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Physical and Chemical Stability of Dexamethasone Sodium Phosphate in Intravenous Admixtures Used to Prevent Chemotherapy-Induced Nausea and Vomiting

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Publication Information

Buga, Ina; Uzoma, Joy; Reindel, Kristin; Rashid, Kateryna; Diep, Tuong; McCartan, Pamela; and Zhao, Fang (2019). "Physical and Chemical Stability of Dexamethasone Sodium Phosphate in Intravenous Admixtures Used to Prevent Chemotherapy-Induced Nausea and Vomiting." *Hospital Pharmacy OnlineFirst*.

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Physical and Chemical Stability of Dexamethasone Sodium Phosphate in Intravenous Admixtures Used to Prevent Chemotherapy-Induced Nausea and Vomiting

Abstract

Purpose: Dilute intravenous (IV) admixtures of dexamethasone sodium phosphate (DSP) are becoming increasingly used in antiemetic regimens to prevent chemotherapy-induced nausea and vomiting (CINV). Based on its chemical structure and previous studies, DSP is known to be susceptible to hydrolysis and oxidation under certain conditions. There are limited data to directly support the selection of IV diluents, storage conditions, and beyond-use dates for the dilute IV solutions of DSP used in the antiemetic regimens. This study was designed to investigate these parameters. **Methods:** A stability-indicating high-performance liquid chromatography (HPLC) method was first developed for the analysis of DSP. Commercially available 100 mg/10 mL DSP injection vials were used to prepare the IV admixtures of DSP in 0.9% sodium chloride injection or 5% dextrose injection. The final DSP concentrations were 0.08 or 0.4 mg/mL, which bracketed the range commonly used in antiemetic regimens. These admixtures were packaged in 50-mL polyvinylchloride (PVC) bags and stored at room temperature or under refrigeration for 14 days. Samples from each IV bag underwent visual, pH, and HPLC assessments on days 0, 1, 3, 7, and 14. **Results:** Immediately after preparation, the IV admixtures of DSP appeared clear, colorless, and free of particulate matters. The initial pH values were 6.4 to 6.8 and 7.0 to 7.8 for samples in 0.9% sodium chloride and 5% dextrose, respectively. The initial DSP concentrations of all samples were within 96% to 100% of the expected values. Over the 14 days of storage at room temperature or refrigeration, no significant change was observed for the visual appearance of any IV bags. The pH of all samples remained within one pH unit from the initial values. The HPLC results confirmed that all samples retained 94% to 100% of original drug concentrations and that no significant degradation products were observed. **Conclusions:** Intravenous admixtures of DSP at 0.08 to 0.4 mg/mL are compatible with 0.9% sodium chloride and 5% dextrose in PVC bags. These admixtures are also chemically and physically stable when stored at room temperature or under refrigeration for up to 14 days.

Disciplines

Pharmacy and Pharmaceutical Sciences

Comments

This is the authors' manuscript version of the article. The final version was published as:

Buga, I., Uzoma, J. I., Reindel, K., Rashid, K., Diep, T., McCartan, P., & Zhao, F. (2019). Physical and Chemical Stability of Dexamethasone Sodium Phosphate in Intravenous Admixtures Used to Prevent Chemotherapy-Induced Nausea and Vomiting. *Hospital Pharmacy*. <https://doi.org/10.1177/0018578719888912>

This was also previously published as a poster at the American Association of Colleges of Pharmacy Annual Meeting in Chicago, Illinois, July 2019: https://fisherpub.sjfc.edu/pharmacy_facpub/331/

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DISCLOSURE:

The authors have no potential conflict of interest to disclose.

ABSTRACT

Purpose: Dilute IV admixtures of dexamethasone sodium phosphate (DSP) are becoming increasingly used in antiemetic regimens to prevent chemotherapy-induced nausea and vomiting (CINV). Based on its chemical structure and previous studies, DSP is known to be susceptible to hydrolysis and oxidation under certain conditions. There is limited data to directly support the selection of IV diluents, storage conditions, and beyond-use dates for the dilute IV solutions of DSP used in the antiemetic regimens. This study was designed to investigate these parameters.

