

Stability of Docetaxel Solution after Dilution in Ethanol and Storage in Vials and after Dilution in Normal Saline and Storage in Bags

Scott E Walker, Flay Charbonneau, and Shirley Law

ABSTRACT

Objective: This study evaluated the stability of a recently marketed formulation of docetaxel in polysorbate 80 diluted with 13% ethanol in water for injection and stored in vials at different temperatures. The stability of docetaxel further diluted in 0.9% sodium chloride (NS) and stored in polypropylene–polyethylene copolymer bags (also known as partial additive bags [PABs]) at room temperature was also evaluated.

Methods: A reverse-phase stability-indicating liquid chromatographic method was developed and validated before the study. On study day 0, 10 vials of the new formulation of the commercially available product were prepared according to the manufacturer's instructions. Six of the vials were stored for 21 days (3 vials at 23°C and 3 vials at 4°C), with drug concentration evaluated several times over the storage period. The remaining 4 vials were further diluted in NS to prepare concentrations equivalent to docetaxel 0.4 mg/mL and 0.8 mg/mL for storage in PABs. A solution of the older formulation of docetaxel at 0.8 mg/mL was also prepared and stored at 23°C in a PAB. All docetaxel solutions stored in PABs at room temperature were unprotected from light. The concentration of docetaxel in the PABs was evaluated over a period of 35 days.

Results: During the study period, all of the study samples retained more than 95.0% of their initial concentration. The concentration changed by less than 5% over the 21-day period for samples stored in vials and by less than 5% over the 35-day study period for samples stored in PABs. Inspection of chromatograms during the stability study failed to reveal any degradation products that were observed during the accelerated degradation.

Conclusion: Solutions of docetaxel 0.4 mg/mL and 0.8 mg/mL prepared in NS and stored in PABs retained more than 95% of the initial drug concentration when stored for 35 days at 23°C. Similarly, docetaxel 10 mg/mL prepared in the ethanol and polysorbate 80 diluent provided by the manufacturer retained more than 95% of the initial docetaxel concentration when stored in vials at either 23°C or 4°C for 21 days.

Key words: docetaxel, Taxotere, stability

RÉSUMÉ

Objectif : Cette étude a évalué la stabilité d'une solution récemment commercialisée de docetaxel dans du polysorbate 80 dilué avec de l'éthanol à 13 % dans de l'eau pour injection et entreposée dans des flacons à différentes températures. La stabilité d'une préparation de docetaxel diluée à nouveau dans du chlorure de sodium à 0,9 % (NS) puis entreposée dans des sacs de copolymère de polypropylène-polyéthylène (aussi connus sous le nom de sacs pour additifs partiels [SAP]) à la température ambiante a également été évaluée.

Méthodes : Une épreuve de stabilité par chromatographie liquide en phase inverse a été mise au point et validée avant l'étude. Au jour 0 de l'étude, 10 flacons de la nouvelle solution du produit commercial ont été préparés selon les instructions du fabricant. Six des flacons ont été entreposés pendant 21 jours (trois flacons à 23 °C et les trois autres à 4 °C), et on a évalué la concentration en médicament de ces flacons plusieurs fois pendant la période d'entreposage. Les préparations des quatre autres flacons ont été diluées à nouveau dans du NS afin de préparer des concentrations de docetaxel équivalent à 0,4 mg/mL et à 0,8 mg/mL dans des SAP. Une solution de l'ancienne composition de docetaxel à 40 mg/50 mL a également été préparée, puis entreposée à 23 °C dans des SAP. Toutes les préparations de docetaxel entreposées dans des SAP à la température ambiante n'ont pas été protégées de la lumière. Les concentrations de docetaxel dans les SAP ont été évaluées sur une période de 35 jours.

Résultats : Au cours de la période de l'étude, tous les échantillons ont conservé plus de 95,0 % de leur concentration initiale. La concentration a varié de moins de 5 % au cours de la période de 21 jours pour les échantillons conservés dans les flacons, et également au cours de la période de 35 jours pour les échantillons conservés dans des SAP. L'inspection des chromatogrammes obtenus par l'épreuve de stabilité n'a pu révéler aucun des produits de dégradation qui avaient été générés durant la dégradation accélérée.

