-dibenzylethylenediamine di-penicillin G were dissolved in 500 ml. formamide at 60° C. 150 ml. water was added slowly with agitation to throw down the dibenzylethylenediamine penicillin. At the end of the addition of water, the mixture was cooled to 0° C., filtered, washed with water, acetone and ether and dried in vacuo. The crystalline dibenzylethylenediamine penicillin was in the form of square and short rectangular plates.

Example 6

5 grams of potassium penicillin were dissolved at 60° C. in the following solvent mixture:

50 ml. formamide
50 ml. isopropyl alcohol
2.5 ml. water

1.20 ml. (110%) of a 1.25 normal aqueous solution of dibenzylethylenediamine diacetate was added slowly to the stirred solution of potassium penicillin and then 50 ml. water to complete crystallization. The mixture was cooled to 0° C. in an ice bath, filtered, washed with water, ace-

tone and ether and dried in vacuo. The product assayed 1170 u./mg. The crystals were in the form of square plates and short rectangles.

Other solvents than isopropyl alcohol may be used, for example, methanol, ethanol, methyl cyanide, diacetone alcohol.

The crystals of N,N'-dibenzylethylenediamine di-penicillin G, suitable for use in the parenteral compositions of the invention, as illustrated by Examples 2 to 6 as given above, have the following physical and optical properties:

1. Crystal habit—tabular (plate-like, square or rectangular).
2. Crystal system—orthorhombic.
3. Length slow, or positive elongation.
4. Index of refraction parallel to the length = 1.56.
5. Index of refraction perpendicular to the length = 1.53.
6. Birefringence strong (.035).
7. Parallel extinction, indicating the optical axes parallel to the crystallographic axes.

In preparing the parenteral compositions of the invention, they may be made up in an oleaginous or aqueous vehicle, or, if desired, they may be in dry form to be reconstituted with the liquid vehicle by the physician at the time of use. For an oleaginous or aqueous suspension for parenteral use, 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. When considering a dry admixture to be reconstituted with water at the time of use, particle sizes may range from about 5 to 40 microns with at least 50% of the particles preferably having a size of about 20 to 40 microns.

The oleaginous vehicle is preferably peanut oil and as a suspending agent one may use beeswax, hydrogenated vegetable oil or aluminum monostearate. A more preferred vehicle is water and, where the aqueous suspension type of composition is desired, one may use 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 non-toxic in the amounts used may be used in place of those mentioned. A preferred suspending agent for the oleaginous vehicle is aluminum monostearate, while sodium carboxymethylcellulose alone or with polyvinylpyrrolidone is preferred with the aqueous vehicles, particularly where a dry admixture is to be made up and later reconstituted with water at the point of use. In the latter case, the suspending agent must be one which will act effectively on the addition of relatively cold water. In referring to polyvinylpyrrolidone, the material meant is that disclosed in the publication bearing that name and dealing with its preparation, properties, and applications, published in 1951 by General Aniline and Film Corp., Development Dept., New York, N. Y.

Oral compositions may utilize either the acicular or the tabular crystalline form of the di-penicillin salt with the latter preferred for liquid compositions since high viscosities are avoided. Particle sizes may range from about 5 to about 150 microns. For liquid compositions, relatively low particle sizes, preferably about 50% having a particle size from about 8 to 10 microns, are used while oral tablets may utilize particle sizes throughout the range first given.

Liquid oral compositions utilizing N,N'-dibenzylethylenediamine di-penicillin have been found to have a surprising utility in the treatment of children, particularly infants too young to swallow medicinal tablets. Oral compositions comprising this penicillin salt in an aqueous vehicle with a mild flavoring agent have found wide acceptance because of the ease of administration. Here-

tofore, any of the known penicillin salts, and even procaine penicillin, has been sufficiently water-soluble to impart the characteristically bitter taste of penicillin to the medicinal.

No flavoring agents could be found strong enough or sufficiently orally acceptable for masking the penicillin bitterness. On the other hand, the oral suspensions containing the diamine salt are so water-insoluble as to be practically tasteless.

As in the case of the parenteral composition, the liquid oral composition may utilize any of the suspending agents disclosed above which are normally useful with an aqueous vehicle, but with sodium salt of carboxymethyl cellulose again being the suspending agent of choice.

