Stability and Compatibility of Granisetron Alone and in Combination with Dexamethasone in 0.9% Sodium Chloride and 5% Dextrose in Water Solutions

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ABSTRACT

Background: Solutions of granisetron, diluted in 0.9% sodium chloride (normal saline [NS]), 5% dextrose in water (D5W), and other common IV solutions, are reportedly stable for at least 3 days when stored at room temperature and 7 days when stored at 4°C. Granisetron is often administered in combination with dexamethasone, and previous reports have demonstrated stability of certain concentrations up to 14 days.

Objective: To evaluate the stability and compatibility of granisetron alone and in combination with dexamethasone at 4°C and at room temperature (23°C) over 35 days.

Methods: Three different stability and compatibility studies were completed. In addition to visual inspection and pH determination, the concentrations of granisetron and dexamethasone in the mixtures were determined by a stability-indicating liquid chromatographic method. In the 24-h room temperature compatibility study, granisetron solutions (0.008 to 0.053 mg/mL) were combined with dexamethasone solutions (0.050 to 0.350 mg/mL) and stored in glass test tubes. Drug concentrations were determined at 0, 2, 6, and 24 h. In the 35-day stability study, granisetron (1 or 3 mg) was mixed with 50 mL of either NS or D5W and stored in polyvinyl chloride (PVC) minibags at 4°C or 23°C. Granisetron concentrations were determined on days 0, 1, 3, 7, 10, 14, 21, 28, and 35. During the 35-day compatibility study, granisetron (1 or 3 mg) and dexamethasone (4 or 10 mg) were mixed with 50 mL of either NS or D5W and stored in PVC minibags at either 4°C or 23°C. Drug concentrations were determined on days 0, 3, 7, 10, 14, 21, 28, and 35.

Results: Granisetron retained greater than 96% and dexamethasone more than 98% of initial concentrations in both NS and D5W when stored in glass test tubes at 23°C for 24 h. When mixed with NS or D5W and stored for 35 days at 4°C or 23°C, granisetron did not degrade to a measurable extent. The granisetron concentration remaining at 35 days was at least 99.8% of the initial concentration (by linear regression). During the 35-day compatibility study, neither granisetron (1 or 3 mg/50 mL) nor dexamethasone (4 or 10 mg/50 mL)

RÉSUMÉ

Historique : Des données montrent que des solutions de granisétron dilué dans du chlorure de sodium à 0,9% (solution salée [NS]), du dextrose à 5 % dans l'eau (D5W) ou d'autres solutions I.V. courantes, seraient stables pendant au moins trois jours lorsqu'elles sont entreposées à la température ambiante et pendant sept jours lorsqu'elles le sont à des températures de 4 °C. En outre, le granisétron est souvent administré en association avec du dexaméthasone; or des données ont aussi montré que le produit, à certaines concentrations, pouvait être stable pendant une période pouvant atteindre 14 jours.

Objectif : Évaluer la stabilité et la compatibilité du granisétron seul et en association avec du dexaméthasone, entreposés à 4 °C et à la température ambiante (23 °C) pendant une période de 35 jours.

Méthodes : Trois études différentes de stabilité et de compatibilité ont été menées. Outre l'inspection visuelle et la détermination du pH, les concentrations de granisétron et de dexaméthasone dans les mélanges ont été déterminés au moyen d'une épreuve de stabilité par chromatographie liquide à haute pression. Dans l'étude de compatibilité de 24 heures à la température ambiante, les solutions de granisétron (de 0,008 à 0,053 mg/mL) ont été mélangées à des solutions de dexaméthasone (de 0,050 à 0,350 mg/mL) et entreposées dans des éprouvettes de verre. La concentration des médicaments a été déterminée à 0, 2, 6 et 24 heures. Dans l'étude de stabilité de 35 jours, le granisétron (1 ou 3 mg) a été mélangé à 50 mL de NS ou de D5W, et les solutions entreposées dans des minisacs de chlorure de polyvinyle (PVC) à 4 °C ou à 23 °C. Les concentrations de granisétron ont été déterminées aux jours 0, 1, 3, 7, 10, 14, 21, 28 et 35. Durant l'étude de compatibilité de 35 jours, le granisétron (1 ou 3 mg) et le dexaméthasone (4 ou 10 mg) ont été mélangés avec 50 mL de NS ou de D5W et les solutions entreposées dans des minisacs de PVC à 4 °C ou à 23 °C. Les concentrations des médicaments ont été déterminées aux jours 0, 3, 7, 10, 14, 21, 28 et 35.

Résultats : Le granisétron a conservé plus de 96 % de sa concentration initiale, comparativement au dexaméthasone qui en a conservé plus de 98 %, tous deux dans des solutions de NS ou

degraded to a measurable extent when stored in PVC minibags at either 4°C or 23°C. On day 35, the lower limit of the 95% confidence interval for granisetron concentration was at least 97.8% and for dexamethasone concentration, at least 91.0%.

Conclusions: All concentrations of granisetron and dexamethasone studied were chemically stable and physically compatible for 35 days when stored at 4°C or 23°C. Therefore, a 35-day expiration date is recommended for combinations of granisetron (1 or 3 mg/50 mL) and dexamethasone (4 or 10 mg/50 mL) in NS or D5W with storage at either 4°C or 23°C. However, expiry dates at any specific institution should take into consideration the bacterial contamination rate within the institution's IV additive program.

Key words: stability, compatibility, granisetron, dexamethasone

de D5W et entreposés dans des éprouvettes de verre à 23 °C pendant 24 heures. Lorsque mélangé à des solutions de NS ou de D5W et entreposé pendant 35 jours à 4 °C ou à 23 °C, le granisétron ne s'est pas dégradé de façon mesurable. Le granisétron a conservé au 35e jour plus de 99,8 % de sa concentration initiale (par régression linéaire). Dans l'étude de compatibilité de 35 jours, ni le granisétron (1 ou 3 mg/50 mL) ni le dexaméthasone (4 ou 10 mg/50 mL) ne se sont dégradés de façon mesurable lorsqu'entreposés dans des minisacs de PVC à 4 °C ou à 23 °C. Au 35e jour, la limite inférieure de l'intervalle de confiance à 95 % pour la concentration de granisétron était au moins 97,8 % et d'au moins 91,0 % pour le dexaméthasone.

Conclusions: Le granisétron et le dexaméthasone, à toutes les concentrations étudiées, ont montré une stabilité chimique et une compatibilité physique pendant 35 jours lorsqu'entreposés à 4 °C ou à 23 °C. Par conséquent, on recommande de ne pas conserver pendant plus de 35 jours les mélanges de granisétron (1 ou 3 mg/50 mL) et de dexaméthasone (4 ou 10 mg/50 mL) dans du NS ou du D5W, qui sont entreposés à 4 °C ou à 23 °C. Toutefois, les dates d'expiration de ces mélanges devraient tenir compte du taux de contamination bactérienne relatif au programme d'additifs aux solutés intraveineux de chaque établissement.