Conclusion : Les solutions de docetaxel à 0,4 mg/mL et à 0,8 mg/mL préparées dans du NS et conservées dans des SAP ont retenu plus de 95 % de leur concentrations initiales de médicament lorsqu'elles étaient entreposées à 23 °C pendant une période de 35 jours. De la même manière, les solutions de docetaxel à 10 mg/mL préparées avec le diluant de polysorbate 80 et d'éthanol fourni par le fabricant ont conservé plus de 95 % de leur concentration initiale de docetaxel lorsqu'elles étaient entreposées à 23 °C ou à 4 °C pendant 21 jours.

Mots clés : docetaxel, Taxotere, stabilité



INTRODUCTION

Docetaxel is an antineoplastic agent that disrupts the microtubular network of cells. It is indicated for patients with locally advanced or metastatic breast cancer, advanced or metastatic non-small-cell lung cancer, or recurrent or metastatic squamous cell carcinoma of the head and neck. The indications for docetaxel have been expanded in recent years, such that in any comprehensive cancer program, docetaxel is likely to be administered every day of the week, primarily to patients with breast cancer, but also routinely to those with prostate and lung cancer.¹

In 2002, a new formulation of docetaxel (Taxotere, Aventis Pharma) was released on the Canadian market. The formulation previously in use and the new formulation have the same medicinal and nonmedicinal ingredients, although in marginally different amounts, volumes, and concentrations.^{2,4} The new formulation does not require refrigerated storage and has a longer shelf life before dilution to 10 mg/mL with the 13% ethanol in water solution supplied by the manufacturer.² However, the manufacturer recommends that after such dilution, the 10 mg/mL docetaxel solution be used within 8 h of preparation, regardless of the storage temperature. After further dilution with either 0.9% sodium chloride (NS) or 5% dextrose in water (to yield an infusion solution), the recommended expiry time is only 4 h.² These expiry times are the same as those recommended by the manufacturer for the previously marketed formulation.^{3,4} However, before release of the new formulation, many Canadian pharmacists had adopted an extended stability period of 28 days at room temperature for infusions prepared with the older formulation, on the basis of data reported in 1999 by Thiesen and Kramer.⁵ Using the manufacturer's shorter recommended expiry date for solutions prepared with the new formulation could contribute to wastage and an increase in overall drug expenditures.^{6,7}

The objective of this study was to evaluate the stability of infusions prepared with the newer formulation of docetaxel, in particular, 10 mg/mL solutions stored for 21 days in vials and 0.4 and 0.8 mg/mL solutions prepared by further dilution of the 10 mg/mL solution in 50 mL NS and stored for 35 days at room temperature in polypropylene–polyethylene copolymer bags (also known as partial additive bags [PABs]).

METHODS

Chromatographic Analysis

The liquid chromatographic system consisted of an isocratic solvent delivery pump (model P4000, Thermo

Separation Products, Fremont, California), which pumped a mixture of methanol (OmniSolv, EMD Chemicals Inc, Gibbstown, New Jersey) and 0.05 mmol/L phosphoric acid (catalogue no. P286, Fisher Scientific, Toronto, Ontario) through a 15 cm x 4.6 mm reverse-phase C₁₈, 3- μ m column (Supelcosil, catalogue no. 58985, Supelco, Oakville, Ontario) at 0.5 mL/min. The ratio of methanol to phosphoric acid (67:33) was held constant during each chromatographic run. The samples were introduced into the liquid chromatographic system using an autoinjector (WISP 712, Waters Scientific, Toronto, Ontario).

The column effluent was monitored with a variable-wavelength ultraviolet detector (UV6000, Thermo Separation Products) at 232 nm. The signal from the detector was integrated and recorded with a chromatography data system (ChromQuest, Thermo Separation Products). The area under the docetaxel peak at 232 nm was subjected to least-squares linear regression and the actual docetaxel concentration in each sample determined by interpolation from the standard curve. Docetaxel concentrations were recorded to the nearest 0.01 mg/mL.

