Chemical Stability of Dimenhydrinate in Minibags and Polypropylene Syringes

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ABSTRACT

Objective: To determine the physical and chemical stability of dimenhydrinate diluted with 0.9% sodium chloride (normal saline [NS]) or 5% dextrose in water (D5W) and stored at either 22°C or 4°C in minibags or polypropylene syringes.

Methods: Solutions of dimenhydrinate (25, 50, and 100 mg/50 mL) were prepared in minibags containing NS or D5W and stored at either 22°C with exposure to light or 4°C with protection from light. Additional samples of dimenhydrinate (25, 50, and 100 mg/10 mL) were prepared in NS and packaged in polypropylene syringes, which were sealed with friction caps and stored at either 22°C with exposure to light or 4°C with protection from light. Solutions stored in minibags were observed and sampled over a 191-day period, and solutions stored in syringes were observed and sampled over a 60-day period. All samples were analyzed in duplicate with a stability-indicating high-pressure liquid chromatography assay.

Results: Throughout the study, all samples remained colourless and free of precipitate. The dimenhydrinate solutions prepared with NS or D5W (25, 50, or 100 mg/50 mL), packaged in minibags, and stored at 22°C with exposure to light were stable for only 7 days. The solutions prepared with NS or D5W (25, 50, or 100 mg/50 mL), packaged in minibags, and stored at 4°C with protection from light were stable for 91 days. The solutions diluted with NS (25, 50, or 100 mg/10 mL) and stored in polypropylene syringes were stable for at least 60 days when stored at either 22°C with exposure to light or 4°C with protection from light.

Conclusions: Institutions should assign an expiry date for dimenhydrinate on the basis of the chemical stability of the drug and the sterile integrity of the finished product under the institution's storage policies.

Key words: dimenhydrinate, stability, dextrose, normal saline, high-performance liquid chromatography

Can J Hosp Pharm 2002;55:307-12

RÉSUMÉ

Objectif : Déterminer la stabilité physique et chimique de la dimenhydrinate, diluée dans un soluté physiologique (NS) ou une solution aqueuse de dextrose à 5 % (D5W), et entreposée à 22 °C ou 4 °C dans des minisacs ou des seringues en polypropylène.

Méthodes : Les solutions de dimenhydrinate (25, 50 et 100 mg/50 mL) ont été préparées dans des minisacs contenant le NS ou la D5W, puis entreposées à 22 °C, non protégées de la lumière, ou à 4 °C, à l'abri de la lumière. Des échantillons de dimenhydrinate (25, 50 et 100 mg/10 mL) ont été préparés dans du NS et aspirées dans des seringues de polypropylène. Les seringues ont ensuite été sellées avec des capuchons rugueux et entreposées à 22 °C, non protégées de la lumière, ou à 4 °C, à l'abri de la lumière. Les solutions contenues dans des minisacs ont été échantillonnées et observées sur une période de 191 jours et les solutions contenues dans des seringues ont été échantillonnées et observées sur une période de 60 jours. Tous les échantillons ont été analysés en double à l'aide d'une épreuve de stabilité par chromatographie liquide à haute pression.

Résultats : Pendant toute la durée de l'étude, tous les échantillons sont demeurés incolores et sans précipité. Les solutions de dimenhydrinate diluées dans le NS ou la D5W (25, 50 ou 100 mg/50 mL), conditionnées dans des minisacs, puis entreposées à 22 °C, non protégées de la lumière, étaient stables pendant seulement sept jours. Les solutions diluées dans le NS ou la D5W (25, 50 ou 100 mg/50 mL), conditionnées dans des minisacs et entreposées à 4 °C, à l'abri de la lumière, étaient stables pendant 91 jours. Les solutions de dimenhydrinate diluées dans le NS (25, 50 ou 100 mg/10 mL) et conditionnées dans des seringues en polypropylène étaient stables pendant au moins 60 jours, lorsqu'elles étaient entreposées à 22 °C, non protégées de la lumière, ou à 4 °C, à l'abri de la lumière.

Conclusions : Les établissements de santé devraient déterminer une date de péremption pour le dimenhydrinate, en se fondant sur la stabilité chimique du médicament et sur l'intégrité du produit fini, conformément aux politiques d'entreposage de l'établissement.

