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Physical and chemical stability of docetaxel infusions in polyolefin bags containing 0.9% sodium chloride or 5% glucose at 5°C and 25°C

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Abstract

Study objectives: To investigate the long-term physical and chemical stability of 0.3 mg/mL and 0.7 mg/mL infusions of docetaxel (Teva) in polyolefin bags containing either 0.9% sodium chloride or 5% glucose, stored under refrigerated (2°C–8°C) and room temperature (25°C) conditions protected from the light.

Methods: The infusions were prepared aseptically and stored at the two temperatures for 56 days. At various time points, chemical stability was determined using a validated stability-indicating, high performance liquid chromatography (HPLC) assay. Physical stability was ascertained in terms of visual appearance, pH, weight change of infusions, and sub-visible particles counts.

Results: Irrespective of drug concentration, diluent type, or storage temperature, docetaxel infusions were compliant with both physical and chemical acceptance criteria over the 56-day study period.

Conclusion: This study has demonstrated the extended stability of docetaxel (Teva) infusions over the concentration range 0.3–0.7 mg/mL in polyolefin bags containing either 0.9% sodium chloride or 5% glucose and stored at either 2°C–8°C or 25°C. These findings will enable pre-preparation and storage of these infusions by Centralised Intravenous Additive Services (CIVAS) units and the application of dose-banding schemes. As with all infusions where physical stability is potentially limited, docetaxel infusions should be carefully inspected for precipitation both before and during use irrespective of the storage period before use.

Keywords

Chemotherapy, docetaxel, dose-banding, high performance liquid chromatography, stability

Introduction

Docetaxel is an anticancer agent belonging to the taxane group. It is semi-synthesised from a substance extracted from the needles of the European yew tree, *Taxus baccata*. Docetaxel is licensed for use in the EU as mono- or combination therapy against cancer of the breast, lung, prostate, head and neck, and stomach [1].

Docetaxel (Teva) is supplied as an 80 mg concentrate containing polysorbate 80 and absolute ethanol co-solvents, and a separate solvent vial of water for injection. Once mixed, a solution of 10 mg/mL is produced and this is further diluted in 5% glucose or 0.9% sodium chloride to a maximum concentration of 0.74 mg/mL. According to the manufacturer, these infusions should be used within four hours at room temperature (< 25°C) [1]. There is a lack of data relating to long-term stability of docetaxel infusions that would support advanced preparation by pharmacy Centralised Intravenous Additive Services (CIVAS) units or would enable inclusion of this drug in dose-banding schemes [3, 4]. Dose-banding requires extended stability as infusions or pre-filled syringes are prepared in advance, often in a CIVAS unit, and then held in the oncology clinic until use [3, 4].

The aim of the study was to investigate the extended physical and chemical stability of docetaxel over the concentration range 0.3–0.7 mg/mL in 5% glucose and 0.9% sodium chloride infusions under refrigerated (5°C ± 3°C) and ambient (25°C ± 1°C) storage conditions over 56 days. Docetaxel is almost insoluble in water and is formulated with ethanol and polysorbate 80 co-solvents to facilitate dissolution. Infusions of docetaxel are effectively supersaturated micellar solutions, and as such are likely to exhibit physical instability over time. Assessment of physical stability was considered to be crucial in this study and this was monitored by visual inspection and by measuring pH, weight change, and sub-visible particle counts. Chemical stability was measured using a validated, stability-indicating high performance liquid chromatography (HPLC) assay.

Materials and methods

Materials

Vials containing docetaxel concentrate 28 mg/mL, (batch number 7221209, expiry 06/2011) and vials containing

docetaxel solvent (batch number 7221209) were supplied by Teva Pharmaceuticals, Leeds, UK. The 250 mL polyolefin (Viaflo®) infusion bags, containing 0.9% sodium chloride (batch number 10E11E2H, expiry 04/2013) and 5% glucose (batch number 10E05E7M, expiry 04/2013) were supplied by Baxter Healthcare, Newbury, UK. All pharmaceuticals were used within their expiry date. All other reagents and chemicals were of analytical or HPLC grade (Fisher Scientific, Loughborough, UK).

