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Intravenous Suitability Studies of Commonly Used Oxacillin Sodium Solutions in the Accufuser® Infusion Device

Min-Jeong Kim[1], Ga-Young Lee[2], Yoo-Sin Park[3], Shin-Hee Kim[3], Sang-Yeon Kim[3], Min-A. Kang[4], Min-Ji Kim[5], Ju-Seop Kang[3]

[1]Korean Minjok Leadership Academy, Gangwon-do, South Korea; [2]Gimpo Foreign Language High School, Gimpo, South Korea; [3]Department of Pharmacology & Clinical Pharmacology Lab, College of Medicine and Division of Molecular Therapeutics Development, Hanyang Biomedical Research Institute, Hanyang University, Seoul, South Korea; [4]Department of Nursing, College of Nursing, Yonsei University, Seoul, South Korea; [5]Korean International School in Beijing, Beijing, China.
Email: jskang@hanyang.ac.kr

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ABSTRACT

Our study compares two commonly used solutions of oxacillin sodium, 5.0 *mg/mL in either* 0.9% *sodium chloride* (*NS*) *or* 5% *dextrose water* (*D*5*W*), *for their continued suitability for IV usage, and stability of active compound over time, when stored at two different controlled temperatures for six weeks. Both solutions were stored in an intravenous infusion device commercially available as Accufuser® and kept at a continuously maintained temperature of either* 4 ± 2˚C (*CT*) *or* 25 ± 2˚C (*RT*). *Suitability for IV administration was assessed by measuring changes in macrographical transparency and pH over time, and drug stability was assessed by measuring changes in oxacillin concentration over time using high-performance liquid chromatography* (*HPLC*). *After* 6 *weeks, concentrations of oxacillin were unchanged in the CT solutions, while both RT solutions showed significant decreases in the concentration of oxacillin after only two weeks. Final concentration compared to starting concentrations after* 6 *weeks at RT, were* 36.57% *in NS, while virtually no oxacillin was detectable in D*5*W. Also pH measurements showed a slight decrement at* 2 *weeks with RT and at* 6 *weeks, there was a significant change in pH in both NS and D*5*W at RT. There was no significant change in color, transparency or appearance after* 6 *weeks in any of the oxacillin solutions stored in the Accufuser® infusion device. In summary, two commonly used IV solutions for oxacillin administration* (5 *mg/mL in NS or D*5*W*) *stored in the Accufuser® showed significant changes over time when maintained at RT, that would make the solutions inappropriate for therapeutic use. Both solutions when maintained in CT were not significantly altered and continued to be appropriate in pH and drug concentration for IV therapy. This suggests that ready-to-use solutions of oxacillin sodium in the Accufuser® infusion device can be kept at CT for up to* 6 *weeks safely but should not be stored at RT due to loss of potency and changes in pH.*

Keywords*: *Intravenous Suitability, Oxacillin Sodium, Accufuser® Infusion Device, HPLC

1. Introduction

The disposable silicon balloon infusion device, Accufuser® is a well-established simplified silicon-based elastomeric device for administration of antibiotics and other drugs 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 and in these patients, drugs are often infused using portable pumps or infusion devices. 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 [1-6]. 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 intravenous suitability and physical and chemical stability of oxacillin sodium (**Figure 1**, 5.0 mg/mL, normal saline, NS and 5% dextrose, D5W) solutions packaged in sterile Accufuser® device stored and evaluated at appropriate intervals up to 6 weeks at different storage conditions with room (RT, 25

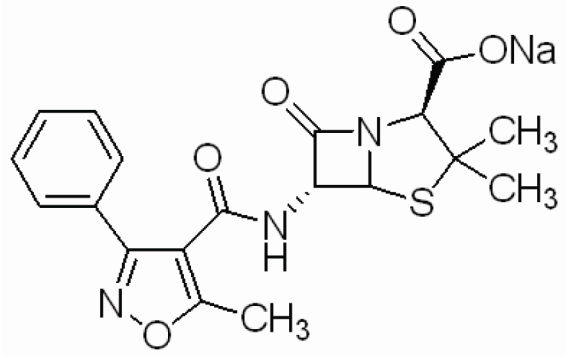


Figure 1. Oxacillin sodium ($C_{19}H_{18}N_3NaO_5S$).

± 2˚C) and cold temperature (CT, 4 ± 2˚C). The study was performed with oxacillin sodium solution that made with NS and D5W because these are the most available infusion solution for oxacillin administration in clinical situations [2,6-10].

