Chemical Stability of Cloxacillin in Sterile Water for Injection (SWFI) Stored in Polypropylene (PP) Syringes (50 and 100 mg/mL) and Glass Vials (250 mg/mL) at 4ºC and 25ºC.

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INTRODUCTION

A 1998 CJHP publication§ evaluated cloxacillin concentrations between 5 and 50 mg/mL in PVC minibags containing 0.9% sodium chloride injection (NS) and 5% dextrose in water (D5W) over 18 days. Although confidence intervals were not used to determine the BUD, the study demonstrated that higher concentrations were less stable and that solutions in D5W (at 23ºC, primarily) were more stable.

Interruptions in minibag supplies necessitated conservation strategies, including compounding cloxacillin in syringes and administration by direct IV injection.

Since we were unaware of any stability data for concentrations greater than 50 mg/mL at either 4ºC or 25ºC in any solution, we completed this study to determine the maximum storage at 4ºC and 25ºC in glass vials and PP syringes. Since Sterile Water for Injection (SWFI) is recommended for reconstitution and dilution, this was the diluent used in the study.

Reference:

§ Walker SE, Dufour A, Iazzetta J. Concentration and Solution Dependent Stability of Cloxacillin Intravenous Solutions. CJHP 1998; 51 (1): 13-19

OBJECTIVES

To evaluate the chemical stability of cloxacillin reconstituted with Sterile Water for Injection (SWFI) at concentrations of 250 mg/mL in glass vials and 50 and 100mg/mL in polypropylene (PP) syringes at 4ºC and 25ºC.

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METHODS

Liquid Chromatographic Method:
The liquid chromatographic system consisted of a mixture of 35% acetonitrile and 65% 0.05 mol/L phosphoric acid with 0.01 M sodium lauryl sulfate. This was pumped through a 15 cm x 4.6 mm reverse-phase SB-CN column (Agilent Zorbax SB-CN) at 1.0 mL/min. The column effluent was monitored at 250 nm.

Assay Validation:
The analytical method was validated to ensure reproducibility, accuracy and assay specificity. The system was shown to be capable of separating cloxacillin from its degradation products (Figure 1). Accuracy and reproducibility of standard curves was tested over 5 days. Inter and intra-day errors of reproducibility were assessed by the coefficients of variation and the standard deviation of regression.

Stability Study:
Vials and syringes were stored at 4ºC and 25ºC. On study day 0, 10g vials of cloxacillin were reconstituted with 40 mL of SWFI (250mg/mL). Vials were further diluted with SWFI to achieve concentrations of 50 and 100mg/mL and drawn into PP syringes. Vials and syringes were stored at 4ºC and 25ºC. Cloxacillin concentration analysis was completed on study days 0, 1, 2, 4, 7, 10, 14, 17 and 21 using a validated stability-indicating liquid chromatographic method with UV detection.

Data Reduction and Statistical Analysis:
Chemical stability was based on the intersection of the lower limit of the 95% confidence interval of the observed degradation rate and the time to achieve 90% of the initial concentration (T-90).

Analysis of variance was used to test differences in degradation rate between the different storage temperatures and container combinations. The 5% level was used as the a priori cut-off for significance.

Figure 1.
Chromatogram A represents a solution of 250 mg/mL solution of cloxacillin in SWFI on study day zero. Chromatogram B was observed after 14 days storage of a 250 mg/mL solution at 4ºC. 91.97% remains. Chromatogram C was observed after 14 days storage of a 250 mg/mL solution at 25ºC. 30.8% of the initial cloxacillin concentration was observed to remain. Degradation products appear at 2.4, 2.7, 3.2, 4.2, 6.0 and 6.5 minutes (arrows) and are separated from cloxacillin which elutes at 4.5 minutes.