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Mots clés : stabilité, compatibilité, granisétron, dexaméthasone

INTRODUCTION

The product monograph for granisetron indicates that solutions containing 1 mg of granisetron in 50 mL of 0.9% sodium chloride (normal saline [NS]), 5% dextrose in water (D5W), or other common IV solutions are stable for at least 24 h when stored at room temperature.[1] However, it has been previously reported that a concentration of 0.056 mg/mL is stable for 3 days at room temperature and 7 days at 4°C.[2] Granisetron was also stable after dilution with NS or D5W in syringes stored at 24°C or 5°C for 14 days.[3] Because granisetron is often administered in combination with dexamethasone, knowledge of the compatibility and stability of this drug combination is important. The stability and compatibility of this combination have been reported previously.[2,4] Pinguet and others[2] demonstrated the compatibility and stability of granisetron 0.05 mg/mL and dexamethasone 0.074 or 0.345 mg/mL in polyvinyl chloride (PVC) bags. Chin and others[4] demonstrated the compatibility and stability of granisetron 0.01 or 0.04 mg/mL and dexamethasone 0.08 or 0.60 mg/mL in PVC bags for up to 14 days at 23°C to 25°C.

The objective of this study was to evaluate the stability of granisetron in NS and D5W and the compatibility of granisetron in combination with dexamethasone in the same diluents over a longer period of time, 35 days, than had previously been reported.

METHODS

Assay Validation

Accelerated Degradation

Degradation products of granisetron were generated with acid and heat. A 1-mL aliquot of granisetron hydrochloride (Kytril 1 mg/mL; SmithKline Beecham, Oakville, Ontario, lot 179K49, expiry August 2002) was mixed with 24 mL of distilled water to prepare a 0.04 mg/mL solution. The solution was acidified to a pH of 0.8 with concentrated hydrochloric acid and then incubated at 79°C for 35 h. Samples were drawn before incubation and at 21 other times during the 35-h period.

Degradation products of dexamethasone were also generated with acid and heat. A 1-mL aliquot of dexamethasone (10 mg/mL; Sabex, Boucherville, Quebec, lot 102307, expiry October 2000) was diluted with distilled water and acidified with hydrochloric acid to achieve a pH of 1.8 and a final volume of 25 mL. The solution was incubated at 90°C for 11 h. Samples were drawn before incubation and at 17 other times during the 11-h period.

Chromatograms for the samples of granisetron and dexamethasone were inspected for the appearance of additional peaks, and the peak for the compound of interest was compared between samples for changes in concentration, retention time, and peak shape.

A modified version of the validated, stability-indicating[5,6] liquid chromatography method previously

reported for dexamethasone,[7-10] was used to evaluate the chromatographic separation of granisetron and its degradation products from dexamethasone and its degradation products. First, the degraded granisetron sample taken at 35 h and the degraded dexamethasone sample taken at 11 h, as described above, were mixed together. Chromatograms of the mixture were inspected for the appearance of additional peaks, and the granisetron and dexamethasone peaks were compared between mixed and individual samples for changes in concentration, retention time, and peak shape. The ultraviolet spectral purity (200 to 365 nm, 6-nm bandwidth, deuterium lamp [UV6000, Thermo Separation Products, Fremont, California]) of the leading edge, middle, and tail of both the granisetron and the dexamethasone peaks in chromatograms of the individual degraded samples, the mixture of degraded samples, and the samples taken at time zero were compared.

Accuracy and Reproducibility of Assay

Following this first phase of evaluation and validation, the accuracy and reproducibility of standard curves for the 2 drugs were tested over 5 days, and system suitability criteria (theoretical plates, tailing, and retention time) were developed to ensure consistent chromatographic performance on each study day. Inter- and intra-day reproducibility were assessed by means of the coefficient of variation of the peak area for samples determined in duplicate, and accuracy was determined on the basis of deviations from the known concentration for both standards and quality control samples.

Preparation of Standard Curves

A minimum of 6 standards and 3 quality control samples were prepared for each of the 2 drugs, granisetron and dexamethasone. Granisetron hydrochloride (Kytril 1 mg/mL) was dissolved in 10 mL of water to make a 0.100 mg/mL stock solution. From this stock, additional standards of 0.075, 0.050, 0.025, 0.019, and 0.010 mg/mL were prepared on each study day and used to construct a standard curve. Quality control samples with concentrations of 0.088, 0.038, and 0.013 mg/mL were also prepared each day. Dexamethasone disodium phosphate 100 mg (Sigma Chemical, St. Louis, Missouri) was dissolved in 10 mL of water to make a 10 mg/mL stock solution. From this stock, standards of 0.600, 0.400, 0.200, 0.150, 0.100, and 0.040 mg/mL were prepared on each study day. These standards, along with a blank, were used to construct a standard curve. Quality control samples with concentrations of 0.500, 0.300, and 0.050 mg/mL were also prepared each day. A 50-µL aliquot of each standard and each quality control sample for each drug was chromatographed in duplicate. The concentration of granisetron and dexamethasone in each stability study sample or quality control sample was determined by interpolation from the standard curve by least-squares linear regression. The concentrations were recorded to the nearest 0.001 mg/mL.

Chromatographic System and Separation

After the formation of degradation products, the chromatographic separation method was evaluated to ensure the separation of granisetron and dexamethasone from their degradation products during simultaneous analysis. The gradient for the chromatographic separation was similar to that used in a compatibility study of dexamethasone and diphenhydramine,[7] but the pH was reduced to improve the shape of the granisetron peak. The initial mobile phase consisted of 24% acetonitrile and 76% 0.05 mol/L phosphoric acid. The ratio of acetonitrile to phosphate buffer was held constant for the first 5 min; the proportion of acetonitrile was then increased to 50% in a linear fashion between the 1st and 15th minute after injection. The mobile phase was pumped at 2.0 mL/min through an Ultrasphere 25 cm x 4.2 mm C_{18}, 5-µm column (distributed in Canada by Beckman, Mississauga, Ontario) with a P4000 gradient pump (Thermo Separation Products, Fremont, California). Granisetron and dexamethasone were detected at 220 nm with a UV 3000 variable-wavelength absorbance detector (Thermo Separation Products, San Jose, California) and chromatograms were recorded directly on computer using ChromQuest software (version 2.1, ThermoQuest Inc. San Jose, California).

Stability and Compatibility Studies

Short-Term Study of Granisetron and Dexamethasone

Two solutions of granisetron, one diluted in NS and the other in D5W, at a concentration of 0.060 mg/mL (from Kytril 1 mg/mL; nominally equivalent to 3 mg/50 mL of solution), were prepared. Two solutions of dexamethasone disodium phosphate, also diluted in NS or D5W, at a concentration of 0.400 mg/mL (10 mg/mL; Sabex, lot 102307, expiry October 2000; nominally equivalent to 20 mg/50 mL of saline), were also prepared. Aliquots of the individual solutions were set

aside, and then the NS solutions were mixed together, and the D5W solutions were also combined, in ratios of granisetron to dexamethasone ranging from 8:1 to 1:8; the mixtures were stored in glass test tubes. In total, 7 solutions containing both granisetron and dexamethasone were prepared for each diluent (NS and D5W). The nominal concentration of the mixtures evaluated appear in Table 1 (for NS) and Table 2 (for D5W). After mixing, each solution was observed for precipitate, colour change, or evolution of gas, and the dexamethasone and granisetron concentrations were determined.

A single container of each granisetron–dexamethasone mixture was prepared and stored at room temperature for 24 h in a glass test tube. Samples were drawn from each study mixture immediately after mixing and at 2, 6, and 24 h. At each sampling time, the samples were inspected visually and the concentrations of granisetron and dexamethasone were determined by liquid chromatography by means of the validated stability-indicating method.

