Stability of docetaxel diluted to 0.3 or 0.9 mg/mL with 0.9% sodium chloride injection and stored in polyolefin or glass containers

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Purpose. The stability of docetaxel diluted to 0.3 or 0.9 mg/mL with 0.9% sodium chloride injection and stored in polyolefin or glass containers was studied.

Methods. Vials of docetaxel injection concentrate were reconstituted with the entire contents of the solvent vial and carefully homogenized to avoid the formation of foam. Solutions were aseptically prepared with nominal docetaxel concentrations of 0.3 and 0.9 mg/mL by adding the appropriate quantities to polyolefin containers or glass bottles, to which had been added the appropriate volume of 0.9% sodium chloride injection, yielding a final volume of 50 mL. Three identical polyolefin containers and one control glass bottle for each concentration were prepared. All test solutions were stored at 19–21°C and protected from light. Chemical stability was measured by using a stability-indicating high-performance liquid chromatographic (HPLC) assay with ultraviolet-light detection. Physical stability was determined by visual inspection.

Results. No evidence of precipitation was observed during the first 24 hours of the study. However, after a day of storage, the HPLC assay revealed large relative standard deviation values for diluted docetaxel solutions in some containers. These values were predictive for the formation of precipitates and compatible with the existence of microprecipitates at 24 hours. These results suggest that the diluted docetaxel infusions were not stable when stored at 19–21°C.

Conclusion. Docetaxel 0.3 and 0.9 mg/mL in 0.9% sodium chloride injection was not physically stable for more than one day when stored at 19-21°C. Docetaxel stability in diluted solutions appears sensitive to slight changes in temperature and degree of agitation.

Index terms: Antineoplastic agents; Chromatography, liquid; Concentration; Containers; Diluents; Docetaxel; Glass; Polyolefin; Precipitation; Sodium chloride; Stability; Storage; Temperature

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Docetaxel is approved for the adjuvant treatment of locally advanced and metastatic breast cancer, non-small-cell lung cancer, and prostate cancer. Docetaxel acts by promoting the assembly of tubulin into stable microtubules and inhibits their disassembly, which leads to a marked decrease of free tubulin and eventually to cancer cell death.

Docetaxel belongs to the taxoid family. It is prepared by a semisynthetic process, beginning with a precursor extracted from the renewable needle biomass of yew trees. Because docetaxel has an extremely poor aqueous solubility, the agent has been formulated in polysorbate 80.

The Taxotere (Sanofi Aventis) brand of docetaxel is a concentrate for infusion and is available in vials containing 20 or 80 mg of docetaxel (anhydrous). The composition of the viscous solution is identical for both vial sizes (40 mg/mL). The accompanying solvent contains 13% ethanol in water for injection.

The European Medicines Agency’s summary of product characteristics for Taxotere states that docetaxel infusion solution should be used within four hours after preparation and should be aseptically administered as a one-hour infusion in room temperature (below 25°C) and normal lighting conditions.

Some studies have found that docetaxel is stable for longer periods.

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Thiesen and Krämer found that docetaxel was chemically and physically stable for four weeks when prepared in polyolefin containers but not in polyvinyl chloride (PVC) bags. A recent study conducted by Jané et al. found that docetaxel was stable for seven days when stored at room temperature or under refrigeration. Dalle et al. found that docetaxel in PVC or low-density polyethylene bags was stable when stored for 48 hours at 6 °C and protected from light and then exposed to light and room temperature for 4 hours.

Because there is considerable variability in the stability data for docetaxel, this study was conducted to determine the stability of docetaxel when diluted in 0.9% sodium chloride injection in polyolefin and glass containers and stored at between 19 °C and 21 °C.

Methods

Sample preparation. Vials of docetaxel injection concentrate (80 mg each) were reconstituted with the entire contents of their accompanying solvent vials and carefully homogenized to avoid the formation of foam. This process yielded a nominal drug concentration of 10 mg/mL.

Solutions were aseptically prepared with nominal docetaxel concentrations of 0.3 and 0.9 mg/mL by adding the appropriate quantities of docetaxel 10-mg/mL solution either to Baxter Viaflo polyolefin containers or to glass bottles to which had been added the appropriate volume of 0.9% sodium chloride injection to result in a final volume of 50 mL.

Three identical polyolefin containers and one control glass bottle for each concentration were prepared. All test solutions were stored at 19–21 °C and protected from light.

High-performance liquid chromatographic assay. A modification of the stability-indicating high-performance liquid chromatographic (HPLC) method developed by Thiesen and Krämer was used for the docetaxel assay. The modification was made to simplify and quicken the method. More complex chromatographic methods to test docetaxel stability have been described elsewhere.

