

UNITED STATES PATENT OFFICE

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PREPARATIONS FOR PENICILLIN THERAPY

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The invention described herein may be manufactured and used by or for the Government for governmental purposes without payment to me of any royalty thereon.

This invention relates to pharmaceutical preparations and more particularly to preparations for penicillin therapy.

The most common method of administering penicillin has been by introducing penicillin in physiologic saline or water through the intramuscular route. This method has not been completely satisfactory since it results in high blood levels of penicillin which endure for only brief periods of time and necessitate frequent injections. The inconvenience to the patient resulting from this method, as well as the personnel administering the penicillin, is readily apparent. A further disadvantage lies in the fact that penicillin in physiologic saline lacks stability and loses its potency during storage particularly at elevated temperatures. In addition to the foregoing objections this method has acted, in a sense, as a barrier in determining the optimum dose and the period of time necessary for treatment.

Numerous attempts have been made to overcome the foregoing disadvantages, but none of them has been entirely satisfactory. Thus, the intermittent intravenous method also results in transitory high levels and necessitates repeated venipunctures. The constant intravenous procedure, although maintaining a satisfactory level, is difficult on the patient and involves the possibility of thrombosis. The constant subcutaneous infusion, the continuous intramuscular drip infusion and the deep infusion into bone marrow, are all inconvenient to the patient and have not been standardized thus far.

One of the objects of the present invention is to provide more useful pharmaceutical preparations containing penicillin than have been available heretofore.

Another object of the present invention is to provide pharmaceutical preparations containing penicillin which, upon administration, produce satisfactory penicillin blood levels for extended periods.

A further object of the invention is to provide pharmaceutical preparations containing penicillin which retain their potency for long periods,

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particularly when stored either at room temperature or elevated temperatures. More specifically, it is an object of this invention to provide a stable pharmaceutical composition containing penicillin in a substantially anhydrous vehicle of beeswax and highly refined peanut oil.

These objects are accomplished by admixing a warm anhydrous vehicle consisting of beeswax in peanut oil with either a crystalline penicillin, for example sodium penicillin, or potassium penicillin, or an amorphous penicillin, for example calcium penicillin, whereby there is obtained a pharmaceutical composition comprising these components which is capable of producing satisfactory blood levels of penicillin for long periods and which is more stable than compositions previously available.

In the practice of the invention, a sterilized, highly refined peanut oil is warmed at a temperature of from 40° to 45° C. Sterilized U. S. P. bleached beeswax is heated separately at a temperature of from approximately 50° to approximately 55° C. until it forms a clear liquid and the warm peanut oil then is mixed therewith. The melt-blending of the components may be augmented by agitation in a warm container or by means of a mechanical blender. The penicillin derivative is placed in a mechanical blender in as powdery a state as possible, and the clear, liquid beeswax peanut oil mixture added thereto at a temperature of from approximately 50° to 55° C. The penicillin derivative and the wax-oil vehicle are blended until a complete homogeneous suspension is obtained. The composition is sufficiently liquid after warming to 55°-60° C. for 3 to 5 minutes that it can be withdrawn from a rubber stoppered bottle with a No. 18 or 19 gauge needle and after allowing to be cooled to room temperature (approximately 25° C.) can be injected with a No. 20.

The peanut oil employed is highly refined and contains the minimum amount of moisture, not more than 0.05 per cent, and readily oxidizable materials. Before compounding, the peanut oil must be sterilized. This may be accomplished by filtering the oil with a Seitz filter, then passing it through a filter consisting of six layers of sterile gauze or a sintered glass filter and thereafter heating the oil for sterilization. This latter step may be effected by autoclaving the peanut

oil at 17-20 pounds steam for approximately 20 to 30 minutes.

The quantity of beeswax employed is limited principally by viscosity considerations with regard to the final product. Effective results have been obtained with beeswax peanut oil vehicles in which the beeswax content ranges from 0.60 to 4.80 per cent by weight. If the beeswax content is increased substantially beyond the upper limit specified, the compositions obtained are too viscous for practical use, and, furthermore, such increased amounts have been found to have no effect upon prolonging the penicillin action. The preferred beeswax content is from 3.2 to 4.8 per cent by weight and within this range the amount may be varied according to the potency of the penicillin derivative employed. It has been found that higher percentages of beeswax within the range given should be employed with penicillin derivatives having high potency. In addition to peanut oil, it has been found in practice that oils other than peanut oil, such as sesame oil, olive oil, corn oil, cottonseed oil, and also animal oils, or mineral oil, may be similarly employed to produce a prolonged penicillin action.