Methods: A stability-indicating high performance liquid chromatography (HPLC) method was first developed for the analysis of DSP. Commercially available 100 mg/10 mL DSP injection vials were used to prepare the IV admixtures of DSP in 0.9% sodium chloride injection or 5% dextrose injection. The final DSP concentrations were 0.08 or 0.4 mg/mL, which bracketed the range commonly used in antiemetic regimens. These admixtures were packaged in 50-mL polyvinylchloride (PVC) bags and stored at room temperature or under refrigeration for 14 days. Samples from each IV bag underwent visual, pH, and HPLC assessments on day-0, 1, 3, 7, and 14.

Results: Immediately after preparation, the IV admixtures of DSP appeared clear, colorless, and free of particulate matters. The initial pH values were 6.4 – 6.8 and 7.0 – 7.8 for samples in 0.9% sodium chloride and 5% dextrose, respectively. The initial DSP concentrations of all samples were within 96 – 100% of the expected values. Over the 14 days of storage at room temperature or refrigeration, no significant change was observed for the visual appearance of any IV bags. The pH of all samples remained within one pH unit from the initial values. The HPLC results confirmed that all samples retained 94 – 100% of original drug concentrations and that no significant degradation products were observed.

Conclusion: IV admixtures of DSP at 0.08 – 0.4 mg/mL are compatible with 0.9% sodium chloride and 5% dextrose in PVC bags. These admixtures are also chemically and physically stable when stored at room temperature or under refrigeration for up to 14 days.

KEY WORDS: Decadron, chemotherapy induced nausea and vomiting, compounding, compatibility, stability, IV, admixture

INTRODUCTION

Dexamethasone is a synthetic glucocorticoid largely used for its anti-inflammatory and immunosuppressive properties.^{1,2} Dexamethasone also possesses antiemetic properties and is recommended by both National Comprehensive Cancer Network (NCCN) and American Society of Clinical Oncology (ASCO) for the prevention of acute and delayed chemotherapy induced nausea and vomiting (CINV).^{3,4} The exact mechanism of how dexamethasone prevents CINV is not well understood, though several possibilities have been postulated.⁵ As a glucocorticoid, dexamethasone reduces the inflammatory responses to chemotherapies and acts directly on the solitary tract nucleus which induces emesis through the central nervous system. Dexamethasone may also inhibit 5-HT neurotransmitters and tachykinin receptors. Finally dexamethasone probably lessens the severity of CINV by mediating the body's stress response and restoring the normal physiological functions. Depending on the emesis risk category of chemotherapy regimens, NCCN and ASCO recommend various antiemetic regimens to prevent CINV.^{3,4} For low emetic risk chemotherapies, dexamethasone can be used as a single-agent antiemetic regimen. For moderate and high emetic risk chemotherapies, dexamethasone should be used in combination with a NK1 antagonist and a 5-HT3 antagonist.

Dexamethasone is available in a variety of dosage forms for different routes of administration.^{1,2,6} Due to the poor aqueous solubility of dexamethasone, the dexamethasone sodium phosphate (DSP) form is used in the injectable dosage forms.^{1,7} To be more explicit, DSP is the disodium salt of the phosphate ester of dexamethasone. The chemical structures of dexamethasone and DSP are shown in Figure 1. DSP injection products are available at 4 and 10 mg/mL concentrations. The strengths and dosages of DSP injection products are expressed based on the dexamethasone phosphate form.

For prevention of CINV, DSP is typically administered intravenously, with doses ranging from 8 – 20 mg prior to chemotherapy, followed by 8 mg by mouth daily for 2 – 4 days.^{3,4} The following intravenous (IV) admixtures of DSP are frequently prepared in 0.9% sodium chloride injection (NS) or 5% dextrose injection (D5W) in polyvinylchloride (PVC) bags. If the overfill and additive volumes are disregarded, the final drug concentration ranges from 0.08 – 0.4 mg/mL.