Mots clés : dimenhydrinate, stabilité, dextrose, soluté physiologique, chromatographie liquide à haute pression

INTRODUCTION

Dimenhydrinate is used in the management of nausea and vomiting in the postoperative patient-controlled analgesia program at the author's institution. In addition, dimenhydrinate is used by the oncology service as an anti-emetic medication in the chemotherapy protocol. For the surgical floors, the drug is prepared in minibags of 0.9% sodium chloride (normal saline [NS]) or 5% dextrose in water (D5W) at concentrations of 25, 50, and 100 mg/50 mL. For oncology patients, prefilled dimenhydrinate syringes (25, 50, and 100 mg/10 mL) are manufactured extemporaneously. A 10-day expiry date is used for both minibag and syringe preparations. This short expiry date prevents the economies of scale that would be gained from batch production.

Dimenhydrinate is the 8-chlorotheophylline salt of diphenhydramine. Cleavage of the ether linkage in diphenhydramine typically occurs under acidic conditions.[1] The ether linkage is more stable under alkaline conditions.

A review of the literature yielded no studies of chemical stability; however, one study[2] reported that the drug was physically stable for 10 days. The present study was undertaken to determine the chemical stability of various concentrations of dimenhydrinate prepared in minibags or polypropylene syringes and stored at either 22°C with exposure to light or at 4°C with protection from light.

METHODS

Assay Validation

To determine the stability-indicating nature of the high-performance liquid chromatography (HPLC) assay, dimenhydrinate samples were forcibly degraded and then assayed for any interfering peaks. Aliquots of dimenhydrinate (125 mg each; Sabex Inc, Boucherville, Quebec, lot 459702D) were added to three 50-mL volumetric flasks. The pH of one solution was adjusted to approximately 1 with concentrated hydrochloric acid (BDH Inc, Toronto, Ontario, lot 109521/11031) to induce acid hydrolysis. The pH of the second solution was adjusted to approximately 12 with 1.0N sodium hydroxide (BDH Inc, lot 9304066) in an attempt to induce alkaline-catalyzed hydrolysis. The third solution was exposed to 807 lx of fluorescent lighting for 165 days. The light intensity was measured with a digital light meter (model 401025, Extech Instruments, Hauppauge, New York). All solutions were analyzed by HPLC at time zero and at 4 subsequent times to determine if peaks for the degradation products interfered with the dimenhydrinate peak. The stock acid and alkaline solutions were heated to 80°C on a Thermix stirring hot plate (model 210T, Fisher Scientific, Nepean, Ontario) to speed degradation after the initial samples had been obtained.

To determine the purity of the dimenhydrinate peaks, multichannel (230 and 254 nm) and ultraviolet (UV) spectral analysis (200–350 nm) was used. The UV spectra of dimenhydrinate USP (Medisca Pharmaceutique Inc, Montreal, Quebec, lot 062297, expiry April 2002) were compared with the UV spectra of the dimenhydrinate peaks from the degraded samples, and correlation coefficients were determined with EZ Chrom software (version 4.01, Shimadzu Corp, Columbia, Maryland). The UV spectra of dimenhydrinate USP were also compared with the UV spectra of the peaks for the degradation products, and correlation coefficients were determined.

The linearity of a concentration versus area response curve, over the range 0.128 to 1.025 mg/mL, was assessed by least-squares linear regression. Accuracy, expressed as percent recovery, was assessed on 4 separate days by analyzing a sample of dimenhydrinate USP solution prepared from a known weight of the drug. Intra-day variation was determined by analyzing 5 replicate samples of dimenhydrinate USP 0.5 mg/mL at time zero and at 16 and 24 h. Mean area ratios from each set of replicate samples were used to determine the coefficient of variation. Comparison of slopes and r^2 values from standard curves and samples of dimenhydrinate USP 0.5 mg/mL on 4 different days were used to assess inter-day variation. These values were analyzed statistically for differences.

To determine the sensitivity of the assay, progressively more dilute solutions of dimenhydrinate were prepared and analyzed, and linear regression was used to determine the smallest concentration capable of producing a detectable peak on the chromatograph while maintaining linearity.