It is found in practice that crystalline sodium penicillin or potassium penicillin, and amorphous calcium penicillin act in a similar manner. Penicillin derivatives of any desired potency may be employed, but it is preferred to use the most potent products available in order to produce satisfactory penicillin blood levels for the longest possible periods of time. Compositions of the penicillin derivative in a vehicle of beeswax and peanut oil have been prepared with the penicillin derivative assaying from 300 to 500, 600 to 800 900 to 1000 or more units per milligram for amorphous penicillin, and as high as 1660 units per milligram for crystalline penicillin, which values are more satisfactory than any penicillin composition that has been available previously. The apparent optimum quantity of penicillin which may be suspended in beeswax and peanut oil and still be satisfactory from the standpoint of viscosity and prolonged therapeutic action is approximately 300 milligrams in sufficient beeswax and peanut oil to provide a volume of one cubic centimeter. While it is preferred to employ the

maximum quantity specified, from 175 to 300 milligrams may be used with good results. The maximum quantity of 300 milligrams of the penicillin derivative occupies a volume of approximately 0.2 cubic centimeter and is admixed, therefore, with approximately 0.8 cubic centimeter of beeswax and peanut oil vehicle to provide a volume of one cubic centimeter. It has been found that a relatively constant amount of penicillin is absorbed from each cubic centimeter of the penicillin-beeswax-peanut oil mixture and by increasing the number of cubic centimeters of the dose only slight additional prolongations were achieved, although a marked increase in the height of the level of penicillin in the blood occurred.

An extended chemical analysis has been made with regard to the compositions hereinabove described. A calcium penicillin, beeswax and peanut oil mixture was prepared with calcium penicillin having a potency of from 300 to 400 units per milligram employing 3.2 per cent by weight beeswax in the vehicle. One cubic centimeter of this preparations containing a total of 100,000 units produced a maximum penicillin blood level of 0.312 unit per cubic centimeter of blood and assayable levels for approximately ten hours after injection. The presence of penicillin in the urine was detectable for 27 hours after the injection. A calcium penicillin beeswax and peanut oil mixture prepared with calcium penicillin assaying from 600 to 800 units per milligram and 4.0 per cent by weight of beeswax provided a preparation containing 200,000 units per cubic centimeter. An intramuscular injection of one cubic centimeter of this preparation produced a maximum penicillin blood level of 1.25 units per cubic centimeter of blood approximately four hours after injection and a blood level in excess of 0.039 unit for more than sixteen hours after injection. The presence of penicillin in the urine was detectable for 96 hours after injection.

The following table, Table I, shows penicillin blood levels produced in fifty cases by a single intramuscular injection of 300,000 units of calcium penicillin in 4.8 per cent beeswax by weight in peanut oil contained in 1 cubic centimeter.

TABLE I

Penicillin blood levels produced by a single intramuscular injection of 300,000 units of calcium penicillin in 4.8 per cent beeswax by weight in peanut oil contained in 1 cc.

Case No.	Time After Injection							Duration of Assayable Level (0.039 Units/cc.)
	½ Hr.	4 Hr.	8 Hr.	12 Hr.	16 Hr.	20 Hr.	24 Hr.	
	Units/cc.	Units/cc.	Units/cc.	Units/cc.	Units/cc.	Units/cc.	Units/cc.	Hours
1-----	0.156	0.625	0.625	0.312	0.156	0.078	0.078	24
2-----	0.321	0.156	0.078	0.156	0.078	0.156	0.156	24
3-----	0.625	2.50	0.312	0.312	0.156	0.039	0.039	24
4-----	1.25	1.25	1.25	0.078	0.078	0.078	0.078	24
5-----	1.25	1.25	0.625	0.625	0.156	0.078	0.078	24
6-----	0.625	1.25	1.25	0.312	0.078	0.039	0.000	20
7-----	1.25	1.25	0.312	0.312	0.156	0.078	0.039	24
8-----	1.25	0.625	0.312	0.312	0.078	0.078	0.078	24
9-----	2.50	2.50	0.625	0.078	0.039	0.039	0.000	20
10-----	0.156	0.625	0.312	0.312	0.156	0.156	0.078	24
11-----	0.312	2.50	2.50	0.312	0.039	0.039	0.039	24
12-----	0.625	2.50	0.312	0.156	0.078	0.078	0.039	24
13-----	0.312	0.625	0.312	0.078	0.039	0.000	0.000	16
14-----	0.625	1.25	1.25	0.156	0.039	0.039	0.078	24
15-----	0.625	1.25	0.625	0.078	0.000	0.000	0.000	12
16-----	0.078	0.156	0.078	0.625	0.312	0.078	0.078	24
17-----	0.312	2.50	1.25	0.078	0.078	0.000	0.000	16
18-----	0.078	0.078	1.25	0.039	0.039	0.039	0.156	24
19-----	0.312	0.625	0.625	0.312	0.039	0.039	0.039	24
20-----	0.156	0.625	0.156	0.156	0.156	0.156	0.312	24
21-----	0.078	0.078	0.156	0.078	0.000	0.000	0.000	12
22-----	0.156	0.625	0.312	0.078	0.078	0.078	0.039	24
23-----	0.625	0.625	0.312	0.156	0.078	0.039	0.039	24