When considering parenteral or liquid oral compositions in addition to the penicillin salt and suspending agent or agents, it has been found useful to have a stabilizer or buffering agent present in order to extend the shelf-life, and a preservative to inhibit bacterial or fungal action. Benzyl alcohol, sodium benzoate as well as the alkyl-p-hydroxy-benzoates are useful preservatives, while suitable buffers or stabilizers for penicillin are CaCO_3 , various mixed phosphate buffers or any of the buffers described in the Alburn et al. Patent No. 2,438,106 issued March 23, 1948. Likewise, if additional properties are desired, one may coat the penicillin particles with a wetting agent such as lecithin to increase the wetting characteristics of the penicillin salt, and, also if desired, emulsifiers, surface-active and defoaming agents may be added, as, for example, 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, etc. Parenteral compositions may also have a substance to render the composition isotonic, for example, sodium chloride. For oral suspensions, suggested additives are coloring, sweetening and flavoring agents where infant acceptability is sought.

The following example illustrates an aqueous composition packaged in a vial and suitable for injection purposes.

Example 7

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

	Grams
Sodium citrate -----	10
Lecithin -----	3
Polyvinylpyrrolidone (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 propyl-p-hydroxybenzoate is then added with agitation until dissolved, followed by the addition of 1.2 grams of sterile methyl-p-hydroxybenzoate with agitation until dissolved.

After this mixture has cooled to 30°C ., 300,000,000 Oxford units of sterile micronized dibenzylethylenediamine di-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 dibenzylethylenediamine di-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 di-penicillin G.

Example 8

A composition similar to that of Example 7 but with a somewhat lower potency and suitable for veterinary use may be made by using 200,000,000 Oxford units of the tabular penicillin salt and increasing the amount of carboxymethylcellulose to 3 grams.

Micronization of the platelets of N,N'-dibenzylethylenediamine di-penicillin G is 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, while pulverization involves comminution with hammer impact devices causing a fragmentation to relatively larger sizes normally ranging upward of about 20 microns in size.

The carboxymethylcellulose may be varied in the above 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. The two suspending agents utilized in Examples 7 and 8 may be changed by using from about 0.05% to 0.2% gelatin, or from about 0.05% to 0.3% agar or gum karaya, or from about 0.1% to 3.0% of dextrin or gum acacia, or from about 0.05% to 1.0% methyl cellulose, or from about 0.05% to 0.5% of carrageen gel, pectin, tragacanth or sodium alginate.

The stabilizer content may vary in the preceding 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 or butyl derivative. One may also substitute 0.9% of benzyl alcohol or from about 0.5% to 1.0% of sodium benzoate or about 0.25 to 0.5% phenol for the preservatives of Example 7.

While sorbitan monopalmitate and its polyoxyalkylene derivative were used in the above examples, one may use in place thereof monolaurate, monostearate or monooleate sorbitans and the corresponding polyoxyethylene derivatives thereof. These wetting agents may be used to the extent of about 0.05% to 0.3% by weight. In place of the sorbitans, or together therewith, one may have from about 0.1% to 3.0% lecithin in suspension. All of these percentages are on a weight basis, in grams per 100 cc. of liquid volume.

The following examples illustrate a few more variations in aqueous suspension compositions suitable for vial packaging.

Example 9

The process of Example 7 was followed but using 300,000,000 Oxford units of pulverized tabular di-penicillin salt crystals with approximately 50% having a particle size ranging from 20 to 40 microns.

The sodium citrate content was varied from 10 to 5 grams and the carboxymethylcellulose content was changed from 1 to 4 grams but deleting the polyvinylpyrrolidone. Instead of the sorbitans previously mentioned, 0.5 gram of sorbitan monostearate and 1 gram of the polyoxyethylene derivative were used. Instead of the preservatives used in Example 7, 0.15 gram of butyl-p-hydroxybenzoate was used.

Example 10

The same procedure as in Example 7 was carried out except that, in place of the suspending agents used there, 1.0 gram of tragacanth was used and instead of the sorbitans disclosed there, 0.5 gram of sorbitan monostearate and the same amount of the corresponding polyoxyethylene derivative was used.

Example 11

Following the same procedure as in Example 7, 625,000,000 Oxford units of tabular, crystalline N,N'-dibenzylethylenediamine di-penicillin G was used for high-

er potency, with 10% being in micronized form and 90% in pulverized form. One gram each of polyvinylpyrrolidone and sodium carboxymethylcellulose was used and, in place of the sorbitans used there, 3 grams of sorbitan monooleate and 2 grams of the corresponding polyoxyethylene derivative were used.