Methods

Preparation of docetaxel infusions

All docetaxel infusions were prepared according to the principles of Good Pharmaceutical Manufacturing Practice in a Class II safety cabinet under 'Grade A' aseptic conditions. Docetaxel infusions, at nominal concentrations of 0.3 mg/mL and 0.7 mg/mL, were prepared in 0.9% sodium chloride and 5% glucose in polyolefin bags. Prior to the addition of the docetaxel solution a volume of diluent equal to the volume of drug solution to be added was first withdrawn from the bags. After addition of docetaxel solution, the bags were gently inverted to ensure mixing.

Six infusions of each concentration and diluent combination were stored in blue polythene overwraps to protect from light and placed at either 5°C ± 3°C in a LEC pharmaceutical grade refrigerator or at 25°C ± 1°C in a Gallenkamp incubator. The infusion bags were removed at specified time points and brought to room temperature prior to sampling and analysis. Samples were withdrawn under aseptic conditions and analysed for physical stability in duplicate (colour and clarity, weight loss, sub-visible particle counts, and pH) and chemical stability in triplicate using a stability-indicating HPLC assay. The remaining infusion of each concentration/diluents combination was held as a spare. All infusion bags, including those designated for chemical analysis or as spares, were visually inspected for clarity and colour.

Samples were analysed immediately after preparation (t = 0) and at the following scheduled time intervals: t = 7, 14, 28, 42, 56 days.

Chromatographic conditions

Docetaxel concentrations were determined using a stability-indicating reverse-phase HPLC method. The system comprised a model PU-2089 Plus pump, a model AS-2057 Plus autosampler with in-line degasser, a model CO-2060 Plus column oven, a model MD-2010 Plus diode array detector, and ChromPass (version1.7403.1) software (all from Jasco Ltd, Essex, UK). Mobile phase comprised 52% acetonitrile: 40% sodium acetate buffer pH 5.0. Docetaxel separation and quantitative analysis were achieved on a Waters Spherisorb® ODS2 5 µm column (2.1 mm x 150 mm, serial number 0161373341) (Waters Ltd, Hertfordshire, UK) with a flow rate of 0.3 mL/min and a 227 nm detection wavelength. The acquisition run-time was seven minutes for each injection. Samples were diluted in distilled water and injected in duplicate 'bracketed' by an injection of a freshly-prepared standard (0.1 mg/mL) stored at 2°C–8°C.

HPLC method validation

Linearity of response

Duplicate injections of seven concentrations over the range 20–160 µg/mL were subjected to the HPLC assay described above. Mean peak height data were fitted by least squares regression to give the equation y = 0.004 x -0.005, r^2 = 0.994.

Intra-day precision

Replicate samples (n = 5) of docetaxel 0.1 mg/mL were injected on the same day using the above assay. The RSD was 0.70%.

Inter-day precision

Replicate samples (n = 5) of docetaxel 0.1 mg/mL were injected on five consecutive days using the above assay. The RSD was 1.24%.

Stability indication

Docetaxel solution (1 mg/mL) was subjected to treatment with either 0.1 M HCl, 0.1 M NaOH, 3% H_2O_2, and heat (all at 50°C for 30 minutes) and then analysed using the above HPLC method. Results are presented in Table 1. No docetaxel peak was seen in the solution subjected to alkaline hydrolysis, either under the above conditions or in repeated experiments using milder conditions (ambient temperature for 10 minutes). Peak purity of the docetaxel peak was > 0.9 in each case. In all cases, no additional peaks were present and no interference of the analyte peak was apparent. It was concluded that the assay was responsive to docetaxel degradation and was suitable for the purposes of this study.

Column performance and peak symmetry were assessed throughout the study using the 2011 British Pharmacopoeial methods [2].Tailing factor ranged from 1.311–1.483 whilst the number of theoretical plates was typically > 2000. This level of performance was considered acceptable for this study.