The concentration of the degradation products of docetaxel (described below) could not be measured quantitatively because of a lack of standards for each of the degradation products. Instead, chromatograms were inspected on each study day for the appearance of degradation products, and the area of these peaks was monitored and compared between days for changes. Change in the amount of degradation product is considered a sensitive indicator of degradation.^{8,9}

Assay Validation

After development of the chromatographic system for docetaxel (see above), the suitability of this method for use as a stability-indicating assay was tested by analyzing solutions obtained by accelerated degradation of docetaxel. A 0.5-mL sample of a 0.5 mg/mL solution of docetaxel (Taxotere, Aventis Pharma Inc, Laval, Quebec; lot 3P732, expiry October 2005; diluted in distilled water, pH 5.0) was placed in a glass vial, which was in turn placed in the autoinjector of the chromatographic system. Two-microlitre samples of this solution were injected and directly chromatographed just before addition of 10 μ L of 1% sodium hypochlorite and at 8 other times over a 705-min period (10, 23, 48, 70, 92, 142, 210, and 705 min) after addition of the sodium hypochlorite. A second sample (25 mL) of the 0.5 mg/mL solution (diluted in distilled water, pH 5.0)



was placed in a glass vial and incubated at 80°C in a water bath. Two-microlitre samples were drawn just before incubation began and at 9 other times over a 67-h period (0.5, 1, 2.25, 3, 4, 5, 20, 25, and 67 h) and were directly chromatographed. The chromatograms were inspected for the appearance of additional peaks, and the docetaxel peak was compared between samples for changes in concentration, retention time, peak shape, and ultraviolet spectral purity (200 nm to 320 nm) relative to a fresh undegraded sample.

Following this first phase of evaluation and validation, the accuracy and reproducibility of standard curves were tested over 5 days, and system suitability criteria (theoretical plates, tailing, and retention time) were developed to ensure consistent chromatographic performance. A standard curve was prepared daily from a fresh vial of docetaxel (Taxotere, lot 3P732, expiry October 2005). Each vial supplied by the manufacturer (80 mg in 2 mL) actually contains 2.36 mL of a 40 mg/mL solution of docetaxel, which was diluted according to the manufacturer's instructions with 7.33 mL of a 13% ethanol solution, also supplied by the manufacturer. This produced approximately 10 mL of a 10 mg/mL solution. Samples of this stock solution were further diluted in methanol and water (60:40) to obtain standards with final concentrations of 1.00, 0.75, 0.38, 0.25, 0.13, and 0.06 mg/mL. When combined with a blank, these standards served to construct a standard curve. A 2- μ L sample of each standard was chromatographed in duplicate. Also, 2 quality control samples of docetaxel (concentrations of 0.50 and 0.19 mg/mL) were chromatographed in duplicate each day, with their concentrations determined and compared to the known concentrations. Intraday and interday errors were assessed by the coefficients of variation (CVs; standard deviation divided by the mean) of the peak areas of both quality control samples and standards.

Stability Study

On study day 0, 10 vials of the new formulation of the commercially available docetaxel product (Taxotere, Aventis Pharma Inc, lot 3P732, expiry October 2005) were diluted with the supplied diluent (13% ethanol in water, lot 2H748, expiry December 2003) according to the manufacturer's instructions. Three of these vials were stored at room temperature (23°C) and 3 were stored in the refrigerator (4°C); the docetaxel concentration was determined in duplicate on study days 0, 1, 3, 4, 7, 10, 14, 17, and 21. The remaining 4 vials were further

diluted in NS to prepare nominal concentrations of 0.4 and 0.8 mg/mL (equivalent to 20 and 40 mg per 50 mL) which were stored in PABs (B Braun Medical Inc, Irvine, California, lot J2D954, expiry July 2003). An additional sample of the older formulation (Taxotere, Rhone-Poulenc Rorer, Ville Saint-Laurent, Quebec, lot 1A154 for docetaxel solution and lot 1C429 for diluent; expiry June 2002) was also prepared according to the manufacturer's instructions and was then further diluted in NS to prepare a nominal concentration of 0.8 mg/mL (equivalent to 80 mg per 100 mL) in a PAB. All PABs were stored at room temperature, unprotected from ambient fluorescent room light during the study. On study days 0, 3, 7, 14, 25, and 35, the concentration of docetaxel was determined in duplicate.