The following example is illustrative of the preparation of a dry admixture to be reconstituted with an aqueous medium for parenteral application at the time of use.

Example 12

Using aseptic technique and precautions, the following ingredients were combined in a suitable sterile container.

Dibenzylethylenediamine di-penicillin G (sterile) tabular crystals: (pulverized, lecithin-coated) potency 1170 units/mg. (maximum 150 microns, average 20 to 40 microns)-----Oxford units--	540,000,000
Dibenzylethylenediamine di-penicillin G (sterile) acicular crystals: (micronized, lecithin-coated) potency 1170 units/mg. (95% of the particles being less than 10 microns) -----Oxford units--	60,000,000
Carboxymethylcellulose (sterile) (type 70—high viscosity) -----grams--	1.5
Polyvinylpyrrolidone (sterile) (K value 26-36) -----grams--	6.0
Sodium citrate, U. S. P. (sterile) -----do-----	20

This mixture is blended for one hour and is then pulverized in a Bantam micropulverizer at 9600 R. P. M. through a 0.035" herringbone screen. To assure uniformity, the mixture is blended for an additional hour. This mixture is also treated with ethylene oxide to insure sterility.

This dry stable material is filled into vials to provide a therapeutic preparation of dibenzylethylenediamine di-penicillin G when reconstituted, in the following manner, and subsequently produces a stable suspension suitable for intramuscular injection into humans or animals.

To the 600,000 Oxford unit single dose vial, add 1.5 cc. of water for injection U. S. P. or physiological saline solution. After moderate shaking the product may be administered intramuscularly through any standard glass syringe equipped with a 22 gauge needle. The entire contents, approximately 2.0 cc. is withdrawn for a single injection of 600,000 Oxford units of dibenzylethylenediamine di-penicillin G. Sufficient excess of all ingredients is provided to permit withdrawal of the entire dose.

To the 1,200,000 Oxford unit single dose vial, add 3.0 cc. of water for injection U. S. P. or physiological saline solution. The resultant suspension provides a single withdrawable dose of approximately 4.0 cc. containing 1,200,000 Oxford units of dibenzylethylenediamine di-penicillin G. This product may be administered as indicated above.

To the 2,400,000 Oxford unit single dose vial, add 6.0 cc. of water for injection U. S. P. or physiological saline solution. The resultant suspension provides a single withdrawable dose of approximately 8.0 cc. containing 2,400,000 Oxford units of dibenzylethylenediamine di-penicillin G. This product may also be administered as indicated above.

Example 13

Following the same procedure as in Example 12, 600,000,000 Oxford units of pulverized tabular crystals were used, with approximately 50% ranging from about 20 to 40 microns in size. In place of the combined suspending agents, 3 grams of sodium carboxymethylcellulose is used. Various dosages could be made up as taught in the preceding example.

Example 14

Also following the same procedure as in Example 12, 180,000,000 Oxford units of micronized tabular penicillin crystals, 95% having a particle size not greater than about 10 microns, and 420,000,000 Oxford units of pulverized tabular penicillin crystals, about 50% ranging from 20 to 40 microns in size, were used. In place of the combined suspending agents, 5 grams of polyvinylpyrrolidone was used and in place of the sodium citrate, 20 grams of potassium citrate was used as a stabilizer. Dosages as taught in Example 12 may then be made up as desired.

The following example is illustrative of an oleaginous, injectable composition utilizing the tabular crystals of N,N'-dibenzylethylenediamine di-penicillin G.

Example 15

To one liter of peanut oil is added 20 grams of powdered commercial aluminum monostearate. This mixture is slowly agitated and heated at an increasing rate of not more than 5° C. per minute. With continued agitation heat to 125° C. whereupon the heating is discontinued but slow agitation is continued until gel cools to room temperature.

Add 300,000,000 Oxford units of micronized, tabular dibenzylethylenediamine di-penicillin G crystals (95% of the particles being less than 10 microns) to 700 cc. of peanut oil with 2% aluminum monostearate (as prepared above) with slow agitation. Then add sufficient quantity of the 2% aluminum monostearate-peanut oil gel to bring the volume of the suspension to one liter. Agitate for one hour to ascertain a homogeneous suspension.

