Stability of Dr. Reddy's Cabazitaxel Following Reconstitution with Manufacturer's Diluent & Dilution with Sodium Chloride and Dextrose 5% in non-PVC non-DEHP bags and Original Glass Vials at 25°C, 4°C and -20°C

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INTRODUCTION

Cabazitaxel (Jevtana®) is a chemotherapy agent used for treating prostate cancer. The product monograph indicates once cabazitaxel is reconstituted with the provided diluent, the solution is stable for 1 hour at room temperature (15-30°C). After the final dilution in the infusion bag with either 0.9% sodium chloride or 5% dextrose, the infusion solution can be stored up to 8 hours at room temperature or 48 hours under refrigerated conditions (2-8°C).

A previous study has reported the stability of Jevtana® to be 8 days when stored at 25°C and 40 days at 4°C[1] and another reported the infusion solution retains >95% for at least 4 week when stored at 25°C[2]. However, neither study used confidence intervals to calculate the beyond-use-date (BUD).

The introduction of a generic version of cabazitaxel (Dr. Reddy) raised questions of the stability of the generic formulation and the validity of extending stability from one brand to another.

OBJECTIVES

The first objective of the study was to evaluate the stability of Dr. Reddy's cabazitaxel formulation diluted to concentrations of 0.1 or 0.26mg/mL with 0.9% sodium chloride (NS) or 5% dextrose (D5W) stored in non-PVC non-DEHP bags over 21 days at room temperature (25°C) and in the refrigerator (4°C).

The second objective was to evaluate stability of Dr. Reddy's cabazitaxel when stored in a freezer (-20°C) over 49 days diluted in NS and D5W to concentrations of 0.1 and 0.26mg/mL stored in non-PVC non-DEHP bags as well as cabazitaxel reconstituted with the manufacturer's diluent to a concentration of 10mg/mL and stored in the original glass vial.

The concentration of cabazitaxel was evaluated during storage at each temperature using a validated, stability indicating, liquid chromatographic method using UV detection.

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[1]: Shao Y, *et al.* Europ J Pharmaceutical Sci. 2014;52:1-11.
[2]: Lazzarini R, *et al.* Europ J Hosp Pharm. 2014;22:150-155.

NONE of the authors of this poster have any personal or financial relationships with any commercial entities that may have a direct or indirect interest in the subject matter of this presentation.
The cabazitaxel used in this study was donated by Dr. Reddy

METHODS

Liquid Chromatographic Method

The liquid chromatographic system consisted of a mixture of 54% acetonitrile and 46% 0.05M phosphoric acid which was pumped through 250mm x 4.6mm reverse-phase C18, 5µm column (Supelcosil ABZ+; Supelco, Toronto, ON) at 1.0 mL/min. The effluent was monitored with UV detection at 230nm.

Assay Validation

The method was evaluated to ensure reproducibility, accuracy and assay specificity. The system was shown to be capable of separating cabazitaxel from its degradation products (Figure 1). Accuracy and reproducibility of standard curves was tested over 5 days. Inter- and intra-day errors of reproducibility were assessed by the coefficients of variation and the standard deviation of regression.

Stability Study

On study day 0, 33 x 60mg vials of cabazitaxel (Dr. Reddy; Lot: H200009; Expiry: Mar-23) were each reconstituted with the supplied diluent, then further diluted in NS or D5W to concentrations of 0.1 and 0.26mg/mL in non-PVC non-DEHP bags. Four bags of each diluent and concentration were stored at 25°C and 4°C. Concentration and physical inspection were completed on study days 0, 1, 2, 3, 4, 5, 7, 9, 11, 14, 18, and 21.

An additional four bags of each diluent and concentration were stored at -20°C along with four vials of cabazitaxel reconstituted with the supplied diluent to a concentration of 10mg/mL and kept in the original glass vials. Concentration and physical inspection were completed on study days 0, 7, 14, 21, 28, 35, 42, and 49.

Data Reduction and Statistical Analysis

The concentration of a solution on a particular day was considered "acceptable" or "within acceptable limits" if it was greater than 90% of the initial concentration (as determined on day 0) and the amount found on that day, with 95% confidence, was also greater than 90% of the initial concentration.

