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Stability and Compatibility of Diphenhydramine Hydrochloride in Intravenous Admixtures: A New Look at an Old Drug

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Abstract

Purpose: Intravenous (IV) admixtures of diphenhydramine are widely used in hospitalized patients to prevent or treat hypersensitivity reactions. However, there is limited data to support the admixture preparation in this manner. This study was designed to investigate the stability and compatibility of diphenhydramine in IV admixtures with a goal to establish a 14-day beyond-use dating with storage under refrigeration. **Methods:** The commercially available 50 mg/mL diphenhydramine hydrochloride injection vials were used to prepare the 0.2 and 1.0 mg/mL IV admixtures in 0.9% sodium chloride injection and 5% dextrose injection in 50 mL polyvinyl chloride (PVC) bags. The IV bags were sealed and stored under refrigeration (2°C-8°C) for the stability study. At each predetermined time point, samples were taken for visual inspection, pH measurement, and analysis by a stability-indicating high-performance liquid chromatography (HPLC) method. **Results:** The freshly prepared IV admixtures appeared clear, colorless, and particulate-free with pH readings of 4.44 to 4.60. The initial drug concentrations of all samples were confirmed by HPLC to be within 101.8% to 103.6% of the label claims. Over the 14 days of the study period, there was no significant change in the appearance or pH values for all stability samples. The HPLC results also confirmed that there was no more than ±2% change of the initial drug concentration in any stability samples. **Conclusion:** Diphenhydramine hydrochloride IV admixtures of 0.2 and 1.0 mg/mL are compatible with 0.9% sodium chloride injection and 5% dextrose injection in PVC bags. These IV admixtures are stable chemically and physically for up to 14 days when stored under refrigeration (2°C-8°C).

Disciplines
Pharmacy and Pharmaceutical Sciences

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Results: The freshly prepared IV admixtures appeared clear, colorless, and particulate-free with pH readings of 4.44 – 4.60. The initial drug concentrations of all samples were confirmed by HPLC to be within 101.8 – 103.6% of the label claims. Over the 14 days of the study period, there was no significant change in the appearance or pH values for all stability samples. The HPLC results also confirmed that there was no more than ±2% change of the initial drug concentration in any stability samples.

Conclusion: Diphenhydramine hydrochloride IV admixtures of 0.2 and 1.0 mg/mL are compatible with 0.9% sodium chloride injection and 5% dextrose injection in PVC bags. These IV admixtures are stable chemically and physically for up to 14 days when stored under refrigeration (2 - 8°C).

Key Words: Benadryl, diphenhydramine, anaphylaxis, compounding, stability, compatibility, IV, admixture

<u>Introduction</u>:

Diphenhydramine, a first-generation H_1 antihistamine introduced back in 1946,[1-2] has been used to treat a variety of conditions, such as allergies, insomnia, motion sickness, and parkinsonism.[3] Currently, systemic diphenhydramine is widely used in therapies as an adjunctive agent to prevent or treat hypersensitivity reactions caused by many agents.[4] In particular, many published studies have used either oral or intravenous (IV) diphenhydramine as part of a premedication series before administering chemotherapy or immunotherapy treatments.[5]

The IV administration of diphenhydramine provides rapid achievement of therapeutic effects and bypasses potential absorption issues. It is an attractive choice for some therapies and can be administered via IV push or IV infusion. While IV push of diphenhydramine would yield a fast onset, it may lead to potential side effects and thus requires additional nursing time to monitor patients. IV infusion of diphenhydramine, as diluted IV admixtures, allows the medication to be safely administered to patients.[3,6]

Even though the IV infusion therapy of diphenhydramine is widely used, there is limited information from the manufacturers or published literature to support the stability and compatibility of diphenhydramine IV admixtures at commonly used dosages.[7-9] A typical dose of 25 to 50 mg of diphenhydramine hydrochloride (HCl) prepared in a commercially available 50 or 100 mL IV bag would result in a theoretical concentration range of 0.25 to 1.0 mg/mL. The actual concentrations would be slightly lower due to bag overfill and additive volume. The purpose of this study was to evaluate the stability and compatibility of 0.2 and 1.0 mg/mL diphenhydramine HCl admixtures in 0.9% sodium chloride injection and 5% dextrose injection in polyvinyl chloride (PVC) IV bags stored under refrigeration (2 - 8°C) for up to 14 days.