TABLE I—Continued

Penicillin blood levels produced by a single intramuscular injection of 300,000 units of calcium penicillin in 4.8 per cent beeswax by weight in peanut oil contained in 1 cc.—Continued

Case No.	Time After Injection							Duration of Assayable Level (0.039 Units/cc.)
	½ Hr.	4 Hr.	8 Hr.	12 Hr.	16 Hr.	20 Hr.	24 Hr.	
	Units/cc.	Units/cc.	Units/cc.	Units/cc.	Units/cc.	Units/cc.	Units/cc.	Hours
24	2.50	1.25	0.156	0.312	0.156	0.039	0.000	20
25	0.312	1.25	0.156	0.078	0.156	0.078	0.039	24
26	0.312	0.625	1.25	0.156	0.078	0.000	0.000	16
27	0.156	0.625	0.156	0.078	0.078	0.039	0.000	20
28	1.25	1.25	1.25	0.312	0.039	0.000	0.000	16
29	0.156	0.078	0.078	0.078	0.078	0.078	0.039	24
30	0.312	1.25	0.625	0.156	0.078	0.039	0.000	20
31	0.312	1.25	0.625	0.039	0.039	0.078	0.039	24
32	0.312	0.625	0.625	0.078	0.039	0.000	0.000	16
33	0.625	1.25	0.625	0.078	0.000	0.039	0.000	20
34	0.625	1.25	0.625	0.078	0.039	0.078	0.039	24
35	0.312	0.625	0.312	0.156	0.078	0.039	0.078	24
36	0.312	0.625	0.625	0.312	0.039	0.156	0.039	24
37	0.625	0.625	2.50	0.078	0.039	0.078	0.078	24
38	0.156	0.156	0.156	0.156	0.039	0.078	0.156	24
39	0.078	0.156	0.039	0.156	0.039	0.078	0.078	24
40	0.312	1.25	0.625	0.312	0.039	0.156	0.078	24
41	0.312	0.312	0.625	0.625	0.078	0.039	0.039	24
42	0.625	1.25	0.625	0.156	0.156	0.039	0.039	24
43	0.625	0.625	0.625	0.312	0.039	0.039	0.156	24
44	0.156	1.25	0.312	0.312	0.156	0.156	0.156	24
45	0.312	0.625	0.625	0.312	0.078	0.039	0.039	24
46	1.25	1.25	0.312	0.312	0.078	0.156	0.078	24
47	0.625	0.625	0.312	0.312	0.078	0.039	0.000	20
48	2.50	1.25	0.156	0.312	0.156	0.000	0.000	12
49	0.625	1.25	0.625	0.078	0.039	0.078	0.039	24
50	0.625	1.25	0.625	0.078	0.039	0.078	0.039	24

Out of the aforesaid 50 cases reported, 35 showed assayable levels were retained for more than 24 hours, 7 showed retention of 20 hours, 5 of 16 hours, and 3 of 12 hours, this last being the shortest retention period that was noted. The lowest assayable level, as will be noted from Table I, is 0.039 unit per cc.

The effect upon maximum penicillin blood levels and the slight prolongation of penicillin action produced by injecting 1, 2 and 3 cubic centimeters of calcium penicillin in 3.2 per cent beeswax in peanut oil containing 100,000, 200,000 and 300,000 units, respectively, has been demonstrated. A maximum penicillin blood level of 0.312 unit per cubic centimeter of blood was reached from 2 to 4 hours after injection and a level in excess of 0.039 unit was maintained for approximately 10 hours with an injection of one cubic centimeter containing 100,000 units. A two cubic centimeter injection containing 200,000 units produced a maximum penicillin blood level of 1.25 units per cubic centimeter approximately 6 hours after injection and a blood level in excess of 0.039 unit per cubic centimeter continued for 14 hours. The three cubic centimeter injection containing 300,000 units produced a maximum penicillin blood level of 1.25 units per cubic centimeter approximately 4 hours after injection and a blood level in excess of 0.039 unit per cubic centimeter induced for only 15 hours.