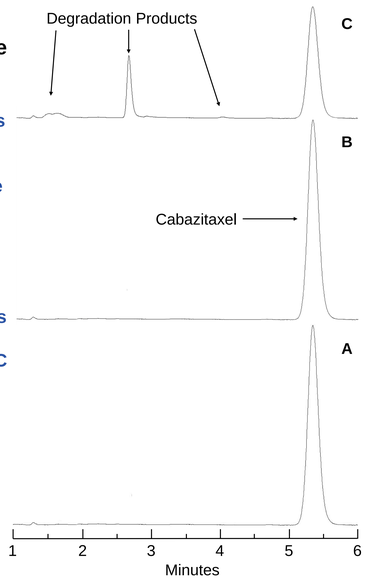
Analysis of variance was used to test differences in degradation rate between the different storage temperatures and container combinations. The 5% level was used as the *a priori* cut-off for significance.

RESULTS

Assay Validation

Assay validation demonstrated that degradation products are separated from cabazitaxel (Figure 1). Standards and quality control samples over the study period showed an average absolute deviation of 0.93% from the expected concentration. Analytical error with replicate measurement (as measured by coefficient of variation) averaged 0.51% within a day, 1.04% between days and the standard deviation of regression averaged 1.63%.

Figure 1. Representative Chromatograms



Chromatogram A represents a solution of 0.26 mg/mL cabazitaxel in NS on day 0. Chromatogram B shows the same sample after 21 days of storage at room temperature with 99% remaining.

Chromatogram C represents a solution of cabazitaxel at pH 1.10 after storage at 60°C for 8 hours with 13% of the initial concentration remaining.

Cabazitaxel eluted at 5.3 minutes and degradation products eluted at 1.6, 2.7, and 4.0 minutes.

Concentration Results

Concentrations on each study day are reported in Tables 1 and 2. All solutions stored at room temperature (25°C), in the refrigerator (4°C), and in the freezer (-20°C) retained more than 95% of the initial concentration for the entire study duration in all diluents and concentrations. The calculated beyond-use-date, with 95% confidence, exceeded the 21 day study period for solutions stored at room temperature and in the fridge, and the 49 day study period for solutions stored in the freezer.

Analysis of variance revealed significant differences in percent remaining due to study day ($p<0.01$), diluent ($p<0.01$) and temperature ($p<0.01$), but not concentration ($p=0.18$). The study was capable of detecting a 0.93% difference in concentration due to study day, temperature, concentration or container.

CONCLUSIONS

Dr. Reddy's cabazitaxel concentrations between 0.1 and 0.26mg/mL, diluted in either NS or D5W and stored in non-PVC non-DEHP minibags are physically and chemically stable for at least 21 days when stored at 25°C, 4°C and at least 49 days when stored at -20°C.

When reconstituted with the manufacturer's diluent to a concentration of 10mg/mL and stored in the original glass vial, Dr. Reddy's cabazitaxel is stable for at least 49 days.

When establishing a BUD, both the stability of the components and the sterility limits established by NAPRA/USP 797 must be considered.

Table 1. Percent Remaining of the Initial Cabazitaxel Concentration when stored at Room Temperature and in Refrigerator.