Long-Term Study of Stability of Granisetron

On study day zero, either 1 mg or 3 mg of granisetron (Kytril 1 mg/mL) was added to 50-mL PVC minibags (0.9% sodium chloride injection USP, Baxter, Mississauga, Ontario, lot WOA18CO, or 5% dextrose injection USP, Baxter, Mississauga, Ontario, lot PS092874, expiry June 2001). Four PVC minibags of each combination of diluent (NS or D5W), granisetron concentration (1 or 3 mg per 50 mL), and storage temperature (refrigerated or room temperature) (32 minibags total) were prepared and stored at 4°C or 23°C for 35 days. Three of each set of 4 bags were designated for liquid chromatographic analysis, and 1 bag was designated for pH determination and physical inspection. Samples were drawn from each study mixture immediately after mixing and after 1, 3, 7, 10, 14, 21, 28, and 35 days of storage. For samples obtained at each sampling time, the concentration of granisetron was determined by liquid chromatography, the pH was determined, and physical inspection (visual) was completed.

Long-Term Study of Stability and Compatibility of Granisetron and Dexamethasone

On study day 0, either 1 or 3 mg of granisetron (from Kytril 1 mg/mL) and either 4 mg of dexamethasone sodium phosphate (4 mg/mL; Sabex, lot 103271, expiry January 2002) or 10 mg of dexamethasone sodium phosphate (10 mg/mL; Sabex, lot 102307, expiry October 2000) was added to 50-mL PVC minibags (0.9% sodium chloride injection USP or 5% dextrose injection USP). Four PVC minibags of each combination of diluent (NS or D5W), granisetron concentration (1 or 3 mg per 50 mL), dexamethasone concentration (4 or 10 mg per 50 mL), and storage temperature (refrigerated or room temperature) (64 minibags total) were prepared and stored at 4°C or 23°C for 35 days. Three of each set of 4 bags were designated for liquid chromatographic analysis, and 1 bag was designated for pH determination and physical inspection. Samples were drawn from each study mixture immediately after mixing and after 3, 7, 10, 14, 21, 28, and 35 days of storage. The concentrations of granisetron and dexamethasone in each of these samples were determined by liquid chromatography, the pH was determined, and physical inspection (visual) was completed.

Physical Inspection and pH

On specific days for each component of the study, samples were drawn from the minibags of each combination of diluent, concentration, and storage temperature and placed in 10 x 75 mm glass test tubes to avoid misinterpretations related to the opacity of the container.

Each sample was inspected visually for particulate matter against separate black and white backgrounds and was also inspected for colour and clarity.

After the physical inspection, the pH of each sample was measured. The pH meter (Accumet model 925, Fisher Scientific, Toronto, Ontario) was equipped with a microprobe glass-body electrode (catalogue no. 13-639-280, Fisher Scientific) and was standardized each day with 2 commercially available buffer solutions (buffer solution pH 7.00, lot SC9008628, expiry January 2001, and buffer solution pH 4.00, lot SC9027695, expiry January 2001; Fisher Scientific). The pH was recorded to the nearest 0.001 of a pH unit but is reported to 0.1 of a pH unit.

Data Reduction and Statistical Analysis

Means (± standard deviation) were calculated for replicated analyses. Reproducibility was assessed by coefficient of variation (standard deviation divided by the mean). After the coefficient of variation was determined for the assay, a power calculation was completed to determine the number of replications required to ensure that the analytical method would be

Table 1. Observed Concentrations of Granisetron and Dexamethasone (as Percent of Initial Concentration) in NS Solutions Stored at Room Temperature (23°C) for 24 h

Time (h)	Drug Combination*; Drug Concentration (as % of Initial Concentration)								
	G 0.060 D 0.000	G 0.000 D 0.400	G 0.053 D 0.050	G 0.045 D 0.100	G 0.036 D 0.160	G 0.030 D 0.200	G 0.024 D 0.240	G 0.015 D 0.300	G 0.008 D 0.350
Granisetron concentrations									
0	100.0	NA	100.0	100.0	100.0	100.0	100.0	100.0	100.0
2	100.0	NA	98.5	98.0	97.6	97.6	99.0	97.0	101.8
6	99.6	NA	100.4	99.6	99.0	97.9	100.2	99.1	102.9
24	99.4	NA	98.8	99.9	98.5	99.1	100.2	98.1	101.9
CV (%)†	0.3		0.9	0.9	1.0	1.1	0.6	1.3	1.2
% remaining at 24 h by linear regression‡	99.5	NA	99.3	99.8	99.5	100.3	100.5	99.3	100.9
Dexamethasone concentrations									
0	NA	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0
2	NA	100.0	103.5	102.0	102.0	100.8	100.5	100.1	99.9
6	NA	101.0	102.8	103.5	103.5	101.3	101.8	102.7	102.0
24	NA	100.3	102.7	103.1	102.9	102.0	102.0	101.0	101.2
CV (%)†	NA	0.5	1.5	1.5	1.5	0.8	1.0	1.2	1.0
% remaining at 24 h by linear regression‡	NA	101.1	102.0	101.9	101.6	101.7	100.7	101.0	100.2

NS = normal saline (0.9% sodium chloride in water), NA = not applicable, CV = coefficient of variation.
*Drug combination given as G for granisetron and D for dexamethasone, with initial nominal concentrations in milligrams per millilitre. For example, G 0.053 D 0.050 indicates an initial nominal concentration of granisetron of 0.053 mg/mL and an initial nominal concentration of dexamethasone of 0.050 mg/mL.
†Variability of estimated concentrations over the 24-h study period, expressed as CV.
‡Calculated from concentrations at 24 h and at time zero, as determined by linear regression, according to the following formula:
[100 x (concentration at 24 h / concentration at time 0)].

Table 2. Observed Concentrations of Granisetron and Dexamethasone (as Percent of Initial Concentration) in D5W Solutions Stored at Room Temperature (23°C) for 24 h

Time (h)	Drug Combination*; Drug Concentration (as % of Initial Concentration)								
	G 0.060 D 0.000	G 0.000 D 0.400	G 0.053 D 0.050	G 0.045 D 0.100	G 0.036 D 0.160	G 0.030 D 0.200	G 0.024 D 0.240	G 0.015 D 0.300	G 0.008 D 0.350
Granisetron concentrations									
0	100.0	NA	100.0	100.0	100.0	100.0	100.0	100.0	100.0
2	100.0	NA	98.8	98.0	97.2	97.2	97.4	96.6	98.5
6	Not done	NA	99.6	100.4	97.3	97.6	97.6	98.4	98.8
24	102.0	NA	100.1	99.4	98.8	98.4	97.9	96.4	99.9
CV (%)†	1.2	NA	0.6	1.1	1.4	1.3	1.2	1.7	0.8
% remaining at 24 h by linear regression‡	102.1	NA	100.7	100.2	100.2	99.8	99.1	97.7	100.7
Dexamethasone concentrations									
0	NA	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0
2	NA	100.0	102.3	101.1	100.5	99.4	99.4	98.9	98.5
6	NA	Not reported	103.8	102.1	Not reported	103.2	Not reported	99.4	101.3
24	NA	99.4	103.5	102.0	101.9	100.0	100.1	99.4	100.2
CV (%)†	NA	0.4	1.7	1.0	1.0	1.7	0.4	0.4	1.2
% remaining at 24 h by linear regression‡	NA	99.4	102.2	101.3	101.7	99.8	100.4	99.9	100.7

D5W = 5% dextrose in water, NA = not applicable, CV = coefficient of variation.
*Drug combination given as G for granisetron and D for dexamethasone, with initial nominal concentrations in milligrams per millilitre. For example, G 0.053 D 0.050 indicates an initial nominal concentration of granisetron of 0.053 mg/mL and an initial nominal concentration of dexamethasone of 0.050 mg/mL.
†Variability of estimated concentrations over the 24-h study period, expressed as CV.
‡Calculated from concentrations at 24 h and at time zero, as determined by linear regression, according to the following formula:
[100 x (concentration at 24 h / concentration at time 0)].