- 4 mg DSP injection in 50 mL NS or D5W (0.08 mg/mL)
- 8 mg DSP injection in 50 mL NS or D5W (0.16 mg/mL)
- 12 mg DSP injection in 50 mL NS or D5W (0.24 mg/mL)
- 20 mg DSP injection in 50 mL NS or D5W (0.4 mg/mL)

As shown in Figure 1, the chemical structure of DSP contains functional groups which are prone to oxidation and acid/base catalyzed hydrolysis.⁸ Compatibility and stability of DSP in IV admixtures has been studied by several research groups,⁸⁻¹⁰ and a USP monograph is available for a compounded DSP injection product at 24 mg/mL.⁶ However, none included dilute solutions at the aforementioned concentration range. There are two main stability concerns about dilute DSP admixture solutions: buffer capacity and sorption to packaging. The manufactured DSP injection products are formulated at pH 7.0 – 8.5, as per USP monograph requirement, mostly with 35 – 75 mM sodium citrate buffer.^{1,6} Upon 25 – 50 fold dilution, the buffer concentration would drop below 3 mM in the IV admixtures. Significant pH change of the DSP IV admixtures away from neutral range can promote oxidation and hydrolysis. In addition, dilute solutions are more susceptible to drug loss due to sorption to packaging materials. The same mass quantity of drug loss translates to an increased percentage loss for dilute solutions.

With the two major concerns described above, the compatibility and stability data from the previous studies may not be extrapolated to the current application. The goal of this study is to directly assess the compatibility and stability of the 0.08 – 0.4 mg/mL DSP IV admixtures in 50-mL PVC bags of 0.9% sodium chloride or 5% dextrose.

METHODS

Materials

All materials for DSP IV admixture preparations were purchased through a pharmacy distributor. The original manufacturers and NDC/Lot information are listed below. Dexamethasone Sodium Phosphate Injection USP, 10 mg/ml, 10 mL vials, Fresenius Kabi (Lake Zurich, IL), NDC#63323-516-10, and Lot#6015699. Sodium Chloride Injection USP, 0.9% (NS), 50-mL PVC bags, Baxter (Deerfield, IL), NDC#0338-0049-11, and Lot#P375915. Dextrose Injection USP, 5% (D5W), 50-mL PVC bags, Baxter, NDC#0338-0017-41, and Lot#P372490.

The water used for all sample preparation and analysis was produced on-site by a Milli-Q Direct 8 system from Millipore Sigma (Burlington, MA), and it met the requirements for Type I ultrapure water. All other solvents and chemicals were purchased from Thermo Fisher Scientific (Waltham, Massachusetts).

Visual Inspection

An IV inspection light box (Cat# 17109) from Health Care Logistics (Circleville, OH), with lighted white and black background, was used for visual inspection.

pH Analysis

A Seven Easy model pH meter from Mettler-Toledo was used with a gel-filled pencil-thin pH electrode from Thermo Fisher Scientific. The pH meter was calibrated daily with standard pH 4 and 7 buffer solutions from Thermo Fisher Scientific.

HPLC Analysis

An HPLC method was developed for DSP to measure drug concentration and monitor drug stability. A Model LC-2010AHT system from Shimadzu Scientific Instruments (Marlborough, MA) was equipped with a Kinetex C18, 5 μ m, 150 \times 4.6 mm column from Phenomenex (Torrance, CA) as the stationary phase. The mobile phase consisted of a 77:23 v/v mixture of 55 mM sodium phosphate buffer (pH 4.0) and acetonitrile. Additional instrument parameters were set as follows: column temperature at 40°C, mobile phase flow rate of 1.0 mL/min, sample injection volume of 10 μ L, UV detection at 230 nm, and analysis run time of 15 minutes. Data collection and processing were performed using the

Shimadzu LC Solution software.

For calibration purposes of the HPLC analysis, pure drug powder is typically used to prepare the standard solutions. However, DSP powder is exceedingly hygroscopic,¹ and the “pure” DSP powder obtained from multiple vendors were found to contain a significant amount of water (~14% w/w) by thermogravimetric analysis. Therefore, the DSP Injection product (10 mg/mL) was used to prepare standards for calibration. The product was assumed to contain 100% of the labeled amount of active ingredient, and it was diluted with water to prepare the standard solutions at 0.064, 0.072, 0.080, 0.088 and 0.096 mg/mL. These concentrations were selected to cover the 80 – 120% range of the expected sample concentration of 0.08 mg/mL from the stability study.