Diluent	D5W	NS	D5W	NS	D5W	NS	D5W	NS
Storage Temperature	4°C	4°C	4°C	4°C	25°C	25°C	25°C	25°C
Nominal Initial Concentration (mg/mL)	0.10	0.10	0.26	0.26	0.10	0.10	0.26	0.26
Actual Initial Concentration (mg/mL ± Coefficient of Variation)	0.11 ± 1.30	0.11 ± 5.15	0.25 ± 0.68	0.26 ± 2.38	0.11 ± 3.51	0.10 ± 3.40	0.25 ± 2.68	0.24 ± 2.12
Study day 1	99.03 ± 0.60	99.15 ± 0.46	100.32 ± 0.30	100.14 ± 0.95	99.91 ± 0.43	100.02 ± 0.51	99.95 ± 0.80	99.61 ± 0.81
Study day 2	98.88 ± 2.58	100.01 ± 0.58	98.97 ± 1.49	99.823±1.24	99.54±1.05	101.55±0.30	98.97±1.48	99.46±0.24
Study day 3	100.22 ± 1.07	99.60 ± 0.65	100.98 ± 1.08	100.24±1.68	100.04±0.90	99.67±0.49	100.42±0.98	99.87±1.65
Study day 4	99.50 ± 0.80	99.46 ± 0.18	99.83 ± 0.54	99.74±0.36	100.11±0.42	101.43±0.63	98.66±1.80	99.16±0.97
Study day 5	100.37 ± 0.97	99.31 ± 1.04	100.88 ± 0.93	100.64±0.65	100.17±0.92	99.86±1.76	100.78±1.26	100.34±1.06
Study day 7	100.14 ± 0.34	100.71 ± 0.57	100.47 ± 0.88	100.99±0.78	102.19±1.70	102.51±1.58	100.60±1.10	101.67±1.67
Study day 9	98.42 ± 0.61	98.42 ± 0.40	98.17 ± 0.07	98.22±0.57	99.13±0.66	99.63±1.01	98.40±1.53	97.93±1.41
Study day 11	99.52 ± 1.05	99.10 ± 0.56	99.54 ± 1.34	99.26±0.57	98.52±0.96	103.25±2.93	98.64±1.95	100.54±0.40
Study day 14	100.39 ± 1.05	99.97 ± 0.55	100.19 ± 1.33	99.91±0.57	96.60±1.55	102.63±4.80	99.03±2.14	101.85±2.76
Study day 18	98.03 ± 0.93	97.83 ± 0.48	99.27 ± 0.73	99.31±0.49	98.93±1.25	103.51±2.51	98.86±2.46	99.52±0.66
Study day 21	98.74 ± 1.23	98.54 ± 0.62	99.68 ± 0.50	99.86±0.56	98.70±1.23	102.89±2.78	99.88±1.29	99.22±0.80
Degradation Rate (%/day) [Slope]	-0.047	-0.067	-0.033	-0.032	-0.105	0.162	-0.035	0.006
Std Deviation of Regression [Sy.x]	0.779	0.695	0.810	0.705	1.166	1.079	0.851	1.133
Confidence Interval for Slope	0.076	0.068	0.080	0.069	0.114	0.106	0.084	0.111
Fastest Degradation Rate	-0.123	-0.135	-0.113	-0.101	-0.219	0.056	-0.118	-0.106
Shortest T-90 in days (95% CI)	81.07	74.11	88.76	98.85	45.65	37.26	84.37	94.55

Table 2. Percent Remaining of the Initial Cabazitaxel Concentration when stored in Freezer.

Diluent	D5W	NS	D5W	NS	MD[1]
Storage Temperature	-20°C	-20°C	-20°C	-20°C	-20°C
Nominal Initial Concentration (mg/mL)	0.10	0.10	0.26	0.26	10
Actual Initial Concentration (mg/mL ± Coefficient of Variation)	0.10 ± 0.98	0.098 ± 2.69	0.24 ± 2.56	0.23 ± 4.92	10.1 ± 1.14
Study day 7	100.72 ± 1.10	102.08 ± 1.46	103.39 ± 2.12	103.07 ± 1.19	98.58 ± 4.52
Study day 14	99.49 ± 0.43	101.60 ± 1.17	102.24 ± 1.70	102.65 ± 1.17	99.91 ± 1.00
Study day 21	98.74 ± 0.95	101.51 ± 0.45	102.56 ± 1.83	103.19 ± 1.40	99.64 ± 0.74
Study day 28	100.15 ± 2.56	101.97 ± 0.32	100.31 ± 2.38	107.74 ± 6.28	98.43 ± 1.47
Study day 35	100.91 ± 1.20	103.55 ± 1.53	102.60 ± 1.18	105.92 ± 4.30	98.04 ± 0.38
Study day 42	102.79 ± 2.04	105.53 ± 1.26	104.40 ± 1.53	105.55 ± 1.24	103.42 ± 2.52
Study day 49	101.18 ± 0.67	101.73 ± 1.97	101.27 ± 1.21	102.09 ± 1.16	99.01 ± 3.60
Degradation Rate (%/day) [Slope]	0.041	0.061	0.019	0.070	0.018
Std Deviation of Regression [Sy.x]	1.073	1.373	1.565	2.325	1.800
Confidence Interval for Slope	0.058	0.074	0.084	0.125	0.097
Fastest Degradation Rate	-0.017	-0.013	-0.065	-0.055	-0.079
Shortest T-90 in days (95% CI)	602.55	743.98	153.08	181.88	125.96

[1]: Manufacturer's provided diluent: 13% (w/w) ethanol in water for injection