Stability of Commonly Used Antibiotics Solutions in the Accufuser® Elastometric Infusion Device under Recommended Storage and Used Conditions

Ga-Young Lee[1,3], Min-Jeong Kim[2,3], Mina Kang[4], Yoo-Sin Park[3], Shin-Hee Kim[3], Sang-Yeon Kim[3] and Ju-Seop Kang[3,*]

[1]*Department of Ciencia, Gimpo Foreign Language High School, Gimposi, 415-871*

[2]*Department of Science, Korean Minjok Leadership Academy, Gangwon, 133-791*

[3]*Department of Pharmacology & Clinical Pharmacology Lab, College of Medicine and Division of Molecular Therapeutics Development, Hanyang Biomedical Research Institute, Hanyang University, Seoul 133-791, South Korea*

[4]*Department of Nursing, College of Nursing, Yonsei University, Seoul 120-752, South Korea*

Abstract: *Objectives:* The stability of two kinds of solution of penicillin G potassium [PEN-K, 10K U/mL in 5% dextrose water, D5W and 50K U/mL in 0.9% sodium chloride in water, NS) into the intravenous infusion device, Accufuser®, storage were evaluated at controlled temperature (CT, 4±2°C and RT, 25±2°C) during 6 weeks.

Methods: Studies were performed using both NS (PEN-K 50K U/mL) and D5W (PEN-K 10K U/mL) injectable solutions. The resulting solutions were transferred to Accufuser® infusion device for storage at CT or RT. Effects of period of storage (from 0 to 6 weeks) and temperature (CT and RT) on the physical appearance and concentrations of PEN-K were determined by visual clarity, pH and antibiotic concentrations by measurement with stability-indicating high-performance liquid chromatography (HPLC) method.

Results: In NS (50 K U/mL) and D5W (10K U/mL) solutions, concentrations of PEN-K were slightly change and remained 94.18 and 83.42% at CT after 1 week, respectively. Otherwise, these were rapidly decreased with time and reached to 74.65 and 75.59% in NS (50K U/mL) and D5W (10K U/mL) solutions at RT after 48 h, respectively. Moderate decrement of pH was observed in cold storage and it was shown no significant changes at 6 weeks in the RT conditions. In CT, no significant changes in physical appearance or color of the solutions were observed during the study.

Conclusion: Two kinds of PEN-K D5W(10K U/mL) and NS(50K U/mL) solution were shown different chemical stability with time in Accufuser® infusion device without any significant physical change and retained about 70% of initial concentration after 48 h in RT and 80 % after 2 weeks in CT, respectively. We suggested that PEN-K solutions of 50K U/mL NS and 10K U/mL D5W in an Accufuser® infusion device should be preferentially applicable only in CT for 48 h in clinical situations.

Keywords: Stability, Penicillin G potassium, Accufuser®, Infusion device.

INTRODUCTION

The disposable silicon balloon infusion device (Accufuser®, Woo Young Medical Co. LTD., Seoul, South Korea) is a well-established simplified silicon-based elastomeric system for administration of antibiotics and other drugs or nutrients that is suitable for patients or caregiver operation, as well as for use by healthcare providers. An increasing number of patients are being treated as outpatients. In these patients, drugs are often infused using portable pumps or infusion devices. In the special situations after curative antitumor treatment [1] or bone marrow transplantation [2], parenteral nutrition with the intravenous devices can enhance survival chances in patients with severe gastrointestinal problems for stabilization of nutritional state and prevention or reduction of progressive weight loss. Therefore, it is necessary that studies determine the physical and chemical stability of its admixtures in this infusion system before they appear in the clinical settings [3-7]. This paper will be to provide such information with commonly used antibiotics solutions in Accufuser® elastomeric infusion device under recommended storage conditions. The purpose of this study was to evaluate the physical and chemical stability of penicillin G potassium (PEN-K, Fig. (**1**)) solutions (10K U/mL, 5% dextrose water, D5W and 50K U/mL, normal saline, NS) packed in sterile Accufuser® infusion device stored and evaluated at appropriate intervals up to 6 weeks at different storage conditions with room temperature (RT, 25±2°C) and cold temperature (CT, 4±2°C). The study was done PEN-K solutions that made with NS and D5W because these are the most available infusion solution for PEN-K administration in clinical situations [4, 8-10].