Visual Inspection and pH

Visual inspection was carried out as samples were drawn for pH analysis on day 0 and day 35. The samples were drawn, placed in a 10 x 75 mm glass test tube and inspected visually for colour and clarity against a black background and a white background. The pH of each solution was then measured and recorded to the nearest 0.001 of a pH unit. 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, Toronto, Ontario). To ensure the accuracy of the pH measurements, the pH meter was standardized on day 0 and day 35 with commercially available buffer solutions (pH 7.00 and 4.00; Fisher Scientific, Nepean, Ontario).

Data Reduction and Statistical Analysis

Means were calculated for analyses completed in duplicate. Error was assessed by CV. Mean concentrations (or percent remaining) for different days were compared statistically by least-squares multiple linear regression, using concentration, formulation, temperature, and study day as sources of error in the analysis of variance (ANOVA) model to determine if there was an association between concentration and time. The 5% level was used as the a priori cut-off for significance, and all references to significance refer to this level. The lower limit of the 95% confidence interval of concentrations determined by linear regression was determined. Docetaxel concentrations were considered acceptable or within acceptable limits if the lower limit of the 95% confidence interval of the mean concentration remaining was greater than 90% of the initial (day 0) concentration.

RESULTS

Accelerated Degradation and Assay Validation

Degradation of docetaxel with sodium hypochlorite occurred relatively quickly, such that less than 53% of the initial docetaxel concentration remained after 23 min. At least 4 degradation products were observed in the chromatograms (Figure 1, chromatogram B). None of these degradation products interfered with quantification of docetaxel. Degradation of docetaxel at 80°C occurs more slowly, and 56% remained after 5 h. At least 6 degradation products were observed in the chromatograms (Figure 1, chromatogram C). Although the relative amounts differed, the primary degradation products obtained with heat were identical with those obtained through degradation with sodium hypochlorite. None of these degradation products interfered with quantification of docetaxel. As a result of the chromatographic separation of these degradation products from docetaxel and the similarity of the ultraviolet spectrum (200 to 320 nm) between a fresh docetaxel sample and docetaxel in a degraded sample, it was concluded that this analytical method was suitable for indicating stability.^{10,11}

Assay validation demonstrated that deviation from the known concentration for quality control samples and standards on any day averaged less than 2%. Analytical error observed with repeated measurements averaged less than 1% within days and less than 2.5% between days.

Analysis of accuracy and reproducibility during the study period indicated that the docetaxel concentration was measured accurately and reproducibly. For accuracy, the mean of duplicate determinations of standards over the study period showed less than 2% deviation from the expected concentration. For analytical reproducibility, the mean of duplicate determinations of standards (as measured by CV) averaged less than 2% within a day and less than 2.5% between days. These results indicate that differences of 10% or more can be confidently detected¹² with acceptable error rates¹³ with duplicate analysis. System suitability criteria developed to ensure continued acceptable chromatographic performance during the study period required that on each study day the concentration of the mobile phase be adjusted to ensure a retention time for docetaxel between 8.2 and 10 min.

Stability of Docetaxel (10 mg/mL) in Vials

During the 21-day study period, all samples retained more than 95.0% of the initial concentration