Table 1: Stability-indicating ability of the HPLC assay for docetaxel

Treatment	Action 1	Action 2	Action 3	Retention time of docetaxel peak	Docetaxel peak height with respect to control (%)	No. of additional peaks
Control	None	2°C–8°C control	None	4.747	N/A	0
Acid hydrolysis	1 mL 0.1 HCl	50°C for 30 min	1 mL 0.1 NaOH	4.800	32.08	0
Alkaline hydrolysis	1 mL 0.1 NaOH	50°C for 30 min*	1 mL 0.1 HCl	N/A	0	0
Oxidation	1 mL 3% H_20_2	50°C for 30 min	None	4.674	103.51	0
Thermal degradation	1 mL water	50°C for 30 min	None	4.634	103.55	0

*No docetaxel was recovered when the alkaline hydrolysis at ambient temperature was repeated with a treatment time of only 10 minutes.

pH measurement

A combination pH electrode and a multi-parameter Orion 5-Star pH meter (Fisher Scientific, Loughborough, UK) calibrated with standard pH 4.0 and 7.0 reference solutions prior to sample measurement was used to measure the pH of duplicate infusions from which the mean was recorded.

Weight change

Infusion bags were weighed before and after sampling on an electronic precision balance (model SG-601, Fisher Scientific, Loughborough, UK, resolution 0.01 g). Percent weight decrease or increase was expressed as the mean of two identical infusion bags.

Visual inspection

Infusions were visually inspected under standard laboratory lighting against dark and light backgrounds for changes in clarity, colour, and presence of particulate matter.

Sub-visible particle counts

Counts of 10 µm and 25 µm diameter particles were performed on 3 x 1 mL infusion samples on a LiQuilaz LS200 Particle Counter (Particle Measuring Technique GB Ltd, Malvern, UK). Average cumulative counts of duplicate infusions were recorded. The instrument was calibrated externally.

Acceptance criteria

Stability of infusions at a given sampling point was confirmed if the following conditions were met:

docetaxel assay: 95–105% with respect to initial drug concentration

pH: change is < 0.5 pH units with respect to initial pH

weight change: < 0.2% w/w

appearance: infusions remain clear and colourless

sub-visual particles: measured for comparative use and to support visual observations.

Results

Data for the physical stability (mean of duplicate infusions) and chemical stability (mean of triplicate infusions) of docetaxel over a period of 56 days under refrigerated and ambient temperatures are presented in Tables 2 and 3 respectively.

At 2°C–8°C all infusions were physically stable over 56 days, see Table 2. There was no change in visual appearance and only very small changes in pH (≤ 0.05 pH units). Sub-visible particle counts were variable throughout the study and the small increases observed did not point to impending visual precipitation. Docetaxel concentrations remained within 95–105% of the initial ($t = 0$) concentration. Additional peaks were not seen in any chromatogram from test samples. Changes in infusion weights were minimal, which excluded the possibility that drug degradation could be masked by moisture loss from the infusions.

Docetaxel infusions stored at 25°C ± 1°C, see Table 3, also showed only minimal changes in pH over the study duration (< 0.15 pH units) whilst sub-visible particle counts were again variable. In two infusions used for physical testing, visible particles were seen floating at $t = 14$ but were not seen at subsequent time points. These were

Table 2: Physicochemical stability of docetaxel (Teva) 0.3 mg/mL and 0.7 mg/mL in 0.9% sodium chloride and 5% glucose at 5°C ± 3°C