Table 3. Observed Concentration of Granisetron in NS and D5W (as Percent of Initial Concentration) after Storage at 23°C or 4°C

	NS				D5W			
	Nominal 1 mg/50 mL*		Nominal 3 mg/50 mL†		Nominal 1 mg/50 mL‡		Nominal 3 mg/50 mL§	
Study Day	23°C	4°C	23°C	4°C	23°C	4°C	23°C	4°C
0	100.0 ± 0.0	100.0 ± 0.0	100.0 ± 0.0	100.0 ± 0.0	100.0 ± 0.0	100.0 ± 0.0	100.0 ± 0.0	100.0 ± 0.0
1	102.5 ± 0.7	103.0 ± 0.4	102.8 ± 0.4	101.5 ± 1.0	101.1 ± 2.5	101.8 ± 1.3	102.5 ± 0.4	102.1 ± 0.9
3	102.1 ± 0.8	101.9 ± 1.2	98.3 ± 0.3	99.1 ± 2.0	101.2 ± 2.9	102.3 ± 0.9	99.7 ± 1.6	97.1 ± 0.5
7	102.1 ± 1.7	102.0 ± 0.4	102.2 ± 0.7	101.5 ± 0.5	100.2 ± 2.6	101.6 ± 1.2	102.3 ± 0.4	100.9 ± 0.5
10	102.4 ± 0.8	100.8 ± 0.6	101.8 ± 0.9	101.7 ± 1.6	99.8 ± 2.1	101.2 ± 0.8	101.9 ± 0.7	102.2 ± 0.3
14	102.7 ± 0.7	101.1 ± 0.4	100.8 ± 0.6	100.2 ± 1.1	100.5 ± 2.0	100.7 ± 0.4	101.0 ± 2.0	101.0 ± 1.8
21	100.4 ± 0.8	101.2 ± 1.1	99.7 ± 0.9	102.1 ± 0.5	100.9 ± 1.3	102.6 ± 0.2	101.0 ± 1.3	101.2 ± 1.6
28	102.2 ± 1.0	99.8 ± 0.4	102.4 ± 1.5	101.6 ± 1.0	102.7 ± 0.9	101.1 ± 1.9	102.7 ± 0.7	101.6 ± 1.7
35	103.5 ± 0.6	99.7 ± 1.7	104.0 ± 1.0	102.6 ± 0.5	102.7 ± 0.8	101.7 ± 2.4	103.9 ± 0.6	103.3 ± 1.0
CV (%)¶	1.1	1.1	1.8	1.1	1.1	0.8	1.3	1.7
% remaining on day 35 by linear regression**	102.8	99.8	102.8	102.5	102.4	101.7	103.2	102.8
Lower limit of 95% CI for % remaining on day 35††	100.2	97.7	98.9	100.3	100.7	99.7	100.6	99.1

NS = normal saline (0.9% sodium chloride in water), D5W = 5% dextrose in water, CV = coefficient of variation, CI = confidence interval.
*Actual initial concentration of granisetron 0.018 mg/mL for minibags stored at both 23°C and 4°C.
†Actual initial concentration of granisetron 0.052 mg/mL for minibags stored at 23°C and 0.051 mg/mL for minibags stored at 4°C.
‡Actual initial concentration of granisetron 0.018 mg/mL for minibags stored at 23°C and 0.017 mg/mL for minibags stored at 4°C.
§Actual initial concentration of granisetron 0.052 mg/mL for minibags stored at both 23°C and 4°C.
¶Variability of estimated concentrations over the 9 sampling days, expressed as CV.
**Calculated from concentrations on day 35 and day 0 as determined by linear regression, according to the following formula:
[100 x (concentration on day 35 / concentration on day 0)].
††Calculated from the lower limit of the 95% CI of the slope of the concentration–time relationship, determined by linear regression, according to the following formula: 100 x [concentration on day 0 + (35 x 95% CI of slope)] / regression-determined intercept for day 0.

able to distinguish between concentrations that differed by at least 10%.[11,12]

Log–linear and linear–linear fits for the data from the accelerated degradation studies were compared for goodness of fit by the maximum likelihood method of Box and Cox.[13,14]

Mean concentrations for each solution were analyzed by least-squares linear regression to determine the percentage of the initial concentration remaining on the last day of the study. Multiple linear regression and analysis of variance (SPSS for Windows, release 5.0.1, 1992; SPSS Inc., Chicago, Illinois) were used to compare differences between diluents, concentrations, and temperatures for similar analytical tests. The 95% confidence interval for the percent remaining on day 35 was calculated for all combinations of diluent, concentration, and temperature from the concentration–time relationship by means of the model derived from multiple linear regression. The 5% level was used as the *a priori* cut-off for significance.

The concentrations of granisetron and dexamethasone were considered within acceptable limits if they did not decrease by more than 10% from the initial concentration as a result of degradation or precipitation. On each study day or at each evaluation period, the samples were visually inspected for colour, clarity, presence of particles, and evolution of gas. If there was no change in colour or clarity and no precipitate was evident, the mixture was considered physically compatible.

RESULTS

Assay Validation

When dissolved in water, adjusted to a pH of 0.8, and heated at 79°C, approximately 25% of the initial concentration of granisetron was lost over 35 h. Granisetron degraded in an apparent first-order fashion (log–linear decline: r^2 = 0.9512 for first-order rate and r^2 = 0.9413 for zero-order rate) to at least 2 other compounds (Figure 1, chromatogram B), which did not interfere with quantification of either granisetron or dexamethasone.

When dissolved in water, adjusted to a pH of 1.8, and heated at 90°C, dexamethasone degraded to less than 30% of the initial concentration over an 11-h period. Dexamethasone degraded in an apparent first-order fashion (log–linear decline: r^2 = 0.9924 for first-order rate and r^2 = 0.9790 for zero-order rate) to at

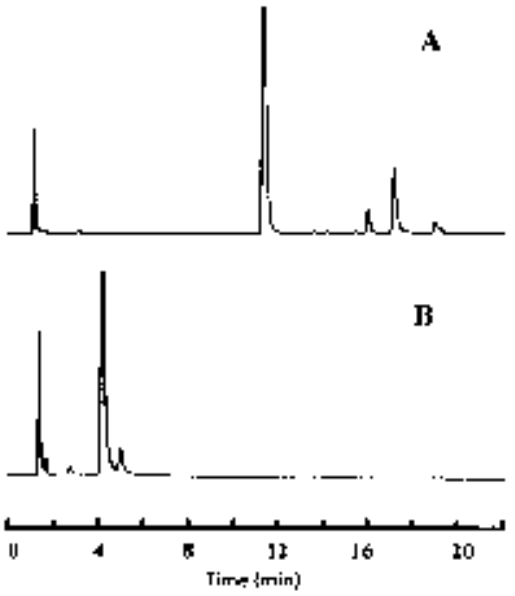

Figure 1. Typical chromatograms of granisetron and dexamethasone) after accelerated degradation. A: Chromatogram of dexamethasone after 11 h incubation at 90°C at pH 1.8. Dexamethasone elutes at 11 min, and 3 degradation products elute between 15 and 20 min. B: Chromatogram of granisetron after 35 h incubation at 79°C at pH 0.8. Granisetron elutes at 4 min, and degradation products elute at 3 and 5 min.

