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PRECIPITATION OF FINE PARTICLE PROCAINE PENICILLIN G

Frank W. Staab, Syracuse, and John M. Kolbas, Tully, N. Y., assignors to Bristol Laboratories Inc., Syracuse, N. Y., a corporation of New York

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This invention relates to a method for producing crystalline procaine penicillins of extremely fine particle size; and, more particularly, to a method for precipitating crystals of procaine penicillin G of a particle size such that the largest dimension of the crystals produced is within the range of from 1 to 5 microns.

In penicillin therapy, the rapid excretion of parenterally administered penicillin in aqueous solution has led to the development of various non-aqueous formulations. These formulations are intended to prolong the therapeutic blood level of penicillin after injection. While these preparations possess the obvious advantages of reducing the frequency of injections and avoiding waste of penicillin, the prolongation of the therapeutic blood level is the most outstanding advantage since it has been generally accepted that a continuous therapeutic level is more effective than intermittent "peak" levels. Among the formulations of the foregoing type which are available are suspensions of procaine penicillins in vegetable oils thickened with aluminum stearates. It has been shown that, in stearate-oil suspensions, one important factor controlling the prolongation of the therapeutic blood level is the particle size of the penicillin compound suspended therein. Thus, it is now recognized that the prolongation effect is greatly improved by employing crystals of procaine penicillin wherein the crystals are less than 50 microns in size. See "Penicillin Formulations: The Efficacy of Oily Injections" by J. C. Floyd, Research Papers, British Pharmaceutical Conference, Blackpool, 1949, pages 747–756. It has been common practice, therefore, in preparing these stearate-oil suspensions of procaine penicillins to subject the crystals of procaine penicillin to a grinding operation employing a "Micronizer" or equivalent grinding equipment. This constitutes an additional operation in the preparation of these products and adds to the cost thereof.

It is, therefore, an object of this invention to prepare crystals of procaine penicillin of a size less than 50 microns adapted for use in metal stearate thickened vegetable oils.

Another object of this invention is to prepare crystals of procaine penicillin of high potency having a particle size such that the largest dimension of any crystal produced is within the range of from 1 to 5 microns by precipitating procaine penicillins from a solution thereof in an organic solvent.

It is another object of this invention to produce highly potent crystals of procaine penicillin G of a size within the range of from 1 to 5 microns

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by adding a warm 30 to 50 percent solution of procaine penicillin G in an organic solvent to about ten volumes of a liquid chlorinated hydrocarbon cooled to between 0–10° C.

The foregoing objects are accomplished by this invention which, briefly, comprises dissolving a procaine penicillin in warm methanol and, thereafter, slowly adding the warm methanol solution of a procaine penicillin to cold carbon tetrachloride with mild agitation. The crystals of the procaine penicillin formed have a particle size such that the largest dimension of the crystals is within the range of from 1 to 5 microns. The crystalline product thus obtained may be recovered by filtering and drying.

The following examples are illustrative of the methods for carrying out this invention:

Example 1.—Fifty grams of procaine penicillin G produced from crude potassium penicillin were dissolved in 100 ml. of methanol by warming the methanol to 35–40° C. The warm methanol solution of procaine penicillin G was then added slowly to one liter of cold (0–10° C.) carbon tetrachloride with mild agitation. The procaine penicillin G precipitated in crystalline form and the crystals were easily filtered off and dried. A recovery of 90% of the procaine penicillin G was obtained by this procedure and the particle size of the crystalline product obtained was below 5 microns. The product thus obtained was suspended in an aluminum stearate gelled vegetable oil; and, upon being injected parenterally, therapeutic blood levels of penicillin were produced for periods in excess of 96 hours.

Example 2.—One hundred grams of procaine penicillin G (D9504) were dissolved in 175 ml. of warm (35–40° C.) methanol and the warm solution added slowly over a period of about 3 minutes to 2 liters of carbon tetrachloride cooled to between 5–7° C. The beaker was washed with 25 ml. of warm methanol and the wash added to the carbon tetrachloride. The mixture thus obtained was moderately agitated for several minutes before crystallization occurred. The agitation was continued for 15 minutes and the crystalline product obtained was filtered off and dried. By this method 92% of the procaine penicillin G was recovered and the crystalline product obtained had a particle size of from 1 to 5 microns. Suspensions of this product in aluminum stearate gelled vegetable oil gave therapeutic blood levels of penicillin, upon injection, for a period of time in excess of 96 hours. The potency of the starting material was 973 O. U. and that of the fine particle size crystalline product was 961 O. U.

Example 3.—The procedure described in Exam-

ple 2 above was duplicated and a recovery of 90% of the procaine penicillin G was obtained. The potency of the procaine penicillin G starting material was 970 O. U. and that of the fine particle size crystalline product obtained was 968 O. U.

The processes described in the foregoing examples produce crystalline procaine penicillin G having a particle size within the range of from 1 to 5 microns. The same methods may be employed to produce fine particle size crystalline procaine salts of other penicillins; such as, for example, penicillins X, F, K and dihydro F and mixtures of naturally occurring penicillins present in the crude products obtained by industrial fermentation methods. While the process has been disclosed employing methanol as the organic solvent for the procaine penicillin and carbon tetrachloride as the precipitant, other organic solvents for procaine penicillin which do not lower the potency of the penicillin may be utilized; and, as well, other low molecular weight liquid chlorinated hydrocarbons may be used to precipitate the procaine penicillin from solution in place of carbon tetrachloride.

We claim:

1. The method of producing crystals of procaine penicillins of high therapeutic potency having a particle size within the range of from 1 to 5 microns which comprises the steps of dissolving a procaine penicillin in one volume of methanol at a temperature of 35 to 40° C., adding the warm methanol solution of procaine penicillin to 5 to 15 volumes of carbon tetrachloride having a temperature of between 0 to 10° C., mildly agitating the mixture to precipitate crystals of the procaine penicillin having a particle size of from 1 to 5 microns, and separating and drying the fine particle size crystalline product.

2. The method of producing crystals of procaine penicillin G of high therapeutic potency having a particle size within the range of from 1 to 5 microns which comprises the steps of dissolving procaine penicillin G in methanol at 35 to 40° C. to form a 30 to 50% solution, adding the warm methanol solution of procaine penicillin G to 5 to 15 volumes of carbon tetrachloride cooled to between 0 to 10° C., mildly agitating the mixture to precipitate crystals of procaine penicillin G having a particle size of from 1 to 5 microns, and separating and drying the fine particle size crystalline product.

3. The method set forth in claim 2 characterized in that the volume of carbon tetrachloride is about ten times that of the methanol solution of procaine penicillin G added thereto.

FRANK W. STAAB.
JOHN M. KOLBAS.

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