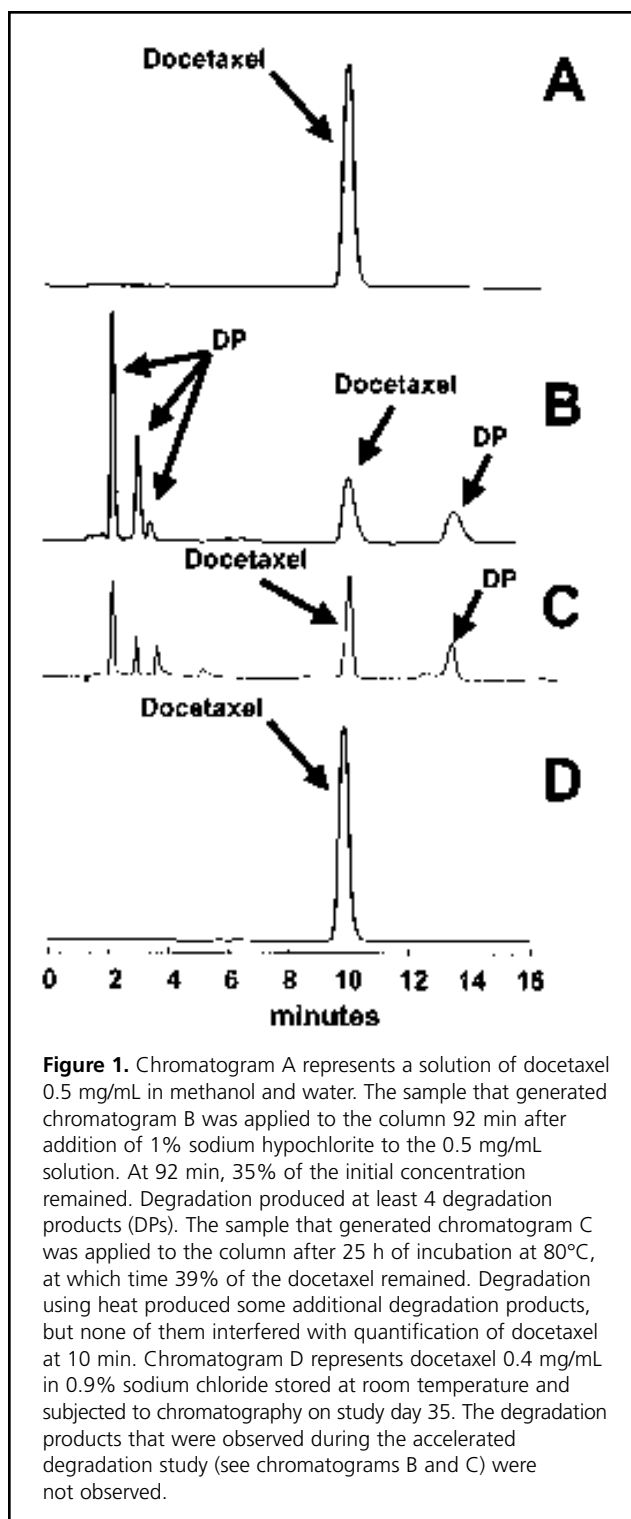


Figure 1. Chromatogram A represents a solution of docetaxel 0.5 mg/mL in methanol and water. The sample that generated chromatogram B was applied to the column 92 min after addition of 1% sodium hypochlorite to the 0.5 mg/mL solution. At 92 min, 35% of the initial concentration remained. Degradation produced at least 4 degradation products (DPs). The sample that generated chromatogram C was applied to the column after 25 h of incubation at 80°C, at which time 39% of the docetaxel remained. Degradation using heat produced some additional degradation products, but none of them interfered with quantification of docetaxel at 10 min. Chromatogram D represents docetaxel 0.4 mg/mL in 0.9% sodium chloride stored at room temperature and subjected to chromatography on study day 35. The degradation products that were observed during the accelerated degradation study (see chromatograms B and C) were not observed.

(Table 1). On day 21, the lowest limit of concentration, with 95% confidence, was calculated as 96.3% (Table 1). Multiple linear regression showed no differences in percent remaining due to temperature ($p = 0.21$) or time ($p = 0.26$), which indicates that there was no trend for