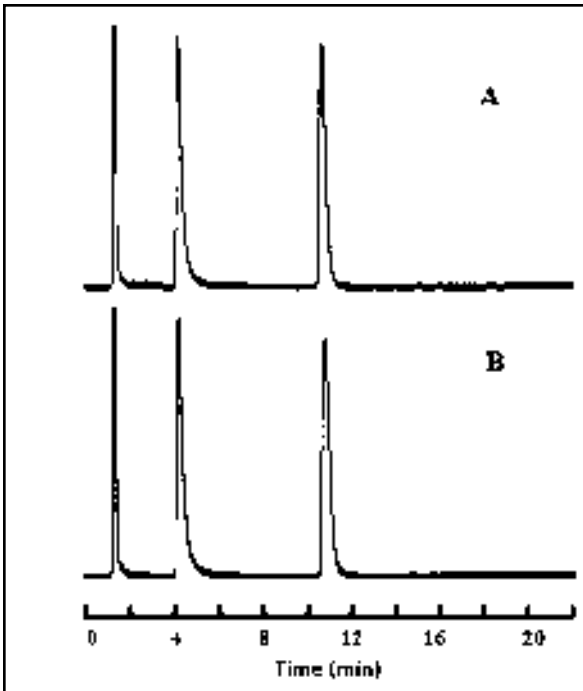

Figure 2. Typical chromatograms of granisetron and dexamethasone mixtures during the study period. A: Chromatogram of sample containing granisetron and dexamethasone on study day 0. B: Chromatogram of a sample containing granisetron and dexamethasone on study day 35. Granisetron elutes at 4 min and dexamethasone at 11 min. Degradation products found during the accelerated degradation study are not readily apparent in these chromatograms and did not increase in quantity during the study period (by day 35).

least 7 other compounds (3 of which are clearly visible in Figure 1, chromatogram A), which did not interfere with quantification of either granisetron or dexamethasone.

The predictable degradation and the chromatographic separation of granisetron and dexamethasone from each other and from their degradation products (Figure 1, chromatograms A and B) demonstrated that the stability of granisetron and dexamethasone could be determined with this analytical method.[5,6]

The standard curves of granisetron consisted of 6 standards from 0.010 to 0.100 mg/mL and 3 quality control samples with concentrations of 0.013, 0.038, and 0.088 mg/mL. Assay error, as assessed by coefficient of variation, was less than 1.5% for all concentrations for both intra- and inter-day reproducibility. Duplicate analysis of the granisetron quality control samples demonstrated that concentrations were estimated with less than 3% deviation between the observed and known concentrations.

The standard curves of dexamethasone consisted of 6 standards from 0.040 to 0.600 mg/mL and 3 quality control samples with concentrations of 0.050, 0.300, and 0.500 mg/mL. Assay error, as assessed by coefficient of variation, was less than 3.0% for all concentrations for both intra- and inter-day reproducibility. Duplicate analysis of the dexamethasone quality control samples demonstrated that concentrations were estimated with less than 3% deviation between the observed and known concentrations.

These analyses indicated that the concentrations of both granisetron and dexamethasone were measured accurately and reproducibly and that differences of 10% or more could be confidently detected with acceptable error rates.[11,12]

Stability and Compatibility Studies

Short-Term Study of Granesiton and Dexamethasone

Solutions of granisetron 0.060 mg/mL, diluted in either NS or D5W, were physically compatible, and concentrations remained above 99% of the initial concentration over the 24-h study period (Tables 1 and 2).

At room temperature, solutions of granisetron (0.008 to 0.053 mg/mL) combined with dexamethasone (0.050 to 0.350 mg/mL) were also physically compatible

Table 4. Observed Concentration of Granisetron in Mixtures with Dexamethasone in NS and D5W (as Percent of Initial Concentration) after Storage at 4°C

	NS				D5W			
Study Day	**G1:D4***	**G1:D10†**	**G3:D4‡**	**G3:D10§**	**G1:D4***	**G1:D10†**	**G3:D4‡**	**G3:D10§**
0	100.0 ± 0.0	100.0 ± 0.0	100.0 ± 0.0	100.0 ± 0.0	100.0 ± 0.0	100.0 ± 0.0	100.0 ± 0.0	100.0 ± 0.0
3	103.1 ± 1.0	102.5 ± 1.0	100.3 ± 0.5	101.1 ± 1.1	101.0 ± 1.0	101.3 ± 1.4	100.0 ± 0.4	102.6 ± 0.8
7	100.9 ± 1.4	101.3 ± 1.0	99.1 ± 0.5	99.8 ± 1.0	100.1 ± 0.7	98.9 ± 0.7	99.0 ± 0.9	101.3 ± 0.3
10	100.7 ± 1.2	102.2 ± 1.0	100.9 ± 0.7	101.6 ± 2.0	100.6 ± 0.7	100.4 ± 0.2	100.8 ± 0.6	102.4 ± 1.2
14	100.4 ± 1.2	98.9 ± 1.1	99.8 ± 1.3	100.0 ± 1.2	98.7 ± 0.9	97.4 ± 1.0	99.1 ± 1.1	101.6 ± 0.5
21	103.5 ± 0.7	102.4 ± 1.3	99.9 ± 0.1	101.7 ± 1.4	102.6 ± 1.4	102.2 ± 1.3	99.1 ± 0.4	102.9 ± 0.8
28	101.9 ± 2.3	101.0 ± 1.5	100.7 ± 0.8	101.7 ± 1.0	106.8 ± 6.0	112.7 ± 8.6	100.4 ± 0.4	104.4 ± 1.2
35	102.8 ± 0.9	102.9 ± 0.8	102.0 ± 0.5	103.4 ± 0.4	101.6 ± 0.7	103.5 ± 0.5	101.3 ± 0.9	104.1 ± 0.5
CV (%)¶	1.3	1.3	0.9	1.2	2.4	4.6	0.9	1.4
% remaining on day 35 by linear regression**	102.8	102.1	101.3	102.8	103.8	106.7	100.5	104.4
Lower limit of 95% CI for % remaining on day 35††	99.9	99.6	98.9	98.7	99.3	99.0	98.3	98.0