This therapeutic preparation is a uniform suspension of dibenzylethylenediamine di-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 dibenzylethylenediamine di-penicillin G.

In place of the 100% micronized penicillin salt one may use a mixture of 40% micronized and 60% pulverized or all pulverized penicillin salt, the latter preferably having a particle size below about 75 microns.

The following example illustrates the preparation of single dose, disposable cartridges for hypodermic injection.

Example 16

Using aseptic technique and precautions throughout add, with constant agitation, the following ingredients to 500 cc. of water:

	Grams
Sodium citrate-----	5
Carboxymethylcellulose (high viscosity)-----	3
Polyvinylpyrrolidone (K value 26-36)-----	3

With constant agitation this mixture is sterilized at 121° C. and 15 lbs. pressure for one hour and cooled immediately to 60° C. 0.1 gram of sterile propyl-p-hydroxybenzoate is then added with agitation until dissolved, followed by the addition of 0.9 gram of sterile methyl-p-hydroxybenzoate with agitation until dissolved.

After this mixture has cooled to 30° C., 170,000,000 Oxford units of sterile micronized tabular dibenzylethylenediamine di-penicillin G crystals (95% of the particles being less than 10 microns) with a potency of about 1170 units/mg. are added with continuous agitation. Then 400,000,000 Oxford units of sterile pulverized tabular dibenzylethylenediamine di-penicillin G crystals (maximum 150 microns, average 20 microns to 40 microns) of similar potency are added with continuous agitation. Sufficient quantity of water for injection, U. S. P., is 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 dibenzylethylenediamine di-penicillin G which is stable

and suitable for intramuscular injections into humans or animals.

Disposable cartridges filled with this material provide an extrudable dose of 600,000 Oxford units in approximately 1.1 ml.

In Example 16, one may vary the ratio of micronized to pulverized penicillin salt, but preferably keeping the latter as the major ingredient, or, if desired, having all pulverized material.

The carboxymethylcellulose may vary in amount from 0.05 to 0.5% while the polyvinylpyrrolidone may be varied from 0.05 to 0.75%. In place of these two agents, one may have from about 0.05% to 0.3% of agar, 3% to 8% dextrin or gum acacia, 0.4% to 1.0% gum karaya, carrageen gel or pectin, 0.3% to 0.8% tragacanth or methyl cellulose, from 1% to 3% gelatin or from 0.05 to 0.75% sodium alginate.

The stabilizer content may be varied from about 0.5% to 5% while the preservatives may range from about 0.12% to 0.25% methyl-p-hydroxybenzoate or from 0.013 to 0.05% of the propyl or butyl ester. In place of these preservatives one may have from 0.25% to 0.5% of phenol.

The wetting agents may be lecithin or any of the sorbitans heretofore suggested in the previously indicated amounts.

An oral liquid suspension particularly suitable for children is illustrated by the following example.

Example 17

To 700 cc. of deionized water the following are added with constant agitation:

	Grams
Sodium citrate.....	5
Sodium carboxymethylcellulose (high viscosity).....	5

With constant agitation sterilize this mixture at 121° C. and 15 lbs. pressure for one hour and cool immediately to 90° C. Add 200 grams of sucrose and 0.25 gram of brilliant crimson red color with continued agitation and maintain the temperature of this mixture at 90° C. for one hour. Cool to 60° C. and add 0.14 grams of sterile propyl-p-hydroxybenzoate with agitation until dissolved, followed by 1.2 grams of sterile methyl-p-hydroxybenzoate with agitation until dissolved. Cool this mixture to 30° C. and add 20 ml. of wild cherry flavor with agitation.

At a temperature of 30° C. to 35° C. add to this gel 60,000,000 Oxford units of sterile micronized dibenzylethylenediamine di-penicillin G tabular crystals (95% of the particles being less than 10 microns) having a potency of about 1170 units/mg. with agitation. Sufficient quantity of deionized water is added to bring the volume of the suspension to one liter and agitation is continued for one hour.

The suspension is passed through a homogenizer to insure wettability and uniformity.

This therapeutic preparation is a uniform, palatable suspension of dibenzylethylenediamine di-penicillin G which is stable and suitable for oral administration into humans and animals. Each 5.0 cc. of this suspension provides a dose of 300,000 Oxford units of dibenzylethylenediamine di-penicillin G.