2. Materials

Oxacillin sodium was purchased from Fluka Co., Milwaukee, MI, 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 all HPLC-grade and were prepared immediately before use.

3. Preparation and Sampling of Solutions

To prepare the test samples, the appropriate amounts of oxacillin sodium 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® device for testing. All manipulations were performed in a biological safety cabinet. The nominal oxacillin sodium concentration for testing was 5.0 mg/mL and triplicate test solutions under each storage test conditions were prepared. The test solutions were stored at RT and CT conditions. Aliquots were taken from each device initially and at the intervals of 48 h, 1, 2, 4, and 6 weeks at RT and CT conditions and determined its concentration by the HPLC method (**Table 1**).

4. Methods

4.1. Physical Stability

The physical stability of the oxacillin infusion solutions was assessed by visual examination and HPLC analysis. Macrographical transparency was performed in normal diffuse fluorescent room light with naked eye and a high-intensity mono-directional light. The pH of solutions was measured with 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 [2,10-13].

Table 1. Study designs based on appointed time for stability test of oxacillin Na solutions in Accufuser® device.

Conditions	Solution \ Time	0 h	48 h	1 wk	2 wks	4 wks	6 wks
RT (25 ± 2˚C)	NS	O*	O	O	O	O	O
		O	O	O	O	O	O
		O	O	O	O	O	O
		O	O	O	O	O	O
	D5W	O	O	O	O	O	O
		O	O	O	O	O	O
		O	O	O	O	O	O
CT (4 ± 2˚C)	NS	O	O	O	O	O	O
		O	O	O	O	O	O
		O	O	O	O	O	O
	D5W	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.

4.2. HPLC Method

4.2.1. HPLC-UV System

The HPLC system [2,13] consisted of an isocratic solvent delivery pump (Model 515, Waters Scientific Co., Milford, MA, USA) which pumped a mixture (v/v, 35/65, pH 3.0) of acetonitrile (ACN) in 0.05 M potassium phosphate through a Capcell Pak C18 UG80 (3.0 × 250 mm, 3 µm, Shiseido Co., Tokyo, Japan) column at infusion rate of 0.8 mL/min. The ratio of ACN to 0.05 M potassium phosphate was 35:65 (pH 3.0) and was held constant during a chromatographic run. The sample volume of 2.0 µL was injected into the HPLC system using an autosampler (Nanospace SI-2, Shiseido Co., Tokyo, Japan). The column effluent was monitored with a variable wavelength ultraviolet detector (Nanospace SI-1, Shiseido Co., Tokyo, Japan) at 220 nm. The integration of chromatogram was performed by dsCHROM® software (Do Nam Instrument Co., Seoul, Korea).

4.2.2. Validation of the HPLC Method

The method was validated for linearity, precision (inter-

day and intra-day), accuracy, and selectivity [10]. The standard plot was constructed for oxacillin sodium in the range of 0.5 - 7.5 mg/mL. The experiment was repeated 3 times on the same day and additionally on 2 consecutive weeks to determine intra- and inter-day precisions. Assays of control solutions at oxacillin sodium solutions (5.0 mg/mL) were undertaken to calculate the intra-day and inter-day variations using external standard method. Linearity was evaluated by serial dilutions of oxacillin sodium solutions with NS and D5W for loading. Linear regression analysis of peak area and drug concentration yielded a correlation >0.99 (range 0.5 - 7.5 mg/mL). The stability of oxacillin infusion solution is determined in disposable silicone balloon infuser (Accufuser®) during 6 weeks of storage under RT and CT. Solutions of oxacillin sodium with concentrations 5.0 mg/mL are prepared with NS and D5W. Two kinds of oxacillin sodium solutions are filled with 10 mL of each in three Accufuser® and stored at room and cold temperature cabinets. Then, each Accufuser® containers are filled with the same volume of different solutions (NS and D5W) and different temperatures (RT and CT) [1,3]. All the samples are stored at RT and CT. Periodically; the samples are evaluated for appearance, visible particles, pH and chromatographic parameters. We analyzed the amount of oxacillin sodium in each two solutions at 0, 48 h, 1, 2, 4, and 6 weeks after making solutions by HPLC-UV system [1,7,10]. On each analysis day, 1.0 mL of samples for chromatographic analysis with a nominal concentration of 5.0 mg was drawn from Accufuser® device and 2.0 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).