NS = normal saline (0.9% sodium chloride in water), D5W = 5% dextrose in water, CV = coefficient of variation, CI = confidence interval.
*G1:D4 represents granisetron at a nominal concentration of 1 mg/50 mL and dexamethasone at a nominal concentration of 4 mg/50 mL. The actual initial concentration of granisetron was 0.017 mg/mL in NS and 0.018 mg/mL in D5W.
†G1:D10 represents granisetron at a nominal concentration of 1 mg/50 mL and dexamethasone at a nominal concentration of 10 mg/50 mL. The actual initial concentration of granisetron was 0.018 mg/mL in NS and 0.017 mg/mL in D5W.
‡G3:D4 represents granisetron at a nominal concentration of 3 mg/50 mL and dexamethasone at a nominal concentration of 4 mg/50 mL. The actual initial concentration of granisetron was 0.054 mg/mL in NS and 0.053 mg/mL in D5W.
§G3:D10 represents granisetron at a nominal concentration of 3 mg/50 mL and dexamethasone at a nominal concentration of 10 mg/50 mL. The actual initial concentration of granisetron was 0.053 mg/mL in NS and 0.052 mg/mL in D5W.
¶Variability of estimated concentrations over the study period, expressed as CV.
**Calculated from concentrations on day 35 and day 0, as determined by linear regression, according to the following formula: [100 x (concentration on day 35 / concentration on day 0)].
††Calculated from the lower limit of the 95% CI of the slope of the concentration–time relationship, determined by linear regression, according to the following formula: 100 x [concentration on day 0 – (35 x 95% CI of slope)] / regression-determined intercept for day 0.

over 24 h. No precipitate was visible in any solution, no colour changes occurred, and no gas was produced on mixing. Furthermore, during the 24-h stability study period, neither dexamethasone nor granisetron degraded to a measurable extent. The dexamethasone concentration remaining at 24 h, as determined by linear regression, was at least 99.4% of the initial concentration (range 99.4% to 102.2%; Tables 1 and 2), and the granisetron concentration remaining at 24 h was greater than 97.7% of the initial concentration (range 97.7% to 102.1; Tables 1 and 2).

Long-Term Study of Stability of Granisetron

Solutions of granisetron (1 or 3 mg in 50 mL) diluted in either NS or D5W were physically compatible and stable, and concentrations remained greater than 97% of the initial concentration on all study days over the 35-day study period when refrigerated or stored at room temperature (Table 3).

During the 35-day stability study period, granisetron did not degrade to a measurable extent. The concentration remaining at 35 days, as determined by linear regression, was at least 99.8% of the initial concentration (range 99.8% to 103.2%; Table 3). On the basis of the 95% confidence interval for the degradation rate determined by linear regression, the amount remaining on day 35 was not less than 97.7% (Table 3). Chromatography demonstrated some evidence of minor amounts of impurities; however, these contaminants did not change in concentration during the study period. The concentration of these impurities was low and therefore they are not readily visible in Figure 2, chromatograms A and B.

Multiple linear regression revealed a significant association between observed granisetron concentration and study day (p = 0.013). However, the difference represented a change of less than 1.17% over the 35-day study period and is not clinically important. All other factors — diluent (NS or D5W; p = 0.591), nominal granisetron concentration (p = 0.678), and temperature (p = 0.229) — did not significantly affect the granisetron concentration.

The initial pH of the solution of 1 mg of granisetron in 50 mL NS was 6.4 and increasing the concentration of granisetron to 3 mg in 50 mL NS increased the initial pH to 6.5. When granisetron was admixed with D5W, the

Table 5. Observed Concentration of Granisetron in Mixtures with Dexamethasone in NS and D5W (as Percent of Initial Concentration) after Storage at 23°C

	NS				D5W			
Study Day	**G1:D4***	**G1:D10†**	**G3:D4‡**	**G3:D10§**	**G1:D4***	**G1:D10†**	**G3:D4‡**	**G3:D10§**
0	100.0 ± 0.0	100.0 ± 0.0	100.0 ± 0.0	100.0 ± 0.0	100.0 ± 0.0	100.0 ± 0.0	100.0 ± 0.0	100.0 ± 0.0
3	102.8 ± 1.3	102.9 ± 1.0	101.8 ± 1.7	102.2 ± 1.8	102.3 ± 1.0	101.2 ± 0.9	101.2 ± 1.5	103.2 ± 0.5
7	101.7 ± 0.5	100.5 ± 0.5	99.7 ± 0.8	99.6 ± 0.4	100.1 ± 0.8	100.0 ± 1.5	99.7 ± 0.3	103.2 ± 1.6
10	102.3 ± 1.8	102.8 ± 1.6	103.5 ± 0.6	102.1 ± 0.3	102.8 ± 1.2	102.0 ± 0.9	102.4 ± 0.7	103.6 ± 0.7
14	100.5 ± 1.3	100.3 ± 3.4	100.4 ± 1.5	99.2 ± 0.3	99.9 ± 0.7	98.9 ± 1.2	99.7 ± 1.9	101.7 ± 1.0
21	103.2 ± 0.9	103.0 ± 0.8	101.0 ± 1.3	102.0 ± 0.9	101.4 ± 0.5	102.9 ± 1.4	101.0 ± 1.1	102.4 ± 0.9
28	110.8 ± 5.0	101.7 ± 1.4	103.0 ± 0.7	102.5 ± 0.5	101.4 ± 1.0	100.2 ± 3.2	102.5 ± 0.1	102.8 ± 1.7
35	101.8 ± 2.5	102.1 ± 1.1	103.1 ± 1.0	102.9 ± 1.2	102.8 ± 0.8	102.6 ± 0.6	103.8 ± 0.2	102.8 ± 0.7
CV (%)¶	3.3	1.2	1.5	1.4	1.2	1.4	1.5	1.1
% remaining on day 35 based on linear regression**	105.6	102.2	103.0	102.7	102.2	102.0	103.1	102.9
Lower limit of 95% CI for % remaining on day 35††	99.7	99.4	98.7	98.4	99.0	98.8	98.1	97.8

NS = normal saline (0.9% sodium chloride in water), D5W = 5% dextrose in water, CV = coefficient of variation, CI = confidence interval.
*G1:D4 represents granisetron at a nominal concentration of 1 mg/50 mL and dexamethasone at a nominal concentration of 4 mg/50 mL. The actual initial concentration of granisetron was 0.016 mg/mL in NS and 0.018 mg/mL in D5W.
†G1:D10 represents granisetron at a nominal concentration of 1 mg/50 mL and dexamethasone at a nominal concentration of 10 mg/50 mL. The actual initial concentration of granisetron was 0.019 mg/mL in NS and 0.018 mg/mL in D5W.
‡G3:D4 represents granisetron at a nominal concentration of 3 mg/50 mL and dexamethasone at a nominal concentration of 4 mg/50 mL. The actual initial concentration of granisetron was 0.052mg/mL in NS and 0.053 mg/mL in D5W.
§G3:D10 represents granisetron at a nominal concentration of 3 mg/50 mL and dexamethasone at a nominal concentration of 10 mg/50 mL. The actual initial concentration of granisetron was 0.053 mg/mL in NS and 0.051 mg/mL in D5W.
¶Variability of estimated concentrations over the study period, expressed as CV.
**Calculated from concentrations on day 35 and day 0, as determined by linear regression, according to the following formula: [100 x (concentration on day 35 / concentration on day 0)].
††Calculated from the lower limit of the 95% CI of the slope of the concentration–time relationship, determined by linear regression, according to the following formula: 100 x [concentration on day 0 – (35 x 95% CI of slope)] / regression-determined intercept for day 0.

initial pH was 6.2 for 1 mg of granisetron in 50 mL and 6.2 for 3 mg of granisetron in 50 mL D5W. During the 35-day stability study of granisetron alone, the maximum change observed on any day (relative to initial pH), was less than 0.2 of a pH unit. All samples at all concentrations and both temperatures were initially clear and colourless and remained so for the entire study period.