Similar results are obtainable using the crystalline penicillin salts, e. g., sodium penicillin and potassium penicillin.

Thus, 300,000 units of these crystalline salts were prepared in the same manner as the amorphous calcium penicillin, that is to say, in 4.8 per cent beeswax and peanut oil contained in one cubic centimeter. The viscosity of the resulting mixes containing crystalline sodium penicillin or crystalline potassium penicillin at room temperature is found to be comparable to the corresponding mixes containing amorphous calcium penicillin. In this connection it may be noted that, in carrying out the present invention,

the preferred viscosity of the penicillin in beeswax peanut oil mix is such that the mixture does not flow at room temperature (25° C.) since it is the viscose preparations which produce levels of penicillin in the blood which endure for 24 hours. It is found in practice that preparations which are liquid at room temperature usually produce assayable levels for only 12 to 16 hours.

About 500 patients with various types of infections usually treated with penicillin were given one or two intramuscular injections of 300,000 units of the crystalline penicillin, beeswax, peanut oil composition of the present invention. About half received the crystalline sodium and the remaining half the crystalline potassium mixture. Most of the patients received a single injection of 300,000 units once in 24 hours. Those who were given two injections daily received them at twelve hour intervals. These patients were both ambulatory and at bed rest. Certain of these individuals received their injection at approximately 4-5 P. M. instead of the usual time of 9 A. M. This is found to be in practice a very important factor in therapy.

Penicillin assays of the blood were carried out at 30 minute and 4 hour intervals for 24 hours or at the 24th hour. This was accomplished on at least 150 patients who received the crystalline sodium and on about an equal number of patients who received the crystalline potassium penicillin beeswax, peanut oil mixture. Of that total number, at least 50 had blood levels determined throughout the 24 hours at intervals mentioned above, and the remaining had them at the 24th hour. The usual minimum and maximum blood levels in the first 12 hours have ranged between 0.156 and 2.5 units per cc. The 2.5 unit levels have been found one-half hour after the injection. During the second 12 hours the minimum and maximum levels have been between 0.039 and 0.156. The value of 0.039 unit is an approximate value usually indicating a level of between 0.039 and 0.078. The results of these studies show that 90 per cent of the three hundred patients had a

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dered dry form. In aqueous solution they are no more stable than is amorphous penicillin. The crystalline salts are as stable in the oil-beeswax vehicle as they are in the powdered form.

The pharmaceutical preparations described herein may be employed to treat gonococcal, pneumococcal and staphylococcal infections as well as other infections which respond to penicillin in physiologic saline. The preparations, furthermore, do not cause patients any discomfort, other than a slight soreness present to pressure, and a single injection daily produces a response heretofore attained only by 8 or more injections a day of penicillin in saline or water. Clinical studies have not revealed gross residual to palpitation in any instance and hematologic studies, including bleeding, clotting and prothrombin time, likewise revealed no adverse effects. Gross and microscopic studies of the tissues at the site of injection show results no different from those found at the site of injection of any medication in oil. The vial containing the penicillin beeswax and peanut oil mixture should be kept for 3 to 5 minutes under the hot water tap at 56° to 60° C. The preparation is shaken at intervals so that there is thorough warming of all the material. At this time the mixture may be withdrawn with an 18-gauge or larger needle into a Luer-Lok syringe and should be allowed to cool to room temperature prior to injection. It is definitely unnecessary to rewarm the syringe. For intramuscular injection a 20-gauge needle should be utilized. The penicillin beeswax, peanut oil mixture should not be forced into the 20-gauge needle until the needle is inserted in the muscle, since the mixture occasionally hardens in the needle making it difficult to inject. Only a completely dry needle and syringe should be used. Disposable cartridges containing 300,000 units in one cubic centimeter of the standard mixture are available, which facilitate the administration of the mixture.

The stability of these preparations is high and they may be maintained at 37° C. for at least 9 months without loss of potency, whereas penicillin in physiologic saline or water begins to lose its potency in five days at this temperature. At room temperature, the penicillin salt, beeswax peanut oil mixture of the present invention may be stored for at least a year without deterioration. In addition, no deterioration of the calcium penicillin beeswax and peanut oil mixture occurs for 24 to 36 hours at 56° C. or for 2 hours at 100° C. The crystalline penicillin salts in beeswax and peanut oil show no deterioration for as long as 128 hours at 100° C. dry heat. The mixtures of the invention, therefore, may be stored in an ice box at room temperature or at a temperature of 37° C. without damage.