Concentration/diluent combination and time (days)	pH[a]	Weight loss/gain (%)[a]	Sub-visible particles/mL[a]		Visual appearance[a]	Docetaxel concentration (% initial concentration remaining (% RSD))[b]
			10 µm	25 µm		
0.3 mg/mL in 0.9% sodium chloride						
0	4.48	-	85.70	1.90	Pass	100% = 0.295 mg/mL (2.52)
7	4.48	-0.005	100.90	1.50	Pass	101.43 (1.39)
14	4.43	0.113	97.50	0.80	Pass	100.86 (0.99)
28	4.46	-0.020	177.00	29.50	Pass	102.10 (0.17)
42	4.47	-0.021	123.85	2.30	Pass	100.06 (1.31)
56	4.44	0.022	131.00	5.35	Pass	102.88 (1.25)
0.3 mg/mL in 5% glucose						
0	4.16	-	101.30	0.90	Pass	100% = 0.292 mg/mL (2.49)
7	4.17	-0.007	93.70	0.70	Pass	101.52 (0.57)
14	4.12	0.093	106.00	4.65	Pass	100.66 (0.42)
28	4.13	-0.019	104.00	10.00	Pass	100.99 (0.32)
42	4.15	0.000	113.50	18.50	Pass	100.96 (0.13)
56	4.15	0.021	96.30	12.00	Pass	102.47 (0.66)
0.7 mg/mL in 0.9% sodium chloride						
0	4.19	-	299.40	8.70	Pass	100% = 0.689 mg/mL (2.10)
7	4.21	-0.009	238.80	1.40	Pass	100.33 (3.19)
14	4.20	0.114	258.35	2.65	Pass	101.41 (3.29)
28	4.18	0.000	427.20	58.15	Pass	100.75 (2.42)
42	4.20	-0.020	263.70	7.80	Pass	101.86 (3.21)
56	4.18	0.021	270.70	11.70	Pass	102.15 (2.56)
0.7 mg/mL in 5% glucose						
0	4.03	-	213.70	4.50	Pass	100% = 0.698 mg/mL (0.51)
7	4.03	-0.005	173.90	2.40	Pass	97.82 (2.63)
14	4.05	0.056	200.00	3.50	Pass	98.93 (2.79)
28	4.03	0.019	177.15	6.50	Pass	100.39 (1.61)
42	4.04	0.000	169.00	10.00	Pass	99.06 (2.59)
56	4.03	0.041	153.50	15.50	Pass	100.95 (2.77)

[a]mean of duplicate infusions; [b]mean of triplicate infusions.

Table 3: Physicochemical stability of docetaxel (Teva) 0.3 mg/mL and 0.7 mg/mL in 0.9% sodium chloride and 5% glucose at 25°C ± 1°C

Concentration/ diluent combination and time (days)	pH[a]	Weight loss/ gain (%)[a]	Sub-visible particles/mL[a]		Visual appearance[a]	Docetaxel concentration (% initial concentration remaining (% RSD))[b]
			10 µm	25 µm		
0.3 mg/mL in 0.9% sodium chloride						
0	4.44	-	32.15	1.50	Pass	100% = 0.277 mg/mL (0.93)
7	4.46	-0.055	107.15	4.35	Pass	101.27 (1.02)
14	4.43	-0.076	37.15	1.25	Pass*	99.07 (0.98)
28	4.44	-0.118	106.15	17.30	Pass	97.97 (0.77)
42	4.42	-0.062	39.70	3.30	Pass	97.55 (0.22)
56	4.42	-0.191	62.50	5.00	Pass	98.01 (0.51)
0.3 mg/mL in 5% glucose						
0	4.11	-	44.50	0.85	Pass	100% = 0.275 mg/mL (0.68)
7	4.13	-0.072	28.00	3.20	Pass	98.70 (0.41)
14	4.08	-0.074	40.85	2.65	Pass	98.92 (0.94)
28	4.14	-0.096	85.50	3.50	Pass	97.38 (0.81)
42	4.09	-0.080	92.70	5.15	Pass	97.42 (0.39)
56	4.02	-0.167	53.50	2.35	Pass	96.78 (0.75)
0.7 mg/mL in 0.9% sodium chloride						
0	4.15	-	45.50	1.30	Pass	100% = 0.644 mg/mL (1.45)
7	4.14	-0.074	96.00	1.50	Pass	101.97 (1.69)
14	4.14	-0.095	47.65	2.80	Pass	98.41 (0.52)
28	4.15	-0.098	66.50	12.35	Pass	99.24 (1.31)
42	4.16	-0.102	93.70	10.80	Pass	98.52 (1.20)
56	4.07	-0.170	61.85	4.50	Pass	98.27 (0.55)
0.7 mg/mL in 5% glucose						
0	4.02	-	96.00	3.00	Pass	100% = 0.634 mg/mL (1.57)
7	3.98	-0.054	77.85	4.65	Pass	101.03 (0.17)
14	4.01	-0.261	72.65	3.65	Pass*	99.16 (0.91)
28	4.00	-0.116	69.00	1.85	Pass	98.23 (0.76)
42	3.93	-0.081	121.70	6.70	Pass	97.68 (0.68)
56	3.85	-0.168	93.70	3.65	Pass	98.34 (1.30)