5. Results

1) No significant changes in physical appearance or clarity of the solutions were observed during the study. The colors of the samples were transparent with no changes of color. The particles are not detected in any samples.

2) Slight decrement of NS and D5W solutions in pH from 5.56 to 5.32 and from 5.55 to 5.45 was observed in cold storage, respectively and shown similar pattern in NS solutions in RT conditions. But it was shown different pattern with significant changes in D5W solution and reached to 3.6 at 6 weeks in the RT conditions (**Table 2**, **Figure 2**).

3) The linearity could be established for oxacillin sodium in the concentration range of 0.5 - 7.5 mg/mL (r^2 = 0.9998, **Figure 3(a)**). **Table 3** lists 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 evident, the R.S.D. values were <1.37% and <2.93% for intra-day and inter-day results, respectively, meaning that the method was sufficiently precise.

Table 2. Validation studies for Intra-day (n = 3) and Inter-day (n = 5) precision.

		RT		CT	
		NS	D5W	NS	D5W
Intra-day (n = 3)	Accuracy (%)	101.01	100.74	100.69	100.81
	R.S.D (%)	0.91	1.23	1.37	0.94
Inter-day (n = 5)	Accuracy (%)	101.01	100.74	100.69	100.81
	R.S.D (%)	2.88	2.71	2.87	2.93

RT; room temperature, CT; cold temperature, NS; normal saline, D5W; injectable 5% dextrose water.

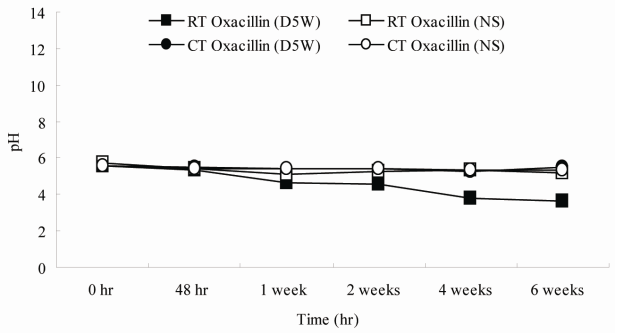
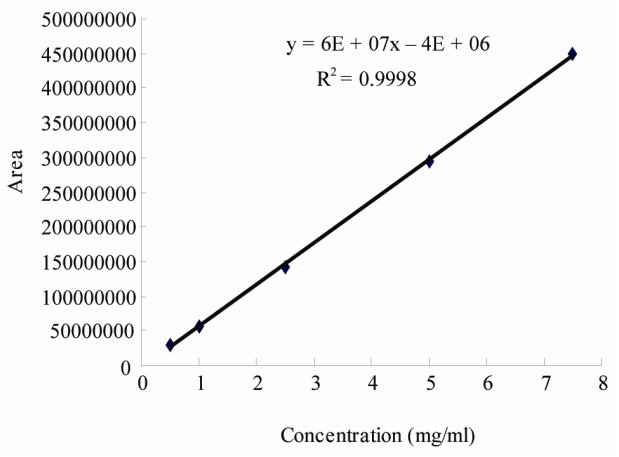


Figure 2. The changing plots of pH of oxacillin 5.0 mg/mL solutions over time of storage.

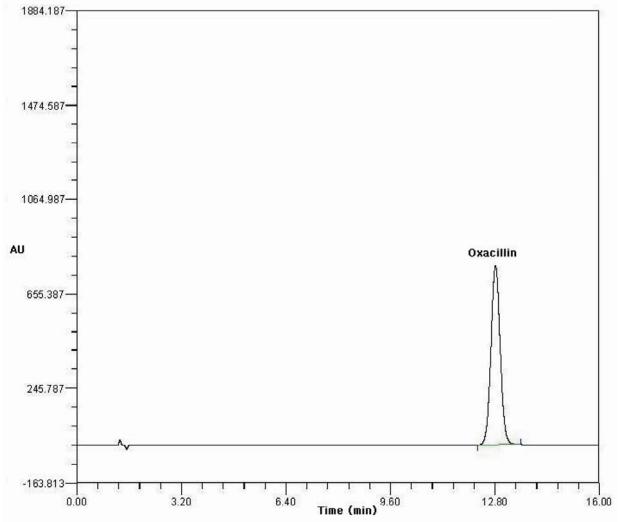
4) The retention time for oxacillin sodium in the chromatogram was about 12.8 min. The typical HPLC chromatogram of oxacillin sodium (5.0 mg/mL) was shown in the **Figure 3(b)**. The initial concentration and the percentages of oxacillin sodium on each appointed analytic point during the study period for each solutions and a storage condition is listed in the **Table 3** and **Figure 4**. The HPLC analysis showed that the amount of oxacillin sodium was remained about initial values at CT up to 6 weeks in NS and D5W solutions. But it was significantly decreased to 36.57% in NS solution and disappeared in D5W solution at 6 weeks at RT.