Methods:

Materials for IV Admixtures

Diphenhydramine HCl Injection, USP, 50 mg/mL, 1-mL vials, were purchased from Fresenius Kabi (NDC#63323-664-16; lot# 6011913). The diluents used to prepare the IV admixtures were obtained from 250 mL bags of 0.9% Sodium Chloride Injection, USP from Baxter (NDC#0338-0049-02, lot# Y234302) and 5% Dextrose Injection, USP from Baxter (NDC#0338-0017-02, lot# Y228320). Sterile empty 50 mL IV bags were not available commercially at the time of the study. Therefore, 50 mL bags of 0.9% Sodium Chloride Injection, USP (NDC#0338-0049-31, lot# P360990) and 5% Dextrose Injection, USP (NDC#0338-0017-11, lot# P349647) were purchased from Baxter. The fluid in each 50 mL bag was completely removed under aseptic conditions prior to packaging of the stability samples. The material of these bags was polyvinyl chloride (PVC).

Materials for High Performance Liquid Chromatography (HPLC) Analysis

A Milli-Q Direct 8 system from Millipore Sigma (Burlington, MA) was used to produce Type I (ultrapure) water. Acetonitrile and trifluoroacetic acid, both HPLC grades, were purchased from Thermo Fisher Scientific (Waltham, MA). Diphenhydramine HCl powder (99% purity) was purchased from Acros Organics (Cat# AC350850250, lot# A0370928) and used as a reference standard for HPLC calibration purpose.

pH Analysis

A Mettler-Toledo SevenEasy model pH meter (Columbus, OH) was used with a gel-filled pencil-thin pH electrode from Fisher Scientific (Cat# 13-620-290). The pH meter was calibrated daily with standard pH 4 and 7 buffer solutions purchased from Fisher Scientific (Cat# SB101-500

and SB107-500).

A reversed-phase HPLC method was developed for diphenhydramine to measure drug concentration and monitor drug stability. A Model LC-2010A system from Shimadzu Scientific Instruments (Marlborough, MA) was equipped with a C18, 3 μm, 100 A, 4.6×150 mm column from Phenomenex (Torrance, CA) as the stationary phase. The mobile phase consisted of water:acetonitrile (63:37) with 0.1% trifluoroacetic acid, and the pH was approximately 2.0. Additional instrument parameters were set as follows: column temperature at 40°C, mobile phase flow rate of 0.6 mL/min, sample injection volume of 5 μL, and UV detection at 220 nm. Data collection and processing was performed by the Shimadzu LC Solution software.

For calibration purpose, five standard solutions of diphenhydramine HCl (0.16, 0.18, 0.20, 0.22, and 0.24 mg/mL) were run on each analysis day. This range encompasses the 80 – 120% of the expected concentration of the HPLC samples. These standards were prepared from the pure diphenhydramine HCl powder dissolved in water. A calibration curve was constructed on each analysis day by plotting the peak area against concentration. The mid-point standard of 0.20 mg/mL was also injected 3 times on each analysis day to monitor the intra-day and inter-day variability of the HPLC method.

Forced Degradation Study

A forced degradation study was performed to confirm that the above HPLC method could separate the potential degradation products from the original drug. As listed in Table 1, four drug samples of 0.20 mg/mL were subjected to different stress conditions of extreme pH, oxidizing agent, heat, and light. Samples #1 and #2 were adjusted to pH 2 and pH 12 by adding 1 M

hydrochloric acid and 1 M sodium hydroxide, respectively. Samples #3 and #4 were both spiked with concentrated hydrogen peroxide to a final concentration of 3%. Samples #1, 2, and 3 were incubated at 60°C, and Sample #4 was exposed to direct sunlight at ambient room temperature. All four samples were monitored by the HPLC analysis until a minimum of 10% degradation was observed in at least one of the four samples.[10-11]

14-Day Stability Study of IV Admixtures

Four IV admixtures of diphenhydramine were prepared for this stability study which included two drug concentrations (0.2 and 1.0 mg/mL) and two diluents (0.9% sodium chloride injection and 5% dextrose injection). To ensure accurate initial drug concentrations and avoid issues due to variable bag overfill volumes, the admixtures were prepared in clean beakers using appropriate measuring devices. To prepare each batch of 0.2 mg/mL diphenhydramine HCl admixture, 0.8 mL of the 50 mg/mL drug solution was mixed with 199.2 mL diluent. To prepare each batch of 1.0 mg/mL diphenhydramine HCl admixture, 4.0 mL of the 50 mg/mL drug solution was mixed with 196.0 mL diluent. Both drug and diluent solutions were aqueous, so the volumes were assumed to be additive and the final volume of each batch was 200 mL. Each admixture batch was filled into 3 replicate bags, 50 mL per bag. Please note that each batch included an overage of 50 mL to account for potential losses due to transfer or void space. The IV bag samples were sealed, labeled, and placed on stability study in a refrigerator (2 – 8°C). All preparation steps described above were carried out under aseptic conditions to minimize contamination.