*Address correspondence to this author at the Department of Pharmacology & Clinical Pharmacology Lab, College of Medicine, Hanyang University, Seoul 133-791, South Korea; Tel: 82-2-2220-0652; Fax: 82-2-2292-6686; E-mail: jskang@hanyang.ac.kr

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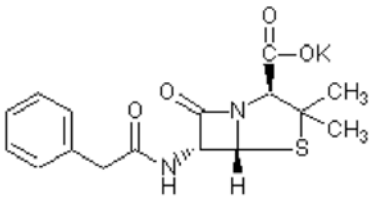


Fig. (1). Chemical Structure of penicillin G potassium ($C_{16}H_{17}N_2O_4S^-K$, MW=372.48, pH=6.0~8.5).

MATERIALS AND METHODS

Materials

PEN-K was purchased from Sigma Co. (St. Louis, MO, USA). Normal saline (NS, 0.9% sodium chloride in water) and 5% dextrose (D5W, injectable 5% dextrose water) were purchased from JW Pharmaceutical Co., Seoul, Korea. Disposable Silicone Balloon Infuser (Accufuser®) was obtained from Woo-Young Medical Co., LTD, Seoul, Korea. Acetonitrile and potassium phosphate were purchased from Sigma-Aldrich Co. (St. Louis, MO, USA). Milli-Q water from Millipore's Milli-Q system (MA, USA) was used throughout the analysis. All chemicals for HPLC analysis were HPLC-grade and were prepared immediately before use.

Preparation and Sampling Solutions

To prepare the test samples, the appropriate amounts of PEN-K were added to a portion of the infusion solution and then were brought to a final volume of 100 mL with NS and D5W. The test solutions were packaged in sterile Accufuser® infusion device for testing. All manipulations were performed in a biological safety cabinet. The nominal PEN-K concentration for the sample used in the testing was 10K U/mL in the D5W solution and 50K U/mL in the NS solutions. Triplicate test solutions under each storage conditions were prepared. The test solutions were stored at RT and CT conditions. Aliquots were removed from each device initially and at the intervals of 48 h, 1, 2, 4, and 6 weeks at RT and CT storage (Table **1**).

Method

The physical stability of the PEN-K infusion solutions was assessed by visual examination and HPLC analysis. Visual examinations were performed in normal diffuse fluorescent room light with unaided eye and a high-intensity mono-directional light. The pH of solutions was measured by a stainless electrode pH meter (Thermo Scientific Co., MA, USA). The drug concentrations were determined using a stability-indicating HPLC assay method based on several literatures. The HPLC system [4] consisted of an isocratic solvent delivery pump (Model 515, Waters Co. Milford, MA, USA) which pumped a mixture of acetonitrile (ACN) in 0.05 M potassium phosphate through a Capcell Pak C18 MG (4.6 x 250 mm, Shiseido Co. Tokyo, Japan) column at 1.1 mL/min. The ratio of ACN to 0.05 M potassium phosphate was 35:65 (v/v, pH 3.0) and was held constant during a chromatographic run. The samples of 1.0 μL were injected into the HPLC system using an autosampler (Nanospace SI-2, Shiseido Co. Ltd., Tokyo, Japan). The column effluent was monitored with a variable wavelength ultraviolet detector (Nanospace SI-1, Shiseido Co., Ltd., Tokyo, Japan) at 220 nm. The integration of chromatogram was performed by dsCHROM® software (Do Nam Instrument Co., Seoul, Korea). The method was validated for linearity, precision (inter-day and intra-day), accuracy, and selectivity [11]. The standard plot was constructed for PEN-K in the range of 2.5K-50K U/mL. The experiment was repeated 3 times on the same day and additionally on two consecutive weeks to determine intra- and inter-day precisions. Assays of quality

Table 1. Study Designs for Stability Testing of PEN-K Solutions in Accufuser® System

Conditions	Unit	Solutions / Time	0 h	48 h	1 wk	2wks	4wks	6wks
RT (25±2℃)	10K	D5W	O	O	O	O	O	O
			O	O	O	O	O	O
			O	O	O	O	O	O
	50K	NS	O	O	O	O	O	O
			O	O	O	O	O	O
			O	O	O	O	O	O
CT (4±2℃)	10K	D5W	O	O	O	O	O	O
			O	O	O	O	O	O
			O	O	O	O	O	O
	50K	NS	O	O	O	O	O	O
			O	O	O	O	O	O
			O	O	O	O	O	O