In the above formulation, the penicillin salt used may be either the acicular or tabular type or mixtures of both with the tabular or mixed types preferred to avoid unduly high viscosities. While the micronized form is disclosed, one may also use pulverized material having a particle size averaging about 20 to 60 microns.

The amount of carboxymethylcellulose may be varied from about 0.05% to 1.0%, and, if desired, one may replace this agent with either 0.1% to 1.5% polyvinylpyrrolidone, 0.05% to 0.4% agar, 1.0% to 8.0% gum acacia or dextrin, 0.3% to 2.0% gum karaya, 0.2% to 0.8% methyl cellulose or carrageen gel, 0.5% to 4.0%

gelatin or from 0.1% to 0.8% pectin, sodium alginate or tragacanth.

Other colors and flavors may be used as, for example, up to about 0.3% of a yellow, orange, blue, green, brown or violet color, and, for flavors, one may use either blackberry, strawberry, raspberry, loganberry, grape, chocolate, vanilla or grenadine or other known flavors in place of the wild cherry flavor of the example.

For sweetening agents, the sucrose content may be varied from about 5% to about 30% or one may use sucrose syrup, or artificial sweetening agents such as saccharin, or either sodium or calcium cyclamate from about 0.5 grain to about 4 grains per 100 cc.

As a stabilizer, one may use from 0.5% to about 5.0% of sodium citrate or any equivalent amount of the buffers mentioned hereinabove. As preservatives, 0.12% to 0.25% of the methyl benzoate, or about 0.014% to about 0.04% of the propyl or butyl benzoates may be used. As a substitute, one may use from about 0.1% to 1% sodium benzoate.

As indicated heretofore, the percentages are based on weight per unit of liquid volume, for example, in grams per 100 cc.

Oral tablets of N,N'-dibenzylethylenediamine di-penicillin G have also been prepared and, where selected ingredients are utilized, the therapeutic effect may be prolonged far beyond the usual effectiveness of penicillin tablets.

Normally, penicillin in tablet form and containing a buffering agent to protect the penicillin against the gastric acidity in the stomach has an effective action for about 3 or 4 hours and, where an extended blood level is desired, the patient must ingest at least six tablets per twenty-four hours around the clock. The present discovery avoids this difficult regime since the effective blood level for a single tablet of the invention (200,000 units) is 12 hours.

It has been discovered that the combination of N,N'-dibenzylethylenediamine with a sugar carrier with or without a disintegrating agent or a binder and made into a hard tablet using the usual tableting lubricant will produce a tablet having prolonged therapeutic action. It does not require a buffering agent and, in fact, the tablet is improved by its absence, showing a longer action without the buffering agent.

The sugar carrier may be either sucrose, lactose or dextrose or mixtures thereof, with sucrose preferred. The disintegrating agent, if one is used, is preferably starch but one may use any other agent which has the characteristic of swelling in an aqueous medium such as sodium carboxymethylcellulose, agar, pectin, gelatin, etc. Where a binder is used, acacia or some other gum may be used. A lubricant is needed for proper tableting conditions and preferred lubricants are either stearic acid or the stearates such as calcium or magnesium stearate. A color may also be added if so desired.

The tablets may range in size from about 5 to not more than 15 grains. The penicillin salt may comprise about 30 to 40% by weight thereof with about 2% lubricant and the remainder, 58 to 68%, being the sugar. If starch or any other disintegrating agent is used, the amount used approximates about 5% by weight, with correspondingly less of the sugar.

The penicillin salt used in the tablet is preferably a micronized crystal of the tabular type although acicular crystals may be used if desired. The latter have been found harder to micronize than the crystals of tabular habit. The particle size may range from about 5 microns upwardly to about 150 microns or somewhat higher. Potencies will range from about 1000 units/mg. up to about 1300 units/mg., with about 1170 units being the average potency. With regard to the tablets, preferred potencies may range from about 50,000 units to about 500,000 units.

The following examples illustrate the preparation of prolonged action penicillin tablets.

Example 18

Approximately 11.25 grams of micronized tabular N,N'-dibenzylethylenediamine di-penicillin G (95% having a particle size below about 10 microns) was combined with 21.0 grams of lactose and 4.4 grams of acacia. This mixture was moistened with about 10 cc. of water and the moistened granulation was passed through a No. 8 screen. To the granulation was added magnesium stearate as a lubricant and the product was passed through a No. 14 sieve. Fines were removed with a No. 40 sieve and the remainder was formed into tablets of approximately 10 grain size containing about 250,000 units per tablet.