Table 1. Observed Concentration (as Mean Percent of Initial Concentration)* of Docetaxel after Dilution in Ethanol–Polysorbate 80 and Storage in Vials

| Study Day | Room Temperature (23°C) | Refrigerated (4°C) |
|--|-------------------------|--------------------|
| Initial concentration (mg/mL) | 10.0±0.03 | 10.2±0.20 |
| Day 1 | 101.0±1.6 | 101.1±1.2 |
| Day 3 | 96.5±1.1 | 96.2±1.7 |
| Day 4 | 101.8±0.6 | 100.7±1.2 |
| Day 7 | 99.8±1.2 | 101.9±1.2 |
| Day 10 | 103.7±1.0 | 102.5±0.5 |
| Day 14 | 101.7±0.8 | 101.3±0.8 |
| Day 17 | 101.3±1.1 | 100.5±1.7 |
| Day 21 | 100.0±0.4 | 99.6±1.1 |
| % remaining on day 21† | 101.5 | 100.9 |
| Lower limit of 95% CI for % remaining on day 21‡ | 96.6 | 96.3 |

CI = confidence interval.

*Concentrations are expressed as mean percent remaining (\pm standard deviation), relative to concentration on day 0. The means were calculated on the basis of analysis of 3 solutions, each prepared in duplicate and analyzed twice; as such, 12 data points were used in the determination of each mean.

†Percent remaining on day 21 is based on linear regression.

‡Estimated lower limit of percent remaining on day 21, with 95% confidence, based on linear regression.

the concentration to consistently change from day to day during the study. Inspection of chromatograms during the stability study failed to reveal any of the degradation products that were observed during assay validation.

All solutions were initially clear and colourless and remained so for the duration of the study. No visible particles were observed in any of the solutions throughout the study period.

Stability of Docetaxel (0.4 and 0.8 mg/mL) in PABs

During the 35-day study period, all samples retained more than 95.0% of the initial concentration (Table 2). On day 35, the lowest limit of concentration, with 95% confidence, was calculated as 95.9%. Multiple linear regression showed no differences in percent remaining due to formulation (new versus old; $p = 0.16$) or time ($p = 0.34$), which indicates that there was no trend for the concentration to consistently change from day to day during the study. However, a statistically significant difference as small as 2.4% (in terms of docetaxel concentration remaining) was detected ($p = 0.041$).

Inspection of chromatograms during the stability study revealed no measurable amounts of the degradation products that were observed during the accelerated portion of the study (Figure 1, chromatograms B and C). Therefore, degradation could not be detected after storage at room temperature. Because no degradation was detected, estimates of the

degradation rate for docetaxel at room temperature could not be determined with confidence for any solution at either concentration. We were therefore unable to detect differences in degradation rates between the new and the older formulation or between solutions stored at room temperature and at 4°C.

All solutions remained clear and colourless for the duration of the study. With the new formulation, the initial pH values for the 0.4 mg/mL solutions in NS ranged from 5.13 to 5.16, whereas those for the 0.8 mg/mL solutions had an initial pH of 4.80. In contrast, with the old formulation, the initial pH for docetaxel 0.8 mg/mL in NS was 6.71. Over the 35-day study period the pH changed by less than 0.06 of a pH unit in the 4 solutions of docetaxel in NS.

DISCUSSION

Although multiple linear regression of docetaxel concentration for solutions stored in PABs revealed statistically significant differences in amount remaining as small as 2.4% between the 0.4 mg/mL and 0.8 mg/mL solutions, these differences were deemed to be of no practical difference in the evaluation of stability. Demonstrating a trend for the docetaxel concentration to decrease was considered more important than demonstrating a statistical difference in concentration between any 2 days. In fact, the random fluctuations in concentration around the initial concentration are not of practical importance and should be considered “noise” or experimental error, even though these differences, as small as 2.4%, were

Table 2. Observed Concentration (as Mean Percent of Initial Concentration)* of Docetaxel after Dilution in 0.9% Sodium Chloride and Storage in Polypropylene–Polyethylene Copolymer Bags at Room Temperature (23°C)