O*: processed sample, RT; room temperature, CT; cold temperature, NS; normal saline, D5W; injectable 5% dextrose water, 10K U/mL; 10,000 U/mL, 50K U/mL; 50,000 U/mL.

control solutions at PEN-K solutions (10K and 50K U/mL) were undertaken to calculate the intra-day and inter-day variations using external standard method. Linearity was evaluated by serial dilutions of PEN-K solutions with NS and D5W. Linear regression analysis of peak area and drug concentration yielded a correlation coefficient >0.99 with range (2.5K-50K U/mL). The stability of PEN-K infusion solution is determined in disposable silicone balloon infusion device (Accufuser®) during 6 weeks of storage under RT and CT conditions [12]. Solutions of PEN-K with concentrations 10K and 50K U/mL is prepared with NS and D5W. Two kinds of PEN-K solutions (10K U/mL in D5W and 50K U/ml in NS) are filled with 10 mL of each in three Accufuser® and stored at room and cold cabinets. Then, each Accufuser® infusion containers are filled with the same volume of different PEN-K solutions (10K U/mL in D5W and 50K U/mL in NS) and different temperatures (RT and CT). Periodically, the samples are evaluated for appearance, visible particles, pH and chromatographic parameters. We analyzed the amount of PEN-K in each two solutions at 0, 48 h, 1, 2, 4, and 6 weeks after preparation of solutions by HPLC-UV system [11, 13]. On each analysis day, 1.0 mL of samples for chromatographic analysis with a nominal concentration of 10K and 50K U/mL was drawn from Accufuser® infusion device and 1.0 µL were directly injected into HPLC system for analysis. The three aliquots of each solution were processed. Statistical analysis was performed using one-way ANOVA with the level of significance set at 0.05 (PCS, version 4.0, Springer-Verlag, New York, USA).

RESULTS

No significant changes in physical appearance or clarity of the solutions were observed in RT and CT conditions during the study. The pH of NS and D5W solutions were significantly ($p<0.05$) decreased from 5.66 and 5.15 to 3.84 and 3.97 in cold storage condition, respectively and shown relatively consistent in the RT storage during 6 weeks (Table **2**). The linearity of the calibration curves of PEN-K showed good linearity over the range of 2.5K~50K U/mL (r^2=0.998, Fig. (**2**)). Table **3** are listed the relative standard deviation (R.S.D.) data obtained on analysis of the samples (n=3) on the same day and on consecutive days (n=5). As it is evident, R.S.D. values were < 1.70% and < 6.31% for intra-day and inter-day results, respectively, meaning that the method was sufficiently precise. The typical HPLC chromatogram of PEN-K (10K and 50K U/mL) was shown in Fig. (**3**). The retention time for PEN-K was about 7.02 min. The initial concentration and the % remaining amount observed at each analytic time for each PEN-K solutions and storage conditions during the study period are listed in Table **4**. The amount of PEN-K was slightly change and remained 94.63 and 100.25% until 48 h and after then significantly ($p<0.05$) decreased to 2.1 and 4.54% in the D5W and NS solutions, respectively in the CT condition. But it was significantly ($p<0.05$) decreased to 75.59 and 74.65% of initial concentration in NS and D5W solutions after 48 h, respectively and disappeared at 1 week in the RT condition (Table **4**).

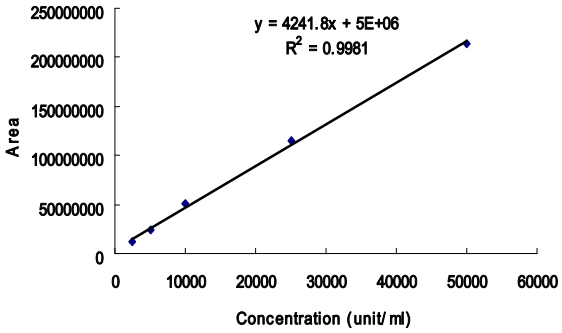


Fig. (2). Calibration curve for the determination of PEN-K concentrations in study solutions. Range (2.5K-50K U/mL), Area=peak area, $E=10^x$.