Long-Term Study of Stability and Compatibility of Granisetron and Dexamethasone

Solutions of granisetron (1 or 3 mg in 50 mL) diluted in either NS or D5W and admixed with either 4 or 10 mg of dexamethasone were physically compatible and stable, with concentrations remaining greater than 97% of the initial concentration on all study days over the 35-day study period when stored in PVC minibags at 4°C or room temperature (Tables 4 and 5).

During the 35-day stability study period, granisetron did not degrade to a measurable extent. The granisetron concentration remaining on day 35, on the basis of linear regression, was at least 100.5% of the initial concentration (range 100.5% to 106.7%; Tables 4 and 5). On the basis of the 95% confidence interval for the degradation rate determined by linear regression, the amount remaining on day 35 was not less than 97.8% and averaged 98.9% (Tables 4 and 5). Multiple linear regression revealed a significant association between the observed granisetron concentration and study day ($p < 0.001$). However, this difference represented a change of less than 2.6% over the 35-day study period and is not clinically important. All other factors — diluent (NS or D5W; $p = 0.986$), nominal granisetron concentration ($p = 0.261$), nominal dexamethasone concentration ($p = 0.252$), and temperature ($p = 0.225$) — did not significantly affect granisetron concentration. Chromatography demonstrated some evidence of minor amounts of impurities; however, these contaminants did not change in concentration during the study period. The concentration of the impurities was low, and therefore they are not readily visible in Figure 2, chromatograms A and B.

During the 35-day stability study period, dexamethasone did not degrade to a measurable extent. The dexamethasone concentration remaining on day

Table 6. Observed Concentration of Dexamethasone in Mixtures with Granisetron in NS and D5W (as Percent of Initial Concentration) after Storage at 4°C

	NS				D5W			
Study Day	**G1:D4***	**G1:D10†**	**G3:D4‡**	**G3:D10§**	**G1:D4***	**G1:D10†**	**G3:D4‡**	**G3:D10§**
0	100.0 ± 0.0	100.0 ± 0.0	100.0 ± 0.0	100.0 ± 0.0	100.0 ± 0.0	100.0 ± 0.0	100.0 ± 0.0	100.0 ± 0.0
3	101.1 ± 0.8	103.1 ± 0.9	99.0 ± 1.3	103.1 ± 1.2	99.4 ± 2.6	103.4 ± 0.1	98.1 ± 0.5	102.8 ± 0.5
7	102.0 ± 0.2	101.4 ± 0.8	101.5 ± 1.0	101.7 ± 0.3	100.7 ± 0.1	101.8 ± 0.9	102.3 ± 0.3	102.0 ± 0.4
10	98.8 ± 1.3	99.0 ± 1.2	100.2 ± 1.5	98.5 ± 2.0	98.0 ± 0.8	98.8 ± 1.0	100.2 ± 1.0	98.1 ± 0.3
14	100.8 ± 1.3	101.8 ± 1.8	101.0 ± 0.8	100.0 ± 3.6	97.1 ± 0.6	101.8 ± 0.8	100.0 ± 1.1	101.4 ± 0.7
21	99.6 ± 2.8	100.7 ± 2.8	97.3 ± 1.3	99.8 ± 3.8	97.1 ± 0.6	101.2 ± 1.9	96.7 ± 1.2	99.3 ± 0.6
28	92.1 ± 6.7	100.5 ± 1.9	101.6 ± 2.1	103.5 ± 0.8	95.9 ± 0.0	112.7 ± 7.4	100.1 ± 1.0	93.6 ± 15.8
35	100.0 ± 0.7	98.8 ± 2.1	98.7 ± 2.9	98.4 ± 2.4	97.5 ± 0.2	97.9 ± 2.6	99.1 ± 1.1	99.0 ± 0.6
CV (%)¶	3.1	1.4	1.5	1.9	1.7	4.6	1.7	2.9
% remaining on day 35 based on linear regression**	96.8	99.6	99.5	100.1	96.1	103.8	98.9	96.7
Lower limit of 95% CI for % remaining on day 35††	95.1	95.7	93.9	94.5	94.4	95.0	93.3	93.8

NS = normal saline (0.9% sodium chloride in water), D5W = 5% dextrose in water, CV = coefficient of variation, CI = confidence interval.
*G1:D4 represents granisetron at a nominal concentration of 1 mg/50 mL and dexamethasone at a nominal concentration of 4 mg/50 mL. The actual initial concentration of dexamethasone was 0.069 mg/mL in NS and 0.072 mg/mL in D5W.
†G1:D10 represents granisetron at a nominal concentration of 1 mg/50 mL and dexamethasone at a nominal concentration of 10 mg/50 mL. The actual initial concentration of dexamethasone was 0.197 mg/mL in NS and 0.192 mg/mL in D5W.
‡G3:D4 represents granisetron at a nominal concentration of 3 mg/50 mL and dexamethasone at a nominal concentration of 4 mg/50 mL. The actual initial concentration of dexamethasone was 0.069 mg/mL in NS and 0.067 mg/mL in D5W.
§G3:D10 represents granisetron at a nominal concentration of 3 mg/50 mL and dexamethasone at a nominal concentration of 10 mg/50 mL. The actual initial concentration of dexamethasone was 0.200 mg/mL in NS and 0.193 mg/mL in D5W.
¶Variability of estimated concentrations over the study period, expressed as CV.
**Calculated from concentrations on day 35 and day 0, as determined by linear regression, according to the following formula: [100 x (concentration on day 35 / concentration on day 0)].
††Calculated from the lower limit of the 95% CI of the slope of the concentration–time relationship, determined by linear regression, according to the following formula: 100 x [concentration on day 0 – (35 x 95% CI of slope)] / regression-determined intercept for day 0.

35, on the basis of linear regression, was at least 96.1% of the initial concentration (range 96.1% to 103.8%; Tables 6 and 7). On the basis of the 95% confidence interval for the degradation rate determined by linear regression, the amount remaining on day 35 was less than 94% for 4 of the 16 storage conditions but nonetheless averaged 95.0% (Tables 6 and 7). Multiple linear regression revealed a significant association between observed dexamethasone concentration and study day (p = 0.037) and nominal dexamethasone concentration (p = 0.001). However, in both cases the difference in the means (day 0 versus day 35 = 2.4%; 4 versus 10 mg dexamethasone = 0.7%) is not clinically important. All other factors — diluent (NS or D5W; p = 0.816), nominal granisetron concentration (p = 0.293), and temperature (p = 0.051) — did not significantly affect the dexamethasone concentration.

The initial pH of the solution of 1 mg of granisetron in 50 mL NS was 6.4 and that of the solution of 3 mg granisetron in 50 mL NS was 6.5. When granisetron was admixed with D5W, the initial pH was 6.2 for 1 mg in 50 mL and 6.3 for 3 mg in 50 mL. The addition of 4 mg of dexamethasone to a 50-mL minibag containing 1 mg of granisetron increased the pH to 6.7 for NS and to 6.6 for D5W. However, the addition of 10 mg of dexamethasone had little further effect on pH. During the 35-day stability and compatibility study of granisetron and dexamethasone, the maximum change observed on any day (relative to the initial pH) was less than 0.1 of a pH unit. In no sample was the change in pH over the 35-day study period greater than 0.2 of a pH unit. All samples at all concentrations and both temperatures were initially clear and colourless and remained so for the entire study period.

