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DOSAGE FORM FOR POTASSIUM PENICILLIN G INTRAVENOUS INFUSION SOLUTIONS

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The chemical stability of potassium penicillin G intravenous infusion solutions is related to the initial pH of the solutions and to the ability of the buffer to maintain a constant pH during aging. It was determined that the 4-5% citrate buffer present in Potassium Penicillin G for Injection, U.S.P. is adequate to maintain the pH at the optimum value of 6.5 when reconstituted for injection. However, the buffer capacity is not adequate to maintain a pH of 6.5 when diluted with a large volume infusion solution. A new dosage form for intravenous infusion is recommended which contains 20% citrate buffer. The recommended dosage form when reconstituted and diluted with either Sodium Chloride Injection, U.S.P. or 5% Dextrose and 0.9% Sodium Chloride Injection, U.S.P. maintains a constant pH and greatly improves the chemical stability of the penicillin. The increased buffer is shown to have little effect on the osmolality of the infusion solution and is expected to reduce the incidence of phlebitis due to the infusion of acidic solutions.

Intravenous infusion therapy has developed in recent years into a major route of drug administration. Approximately 40% of the 63 million

intravenous infusion solutions annually administered in United States hospitals contain one or more additives[1]. These parenteral solutions are usually prepared in the hospital by adding the appropriate volume of an injection dosage form to a large volume infusion solution. As the dosage form requirements for optimum drug delivery vary with the route of administration, it was decided to compare the chemical stability of a drug in a dosage form designed for the injection of a concentrated solution with the chemical stability of the same drug when diluted for infusion therapy. Potassium penicillin G was selected for this study because of its well documented stability problems[2] and its frequent administration as either an injection or infusion. The objective was to improve the chemical stability of potassium penicillin G when administered as an intravenous infusion and to illustrate the differences between a dosage form designed for injection and one designed for intravenous infusion therapy.

METHODS

The chemical stability at 25°C of potassium penicillin G was studied in Sodium Chloride Injection, U.S.P.[3] and 5% Dextrose and 0.9% Sodium Chloride Injection, U.S.P.[3]. All studies were performed on a single lot of each solution.

Potassium Penicillin G for Injection, U.S.P.[4], 5 million units as well as mixtures of 5 million units of potassium penicillin G[5] with various concentrations of citrate buffer were used. The potassium penicillin G intravenous infusion solutions were prepared by reconstituting the appropriate penicillin dosage form with infusion solution and adding the reconstituted penicillin solution to 1 liter of infusion solution.

The concentration of intact penicillin G was determined after reconstitution and during storage by a modified iodometric assay[6]. This assay procedure had a standard deviation of 4%. The pH of the solution was determined with a Sargent-Welch pH Meter, Model NX[7]. The osmolality of the solutions was determined by an Advanced Osmometer, Standard Laboratory Model[8].

RESULTS AND DISCUSSION

Unbuffered solutions of potassium penicillin G in Sodium Chloride Injection, U.S.P. or in 5% Dextrose and 0.9% Sodium Chloride Injection, U.S.P. do not possess adequate chemical stability to permit administration by intravenous infusion. As seen in Table I, all the unbuffered solutions studied lost from 11 to 40% of their potency within 24 hours. It is important to note that the most stable solutions of potassium penicillin G had an initial pH of 6.2 which is close to the pH of maxium stability for potassium penicillin G of 6.5[2]. The other solutions had lower initial pH's and greater losses of potency occurred during the aging of these unbuffered solutions.

TABLE I
Stability of Unbuffered Potassium Penicillin G in Infusion Solutions

5 million Units Potassium Penicillin G in 1 liter of Sodium Chloride Injection, U.S.P.

Hours at 25°C	Abbott % Initial	Abbott pH	Baxter % Initial	Baxter pH	Cutter % Initial	Cutter pH
0	100	6.2	100	6.0	100	6.2
24	89	5.1	84	4.8	88	5.0
48	64	4.5	48	4.4	64	4.5

5 million Units Potassium Penicillin G in 1 liter of 5% Dextrose and 0.9% Sodium Chloride Injection, U.S.P.