HPLC Assay

The chromatographic system had an isocratic solvent delivery pump (model LC-10AS, Shimadzu Corp, Kyoto, Japan), and signals were monitored with a photodiode array detector (model SPD-M6A, Shimadzu Corp, Kyoto, Japan) set at 230 nm. The mobile phase was prepared by mixing 35 volumes of HPLC-grade acetonitrile (BDH Inc, lot 34242) with 65 volumes of an aqueous solution containing 25 mmol/L potassium dihydrogen orthophosphate (BDH Inc, lot 82594-1628)

and 2 mL/L of triethylamine (A&C American Chemical Ltd, Montreal, Quebec, lot 4288/4090/931014). The pH of the final solution was adjusted to 2.2 with concentrated orthophosphoric acid (BDH Inc, lot 91892). The mobile phase was pumped through a 4.0 mm x 25 cm, 5-µm C_{18} column (Luna ODS [octadecylsilane] 18[2], Phenomenex, Torrance, California) at a rate of 1.5 mL/min. An auto-injector (model SIL10A_{XL}, Shimadzu Corp, Kyoto, Japan) was used to inject 25-µL samples. Methyl hydroxybenzoate (1.0 mg/mL; BDH Inc, lot 101824/12313) was used as the internal standard.

Stability Study

Dimenhydrinate (50 mg/mL; Sabex Inc, lots 18909A and 449709A) was further diluted with preservative-free NS (Abbott Laboratories, Montreal, Quebec, lots 20-060-NA and 21-145-NA) or D5W (Abbott Laboratories, lots 20-108-NA and 32-310-NA) to either 25, 50, or 100 mg/50 mL and stored in mini-bags at either 22°C with exposure to light (807 lx) or 4°C with protection from light for 191 days.

Three 5-mL samples were collected from each of the minibags immediately after preparation and on days 7, 14, 30, 60, 91, and 191. The samples were visually inspected for colour change and presence of particulate matter and then frozen at –72°C in a scientific freezer (model 8433, Forma Scientific Inc, Marietta, Ohio).

Dimenhydrinate (50 mg/mL; Sabex Inc, lots 18909A and 449709A) was further diluted with preservative-free NS (Abbott Laboratories, lots 20-060-NA and 21-145-NA) to either 25, 50, or 100 mg/10 mL and packaged in polypropylene syringes (Becton-Dickinson and Company, Franklin Lakes, New Jersey), which were sealed with friction caps (Sherwood Medical, St Louis, Missouri). The syringes were stored at either 22°C with exposure to light (807 lx) or 4°C with protection from light.

Samples (5 mL) were collected in triplicate from the syringes immediately after preparation and on days 7, 14, 21, 28, and 60. The samples were visually inspected for colour change and presence of particulate matter and then frozen at –72°C in the scientific freezer.

On the day of the analysis, all samples were thawed, an internal standard was added to each, and all were diluted with mobile phase. Each sample was then analyzed in duplicate. A calibrated pH meter with a silver and silver chloride electrode (Accumet 25, Fisher Scientific) was used to monitor each sample for any change in pH. Solutions that retained 90% or greater of initial concentration were considered stable.

RESULTS

Assay Validation

Acid-catalyzed hydrolysis produced the most significant deterioration of dimenhydrinate (Figure 1, panel II); however, separation of the degradation products and dimenhydrinate peaks was adequate. Base-catalyzed hydrolysis (Figure 1, panel III) produced limited degradation even after extended heating. Dimenhydrinate exposed to fluorescent light for 165 days (Figure 1, panel IV) showed no signs of chemical degradation. Multichannel and UV spectral analysis confirmed the purity of all dimenhydrinate peaks. Comparison of the dimenhydrinate peaks to reference material indicated good correlation (>0.99). UV spectral comparison of the dimenhydrinate peaks and the degradation product peaks showed limited correlation (<0.80). Both spectral analysis and retention times indicated that the degradation products were distinct from dimenhydrinate.

The concentration versus area ratio curve was linear over the range of 0.128 to 1.025 mg/mL (r^2 = 0.9996). An average recovery of 101.3% was achieved with a coefficient of variation of 1.67%. When the area ratios of samples were compared, coefficients of variation for intra-day and inter-day analysis were 0.12% and 2.45% respectively. The coefficient of variation between slopes and the r^2 value for 4 standard curves were 2.02% and 0.04% respectively. The sensitivity of the assay was 15.6 µg/mL, which corresponds to 390 ng of dimenhydrinate injected onto the column.