The foregoing results indicate that the action of penicillin may be prolonged greatly by intramuscular injection of the penicillin salt, beeswax and peanut oil mixture. It also has been found that these mixtures may be administered orally to patients and produce therapeutic levels in the blood as well as satisfactory clinical response.

The function of the beeswax in the present composition appears to be a shielding effect on the penicillin salt employed, inhibiting excessively rapid absorption of the penicillin salt. It is found in practice that the beeswax is a necessary constituent in the present composition since injections of 300,000 units of the penicillin salts in peanut oil without beeswax are found to produce adequate blood levels for only about 6 hours.

While it has been indicated above herein that peanut oil is the preferred oil vehicle for the beeswax, it has also been mentioned that other oils such as corn oil, sesame oil, cottonseed oil and mineral oil may be employed as the vehicle, with whatever variation of the proportion of beeswax that is found necessary to effect the desired prolongation of the penicillin salt. However, oils derived from animal origins also may be employed. Generally speaking, an oil derived from any source, which oil has a kinematic viscosity at 100° F. of not more than approximately 42 centistokes, may be employed for the purposes of the present invention.

It will be understood also that the invention is not limited necessarily to the specific penicillin salts herein disclosed, that is, crystalline sodium penicillin, crystalline potassium penicillin and amorphous calcium penicillin, these three components being the commercially available penicillin salts at the present time. However, the data and examples herein given are intended to be exemplary only in character, the invention being directed essentially to the incorporation of an available penicillin salt in the beeswax oil mixture disclosed herein.

It will be apparent, therefore, that the invention is capable of being employed with varying constituents such as, for example, different salts of penicillin and different oil vehicles having the specified viscosity, peanut oil being, however, the preferred vehicle. It is thought to be apparent from the foregoing that the invention is capable of modification as will become apparent to one skilled in the art, as determined by given conditions of use, and that, therefore, it is intended and desired to embrace within the scope of this invention such modifications and changes as may be necessary to adapt it to varying conditions and uses, as defined by the scope of the appended claims.

The present application is a continuation-in-part of my copending application Serial No. 609,316, filed August 3, 1945, now abandoned, for Pharmaceutical preparations and method of making the same.

Having thus described my invention, what I claim as new and wish to secure by Letters Patent is:

1. A stable, injectable antibiotic preparation each cubic centimeter of volume of which consists of at least 100,000 units of a water-soluble penicillin salt homogeneously dispersed in a mixture of a sterilized vegetable oil having a kinematic viscosity at 100° F. of not more than 42 centistokes and beeswax of which the beeswax constitutes about 3.2-4.8% by weight, each such cubic centimeter of volume of such preparation having the capacity of maintaining an adequate penicillin blood level for a period of at least 8 hours when injected into a patient as a single dosage.

2. A stable, injectable antibiotic preparation each cubic centimeter of volume of which consists of approximately 300,000 units of a water-soluble penicillin salt homogeneously dispersed in a mixture of sterilized peanut oil and beeswax of which the beeswax constitutes about 4.8% by weight, each such cubic centimeter of volume of such preparation having the capacity of maintaining an adequate penicillin blood level for a period of about 24 hours when injected into a patient as a single dosage.

3. A stable, injectable antibiotic preparation each cubic centimeter of volume of which consists of approximately 300,000 units of sodium penicillin

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lin homogeneously dispersed in a mixture of sterilized peanut oil and beeswax of which the beeswax constitutes about 4.8% by weight, each such cubic centimeter of volume of such preparation having the capacity of maintaining an adequate penicillin blood level for a period of about 24 hours when injected into a patient as a single dosage.

4. A stable, injectable antibiotic preparation each cubic centimeter of volume of which consists of approximately 300,000 units of potassium penicillin homogeneously dispersed in a mixture of sterilized peanut oil and beeswax of which the beeswax constitutes about 4.8% by weight, each such cubic centimeter of volume of such preparation having the capacity of maintaining an adequate penicillin blood level for a period of about 24 hours when injected into a patient as a single dosage.

5. A stable, injectable antibiotic preparation each cubic centimeter of volume of which consists of approximately 300,000 units of calcium penicillin homogeneously dispersed in a mixture of sterilized peanut oil and beeswax of which the beeswax constitutes about 4.8% by weight, each

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such cubic centimeter of volume of such preparation having the capacity of maintaining an adequate penicillin blood level for a period of about 24 hours when injected into a patient as a single dosage.

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