The predefined study time points for this study were 0, 1, 3, 7, and 14 days. At each study time point, the admixture bags were first visually inspected for color, clarity, and particulate matters. For the HPLC analysis and pH measurement, a 1 mL aliquot was aseptically withdrawn from each admixture bag and placed into a microcentrifuge tube. For the 0.2 mg/mL stability samples, 100 μL

was transferred from the microcentrifuge into HPCL vials with inserts for direct HPLC analysis. For the 1.0 mg/mL stability samples, 100 μL was transferred into regular HPLC vials and diluted to 0.2 mg/mL with 400 μL water prior to HPLC analysis. The remaining 900 μL stability sample in each microcentrifuge tube was used directly for pH measurement.

Results and Discussion:

General Considerations

Diphenhydramine is available commercially as a variety of dosage forms[2,3] prepared from either the hydrochloride (HCl) and citrate salt forms.[7,12] All product strengths are labeled based on the salt form (not the free base).[7,12] The only parenteral product available is a 50 mg/mL diphenhydramine HCl solution packaged in 1-mL vials or prefilled syringes.[2,3,7] Accordingly to the package inserts,[7] the solution is adjusted to pH 4.5 – 6.0 with either sodium hydroxide or hydrochloric acid and contains no other excipients. This 50 mg/mL parenteral solution is considered the most suitable drug source to prepare any desired IV admixtures because of its sterile product quality and simple formulation. Although the USP grade of diphenhydramine HCl powder is available commercially and can technically be used to prepare IV admixtures followed by sterilization, the resulting preparations would be considered high-risk for potential microbial contamination.[13]

Diphenhydramine is a small organic molecule with the chemical structure shown in Figure 1 as the HCl salt.[7] The main stability concerns are the potential hydrolysis of the ether group and oxidation of the ether and aromatic groups. The drug has an ionizable tertiary amine group with a $pK_a \sim 9$.[14] The HCl salt is freely soluble in water (100 – 1000 g/mL),[7,14] so there are minimal concerns for precipitation at the desired concentration range of 0.2 – 1.0 mg/mL for IV admixtures. However, drug loss due to sorption to plastic IV bag materials may become problematic for dilute drug solutions.

HPLC Method and Forced Degradation Study

With the HPLC method conditions described in the Methods section, diphenhydramine exhibited a consistent retention time of 6.4 – 6.5 minutes. A representative chromatogram is shown

in Figure 1. The calibration curves were found to be linear over the concentration range of the standards (0.16 – 0.24 mg/mL) with R^2 = 0.989 or better. The intra-day coefficient of variation (CV) was within 0.162%, and the inter-day CV over the study period was within 0.534%.

The results of the forced degradation study are summarized in Table 1. Significant drug degradation (>80%) was observed in the samples spiked with 3% H_2O_2 within 24 hours. Moderate amount of degradation (<20%) also occurred in samples exposed to extreme pH. In all samples, the degradation product peaks were well separated from the original drug peak. Therefore, this HPLC method was considered stability-indicating and suitable for the planned 14-day stability study of the IV admixtures.

14-Day Stability Study of IV Admixtures

Four diphenhydramine HCl IV admixtures were evaluated for the 14-day stability study. These admixtures included two drug concentration levels of 0.2 and 1.0 mg/mL in two commonly used IV vehicles of 0.9% sodium chloride and 5% dextrose. At the initiation of the stability study, all IV bags appeared as clear and colorless solutions with no visible particulate matters. The pH and HPLC results are presented in Table 2 and Table 3. The initial pH readings of the four admixtures ranged from 4.44-4.60, and these values were consistent to the pH range of the source drug solution (4.5-6.0)[7,12] and vehicles (4.5-7.0 for sodium chloride injection and 3.2-6.5 for dextrose injection)[15,16]. The initial drug concentrations of the four admixtures matched closely to the expected values, representing 101.8 – 103.6% of the label claims.

Over 14 days of storage under refrigeration, all stability samples remained clear, colorless, and free of visible particulates. As shown in Table 2, a small drift of 0.55 pH unit was observed for the 0.2 mg/mL admixture in 5% dextrose, and no significant changes in pH were observed for the other three admixtures. As shown in Table 3, the HPLC data suggested that all admixtures retained

98.6 – 100.8 % of their initial drug concentrations. In addition, all the HPLC chromatograms were examined carefully for potential degradation products or leachables from packaging, and no new peaks were observed in any samples.

Overall, the study results suggested that 0.2 – 1.0 mg/mL diphenhydramine hydrochloride IV admixtures are compatible in 0.9% sodium chloride injection and 5% dextrose injection in PVC bags. These IV admixtures are stable chemically and physically for up to 14 days under refrigeration.

