ORIGINAL RESEARCH

Evaluation of the maximum beyond-use-date stability of regular human insulin extemporaneously prepared in 0.9% sodium chloride in a polyvinyl chloride bag

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Background: Regular human insulin 100 units added to a sufficient quantity of 0.9% sodium chloride, to yield a total volume of 100 mL within a polyvinylchloride bag, is accepted to be stable for 24 hours due to physical denaturation and chemical modification. The objective of this study was to evaluate the extended stability of such extemporaneously prepared regular human insulin, stored under refrigeration, to the maximum beyond-use-date allowed by United States Pharmacopeia chapter 797.

Methods: At time "0" three admixtures of regular human insulin were prepared by withdrawing 1 mL of regular human insulin with a concentration of 100 units/mL and adding it to a sufficient quantity of 0.9% sodium chloride for injection in a polyvinylchloride bag to yield a total volume of 100 mL. The three admixtures were stored under refrigeration (2°C–8°C [36°F–46°F]), and one sample of each admixture was withdrawn and tested in duplicate at 0, 6, 24, 48, 72, 144, 168, 192, 216, 240, 312, and 336 hours. Utilizing high performance liquid chromatography, each sample underwent immediate testing. The time points were stable if the mean concentration of the samples exceeded 90% of the equilibrium concentration at 6 hours.

Results: The equilibrium concentration was 0.89 units/mL. Time points were stable if the mean concentration was at least 0.80 units/mL. All time points retained at least 90% of the equilibrium concentration, with the exception of hour 168 (0.79 ± 0.03 units/mL). At 192 hours the mean concentration was 0.88 ± 0.03 units/mL. At 336 hours the mean concentration was 0.91 ± 0.02 units/mL.

Conclusion: Based on these results, regular human insulin 100 units added to 0.9% sodium chloride for injection in a polyvinylchloride bag to yield a total volume of 100 mL is stable for up to 336 hours when stored at 2°C–8°C (36°F–46°F).

Keywords: insulin, stability, storage, temperature, USP 797, sodium chloride, polyvinylchloride

Introduction

In the hospital setting, patients often require continuous infusions of intravenous (IV) regular human insulin. Our standard preparation of IV insulin for infusion consists of 100 units regular human insulin added to a sufficient quantity of 0.9% sodium chloride to yield a total volume of 100 mL. Due to the physical denaturation and chemical modification occurring during insulin admixture within a polyvinylchloride (PVC) bag, a concentration of 100 units/100 mL is accepted to be stable for 24 hours.[1–3] A recent pilot analysis demonstrates insulin stability for up to 7 days when stored under refrigeration.[4]

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SAMPLE

Insulin regular in 0.9% sodium chloride 100 units/100 mL

Bag # (1, 2, 3)

Sample # (1, 2, 3)

Date

Hour (__)

For stability testing use only

Figure 1 Sample label.

In regulations set forth by the United States Pharmacopeia chapter 797 (USP 797) guidelines, all extemporaneous admixtures must be manufactured in a certified clean room.[5] This decreases the risk of contaminants and increases the uniformity of the products produced. The maximum beyond use date allowed in the absence of end-product sterility testing is 14 days (336 hours) for a given product.[5]

The purpose of this study was to evaluate the extended stability of extemporaneously prepared regular human insulin 100 units in 0.9% sodium chloride at a total volume of 100 mL under refrigeration to the maximum beyond-use-date USP 797 allows.

Methods
Preparation of insulin admixtures
From an unopened vial of regular human insulin, 1 mL was withdrawn and added to a sufficient quantity of 0.9% sodium chloride for injection in a PVC bag to yield a total volume of 100 mL. A total of 8 mL of overfill was removed from each PVC bag prior to the addition of insulin to account for the additional volume (7 mL of overfill plus 1 mL of insulin). This process was repeated using new, unopened insulin vials to provide a total of three IV insulin admixtures. Since USP allows ±10% error on all US Food and Drug Administration-approved products, we used different vials for each admixture to account for variance. Once completed, all admixtures were affixed with labels with instructions to store under refrigeration at 2°C–8°C (Figure 1).

Sampling analysis of insulin admixtures
Sampling from each of the three admixtures occurred at 0, 6, 24, 48, 72, 144, 168, 192, 216, 240, 312, and 336 hours. All samples were analyzed by the process of high performance liquid chromatography, which was completed by DYNALABS (Saint Louis, MO, USA). Each sample underwent immediate testing in duplicate.[6]

Statistical analysis
The average of all samples from all three admixtures at each time point yielded the overall mean concentration. A time point was considered stable if the mean concentration of the samples exceeded 90% of the equilibrium concentration at 6 hours.[7–10]

Results
At 6 hours, the equilibrium concentration was determined to be 0.89 units/mL (Table 1). Based on our definition of stability, admixtures were stable at each time point if the concentration of insulin was greater than 0.8 units/mL. All time points retained at least 90% of the equilibrium concentration with

Table 1 Mean insulin concentrations of triplicate insulin samples in 0.9% sodium chloride stored at 2°C–8°C