Forced Degradation Study

A forced degradation study of DSP was carried out to verify that the HPLC method developed was indeed stability indicating. The conditions used to force degradation were adopted from the industry best practice¹¹ and were summarized in Table 1, which included combinations of extreme pH, oxidative stress, high temperature, and/or sun light. The samples were prepared by diluting the DSP Injection product (10 mg/mL) with water in volumetric flasks to a final concentration of 0.8 mg/mL. Suitable amount of acid (1N HCl), base (1N NaOH), or 30% hydrogen peroxide was added to the respective sample before the final volume was brought to the qs mark with water. Samples were properly sealed and placed in the respective heat/light conditions. Aliquots from samples were taken frequently for HPLC analysis until at least 10% degradation was observed in any samples.¹¹

14-Day Stability Study of DSP IV Admixtures

IV admixtures of 0.08 and 0.4 mg/mL DSP were prepared in 0.9% sodium chloride injection (NS) and 5% dextrose injection (D5W). Due to the variable overfill volumes in the commercially available IV bags, it is not possible to achieve accurate and consistent initial drug concentrations in all bags by following the routine compounding procedures. Instead, the DSP solutions were prepared in beakers first and then filled into empty IV bags. Please note that sterility was not a requirement for this study which focused on the physical and chemical stability. Nevertheless, a biological safety cabinet and aseptic techniques were used in the preparation of the solutions and IV bags to minimize contamination. One batch of solution was prepared for all replicate IV bag samples to improve the consistency. For the preparation of each batch of 0.08 mg/mL DSP admixture, 2.64 mL of the 10 mg/mL drug source

solution was mixed with 327.36 mL of NS or D5W. For the preparation of each batch of 0.4 mg/mL DSP admixture, 13.20 mL of 10 mg/mL drug source was mixed with 316.80 mL of NS or D5W. Assuming no volume contraction, the total volume of each solution was 330 mL which included a 10% overage for the IV bag preparations.

The DSP solutions were separately filled into 50-mL PVC bags and sealed. At the time of the study, there were no commercially available empty sterile PVC bags. Therefore, the 50-mL NS and D5W bags were completely emptied and used for the respective DSP solutions. Six replicate bags were prepared for each solution, yielding a total of 24 bags. For the 14-day stability study, three bags of each solution were stored at room temperature (20 – 23°C) and the other three under refrigeration (2 – 8°C).

The time points for the stability evaluation were Day 0 (immediately after preparation), Day 1, Day 3, Day 7 and Day 14. At each time point, the bags were inspected visually for color, clarity, microbial growth, and particulates. A 1-mL sample was withdrawn aseptically from each bag for pH measurement and HPLC analysis. The 0.08 mg/mL samples were analyzed directly by HPLC. The 0.4 mg/mL samples were diluted to 0.08 mg/mL with water prior to the HPLC analysis.

RESULTS AND DISCUSSION

Clarification of Drug Chemical Forms and Strengths

Dexamethasone is a small organic molecule drug with different chemical forms used in commercial dosage forms for various delivery routes.^{1,6} The forms relevant to this study are discussed below. The pure drug substance of dexamethasone is a white crystalline powder that is practically insoluble in water (≤ 0.1 mg/mL).^{1,12} Dexamethasone phosphate is a water soluble phosphate ester of dexamethasone with two added acidic groups (pK_a values of 1.89 and 6.4).¹³ Dexamethasone sodium phosphate (DSP) is the disodium salt of dexamethasone phosphate, and it is freely soluble in water (100 – 1000 mg/mL).^{1,12} The chemical structures and molecular weight values of dexamethasone and DSP are shown in Figure 1.

Due to the poor aqueous solubility of dexamethasone, DSP is used in injection products.^{1,7} According to the definition stated in the USP monograph of DSP injection products, the drug strength is labeled based on the amount of dexamethasone phosphate (not the dexamethasone or disodium salt).⁶ For example, the 10 mg/mL DSP injection product contains actually 10.93 mg/mL DSP, which is equivalent to 10 mg/mL dexamethasone phosphate or 8.33 mg/mL dexamethasone. All drug strengths and dosages of the DSP IV admixtures described in this article follow the same practice as defined in USP.

HPLC Method and Forced Degradation Study

With the HPLC parameters described in the Methods section, DSP exhibited a retention time of 6.1 minutes. A representative chromatogram of the 0.08 mg/mL DSP standard is shown in Figure 2. The daily calibration curves were linear over the concentration range of the standards (0.064 – 0.096 mg/ml) with R^2 values greater than 0.990. The intra-day and inter-day coefficients of variation were all within 2%.