| Study Day | New Formulation | | Old Formulation | |
|--|-----------------------|------------------------|-----------------|--------------|
| | 0.4 mg/mL (first bag) | 0.4 mg/mL (second bag) | 0.8 mg/mL | 0.8 mg/mL |
| Observed initial concentration (mg/mL) | 0.376±0.0005 | 0.393±0.0025 | 0.634±0.0005 | 0.778±0.0003 |
| Day 3 | 100.3±0.7 | 100.9±0.7 | 98.0±0.5 | 97.1±0.2 |
| Day 7 | 103.5±0.8 | 103.9±0.0 | 99.9±0.4 | 98.2±0.1 |
| Day 14 | 106.0±0.4 | 106.9±0.6 | 102.2±0.4 | 98.7±0.3 |
| Day 25 | 99.5±0.3 | 99.1±1.6 | 99.8±0.2 | 98.2±0.6 |
| Day 35 | 104.9±0.2 | 105.0±0.9 | 100.8±0.4 | 97.2±1.7 |
| % remaining on day 35† | 103.9 | 103.9 | 100.9 | 97.5 |
| Lower limit of 95% CI for % remaining on day 35‡ | 99.6 | 99.1 | 98.9 | 95.9 |

CI = confidence interval.

*Concentrations are expressed as mean percent remaining (± standard deviation), relative to concentration on day 0. The solution in each bag was analyzed in duplicate, and each analysis was replicated; as such, 4 data points were used in the determination of each mean.

†Percent remaining on day 35 is based on linear regression.

‡Estimated lower limit of percent remaining on day 35, with 95% confidence, based on linear regression.

statistically significant. Linear regression indicated that the docetaxel concentration in a vial on day 21 and the docetaxel concentration in a PAB on day 35 was within 4% of the initial concentration and that deviations on any day did not exceed 5%. Assuming no degradation and assuming that all study day determinations represent estimates of an unchanging concentration, the interday reproducibility (expressed as CV) was 1.8% during the evaluation of storage in vials and 2.8% during the evaluation of storage in PABs. This is very similar to the interday reproducibility of 2.5% that was observed with the standards, which is equivalent to assay error.

Given that only small changes in docetaxel concentration were detected under these storage conditions, assurance of the specificity of the analytical method is very important. In addition to our demonstration that the method was accurate and reproducible, the specificity of the analytical method was demonstrated during the accelerated degradation studies (Figure 1). In these studies, a reduction in docetaxel concentration was observed as the concentration of apparent degradation products increased. Furthermore, the samples that we used for degradation at 80°C simulated closely our study samples (similar concentration and pH); therefore, the degradation process used here probably produced degradation products similar to those that would be produced in study samples over a prolonged period (e.g., several years). The separation and detection of intact drug in the presence of degradation compounds must be assured before the method can be

considered suitable for indicating stability,^{10,11} as was shown here for docetaxel (see Figure 1).

The expiry dates determined in this study should be implemented in practice only after due consideration of sterility and the contamination rate of individual IV additive programs. Extension of the expiry date for this product beyond 4 h following dilution in NS is of considerable importance to efficiency. Extension of the docetaxel expiry date to 35 days in our IV additive service has eliminated wastage.

In conclusion, vials of docetaxel diluted according to the manufacturer's instructions to prepare a 10 mg/mL ethanol and polysorbate 80 solution retained more than 95% of their initial concentration when stored at either 4°C or 23°C for 21 days. In addition, docetaxel solutions that were further diluted with NS to concentrations of 0.4 or 0.8 mg/mL and stored in PABs at room temperature retained more than 95% of their initial concentration for 35 days.

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Scott E Walker, MScPhm, FCSHP, is Co-ordinator of Research and Quality Control in the Department of Pharmacy and Division of Clinical Pharmacology at Sunnybrook Health Sciences Centre and is an Associate Professor, Faculty of Pharmacy, University of Toronto, Toronto, Ontario. He is also an Associate Editor with *CJHP*.

Flay Charbonneau, BScPharm, is Pharmacy Manager, Toronto Sunnybrook Regional Cancer Centre, Sunnybrook Health Sciences Centre, Toronto, Ontario.

Shirley Law, DipPharmTech, is a Research Assistant in Quality Control, Department of Pharmacy, Sunnybrook Health Sciences Centre, Toronto, Ontario.


Address correspondence to:

Scott Walker
 Department of Pharmacy
 Sunnybrook Health Sciences Centre
 2075 Bayview Avenue
 Toronto ON
 M4N 3M5

e-mail: scott.walker@sunnybrook.ca

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