DISCUSSION AND CONCLUSION

In order to verify the effects of mixing other drugs with penicillin in a range of intravenous media in hospital pharmacy settings, the stability assays are essential for the detection and measurement of interactions, which are often unaccompanied by visual changes. The expiry date of IV medications after reconstitution or dilution is often limited to about 24 h because of the potential for breaks in sterility. However, when reconstitution and dilution are carried out in an absolute sterile environment, according to USP Chapter 797

Table 2. The Change of pH (Mean±SD, n=3) of PEN-K (10K and 50K U/mL) Solutions According to Storage Time

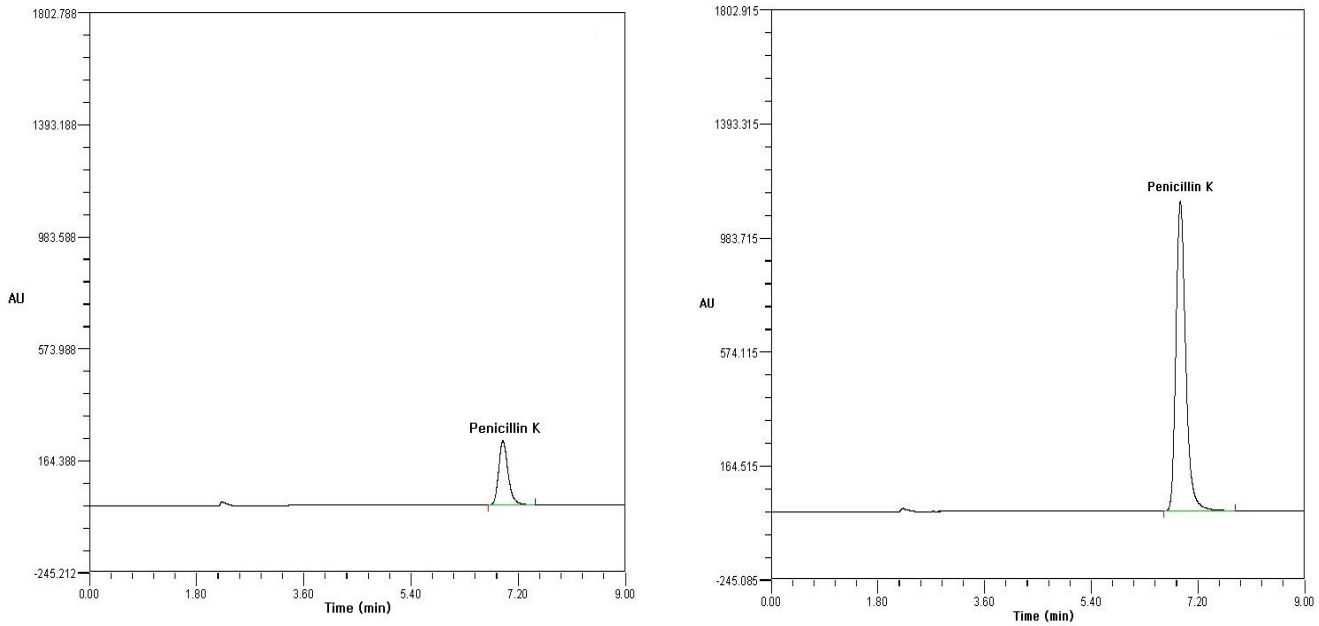
Time \ Group	[1)]RT PEN-K		[2)]CT PEN-K	
	10K U [3)]D5W	50K U [4)]NS	10K U D5W	50K U NS
0 h	5.03±0.03*	5.69±0.09	5.15±0.03	5.66±0.03
48 h	4.43±0.03	4.29±0.01	5.04±0.08	5.43±0.02
1 week	4.59±0.02	4.40±0.01	4.46±0.05	4.50±0.01
2 weeks	4.84±0.03	4.65±0.01	4.27±0.03	4.09±0.01
4 weeks	4.09±0.05	4.00±0.01	4.00±0.01	3.87±0.01*
6 weeks	5.32±0.02	5.11±0.02	3.97±0.01*	3.84±0.00*

[1)]RT; room temperature, [2)]CT; cold temperature, [3)]NS; normal saline, [4)]D5W; 5% dextrose water, * $p<0.05$ vs. 0 h.