Hours at 25°C	Abbott % Initial	Abbott pH	Baxter % Initial	Baxter pH	Cutter % Initial	Cutter pH
0	100	5.2	100	5.2	100	5.6
24	60	4.5	63	4.4	81	4.7
48	25	4.3	19	4.2	47	4.4

The effect of pH on the chemical stability of penicillin is widely recognized[2]. For this reason, penicillin solutions which are not administered immediately after reconstitution should always contain a buffer system. Potassium Penicillin G for Injection, U.S.P. contains penicillin and 4-5% citrate buffer. The buffer is designed to maintain the most stable pH after reconstitution and thereby provide the maximum reconstituted stability. Thus when a vial of Potassium Penicillin G for Injection, U.S.P. is reconstituted for use as an injection, the buffer capacity is adequate to permit the solution to be stored in the refrigerator for one week without significant loss of potency.

In order to determine the stability of potassium penicillin G as normally used in intravenous infusion solutions, a vial of Potassium Penicillin G for Injection, U.S.P. containing 5 million units was reconstituted and added to 1 liter of Sodium Chloride Injection, U.S.P. or 1 liter of 5% Dextrose and 0.9% Sodium Chloride Injection, U.S.P. As seen in Table II, the stability at 25° is greatly improved compared to the unbuffered solution. All of the solutions retained at least 90% of their potency for 48 hours. However, a decrease of 0.6 to 0.8 pH units was observed in all solutions. The solutions having initial pH's of approximately 6.5 were more stable than those solutions whose initial pH was 6.0.

The initial pH of potassium penicillin G intravenous infusion solutions has a significant effect on chemical stability. A solution containing 5 million units of potassium penicillin G was prepared by reconstituting Potassium Penicillin G for Injection, U.S.P., with 1 liter of Sodium Chloride Injection, U.S.P. or 1 liter of 5% Dextrose and 0.9% Sodium Chloride Injection, U.S.P. Each solution was divided into 3 portions and the pH of each portion adjusted with NaOH or HCl

solutions to pH 6.5, 6.0 or 5.5. Table III confirms that the most stable infusion solution has an initial pH of 6.5. The loss of potency increased as the initial pH deviated from pH 6.5. However, a significant downward drift in pH occurred even at pH 6.5.

TABLE II

Stability of Potassium Penicillin G for Injection, U.S.P. in Infusion Solutions

5 million Units Potassium Penicillin G in 1 liter of Sodium Chloride Injection, U.S.P.

Hours at 25°C	Abbott % Initial	Abbott pH	Baxter % Initial	Baxter pH	Cutter % Initial	Cutter pH
0	100	6.9	100	6.6	100	6.9
24	96	6.4	95	6.2	98	6.4
48	94	6.1	94	5.9	94	6.1

5 million Units Potassium Penicillin G in 1 liter of 5% Dextrose and 0.9% Sodium Chloride Injection, U.S.P.

Hours at 25°C	Abbott % Initial	Abbott pH	Baxter % Initial	Baxter pH	Cutter % Initial	Cutter pH
0	100	6.0	100	6.0	100	6.4
24	97	5.7	95	5.7	97	6.1
48	92	5.2	91	5.2	94	5.8

TABLE III

Stability of Potassium Penicillin G for Injection, U.S.P. in Infusion Solutions with Various Initial pH's

5 million Units Potassium Penicillin G for Injection, U.S.P. in 1 liter Abbott's Sodium Chloride Injection, U.S.P., Adjusted to pH:

Hours at 25°C	6.5 % Initial	6.5 pH	6.0 % Initial	6.0 pH	5.5 % Initial	5.5 pH
0	100	6.5	100	6.0	100	5.5
24	95	6.1	98	5.5	86	5.0
48	93	5.7	90	5.0	57	4.5

5 million Units Potassium Penicillin G for Injection, U.S.P. in 1 liter Abbott's 5% Dextrose and 0.9% Sodium Chloride Injection, U.S.P., Adjusted to pH:

