Chemical Stability of Epinephrine Diluted in 0.9% Sodium Chloride and Stored in Polypropylene (PP) Syringes at 4°C and 25°C.

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INTRODUCTION

Inpatient hospital pharmacies must compound intravenous products and assign an appropriate beyond-use-date (BUD) as per NAPRA standards, when products are not commercially available. Having infusions available as ready-to-administer (RTA) products on nursing units is important for safe and timely administration of medication.

Pediatric patients require lower concentrations than adults. Multiple publications have demonstrated the stability of epinephrine, but none at a concentration of 10 mcg/mL with storage in polypropylene syringe at 4C or 25C for longer than 7 days.

Since the stability of epinephrine has not been reported at concentrations of 10 mcg/mL for longer than 7 days, we require such data to be in compliance with current NAPRA/USP regulations.

OBJECTIVES

The objective of this study was to evaluate the chemical stability epinephrine prepared in polypropylene syringes at a concentration of 10 mcg/mL in 0.9% sodium chloride at both room temperature and in the refrigerator.

The concentration of epinephrine was evaluated during storage using a validated, stability indicating, liquid chromatographic method using UV detection.

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METHODS

Liquid Chromatographic Method

The liquid chromatographic system consisted of a mixture of 3% acetonitrile and 97% 0.05 mol/L phosphoric acid which was pumped through a 15 cm x 4.6 mm reverse-phase C18, 5-µm column (Supelcosil ABZ+plus, Sigma-Aldrich, Oakville, ON) at 1.0 mL/min. The effluent was monitored at 280 nm.

Assay Validation

A chromatographic separation was developed and evaluated to ensure reproducibility, accuracy and assay specificity. The system was shown to be capable of separating epinephrine 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

On study day 0, 10mL solutions of 10 mcg/mL concentrations of epinephrine were prepared in BD polypropylene (PP) syringes using ERFA Canada; Epinephrine Injection (Lot F7J025; Expiry April 2019). Three units of 1 syringe from each batch (n=3) were stored at room temperature (25°C) and 3 were stored at 4°C. Concentration analysis was completed on study days 0, 2, 7, 14, 21, 28, 42, 56, 72 and 91 using the validated stability-indicating liquid chromatographic method with UV detection.

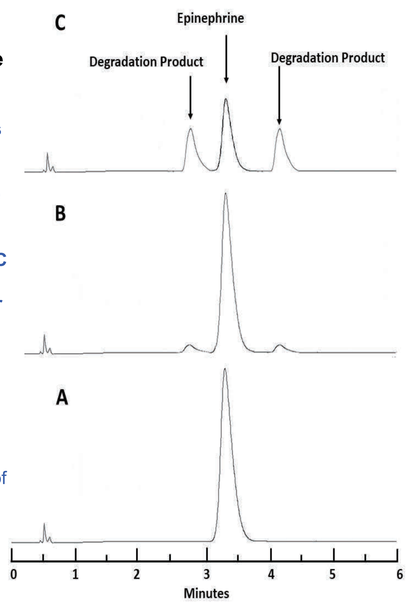
Data Reduction and Statistical Analysis

Chemical stability was based on the intersection of the lower limit of the 95% confidence interval of the observed degradation rate, determined by linear regression, and the time to achieve 90% of the initial concentration. Multiple linear regression analysis was used to test differences in degradation rate between temperatures and study day.

Figure 1. Representative Chromatograms

Chromatogram A represents a 10 mcg/mL epinephrine solution on study day zero. Chromatogram B shows the same sample after 91-days storage at 4C with 89.62% remaining. Chromatogram C represents a 10 mcg/mL solution of epinephrine after 91-days storage at 25C with 37.24% remaining.

Epinephrine elutes at 3.4 minutes and degradation products elute at 2.7 minutes and 4.2 minutes. Neither interferes with measurement of epinephrine, allowing epinephrine to be quantified specifically. The method was judged stability-indicating.



CONCLUSIONS

In this study the concentration was observed to change by more than 10% during the 91-day study period and the BUD, calculated with 95% confidence, was 71.40 days for solutions stored a 4C but only 12.77 days for solutions stored at 25C.

When establishing a BUD in your institution, the sterile compounding environment and sterility testing of the final product must be considered.

We conclude that 10 mcg/mL solutions of epinephrine diluted in 0.9% sodium chloride at in the refrigerator in polypropylene BD syringes are physically and chemically stable for 63 days (7 weeks). This will allow the syringe to be stored for up to 24 hours at RT and still retain more than 90% of the initial concentration (90.46%), with 95% confidence.

RESULTS

Concentration Results

Concentrations on each study day are reported in Table 1 and were observed to vary by ~11% or less from the initial concentration throughout the 91-day study period at 4C and by more than 60% at 25C.

Multiple linear regression revealed significant differences in percent remaining due to study day ($p<0.001$) and temperature ($p = 0.00186$). The calculated T-90, with 95% confidence, was 71.40 days for solutions stored a 4C but only 12.77 days for solutions stored at 25C.

Assay Validation

The analytical method separated degradation products from epinephrine such that the concentration was measured specifically, accurately (deviations from known averaged 2.13%) and reproducibly (replicate error averaged 0.48% [CV(%)]). The analytical method was judged to be stability-indicating.

Table 1. Percent Remaining of the Initial Epinephrine Concentration.

Container	Syringe	Syringe
Temperature	4C	25C
Nominal Concentration (µg/mL)	10ug/mL	10ug/mL
Study Day \ Initial concentration (µg/mL)	9.81	9.70
0	100.00±0.79	100.00±0.59
2	100.80±1.45	99.22±0.86
7	99.41±0.88	98.92±0.68
14	99.22±0.74	95.89±0.70
21	98.11±0.76	92.04±0.60
28	97.28±0.21	86.94±1.11
42	95.05±0.65	78.33±1.14
56	93.10±0.91	67.52±1.28
72	90.66±0.71	50.68±0.74
91	89.62±1.12	37.24±0.66
Rate of Change of Concentration (%/day – Slope)	-0.1276	-0.7036
Standard Deviation of Regression (Sy.x)	0.505	3.227
Confidence Interval for slope	0.01246	0.07956
Fastest Slope 95% Confidence	-0.1401	-0.7831
Upper Limit95% Confidence	-0.1151	-0.6240
Shortest T-90 (95% CI) days	71.40	12.77

1. Concentrations are shown as mean ± coefficient of variation, expressed as a percentage.