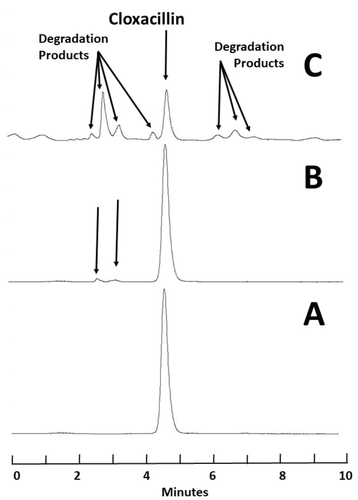
CONCLUSIONS

This study demonstrated that cloxacillin solutions in vials (250mg/mL) and syringes (50 and 100mg/mL) can be stored for up to 14 days if continuously stored at 4ºC and 2 days at 25ºC. If the syringes are exposed to room temperature, the maximum storage is 7-days at 4ºC, allowing a maximum of 12 hours exposure at 25ºC during this 7-day period. Under these conditions syringes would retain more than 93.5% of the initial concentrations and vials would retain more than 91% of the initial concentration.

RESULTS

Table 1. Percent Remaining of the Initial Cloxacillin Concentration.

Container	Syringe	Syringe	Syringe	Syringe	Glass vial	Glass vial
Temperature	4ºC	25ºC	4ºC	25ºC	4ºC	25ºC
Nominal concentration (mg/mL)	50	50	100	100	250	250
Study Day \ Actual concentration (mg/mL)	49.55	49.46	99.68	99.79	249.88	249.98
0	100.00±0.26	100.00±0.27	100.00±0.16	100.00±0.05	100.00±0.05	100.00±0.03
1	99.64±0.22	95.16±0.23	99.63±0.16	93.88±0.18	99.62±0.04	93.52±0.60
2	99.24±0.17	91.20±0.37	99.10±0.04	89.42±0.05	99.04±0.15	86.54±0.15
4	98.88±0.13	81.70±2.13	98.85±0.15	78.77±0.23	98.68±0.26	75.80±0.10
7	97.90±0.10	70.98±0.18	96.89±0.37	69.13±0.71	96.58±0.10	63.59±0.84
10	96.48±0.09	57.61±0.27	96.29±0.14	53.87±0.96	94.34±0.26	50.93±0.94
14	94.62±0.33	41.37±0.89	94.14±0.22	36.07±0.80	91.97±0.46	30.89±0.58
17	92.96±0.30	29.48±1.98	91.65±0.38	22.80±1.31	90.77±0.45	19.98±2.63
21	91.16±0.56	9.96±2.07	88.78±1.00	1.87±2.77	88.03±0.05	0.04±36.29
Rate of Change of Concentration (%/day – Slope)	**-0.4206**	**-4.2040**	**-0.5117**	**-4.5501**	**-0.5787**	**-4.6337**
Intercept	100.317	99.663	100.467	99.069	100.335	97.051
Correlation (r)	-0.995	-1.000	-0.987	-0.999	-0.997	-0.999
Standard Deviation of Regression (Sy.x)	0.355	0.930	0.666	1.420	0.356	1.875
Confidence Interval for slope	**0.03942**	**0.10321**	**0.07390**	**0.15757**	**0.03952**	**0.20799**
Fastest Slope 95% Confidence	**-0.4600**	**-4.3072**	**-0.5856**	**-4.7077**	**-0.6182**	**-4.8417**
Upper Limit 95% Confidence	-0.3811	-4.1008	-0.4378	-4.3926	-0.5392	-4.4257
Shortest T-90 (95% CI) days	21.74	2.32	17.08	2.12	16.18	2.07



Assay Validation:
The analytical method separated degradation products from cloxacillin (Figure 1) and measured the concentration specifically, accurately (average: 2.34%) and reproducibly (intra-day CV(%): 0.56%; or Standard deviation of regression (Sy.x): 1.10%).

Concentration Results:
During the study at 4ºC, 50 mg/mL solutions retained more than 90% of the initial concentration for the entire study period (21 days), 17 days at 100 mg/mL and 14 days at 250 mg/mL. Multiple linear regression revealed significant differences in percent remaining due to study day ($p<0.001$) and temperature ($p<0.001$) but not concentration ($p=0.679$) or container ($p=0.803$). The calculated T-90, with 95% confidence exceeded the 14 day study period for all concentrations at 4ºC and 2 days at 25ºC.

Due to the difference in the degradation rate (8-10 fold) at 4ºC and 25ºC, time at room temperature should be limited to 12 hours, placing constraints on compounding-time and the ability to recycle syringes.