Hours at 25°C	6.5 % Initial	6.5 pH	6.0 % Initial	6.0 pH	5.5 % Initial	5.5 pH
0	100	6.5	100	6.0	100	5.5
24	98	6.1	97	5.7	88	5.0
48	95	5.8	92	5.2	63	4.5

It is apparent that penicillin intravenous infusion therapy can be improved if a buffer with sufficient buffer capacity is present to produce and maintain an infusion solution at pH 6.5. A series of penicillin powders was prepared containing 5 million units of potassium penicillin G but with citrate buffer concentrations ranging from 5 to 30%. These powders were reconstituted and added to 1 liter of 5% Dextrose and 0.9% Sodium Chloride Injection, U.S.P. The initial pH of each solution was 6.5. The change in pH after 2 days storage at 25° is directly related to the buffer concentration (Fig. 1). As high concentrations of citrate buffer may have catalytic effects[9], it was decided that a buffer concentration which would maintain the pH within 0.1 unit of the initial pH would improve stability with a low risk of introducing undesired effects. Figure 1 indicates that a 20% citrate buffer will maintain a 1 liter infusion solution at pH 6.5 ± 0.1 for 48 hours at 25°. Thus a powder consisting of 5 million units of potassium penicillin G with 20% citrate buffer was selected as the optimum dosage form for intravenous infusion. This dosage form was expected to adequately control the pH of a 1 liter infusion solution and produce maximum chemical stability.

In order to confirm this hypothesis, a powder containing 5 million units of potassium penicillin G and 20% citrate buffer in a ratio of 27 parts sodium citrate, anhydrous to 1 part citric acid, anhydrous was prepared. This powder was reconstituted and added to 1 liter of Sodium Chloride Injection, U.S.P. and 1 liter of 5% Dextrose and 0.9% Sodium Chloride Injection, U.S.P. The pH of each potassium penicillin G-Sodium Chloride Injection, U.S.P. solution was between pH 6.4 and 6.5 (Table IV). The pH of the potassium penicillin G-5% Dextrose and 0.9% Sodium Chloride Injection, U.S.P. solution was between pH 6.25 and 6.35. The