Tablets of the type hereinabove described gave prolonged blood levels lasting approximately 12 hours.

Example 19

Tablets were prepared by combining 11.5 grams of N,N'-dibenzylethylenediamine di-penicillin G with 25 grams of sucrose. The mixture was moistened with acetone and the granulation was passed through a No. 12 sieve. 100 mg. of magnesium stearate was added and tablets were compressed into approximately 200,000 unit potencies of about 10 grain size.

Example 20

Following the above procedures, 200,000 unit tablets of about 6.5 grain size were prepared by combining about 170 mg. of pulverized, tabular N,N'-dibenzylethylenediamine di-penicillin G (average particle size from 20 to 40 microns) with about 225 mg. of four X-sucrose (containing about 3% starch), approximately 10 mg. of calcium stearate and about 16 mg. of corn starch. Sufficient brilliant crimson color was added to impart a pink color to the tablet.

Tablets made up as described here also produced prolonged blood levels lasting for at least 12 hours.

We claim:

1. A process for preparing a therapeutic composition comprising crystallizing N,N'-dibenzylethylenediamine di-penicillin from a formamide medium, isolating from said formamide medium tabular crystals of the penicillin salt, comminuting said crystals to obtain crystal particle sizes of less than about 150 microns and combining said comminuted crystal particles with an agent of the group consisting of suspending agent and carrier for said crystals.

2. The process for preparing a therapeutic composition comprising crystallizing N,N'-dibenzylethylenediamine di-penicillin G from a water-formamide medium wherein the formamide is present to an extent of at least about 15%, isolating from said liquid medium penicillin crystals in substantially plate-like, tabular form, comminuting said crystals to obtain crystal particle sizes ranging from about 5 to not more than about 150 microns in size and com-

mining said comminuted crystals with a suspending agent for said crystals.

3. The process of claim 2; wherein the suspending agent comprises a non-toxic salt of carboxymethylcellulose.

4. A prolonged-action therapeutic composition comprising the combination of N,N'-dibenzylethylenediamine di-penicillin G in tabular form and reduced to a particle size from about 5 to not more than 150 microns combined with a non-toxic agent of the group consisting of suspending agent and carrier for said diamine salt.

5. A prolonged-action therapeutic composition comprising tabular, plate-like crystals of N,N'-dibenzylethylenediamine di-penicillin G, said tabular crystals having a particle size of about 5 to not more than 150 microns, and a non-toxic carboxymethylcellulose suspending agent for said tabular crystals.

6. A prolonged-action therapeutic composition for oral use comprising substantially tasteless, crystalline N,N'-dibenzylethylenediamine di-penicillin-G, said penicillin salt in tabular form and reduced to a particle size of about 5 to about 40 microns, an aqueous vehicle, and sodium carboxymethylcellulose as a suspending agent for the penicillin salt in said liquid vehicle.

7. A prolonged-action therapeutic composition for parenteral use comprising a minor amount of finely divided crystals of N,N'-dibenzylethylenediamine di-penicillin G having a particle size of about 5 to about 15 microns commingled with a major amount of relatively large, tabular crystals of said penicillin salt averaging from about 20 to about 40 microns in size, and a suspending agent for said penicillin compound.

8. A prolonged-action therapeutic composition comprising a dry admixture of tabular N,N'-dibenzylethylenediamine di-penicillin G having a particle size not greater than about 150 microns and a non-toxic salt of carboxymethyl cellulose.

9. A prolonged-action therapeutic composition comprising the combination of tabular N,N'-dibenzylethylenediamine di-penicillin G having a particle size not greater than about 150 microns and a non-toxic carrier therefor.

10. A prolonged-action therapeutic tablet for oral medication comprising the combination of tabular N,N'-dibenzylethylenediamine di-penicillin having a particle size not greater than about 150 microns and a carbohydrate carrier therefor.

11. The process of claim 1; wherein the agent comprises a non-toxic carrier for the penicillin salt.

References Cited in the file of this patent

UNITED STATES PATENTS

2,619,447	Malcolm	Nov. 25, 1952
2,627,491	Szabo et al.	Feb. 3, 1953
2,637,679	Gaunt	May 5, 1953