Stability Study

The results of stability testing for the various solutions of dimenhydrinate prepared in minibags and syringes are summarized in Tables 1 and 2 respectively. Dimenhydrinate solutions diluted to 25, 50, or 100 mg/50 mL with NS or D5W, packaged in minibags, and stored at 22°C with exposure to light were stable for only 7 days. All minibag solutions stored at 4°C with protection from light were stable for 91 days. Minor degradation peaks were observed in these solutions (Figure 1, panel I), but the major acid-generated degradation peak (peak A) was not observed. All solutions of dimenhydrinate packaged in polypropylene syringes were stable for at least 60 days. There were no significant differences in stability between solutions stored at 22°C with exposure to light and those stored at 4°C with protection from light. There was no colour development or precipitate formation in any of the

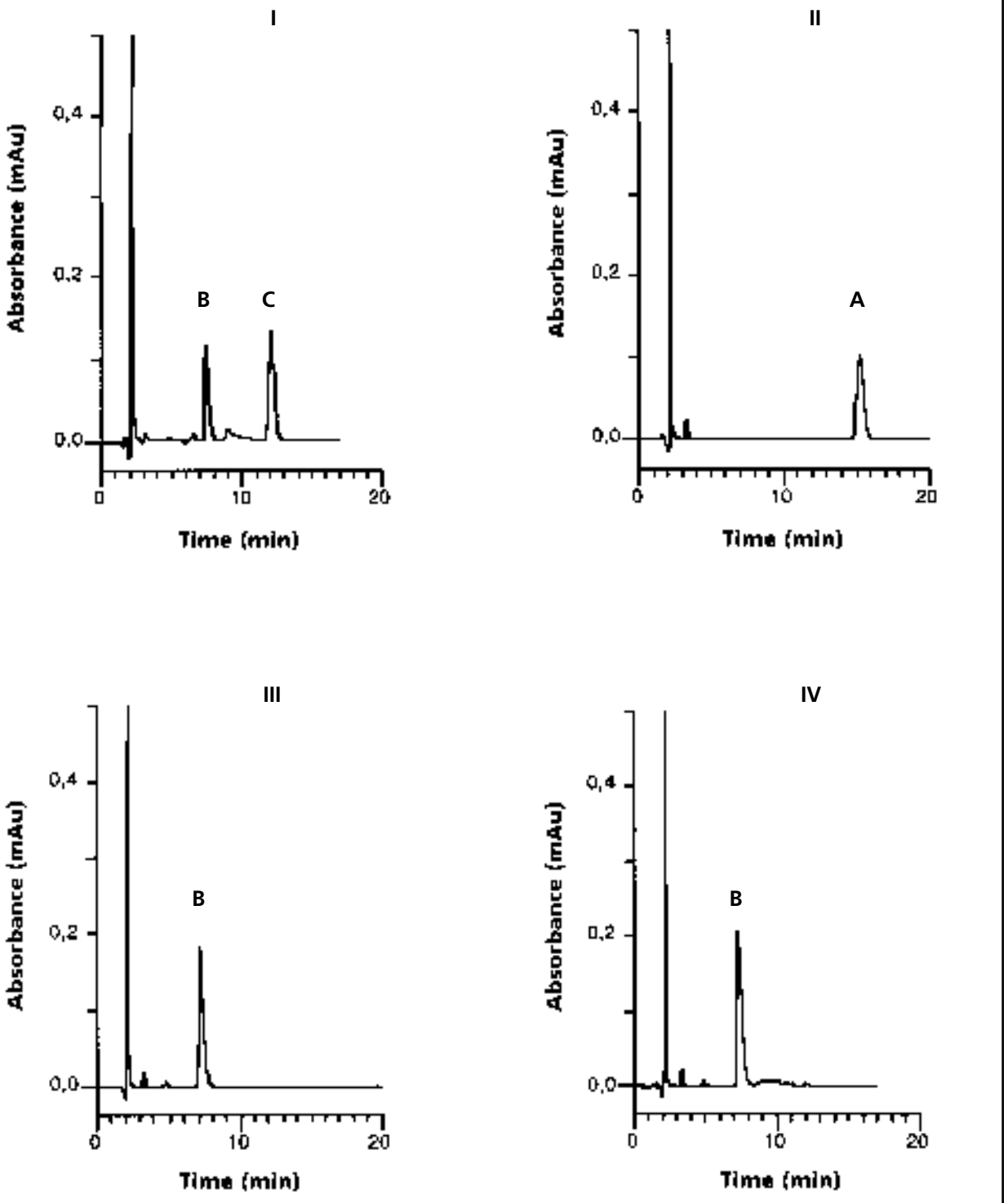

Figure 1. Sample chromatographs of dimenhydrinate. I. Dimenhydrinate 0.5 mg/mL (25 mg/50 mL) in D5W stored at 22°C for 91 days. II. Dimenhydrinate after exposure to acid. III. Dimenhydrinate after exposure to alkali. IV. Dimenhydrinate after exposure to fluorescent light. Peak A is a dimenhydrinate degradation product, peak B is dimenhydrinate, and peak C is methyl hydroxybenzoate (the internal standard). mAu = milli-absorbance units.

Table 1. Observed Concentration of Dimenhydrinate in NS and D5W after Storage in Minibags