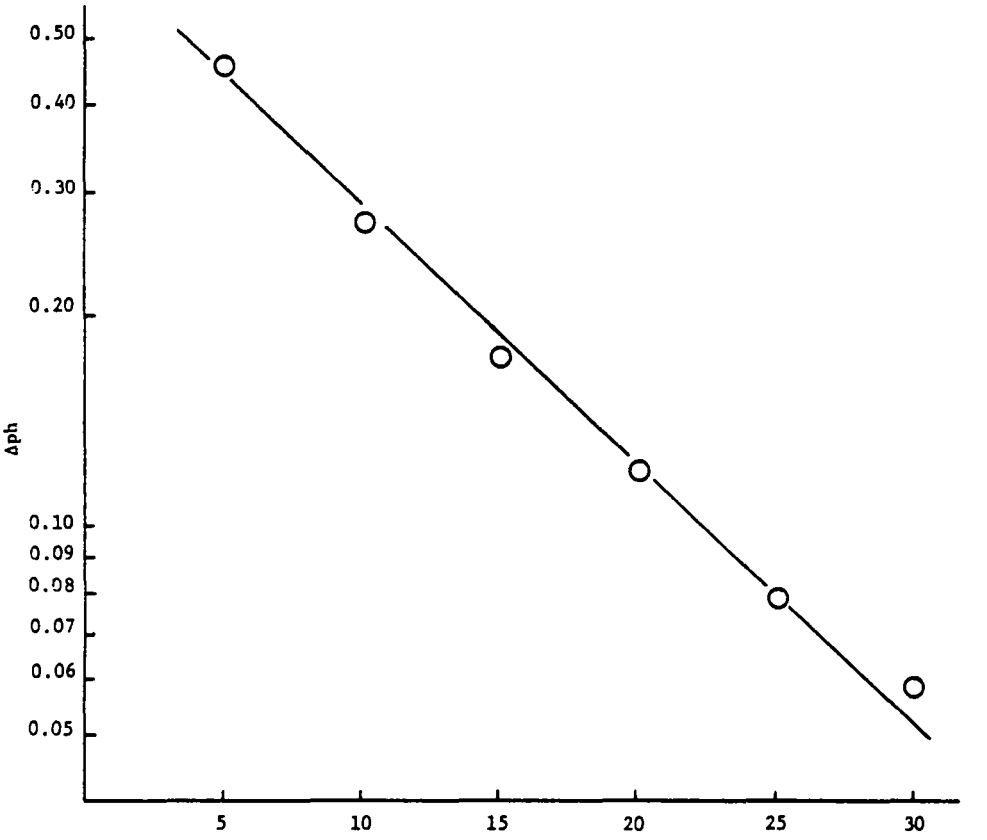

FIGURE I

Change in pH during 48 hours at 25°C for Potassium Penicillin G-5% Dextrose and 0.9% Sodium Chloride Injection Infusion Solutions containing various concentrations of citrate buffer.

initial pH of each solution was adjusted to 6.5 with sodium hydroxide solution. The solutions were aged at 25° and their potency and pH determined at 24 and 48 hours. Table IV indicates that virtually no loss of potassium penicillin G occurs in 24 hours when 5 million units

TABLE IV
Stability of Potassium Penicillin G Containing 20% Citrate Buffer in Infusion Solutions

5 million Units Potassium Penicillin G in 1 liter of Sodium Chloride Injection, U.S.P.

Hours at 25°C	Abbott (6.44)[a] % Initial	pH	Baxter (6.46)[a] % Initial	pH	Cutter (6.40)[a] % Initial	pH
0	100	6.5	100	6.5	100	6.5
24	98	6.5	99	6.4	99	6.4
48	97	6.4	98	6.3	98	6.4

5 million Units Potassium Penicillin G in 1 liter of 5% Dextrose and 0.9% Sodium Chloride Injection, U.S.P.

Hours at 25°C	Abbott (6.32)[a] % Initial	pH	Baxter (6.26)[a] % Initial	pH	Cutter (6.32)[a] % Initial	pH
0	100	6.5	100	6.5	100	6.5
24	100	6.4	99	6.4	99	6.4
48	99	6.3	98	6.4	98	6.4

[a] pH before adjustment with standard NaOH.

of potassium penicillin G with 20% buffer is added to 1 liter of infusion solution manufactured by 3 different pharmaceutical companies. Thus it appears that penicillin infusion therapy could be improved if a potassium penicillin G dosage form was available which was designed for intravenous infusion. This new dosage form should contain potassium penicillin G, buffered with 20% citrate buffer. The ratio of sodium citrate to citric acid should be selected to produce pH 6.35-6.65 after dilution with 1 liter of infusion solution. The results of this study indicate that a ratio of 27-30 parts sodium citrate, anhydrous to 1 part citric acid, anhydrous should produce the desired pH. Initial pH's of approximately 7.0 were obtained when 20% sodium citrate was used.

This new dosage form would contain an adequate buffer capacity to control the pH of the intravenous infusion solution. The buffer capacity (Δml of 0.1N HCl/ΔpH) of a series of solutions was determined by measuring the volume of 0.1 HCl needed to cause the pH of 20 ml. of solution to

drop 0.5 units. As seen in Table V the buffer capacity of Potassium Penicillin G for Injection, U.S.P., 5 million units is 1.0 when diluted to 250,000 units/ml. or 1.6 when diluted to 500,000 units/ml. When Potassium Penicillin G for Injection, U.S.P., 5 million units is used to prepare an infusion solution, the buffer capacity is virtually lost. However, the recommended dosage form containing 20% citrate buffer has a buffer capacity of 0.2 when diluted to 1 liter with either Sodium Chloride Injection, U.S.P. or 5% Dextrose and 0.9% Sodium Chloride Injection, U.S.P. As was noted earlier, this buffer capacity will maintain the desired pH for at least 48 hours at 25°C.