Table 3. Intra-day (n=3) and Inter-day (n=5) Intra-day (n=3) and Inter-day (n=5) validation studies of PEN-K solutions in Accufuser® System

Parameter \ Group		RT[1] Penicillin K (25℃±2)		CT[2] Penicillin K (4℃±2)	
		10K U, D5W[3]	50K U, NS[4]	10K U, D5W	50K U, NS
Intra-day (n=3)	Accuracy (%)	108.22±2.30*	112.21±3.08	109.36±6.78	111.29±1.42
	R.S.D. (%)	1.70±0.68	0.63±0.49	1.48±0.40	1.23±0.99
Inter-day (n=5)	Accuracy (%)	108.22±0.41	112.21±0.53	109.36±0.58	111.29±0.89
	R.S.D. (%)	2.63±0.45	2.79±0.33	6.31±0.82	1.55±0.96

RT; room temperature, CT; cold temperature, NS; normal saline, D5W; injectable 5% dextrose water, R.S.D.; relative standard deviation.



(A) PEN-K(10K U/mL)

(B) PEN-K(50K U/mL)

Fig. (3). Chromatogram for control solution (NS and D5W) containing PEN-K (10K and 50K U/mL). AU (absorbance units).

Table 4. The Changes of amount (mean±SD, %) of PEN-K(10K and 50K U/mL) in various solutions (NS and D5W) According to Storage Conditions and Periods

Time \ Group	RT[1] PEN-K		CT[2] PEN-K	
	10K U, D5W[3]	50K U, NS[4]	10K U, D5W	50K U, NS
0 h	100.00±2.81	100.00±0.80	100.00±2.07	100.00±0.59
48 h	75.59±1.45*	74.65±1.02*	94.63±2.88	100.25±0.47
1 week	0	0	83.42±2.03	94.18±1.07
2 weeks	0	0	72.23±1.95*	77.45±0.73*
4 weeks	0	0	20.74±0.28*	19.43±0.48*
6 weeks	0	0	2.10±0.82*	4.54±0.49*

[1] RT: room temperature, [2] CT: cold temperature, [3] NS: normal saline, [4] D5W: injectable 5% dextrose water, *p<0.05 vs. 0 h.

recommendations [14], the expiry dates of many stable compounds can be extended from 24 h to 14 days [14, 15]. Extending the expiration date could reduce wastage of many drugs [16, 17] and might increase the convenience for an ambulatory patient by eliminating the need for frequent visits to a clinic by home care nurse to obtain additional doses [17]. According to an increasing number of patients were treated as outpatient, many of these patients receive their medications or intravenous nutrients by infusion using portable pumps or infusion devices [18]. Therefore, reliable and widely available stability information for the Accufuser® infusion device is inevitable and then undertaken to determine the stability of commonly used PEN-K when stored in the Accufuser® infusion device according to recommended storage conditions. The resultant solutions were examined for visual clarity and both pH and antibiotic concentrations were measured at 0 h, 48 h, 1, 2, 4, and 6 weeks later in different temperature conditions. No visible precipitation or change in color or clarity was observed in any kinds of PEN-K solutions in CT and RT storage during the study. When PEN-K solutions are prepared according to the sponsor's opinion to achieve concentrations of 10K U/mL in D5W and 50K U/mL in NS and analyzed PEN-K solutions that stored in an Accufuser® infusion device and retained 2.1 and 4.54% during 6 weeks in the CT conditions, respectively and disappeared completely after 1 weeks at RT storage, respectively. Otherwise, when PEN-K solutions (NS with 50K U/mL and D5W with 10K U/mL) is made according to same conditions except storage temperature and stored in an Accufuser® infusion device and retained only 74.65 and 75.59% in the RT storage within 48 h, respectively. The inactivation was also accentuated by the fact that the experiments were performed at RT rather than at CT conditions. Therefore, PEN-K solutions (D5W with 10K U/mL and NS with 50K U/mL) in an Accufuser® infusion device were both chemically stable and physically compatible for 48 h at CT storage.

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