The results of the forced degradation study are summarized in Table 1. Significant drug degradation ($> 45\%$) was observed in three out of the four samples after 24 hours, and the degradation products were separated from the original drug peak by the HPLC method. Therefore, the HPLC method was considered as stability indicating and suitable for the 14-day stability study of the DSP IV admixtures.

14-day Stability Study of DSP IV Admixtures

The freshly prepared IV admixtures of DSP appeared clear, colorless, and free of particulate matters. As shown in Table 2, the initial pH values were 6.4 – 6.8 and 7.0 – 7.8 for samples in 0.9% sodium chloride injection and 5% dextrose injection, respectively (Table 2). The initial DSP concentrations of all samples were within 96 – 100% of the expected values (Table 3).

Over the 14 days of storage at room temperature or refrigeration, no significant change was observed for the visual appearance of any IV bags. The pH of all samples remained within one pH unit from the initial values (Table 2). The HPLC results confirmed that all samples retained 94 – 100% of original drug concentrations (Table 3). No new degradation product peaks were observed in any HPLC chromatograms.

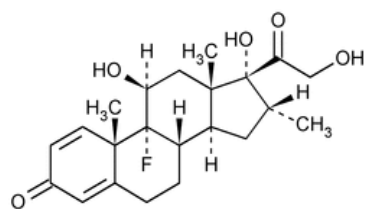
The results demonstrate that IV admixtures of DSP at concentrations between 0.08 – 0.4 mg/mL are compatible with 0.9% sodium chloride injection and 5% dextrose injection in PVC bags. These admixtures are also chemically and physically stable when stored at room temperature or under refrigeration for up to 14 days.

It is important to point out several limitations of this exploratory study for future applications of the study conclusions. There are multiple FDA approved DSP injection products on the market, and the formulations vary slightly in terms of the preservative, anti-oxidant, and buffer systems.¹ For this study, the authors selected the source product which represented the most common formulation with sodium citrate as the buffer, sodium sulfite as the anti-oxidant, and benzyl alcohol as the preservative. This study also focused on the physical and chemical stability of DSP. Therefore, the DSP admixture solutions were initially prepared in batches outside the IV bags to accurately control the starting drug concentration, and microbiological testing was not performed. It should be emphasized that any IV admixtures for direct patient use should be prepared as individual doses in the IV bags, following all sterile compounding and testing requirements specified in the USP <797>.¹⁴ Pharmacists should also be mindful of the bag overfill volume and drug additive volume in their calculations to ensure the accuracy of the DSP concentrations in the final admixture solutions.

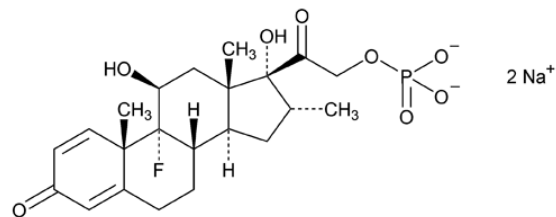
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Figure 1. Chemical structures and molecular weight (MW) values of dexamethasone and dexamethasone phosphate disodium (DSP).^{1,6} Note: the MW of dexamethasone phosphate is 472.



Dexamethasone
MW: 392



Dexamethasone Sodium Phosphate (DSP)
MW: 516

Figure 2. A representative chromatogram of 0.08 mg/mL DSP standard.

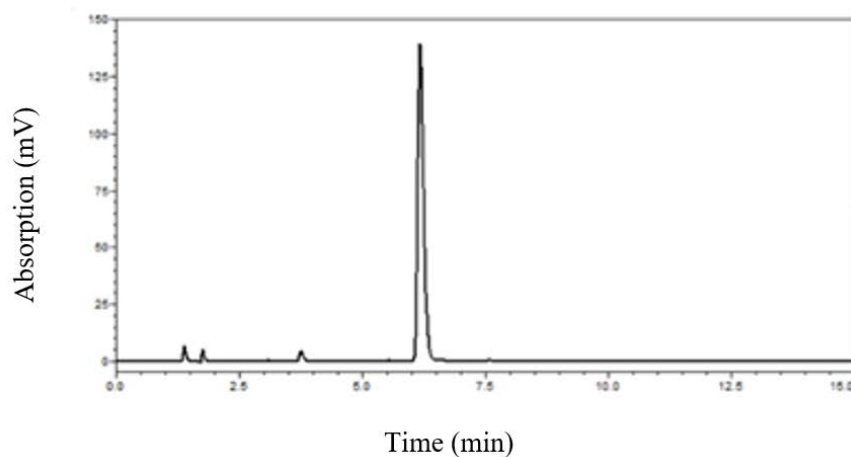


Table 1. Forced Degradation Study Conditions and Results. The initial DSP concentration was 0.08 mg/mL.