The osmolality of the potassium penicillin G-Sodium Chloride Injection, U.S.P., intravenous infusion solution is only increased from 308 to 313 mOsm./Kg. when the buffer concentration is increased from 5 to 20%

TABLE V
Buffer Capacity of Intravenous Infusion Solutions

Solution	Buffer Capacity[a]
Potassium Penicillin G for Injection, U.S.P., 5 million Units diluted to 250,000 U/ml for Injection	1.0
Potassium Penicillin G for Injection, U.S.P., 5 million Units diluted to 500,000 U/ml for Injection	1.6
Potassium Penicillin G for Injection, U.S.P., 5 million Units in 1 liter Sodium Chloride Injection, U.S.P.	0.02
Potassium Penicillin G for Injection, U.S.P. 5 million Units in 1 liter 5% Dextrose and 0.9% Sodium Chloride Injection, U.S.P.	0.08
Potassium Penicillin G with 20% citrate buffer, 5 million Units in 1 liter Sodium Chloride Injection, U.S.P.	0.20
Potassium Penicillin G with 20% citrate buffer, 5 million Units in 1 liter 5% Dextrose and 0.9% Sodium Chloride Injection, U.S.P.	0.22

[a] Δml 0.1 N HCl/ΔpH

(Table VI). Similarly, the osmolality of the potassium penicillin G-5% Dextrose and 0.9% Sodium Chloride Injection, U.S.P., intravenous infusion solution only increased by 7 mOsm./Kg. when the new dosage form was used in place of Potassium Penicillin G for Injection, U.S.P. The small effect on osmolality caused by increasing the concentration of citrate buffer from 5 to 20% was confirmed when the osmolality of a solution of citrate buffer equivalent to the concentration of citrate buffer in Potassium Penicillin G for Injection, U.S.P., 5 million units dissolved

TABLE VI
Osmolality of Intravenous Infusions

Solution	Osmolality (mOsm./Kg.)
Sodium Chloride Injection, U.S.P.	287
Potassium Penicillin G for Injection, U.S.P., 5 million Units in 1 liter Sodium Chloride Injection, U.S.P.	308
Potassium Penicillin G with 20% citrate buffer, 5 million Units in 1 liter Sodium Chloride Injection, U.S.P.	313
5% Dextrose and 0.9% Sodium Chloride Injection, U.S.P.	564
Potassium Penicillin G for Injection, U.S.P., 5 million Units in 1 liter 5% Dextrose and 0.9% Sodium Chloride Injection, U.S.P.	588
Potassium Penicillin G with 20% citrate buffer, 5 million Units in 1 liter 5% Dextrose and 0.9% Sodium Chloride Injection, U.S.P.	595
Potassium Penicillin G for Injection, U.S.P., 5 million Units diluted with H_2O to 250,000 U/cc for Injection	900
Potassium Penicillin G for Injection U.S.P., 5 million Units diluted with H_2O to 500,000 U/cc for Injection	1934
Citrate Buffer in Potassium Penicillin G for Injection (5%) in 1 liter H_2O	2
Citrate Buffer in recommended dosage form (20%) in 1 liter H_2O	10

in 1 liter of H_2O was 2 mOsm./Kg. The osmolality only increased to 10 mOsm./Kg. when the citrate buffer concentration was increased to the proposed 20%. Thus the new dosage form when used for intravenous infusion should not be irritating and should not increase the possibility of phlebitis due to osmolality. A decrease in the incidence of phlebitis may ultimately be observed due to the maintenance of a neutral pH.

The results of this study can be directly applied to the improvement of potassium penicillin G infusion therapy. It may also be possible to improve the intravenous infusion therapy of other drugs whose chemical stability is pH dependent. The dosage form used to prepare infusion solutions of these drugs should contain a buffer system which will bring the pH of the infusion solution to the pH of maximum stability of the drug. It should do this in spite of the widely varying pH of infusion solutions. In addition, it must have adequate buffer capacity to maintain the pH of maximum stability for 24 to 48 hours after dilution with the infusion solution.

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