6. Discussion and Conclusions

No visible precipitation or change in color or clarity was observed in any kinds of oxacillin solutions during the study. We observed that the intravenous suitability and stability of oxacillin is affected by temperature of storage (more stable in CT than RT) and solution (stable in NS than D5W). When oxacillin solution is made according to the sponser's opinion to achieve concentrations of 50



(a)



(b)

Figure 3. (a) Calibration curve for the determination of oxacillin sodium concentrations (0.5 - 7.5 mg/mL), area = peak area, E = 10^x; (b) Chromatogram for study solution (NS and D5W) containing oxacillin sodium (5.0 mg/mL) AU (absorbance units).

mg/mL in NS and D5W and analyzed oxacillin 5.0 mg/mL solutions after 10 times dilution of each solution that stored in an Accufuser® and retained 36.57% and 0.00% at RT up to 6 weeks, respectively. Otherwise, when oxacillin solution is made according to the sponser's opinion to achieve concentrations of 50 mg/mL in NS and D5W and analyzed 5.0 mL solutions after 10 times dilution of each solution that stored in an Accufuser® and retained 104.95% and 102.14% at RT up to 6 weeks, respectively. Therefore, 5.0 mg/mL of oxacillin sodium solutions of NS and D5W were stored in CT and stable and retained about their initial concentration into Accufuser® up to 6 weeks, but shown unstable and its concentrations significantly decreased after 1 week in RT conditions. In conclusion, two commonly used IV solutions for oxacillin administration (5 mg/mL in NS or D5W) stored ready to use in the Accufuser® showed significant changes over time when maintained at RT, that would make the solutions inappropriate for therapeutic use. Both solutions when maintained in CT were not significantly altered and continued to be appropriate in pH and drug concentration for IV therapy. This suggests that ready-to-use solutions of oxacillin sodium in the Accufuser® infusion device can be kept at CT for up to 6 weeks safely but should not be stored at RT due to loss of potency and changes in pH.

Table 3. The changes of concentrations (mean ±SD, %) of oxacillin in various solutions (NS and D5W) according to storage temperature (RT and CT) and periods.

Group / Time	RT[1] oxacillin (25 ± 2˚C)		CT[2] oxacillin (4 ± 2˚C)	
	NS[3]	D5W[4]	NS	D5W
0 h	100.00 ± 0.49*	100.00 ± 1.21	100.00 ± 0.32	100.00 ± 0.29
48 h	100.40 ± 0.60	100.24 ± 1.17	101.30 ± 0.50	98.37 ± 1.78
1 wk	92.81 ± 0.47	71.49 ± 0.60	96.91 ± 0.31	98.19 ± 1.73
2 wks	72.64 ± 1.29*	37.28 ± 1.76*	98.32 ± 0.42	98.85 ± 0.50
4 wks	73.29 ± 1.27*	2.42 ± 0.01*	106.24 ± 0.19	104.26 ± 0.96
6 wks	36.57 ± 14.10*	0.00 ± 0.00	104.95 ± 1.35	102.14 ± 2.07

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

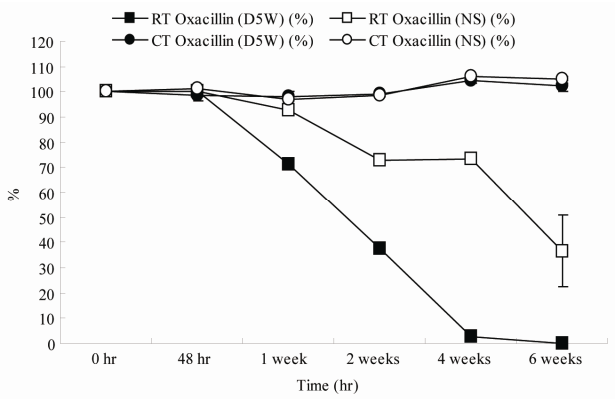


Figure 4. The changes of amount (mean ±SD, %) of oxacillin in various solutions (NS, D5W) according to storage temperature (RT and CT) and periods.

7. Acknowledgements

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