Initial Concentration (mg/50 mL)	Diluent	Storage Temp. (°C)*	Sample Day; % of Initial Concentration Remaining†					
			Day 7	Day 14	Day 30	Day 60	Day 91	Day 191
Nominal 25								
28.3 ± 1.1	NS	22	97.6 ± 2.4	87.8 ± 1.2	87.9 ± 1.4	84.6 ± 0.6	87.6 ± 1.6	NA
27.0 ± 0.7	NS	4	96.4 ± 0.8	94.2 ± 1.1	91.8 ± 1.9	91.6 ± 0.9	90.9 ± 0.9	94.1 ± 2.4
28.8 ± 1.0	D5W	22	92.6 ± 0.4	88.9 ± 0.1	84.4 ± 2.6	87.2 ± 1.7	97.5 ± 2.7	NA
30.6 ± 0.2	D5W	4	100.4 ± 0.6	95.8 ± 0.6	95.8 ± 1.2	94.6 ± 0.7	93.3 ± 1.4	92.9 ± 1.0
Nominal 50								
63.7 ± 0.4	NS	22	92.5 ± 0.5	87.5 ± 0.5	79.2 ± 0.5	77.9 ± 0.8	75.2 ± 0.6	NA
61.6 ± 1.4	NS	4	100.0 ± 0.8	96.4 ± 0.4	96.1 ± 0.4	93.4 ± 1.3	90.2 ± 0.8	89.9 ± 1.5
60.0 ± 2.4	D5W	22	93.0 ± 2.0	83.2 ± 0.7	79.8 ± 0.7	74.0 ± 0.5	71.1 ± 1.8	NA
65.7 ± 1.5	D5W	4	95.5 ± 0.8	NA	94.2 ± 0.2	91.6 ± 0.9	90.7 ± 0.8	91.6 ± 0.4
Nominal 100								
129.8 ± 1.4	NS	22	91.5 ± 1.5	86.3 ± 1.2	81.4 ± 1.2	76.5 ± 1.7	67.0 ± 0.8	NA
120.3 ± 0.5	NS	4	100.7 ± 1.0	97.7 ± 0.7	98.4 ± 0.2	93.9 ± 0.4	92.6 ± 0.9	96.7 ± 0.7
124.1 ± 1.3	D5W	22	91.5 ± 0.6	86.0 ± 0.7	80.4 ± 0.4	72.5 ± 0.6	66.5 ± 1.5	NA
120.0 ± 0.2	D5W	4	100.7 ± 0.2	99.0 ± 0.7	97.5 ± 0.3	94.5 ± 1.3	96.2 ± 2.2	101.8 ± 2.5

NS = normal saline (0.9% sodium chloride in water), D5W = 5% dextrose in water, NA = not assayed.
*Samples stored at 22°C were constantly exposed to 807 lx of fluorescent light. Those stored at 4°C were protected from light.
†Mean ± standard deviation of 6 determinations.