DISCUSSION

This study has demonstrated, as have previous reports,[2-4] that granisetron is a stable compound. During the accelerated degradation study, approximately 25% of the initial granisetron concentration was lost at a pH of 0.8 during incubation at 79°C over 35 h. Granisetron was also stable over a 35-day period, in both NS and D5W solutions, even when stored at room temperature. The lower limit of the 95% confidence interval of multiple-variable least-squares linear regression demonstrated a change of less than 3% in granisetron

Table 7. Observed Concentration of Dexamethasone in Mixtures with Granisetron in NS and D5W (as Percent of Initial Concentration) after Storage at 23°C

	NS				D5W			
Study Day	**G1:D4***	**G1:D10†**	**G3:D4‡**	**G3:D10§**	**G1:D4***	**G1:D10†**	**G3:D4‡**	**G3:D10§**
0	100.0 ± 0.0	100.0 ± 0.0	100.0 ± 0.0	100.0 ± 0.00	100.0 ± 0.0	100.0 ± 0.0	100.0 ± 0.0	100.0 ± 0.0
3	100.5 ± 2.4	102.2 ± 1.1	97.5 ± 0.4	102.5 ± 0.96	100.6 ± 1.7	102.3 ± 0.4	98.1 ± 0.2	102.2 ± 1.9
7	102.2 ± 0.6	103.1 ± 1.0	100.9 ± 0.8	101.1 ± 0.41	102.0 ± 0.5	102.8 ± 1.0	102.8 ± 0.2	102.2 ± 1.3
10	100.6 ± 1.5	100.7 ± 0.4	100.9 ± 1.5	100.8 ± 2.81	102.2 ± 1.9	100.1 ± 0.3	100.2 ± 1.2	102.4 ± 1.8
14	100.1 ± 2.0	102.7 ± 1.0	98.4 ± 0.7	100.7 ± 0.37	101.2 ± 1.5	100.1 ± 3.0	100.9 ± 1.2	100.8 ± 2.5
21	98.3 ± 1.7	100.0 ± 1.2	96.5 ± 0.9	98.6 ± 1.6	98.2 ± 1.1	101.6 ± 1.4	98.5 ± 1.0	100.3 ± 2.2
28	93.7 ± 16.1	103.8 ± 0.3	101.8 ± 0.9	103.6 ± 1.2	100.7 ± 3.5	103.4 ± 0.7	101.6 ± 0.9	103.5 ± 1.2
35	102.0 ± 1.3	100.8 ± 0.8	100.9 ± 0.8	98.9 ± 1.5	102.3 ± 0.3	100.5 ± 0.5	98.7 ± 2.9	96.9 ± 0.5
CV (%)¶	2.1	1.5	1.9	1.7	1.4	1.3	1.6	2.1
% remaining on day 35 based on linear regression**	98.4	101.9	100.3	100.3	101.1	101.6	99.8	99.7
Lower limit of 95% CI for % remaining on day 35††	91.0	97.7	95.1	95.5	97.2	97.8	95.2	94.4

NS = normal saline (0.9% sodium chloride in water), D5W = 5% dextrose in water, CV = coefficient of variation, CI = confidence interval.
*G1:D4 represents granisetron at a nominal concentration of 1 mg/50 mL and dexamethasone at a nominal concentration of 4 mg/50 mL. The actual initial concentration of dexamethasone was 0.070 mg/mL in NS and 0.071 mg/mL in D5W.
†G1:D10 represents granisetron at a nominal concentration of 1 mg/50 mL and dexamethasone at a nominal concentration of 10 mg/50 mL. The actual initial concentration of dexamethasone was 0.209 mg/mL in NS and 0.198 mg/mL in D5W.
‡G3:D4 represents granisetron at a nominal concentration of 3 mg/50 mL and dexamethasone at a nominal concentration of 4 mg/50 mL. The actual initial concentration of dexamethasone was 0.069 mg/mL in NS and 0.068 mg/mL in D5W.
§G3:D10 represents granisetron at a nominal concentration of 3 mg/50 mL and dexamethasone at a nominal concentration of 10 mg/50 mL. The actual initial concentration of dexamethasone was 0.175 mg/mL in NS and 0.177 mg/mL in D5W.
¶Variability of estimated concentrations over the study period, expressed as CV.
**Calculated from concentrations on day 35 and day 0, as determined by linear regression, according to the following formula: [100 x (concentration on day 35 / concentration on day 0)].
††Calculated from the lower limit of the 95% CI of the slope of the concentration–time relationship, determined by linear regression, according to the following formula: 100 x [concentration on day 0 – (35 x 95% CI of slope)] / regression-determined intercept for day 0.

concentration when the drug was stored alone or in combination with dexamethasone over 35 days. In studies where no change in the concentration of the compound of interest can be detected, assurance that the analytical method is specific for the compound of interest is important. This was demonstrated in the accelerated degradation portion of the study, during which degradation products could be separated from both dexamethasone and granisetron. The ability to separate the degradation products of both granisetron and dexamethasone from each of the undegraded drugs and the ultraviolet spectral purity of the 2 drugs indicated that this method was specific for the compounds of interest and was therefore suitable for indicating stability.

Dexamethasone is also a fairly stable compound. During the accelerated study, approximately 70% of the initial dexamethasone concentration was lost at a pH of 1.8 during incubation at 90°C. Dexamethasone was also stable over a 35-day period, in both NS and D5W, even when stored at room temperature. The lower limit of the 95% confidence interval of multiple-variable least-squares linear regression demonstrated a change of less than 7% in dexamethasone concentration when the drug was stored in combination with granisetron over 35 days. Previous studies have also shown that dexamethasone is stable during storage at room temperature for as long as 91 days.[8] The current study has also demonstrated the chemical compatibility of dexamethasone in combination with granisetron over 35 days. Several previous studies have demonstrated incompatibilities when dexamethasone was combined with other drugs, including hydromorphone,[7] diphenhydramine,[7] dolasetron,[9] and midazolam.[10]

In this study, granisetron and dexamethasone were chemically stable and physically compatible with each other in all combinations of diluent, concentration, and temperature that were tested. Because granisetron is an effective anti-emetic and because many prophylactic nausea and vomiting protocols use a 5-hydroxytryptamine receptor antagonist in combination with dexamethasone, knowledge of the compatibility and stability of this combination of drugs is important. Such information will be of value to pharmacists and nurses

working in the hospital setting. If these medications are compatible, the time required for nurses to administer a course of drug therapy will be reduced and the number of IV sites required may also be reduced, when the 2 agents must be given together or administered sequentially. Furthermore, it is generally accepted that extension of the expiry date will reduce wastage.[15,16] Although wastage also depends on the frequency of usage by individual patients and the interval between patients requiring a particular drug, the ability to extend the expiry date is an important component of waste reduction.[16]

On the basis of the results of this study, a 35-day expiration date is recommended for granisetron 0.008 to 0.053 mg/mL and dexamethasone 0.050 to 0.350 mg/mL in NS or D5W when stored at either 4°C or 23°C. Such solutions retained more than 90% of their original concentrations over the 35-day study period. However, expiry dates at any specific institution should take into account the known bacterial contamination rate within the institution's IV additive program.

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