The instrumentation included a binary-flow solvent-delivery system, a C18 column maintained at room temperature, a variable-volume injector, an ultraviolet-light detector, and a recording integrator. The mobile phase consisted of acetonitrile and water (50:50, v/v) in isocratic mode. The mobile phase was filtered, and an in-line degasser was used. The flow rate was set at 1.0 mL/min, and the detector was set at 232 nm; the run time was nine minutes.

The analytic method for docetaxel was demonstrated to be stability indicating by accelerated degradation. Sample solutions of docetaxel 0.5 mg/mL were exposed to ultraviolet light for 72 hours. Also, the pH of docetaxel 0.3-mg/ml solutions was adjusted to 11 with 2 N sodium hydroxide and to 0.5 with 1 N hydrochloric acid and stored for 2 and 36 hours, respectively. Finally, samples of 0.3–mg/mL docetaxel sample solutions were oxidized with 3% hydrogen peroxide for 48 hours. Complete degradation of the parent compound was observed within the basic solution, approximately 45% degradation was observed within the acid solution, 41% degradation was observed within the oxidized solution, and 92–100% degradation was observed with ultraviolet-light exposure. There was no interference with the peak of the intact drug by the degradation product peak. The standard peak for docetaxel appeared at 4.58 minutes. Unidentified degradation peaks at 1.5 minutes were noted after oxidation, basic degradation, and ultraviolet-light exposure; another peak appeared at 5.071 minutes after ultraviolet-light exposure.

Preparation of standard solution and standard curve. A stock solution containing 2 mg of docetaxel per milliliter was prepared in HPLC-grade ethanol and stored at ~70 °C in glass vials until use. A working solution of 1 mg/mL was obtained by diluting with HPLC-grade water. Standard samples of docetaxel were prepared by diluting the working solution with water to 0.1, 0.2, 0.3, 0.4, 0.6, 0.7, 0.9, and 1 mg/mL. Three external quality-control samples were prepared and assayed in every run (0.25, 0.5, and 0.8 mg/mL). The standard curve was produced using linear regression of the peak areas of docetaxel against the docetaxel concentration. The standard curve was linear (r^2 > 0.998) over the working range of concentrations. The linearity of the method was evaluated in triplicate at the eight concentrations listed above. The limit of quantification was 0.1 mg/mL, with less than 20% deviation from the nominal value.

The precision and accuracy of the analytic method were assessed by processing the quality controls in quintuplicate in three different runs. For the 0.25-mg/mL quality controls, the within-day relative standard deviation (RSD) was 1.4–1.7%, the interday RSD was 2.5%, and the mean ± RSD measured percentage was 101.0 ± 2.5%. For the 0.5- and 0.8-mg/mL controls, the corresponding values were 0.2–0.7%, 3.0%, and 101.0 ± 3.0% and 0.4–1.1%, 5.9%, and 97.7 ± 5.9%, respectively.

Sample analysis. Samples of 1.5 mL were withdrawn immediately after the preparation of test solutions and after 1, 7, and 14 days and assayed immediately without being filtered or diluted. The bottles were agitated for a few minutes in a rotating shaker before a sample for analysis was withdrawn. Five microliters of the samples was injected into the HPLC system. HPLC determinations were performed in triplicate for each sample of each test solution. Assay samples were removed aseptically from the infusion bags and glass
bottles; however, sterility was not evaluated and was not analyzed in this study.

Physical stability was determined by visual inspection with the unaided eye. Test solutions were visually examined in normal laboratory fluorescent light for color change and evidence of precipitation whenever aliquots were withdrawn.

**Data analysis.** The stability of docetaxel was assessed by measuring the percentage of the initial concentration remaining at the end of each time interval. The initial concentration of docetaxel was defined as 100%. Stability was defined as retention of at least 90% of the initial docetaxel concentration.6,7

**Results and discussion**

Diluted docetaxel infusions showed limited physical stability when 0.9% sodium chloride was used as the vehicle and solutions were stored between 19 °C and 21 °C, independent of the storage container used (Table 1). Precipitation was a generalized phenomenon at day 7, especially in glass containers.