Time (hour)	Bag 1*	Bag 2*	Bag 3*	Combined*	Considered stable**
0	0.92 (0.04)	0.91 (0.01)	0.93 (0.03)	0.92 (0.02)	Yes
6	**0.88 (0.01)**	**0.89 (0.04)**	**0.91 (0.02)**	**0.89 (0.02)**	Yes
24	0.83 (0.03)	0.86 (0.04)	0.87 (0.02)	0.85 (0.03)	Yes
48	0.84 (0.01)	0.82 (0.03)	0.87 (0.01)	0.84 (0.03)	Yes
72	0.78 (0.03)	0.83 (0.01)	0.84 (0.08)	0.82 (0.05)	Yes
144	0.85 (0.02)	0.84 (0.03)	0.90 (0.04)	0.87 (0.04)	Yes
168	0.79 (0.01)	0.82 (0.03)	0.77 (0.00)	0.79 (0.03)	No
192	0.87 (0.00)	0.86 (0.03)	0.91 (0.03)	0.88 (0.03)	Yes
216	0.82 (0.04)	0.89 (0.01)	0.95 (0.02)	0.89 (0.06)	Yes
240	0.81 (0.03)	0.86 (0.05)	0.86 (0.02)	0.84 (0.04)	Yes
312	0.82 (0.06)	0.90 (0.00)	0.91 (0.00)	0.88 (0.05)	Yes
336	0.91 (0.01)	0.90 (0.00)	0.92 (0.02)	0.91 (0.02)	Yes

Notes: *Represents data presented as mean (standard deviation); **time points were considered stable if the mean concentration of the samples exceeded 90% of the equilibrium concentration at 6 hours (shown in bold).
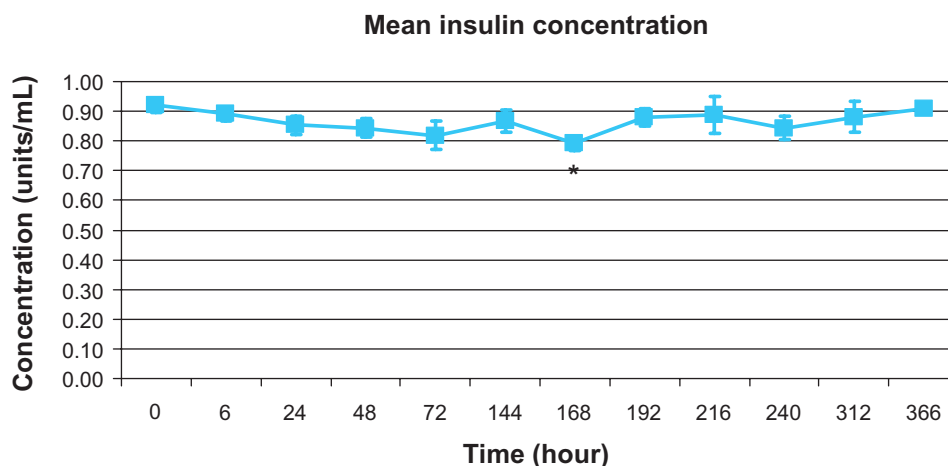
Mean insulin concentration

Figure 2 Mean concentration of insulin 100 units prepared in a total volume of 100 mL 0.9% sodium chloride stored at 2°C–8°C.
Notes: Data are expressed as mean ± standard deviation; *represents the 168-hour time point sample, which did not maintain the equilibrium concentration.

the exception of the 168-hour sample (0.79 ± 0.03 units/mL), but at the next time point, 192 hours, the mean concentration was 0.88 ± 0.03 units/mL. At 336 hours, the concentration was 0.91 ± 0.02 units/mL (Figure 2).

Discussion

To our knowledge, this is the only analysis to suggest extemporaneously prepared regular human insulin 100 units added to a sufficient quantity of 0.9% sodium chloride to yield a total volume of 100 mL is stable for up to 336 hours under refrigeration. In our recent pilot analysis, we showed stability for up to 168 hours.[4] In response to the critique of that pilot analysis, the current analysis had three modifications: (1) high performance liquid chromatography was utilized for stability testing, (2) the samples were never frozen, and (3) each sample was tested in duplicate.[4] The current analysis samples extended to 336 hours, which is the maximum beyond-use-dating allowed by USP 797.

All samples underwent high performance liquid chromatography testing, which is the standard method to ensure product stability. All samples underwent immediate testing in duplicate to provide inter-sample accuracy as well as ensure precision of the values obtained, and all samples were stored under refrigeration, not frozen.

Previously, all IV insulin admixtures at our institution had a 7-day expiration date.[4] Based on these results, we have extended the expiration date of all extemporaneously prepared bags of regular human insulin to 14 days under refrigeration.

There are approximately 400,000 admixtures prepared annually within our pharmacy sterile products room. The ability to prepare and stock common medications saves time

by reducing the need to prepare patient-specific medications on demand, decreasing waste from products that readily expire, and allowing for ease of availability of emergent medications. This extended stability data provides not only improved operational management, but also increased availability of medication for immediate use and urgent patient care.

Conclusion

Based on these results, regular human insulin 100 units added to 0.9% sodium chloride for injection in a PVC bag to yield a total volume of 100 mL is stable for up to 336 hours when stored at 2°C–8°C (36°F–46°F).

Disclosure

The authors report no conflicts of interest in this work.

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