*In both cases the particles seen in the physical testing bags were 'floating'. The solutions were otherwise clear, colourless, and free from haze; [a]mean of duplicate infusions; [b]mean of triplicate infusions.

attributed to small fragments from the addition port septum of the infusion bags. All infusions were chemically stable with docetaxel concentrations remaining within ± 5% of the $t = 0$ concentration. Infusion weight changes were small except for a single, isolated decrease of 0.261% between day 7 and 14 of the 0.7 mg/mL in 5% glucose infusion at room temperature.

Discussion

Prolonged stability of docetaxel infusions of varying concentrations would enable an extended shelf life to be assigned to pre-prepared infusions. This would then allow inclusion in dose-banding schemes. These schemes allow prospective, rather than retrospective, microbiological and chemical quality control testing and therefore enhanced safety, a reduction in patient waiting times since the chemotherapy is prepared in advance, and decreased drug wastage in the case of therapy deferral [3, 4]. The platinum-based drug carboplatin has recently been subjected to similar extended stability studies [5] and, as a result, clinically relevant dose-banding regimens have been proposed [6].

Only one infusion failed to comply fully with the acceptance criteria for physical stability. The mean decrease (-0.261%) in weight of the room temperature 0.7 mg/mL in 5% glucose infusion at day 14, see Table 2, was attributed to the weight change of a single bag. The second bag of the infusion pair showed almost zero weight change. No other weight changes for this bag were outside the acceptance criteria at subsequent sampling times and it was concluded that this sample reading was an artefact. Potential explanations could be related to the presence of condensate on the bag surface when the initial weight was recorded, or to operator error. Careful inspection of the infusion did not identify any leaks.

The few particles seen in the two infusion bags stored at ambient temperature at day 14 were described as 'floating' particles, see Table 3, and did not resemble drug precipitate. The solutions were otherwise clear and colourless. It is likely the particles were fragments of the septum cored out during repeated sampling. They were not seen at later time points and an explanation for this could be that they were removed during the subsequent sample extraction. It was concluded that this was neither microbiological growth nor drug precipitation and as a result both bags were allowed to remain in the study.

Except for the occasions mentioned above the acceptance criteria for chemical and physical stability of all infusions were

met at all sample points throughout the study. These findings are in agreement with those found by Thiesen and Krämer [7], who assigned a 28-day shelf life to docetaxel infusion.

Sub-visible particle counts were measured for comparative use and to support visual observations. It was thought that increased counts might be predictive of imminent precipitation, particularly in the case of particles > 25 µm diameter. Measuring this parameter is particularly useful for infusions prepared in semi-opaque polyolefin bags, as in this case. Throughout the 56 days of the study, the counts exhibited small fluctuations, but no obvious trends emerged. In contrast, measuring this parameter in studies on paclitaxel infusions provided some degree of predictive capacity [8]. Many of the counts exceed the British Pharmacopoeial limits of ≤ 25/mL for 10 µm and ≤ 3/mL for 25 µm for infusions with a volume of more than 100 mL [9].In the experience of the authors, virtually all cytotoxic infusions prepared by pharmacy CIVAS units exceed pharmacopoeial limits for sub-visual particles, although in practice these are rarely measured.