Table 2. Observed Concentration of Dimenhydrinate in NS after Storage in Polypropylene Syringes with Friction Caps

Initial Conc'n (mg/10 mL)	Storage Temp. (°C)*	Sample Day; % of Initial Concentration Remaining†				
		Day 7	Day 14	Day 21	Day 28	Day 60
Nominal 25						
24 ± 1	22	97.4 ± 1.0	97.3 ± 0.9	94.8 ± 1.4	95.6 ± 0.5	92.6 ± 0.8
24 ± 1	4	99.8 ± 1.9	98.4 ± 0.6	99.2 ± 1.6	98.7 ± 1.7	98.1 ± 1.8
Nominal 50						
49 ± 1	22	99.7 ± 1.2	97.7 ± 1.1	98.1 ± 1.1	96.1 ± 0.3	95.4 ± 0.4
43 ± 1	4	99.9 ± 1.7	97.9 ± 1.5	98.8 ± 1.1	97.8 ± 0.8	96.9 ± 0.6
Nominal 100						
100 ± 1	22	98.1 ± 0.6	98.1 ± 1.2	96.8 ± 0.7	97.5 ± 0.3	95.7 ± 0.5
99 ± 1	4	100.6 ± 0.4	100.7 ± 0.4	100.7 ± 0.9	100.5 ± 1.0	98.0 ± 0.5

NS = normal saline (0.9% sodium chloride in water).
*Samples stored at 22°C were constantly exposed to 807 lx of fluorescent light. Those stored at 4°C were protected from light.
†Mean ± standard deviation of 6 determinations.

dimenhydrinate samples over the course of the study, and the pH of the dimenhydrinate solutions did not change significantly.

DISCUSSION

Some minor degradation peaks appeared in some of the day zero samples after storage at –72°C. These impurities may have been present in the commercial product before the samples were prepared. The dimenhydrinate peaks remained pure after frozen storage for up to 191 days, as confirmed by multichannel and UV spectral analysis of day zero samples. The number of minor peaks increased over the course of the study (Figure 1, panel I), but none of the major degradation peaks appeared.

There was adequate separation between the peaks for dimenhydrinate, the internal standard, and the degradation products in chromatographs produced from the degradation samples (Figure 1, panels II, III, and IV). In the acid-degraded sample, the dimenhydrinate peak disappeared completely, with no emergence of interfering peaks. The alkali-degraded sample showed limited degradation of dimenhydrinate even after heating for 139 h. Exposure of dimenhydrinate to fluorescent lighting for 165 days produced no interfering peaks. The purity of all dimenhydrinate peaks was confirmed by multichannel and UV spectral

analysis. Comparison of dimenhydrinate peaks with reference material indicated good correlation whereas comparison with the degradation peaks showed limited correlation.

For solutions stored at 22°C, the ports of all minibags showed signs of physical deterioration at day 191, so samples were not collected at this time. Increases in the concentration of drug at 91 days (relative to the concentration at previous sampling times) for some of the samples stored at 22°C (see Table 1) may have resulted from evaporation of solution from the bag (i.e., the solution assayed at day 91 was more concentrated than solutions assayed earlier). Institutions should review or develop policies on storage of minibags without overwrap, at room temperature and 4°C, based on the rate of evaporation of the solution from the container and physical breakdown of the minibags.

In conclusion, a stability-indicating HPLC assay was developed for analysis of dimenhydrinate. Solutions of dimenhydrinate diluted with NS or D5W to 25, 50, or 100 mg/50 mL and packaged in minibags were chemically stable for 7 days at 22°C with exposure to light. Similar minibag solutions stored at 4°C with protection from light were stable for 91 days. Solutions of dimenhydrinate diluted with NS to 25, 50, or 100 mg/10 mL and packaged in polypropylene syringes sealed with friction caps were chemically stable for at least 60 days when stored at either 22°C with exposure to light or 4°C with protection from light. Institutions should assign an expiry date for dimenhydrinate that is based on the chemical stability of the drug, that assures the sterile integrity of the finished product, and that conforms with the institution's policy for minibag storage under specific storage conditions.

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Acknowledgements

This project was funded internally by the Department of Pharmaceutical Services, The Ottawa Hospital (Civic Campus), Ottawa, Ontario.

The project was awarded the 1998/99 CSHP Baxter Award.