Stress condition	% DSP remaining after 24 hours
pH 2 and 60°C	96.3%
pH 12 and 60°C	44.9%
3% H ₂ O ₂ and 60°C	32.4%
3% H ₂ O ₂ and sunlight	57.3%

Table 2. pH Results of the 14-Day Stability Study (n = 3).

Sample	pH				
	Day 0	Day 1	Day 3	Day 7	Day 14
0.08 mg/mL in NS Room Temperature	6.42 ± 0.02	6.88 ± 0.20	6.33 ± 0.04	6.05 ± 0.20	5.86 ± 0.23
0.08 mg/mL in NS Refrigeration	6.43 ± 0.02	6.11 ± 0.18	6.10 ± 0.09	6.27 ± 0.02	5.98 ± 0.06
0.4 mg/mL in NS Room Temperature	6.75 ± 0.06	7.01 ± 0.06	6.82 ± 0.02	6.71 ± 0.04	6.74 ± 0.02
0.4 mg/mL in NS Refrigeration	6.82 ± 0.02	6.61 ± 0.28	6.76 ± 0.08	6.83 ± 0.03	6.60 ± 0.08
0.08 mg/mL in D5W Room Temperature	7.76 ± 0.48	7.29 ± 0.08	7.12 ± 0.03	7.13 ± 0.06	6.91 ± 0.41
0.08 mg/mL in D5W Refrigeration	7.00 ± 0.11	7.05 ± 0.12	6.84 ± 0.01	6.94 ± 0.04	6.88 ± 0.07
0.4 mg/mL in D5W Room Temperature	7.35 ± 0.06	7.43 ± 0.07	7.39 ± 0.12	7.35 ± 0.11	6.80 ± 0.10
0.4 mg/mL in D5W Refrigeration	7.26 ± 0.01	7.70 ± 0.70	7.36 ± 0.05	7.23 ± 0.01	7.00 ± 0.03

Table 3. HPLC Results of the 14-Day Stability Study (n = 3).

Sample	Initial Drug Concentration (mg/ml)	% Initial Concentration Remaining			
		Day 1	Day 3	Day 7	Day 14
0.08 mg/mL in NS Room Temperature	0.0774 ± 0.0006	99.2 ± 0.7	99.7 ± 0.7	99.8 ± 0.7	100.4 ± 0.6
0.08 mg/mL in NS Refrigeration	0.0778 ± 0.0002	99.5 ± 0.2	99.8 ± 0.3	99.9 ± 0.2	99.9 ± 0.1
0.4 mg/mL in NS Room Temperature	0.3970 ± 0.0077	94.9 ± 0.3	96.5 ± 0.3	96.0 ± 0.3	96.1 ± 0.4
0.4 mg/mL in NS Refrigeration	0.3979 ± 0.0110	94.7 ± 0.3	95.0 ± 0.9	95.1 ± 0.8	95.7 ± 1.0
0.08 mg/mL in D5W Room Temperature	0.0769 ± 0.0007	99.5 ± 0.2	99.6 ± 0.0	99.6 ± 0.1	100.2 ± 0.1
0.08 mg/mL in D5W Refrigeration	0.0775 ± 0.0004	99.5 ± 0.2	99.6 ± 0.2	99.4 ± 0.5	99.7 ± 0.3
0.4 mg/mL in D5W Room Temperature	0.3912 ± 0.0043	97.6 ± 0.3	99.0 ± 0.7	98.7 ± 0.0	98.8 ± 0.8
0.4 mg/mL in D5W Refrigeration	0.3944 ± 0.0035	97.3 ± 0.2	97.7 ± 0.4	97.8 ± 0.3	97.7 ± 0.4