Under the acidic conditions of the infusions (pH 3.93–4.48), docetaxel demonstrated chemical stability in polyolefin bags. All infusions remained within 95–105% of the initial concentration. This is in accordance with results from a 28-day room temperature study by Thiesen and Krämer [7]. Unlike infusions of the related drug paclitaxel, storage temperature had no affect on stability. Donyai and Sewell [8] found significant precipitation and concomitant decreases in paclitaxel concentration occurred more frequently at ambient, rather than refrigerated, temperatures. Although docetaxel precipitation was not observed in this study, we recognise that the number of infusions included in this study (six infusions for each concentration/diluent/temperature combination) was, of necessity, limited. It is also accepted that various factors can influence the tendency of infusions of this type to crystallise, resulting in significant variation between infusion bags [10]. Such factors can include the method of preparation, consistency of storage temperature, and the sub-visual particulate-load of diluent infusions. For these reasons, we strongly advise pharmacy and nursing staff to follow the precautions described below.

Conclusion

The results from this study demonstrate that polyolefin bags containing docetaxel (Teva) infusions over the concentration range 0.3–0.7 mg/mL in either 0.9% sodium chloride or 5% glucose are chemically and physically stable for up to 56 days when stored at either 2°C–8°C or 25°C and protected from light. As a consequence, advanced preparation by pharmacy CIVAS units and the application of dose-banding schemes for this drug can be supported.

Microbiological assessment was not part of this investigation, but as with all pharmacy prepared infusions the ability of the CIVAS unit to ensure sterility during preparation must be thoroughly validated and monitored, especially for infusions stored at room temperature. Accordingly, the authors recommend that unless extended storage times are essential, a maximum shelf life of 28 days should be assigned to docetaxel infusions. We also strongly advise that all infusions are carefully examined for visual precipitation prior to use and at intervals during infusion. These precautions will be standard practice in many institutions. Since Teva-manufactured docetaxel was used in this study, the results obtained are only valid for infusions prepared using drug from this manufacturer.

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References

1. SPC for Docetaxel Teva 80 mg concentrate. Available from: http://www.ema.europa.eu. [Accessed 2011 January 05].
2. Appendix III. Chromatographic Separation Techniques. British Pharmacopoeia. 2011. Available from: http://www.pharmacopoeia.co.uk. [Accessed 2011 January 11].
3. Kaestner S, Sewell G. Pharmacoeconomic aspects of dose-banding. Hosp Pharm Eur. 2006;26:33-4.
4. Kaestner S, Sewell G. Dose-banding of cancer chemotherapy. Hosp Pharm Eur.2010;51:31-2.
5. Kaestner S, Sewell G. A sequential temperature cycling study for the investigation of carboplatin infusion stability to facilitate 'dose-banding'. J Oncol Pharm Pract. 2007;13(2):119-26.
6. Kaestner S, Sewell G. Dose-banding of carboplatin: rationale and proposed banding scheme. J Oncol Pharm Pract. 2007;13(2):109-17.
7. Thiesen J, Krämer I. Physico-chemical stability of docetaxel premix solution and docetaxel infusions in PVC bags and polyolefine containers. Pharm World Sci. 1999;21(3):137-41.
8. Donyai P, Sewell G. Physical and chemical stability of paclitaxel infusions in different container types. J Oncol Pharm Pract. 2006;12(4):211-22.
9. Appendix XIII A. Particulate Contamination: Sub-visible Particles. British Pharmacopoeia 2011. Available from: http://www.pharmacopoeia.co.uk. [Accessed 2011 January 17].
10. Acott SR, Hart M. Physical and chemical stability of Taxotere 1-vial 20 mg/1 mL infusion solution following refrigerated storage. Eur J Oncol Pharm. 2010;4(3):24-6.