No evidence of precipitation was observed in any of the solutions within the first 24 hours of the study. However, after a day of storage, the assay revealed concentrations with large standard deviations for some containers. Precipitates were apparent at seven days in both glass bottles and in one of the polyolefin containers originally holding docetaxel 0.9 mg/mL. At the same study time, one polyolefin container originally containing docetaxel 0.3 mg/mL had lost nearly half its drug content and had substantial variability among its triplicate assays; no precipitate was evident at the time. One week later, a precipitate was apparent in the container. The values obtained with the HPLC assay were predictive for the formation of precipitates and compatible with the existence of microprecipitates at the moment of the assay at 24 hours. No sign of chemical instability was detected in the test solutions containing less than 90% of the initial docetaxel concentration.

The results of this study support the administration of Taxotere within four hours of preparation, the limit specified in the product's technical brochure. However, there is a clear discrepancy between the results of this study and previously published data.2-4 Physical rather than chemical stability seems to be the important issue. When the assay showed that less than 90% of initial docetaxel was present, only one peak corresponding to intact docetaxel appeared in chromatograms. No published reports provide evidence of chemical degradation of docetaxel in diluted solutions for infusion. The loss of docetaxel reported by Thiesen and Krämer2 was attributed to physical instability.

The instability observed cannot be explained by the composition of the containers, since these materials do not promote degradation or precipitation of docetaxel.2,3 Other conditions, such as temperature and agitation, could explain the findings of the current study.

The temperature in these experiments, maintained under 21 °C, was lower than that used by Thiesen and Krämer2 (25 °C). All containers in this study were prepared simultaneously and stored together. Test solutions were kept in the centralized i.v. admixture area, where temperature is strictly maintained at 19–21 °C. Another important difference is that the diluted solutions used in this study were agitated before samples were withdrawn for analysis.

These two differences combined could lead to the formation of crystallization nuclei, a critical event that accelerates precipitation in supersaturated solutions of drugs with poor water solubility. The physical instability observed in glass contain-

| Table 1. Stability of Docetaxel 0.3 and 0.9 mg/mL in 0.9% Sodium Chloride Injection* |
|---------------------------------|------------------|------------------|------------------|
| **Nominal Docetaxel Concentration and Container** | **Actual Initial Docetaxel Concentration (mg/mL)** | **Mean ± S.D. % Initial Concentration Remaining** |
| | **1 Day** | **7 Days** | **14 Days** |
| 0.3 mg/mL | | | |
| Polyolefin 1 | 0.322 ± 0.004 | 101.0 ± 1.1 | 100.6 ± 1.1 | 99.8 ± 1.2 |
| Polyolefin 2 | 0.322 ± 0.002 | 100.6 ± 0.3 | 99.5 ± 0.2 | 99.3 ± 0.5 |
| Polyolefin 3 | 0.312 ± 0.005 | 108.8 ± 13.4 | 55.3 ± 37.7 | Precipitate |
| Glass | 0.307 ± 0.003 | 93.9 ± 8.9 | Precipitate | Precipitate |
| 0.9 mg/mL | | | |
| Polyolefin 1 | 0.869 ± 0.006 | 99.9 ± 0.8 | 99.5 ± 0.6 | Precipitate |
| Polyolefin 2 | 0.882 ± 0.006 | 99.9 ± 0.5 | 100.0 ± 0.9 | Precipitate |
| Polyolefin 3 | 0.883 ± 0.004 | 100.7 ± 1.7 | Precipitate | Precipitate |
| Glass | 0.883 ± 0.005 | 100.2 ± 3.6 | Precipitate | Precipitate |

*Mean ± S.D. calculated from triplicate assays on single samples from each container.
ers stresses the importance of storage temperatures under 21 °C and agitation—rather than container composition—as contributing factors to docetaxel physical instability. Agitation and refrigeration were specifically avoided in the study by Thiesen and Krämer, which may explain the absence of precipitation in their solutions.

The European Medicines Agency’s scientific discussion for the approval of Taxotere reported that a study showed that docetaxel infusion solution (in 0.9% sodium chloride or 5% dextrose injection) remained clear for up to six hours after preparation, whether stored in PVC or polyolefin bags. These results contributed to the recommendation that the infusion solution be administered within four hours of preparation. This seems short in light of the longer periods specified for the chemically related drug paclitaxel.

Published data and the results of the current study suggest that the physical stability of diluted docetaxel solutions is very labile and can be strongly affected by small variations in handling conditions. Because it is difficult to maintain very-well-controlled conditions in clinical practice and outside the pharmacy, it is not advisable to store docetaxel infusion solutions for periods exceeding the time (four hours) established by the manufacturer.

**Conclusion**

Docetaxel 0.3 and 0.9 mg/mL in 0.9% sodium chloride injection was not physically stable for more than one day when stored at 19–21 °C. Docetaxel stability in diluted solutions appears sensitive to slight changes in temperature and degree of agitation.

**References**