The authors would like to point out that the diphenhydramine admixtures were batched in beakers prior to packaging into IV bags in this study. This approach was used in order to achieve the accurate and consistent starting drug concentrations in the IV bags. The actual IV admixtures for patient use should be prepared as individual doses directly in the IV bags, following all pertinent requirements in USP general chapter 797 for sterile compounding.[13] It is also advised to verify the overfill volume of IV bags to ensure that the final drug concentration in the admixture is within the 0.2 – 1.0 mg/mL range covered in this study.

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Figure 1. A representative HPLC chromatogram of 0.2 mg/ml diphenhydramine HCl standard
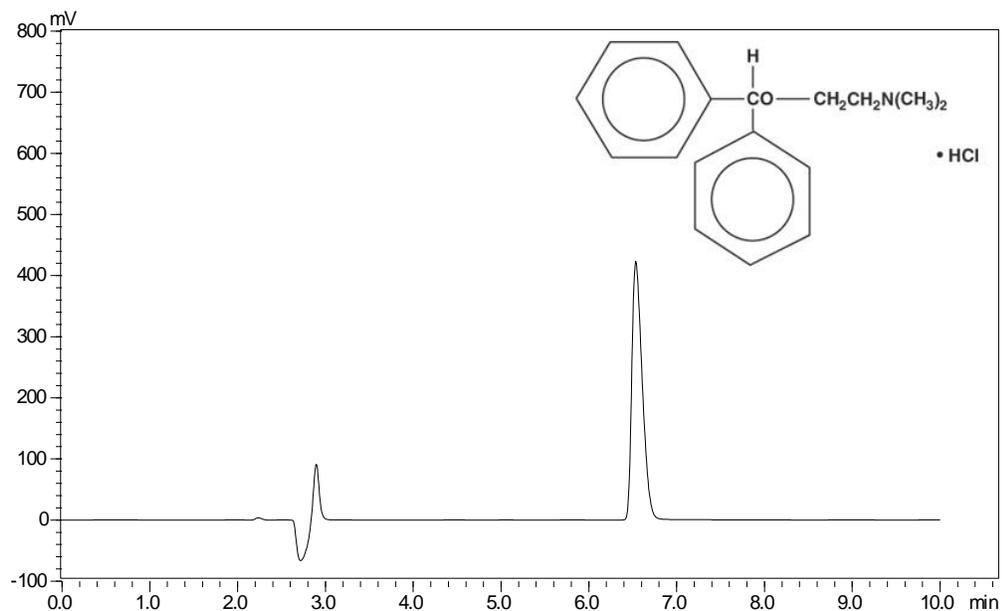solution and the chemical structure of diphenhydramine HCl

Table 1. Forced Degradation Study of Diphenhydramine HCl

Sample #	Stress Conditions	% Drug Remaining after 24 Hours
1	pH 2 and 60°C	82.3%
2	pH 12 and 60°C	94.8%
3	3% H_2O_2 and 60°C	6.6%
4	3% H_2O_2 and sun light	18.9%

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

Sample	pH				
	Day 0	Day 1	Day 3	Day 7	Day 14
0.2 mg/mL in 0.9% Sodium Chloride Injection	4.57 ± 0.05	4.57 ± 0.04	4.61 ± 0.03	4.57 ± 0.04	4.60 ± 0.01
1.0 mg/mL in 0.9% Sodium Chloride Injection	4.60 ± 0.09	4.65 ± 0.12	4.62 ± 0.05	4.61 ± 0.06	4.60 ± 0.05
0.2 mg/mL in 5% Dextrose Injection	4.44 ± 0.02	4.46 ± 0.09	4.61 ± 0.11	4.84 ± 0.12	4.99 ± 0.06
1.0 mg/mL in 5% Dextrose Injection	4.60 ± 0.04	4.65 ± 0.04	4.87 ± 0.06	4.66 ± 0.04	4.69 ± 0.04

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

Sample	Initial Drug Concentration (mg/mL)	% Initial Concentration Remaining			
		Day 1	Day 3	Day 7	Day 14
0.2 mg/mL in 0.9% Sodium Chloride Injection	0.2052 ± 0.0004	100.6 ± 0.4	100.0 ± 0.4	100.8 ± 0.5	100.6 ± 0.4
1.0 mg/mL in 0.9% Sodium Chloride Injection	1.035 ± 0.007	100.5 ± 0.6	100.2 ± 0.6	100.5 ± 0.2	99.5 ± 1.5
0.2 mg/mL in 5% Dextrose Injection	0.2037 ± 0.0001	100.6 ± 0.3	100.4 ± 0.2	101.1 ± 0.3	100.8 ± 0.3
1.0 mg/mL in 5% Dextrose Injection	1.036 ± 0.006	98.6 ± 1.8	100.5 ± 0.2	99.5 ± 0.2	99.3 ± 0.6