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Physical and chemical stability of paclitaxel infusions in different container types

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Objectives. To determine the physicochemical stability of generic (Teva Pharmaceuticals) paclitaxel infusions (0.3 and 1.2 mg/mL) in 0.9% sodium chloride or 5% glucose in polyolefin (Viaflo®), low-density polyethylene (Ecoflac®), and glass containers at 2–8 and 25°C.

Methods. Paclitaxel infusions of various concentration/diluent/container combinations were prepared. Containers were light-protected and incubated at test temperatures with further analysis at predetermined intervals of 1–3 days for up to 30 days. Infusions were monitored for pH, weight loss, precipitation, colour change, and subvisual particulates as indicators of physical stability, and assayed for drug concentration to determine chemical stability.

Results. Precipitation was the limiting factor. Infusions of paclitaxel (0.3 mg/mL) in 0.9% sodium chloride remained stable for 13, 16 and 13 days at 2–8°C in polyolefin, low-density polyethylene and glass containers, respectively; in 5% glucose for 13, 18, and 20 days, respectively. At 25°C, paclitaxel infusions (0.3 mg/mL) remained stable for 3 days in all diluent/container combinations with the exception of 5% glucose in glass, where stability reached 7 days. Paclitaxel infusions (1.2 mg/mL) in 0.9% sodium chloride remained stable for 9, 12, and 8 days at 2–8°C in polyolefin, low-density polyethylene and glass containers, respectively; in 5% glucose for 10, 12, and 10 days, respectively. At 25°C, paclitaxel 1.2 mg/mL remained stable for 3 days in all diluent/container combinations with the exception of glass, where stability reached 5 days in 0.9% sodium chloride diluent, and 7 days in 5% glucose.

Conclusion. Paclitaxel stability was influenced by storage temperature, with longer shelf-life at 2–8°C, and also by drug concentration, where 0.3 mg/mL infusions were more stable than 1.2 mg/mL for all diluent/container combinations. Physical stability (precipitation) was the limiting parameter in each case. ***J Oncol Pharm Practice (2006) 12: 211–222.***

Key words: compatibility; generic; infusion; paclitaxel; stability

Introduction

Paclitaxel, a potent chemotherapeutic agent, was discovered during a large-scale screening programme conducted by the National Cancer Institute in the 1960s, and was initially extracted and isolated from the bark of Western Yew (*Taxus brevifolia*).[1] Since its discovery, paclitaxel has been indicated in the treatment of a variety of cancers, such as advanced ovarian and breast cancer, non-small cell lung cancer and AIDS-related Kaposi's sarcoma.[2–4]

The extreme lipophilicity of paclitaxel,[5–7] presented difficulties in developing stable parenteral formulations for iv infusion. To circumvent this problem, commercially available paclitaxel injection is formulated in a 50:50 solvent mixture of cremophor EL and dehydrated ethanol.[8] However, cremophor EL causes severe hypersensitivity reactions in

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patients and pre-medication with corticosteroids, antihistamines and H_2-antagonists is required.[9,10] Furthermore, cremophor EL is incompatible with some plastics and is known to leach diethylhexylphthalate (DEHP) plasticisers from polyvinyl chloride (PVC) infusion bags and administration sets.[11,12] It is, therefore, recommended that paclitaxel infusion is prepared and administered in non-PVC containers.

For administration, paclitaxel concentrate is diluted in infusions of 0.9% sodium chloride or 5% dextrose to achieve a final concentration of 0.3–1.2 mg/mL.[13–15] Adequate physical and chemical stability of infusions under clinically relevant conditions is essential to ensure safety and efficacy. Physical stability of paclitaxel infusions is the limiting factor, resulting in precipitate formation on storage,[16] particularly where the paclitaxel concentration exceeds 0.6 mg/mL.[17] However, long-term infusion stability is required for the development of dose-banding strategies,[18] and to avoid wastage on occasions when treatment is delayed after the infusion has been prepared.

In this study, the stability of infusions prepared from a generic paclitaxel presentation (Teva Pharmaceuticals) was investigated. Low-density polyethylene containers were included as a non-PVC alternative to polyolefin, but with a lower environmental impact. Glass containers were included because of continued use in some European countries. The objective of this work was to determine the physical and chemical stability of paclitaxel infusion at concentrations of 0.3 and 1.2 mg/mL in 0.9% sodium chloride or 5% glucose under storage at 5 and 25°C in polyolefin infusion bags, low-density polyethylene Ecoflac® containers, and glass bottles.

Materials and methods

Materials

Vials containing paclitaxel 6 mg/mL (batch No. A417745, expiry 3/2007) were supplied by Teva Pharmaceuticals (Leeds, UK). The polyolefin (Viaflo®) infusion bags, containing 0.9% sodium chloride 250 mL (batch No. 03F10E1D, expiry 05/2006) and 5% glucose 250 mL (batch No. 03E24E1E, expiry 04/2006), were supplied by Baxter Healthcare (Berkshire, UK). Glass containers of 0.9% sodium chloride 250 mL (batch No. 04F0262, expiry 05/07) and 5% glucose 250 mL (batch No. 02L2171, expiry 10/05) were supplied by B Braun (Sheffield, UK). Low-density polyethylene (Ecoflac®) containers of 0.9% sodium chloride 500 mL (batch No. 4124A141, expiry 02/2007) and 5% glucose 500 mL (batch No. 4185A142, expiry 03/2009) were supplied by B Braun Melsungen AG (Melsungen, Germany). All pharmaceuticals were used within their expiry date.

All other chemicals and reagents were of analytical grade or high-performance liquid chromatography (HPLC) grade.

Preparation of paclitaxel infusions

All paclitaxel infusions were prepared under European Grade A aseptic conditions in a Class II safety cabinet by trained and validated personnel, in accordance with the principles of Good Manufacturing Practice. Paclitaxel infusions, at concentrations of 0.3 and 1.2 mg/mL, were prepared in 0.9% sodium chloride or 5% glucose in polyolefin, low-density polyethylene and glass containers. In each instance, a volume of the diluent equal to the volume of paclitaxel solution added was first withdrawn. After adding the drug concentrate, the containers were gently inverted to promote adequate mixing. Particular care was taken to avoid excessive agitation of test infusions.

Methods

Incubation of test infusions

Triplicate infusions of each concentration/diluent/container-type combination were placed in blue polythene over-wraps to protect from light and stored at the desired study temperatures using a LEC pharmacy refrigerator (5°C) or a laboratory incubator (25 ± 0.5°C). The infusions were removed at selected time intervals (see below), and equilibrated to room temperature prior to analysis (in triplicate). Samples were analysed for physical stability (pH, and weight loss, visible and subvisual particulates) and chemical stability (HPLC assay) immediately after preparation ($t = 0$), and subsequently at the following scheduled time intervals:

- Paclitaxel (0.3 mg/mL) in polyolefin and glass containers: $t = 0$, 3, 7, 10, 13, 15, 20 and 30 days at 2–8 and 25°C.
- Paclitaxel (1.2 mg/mL) in polyolefin and glass containers: $t = 0$, 3, 5, 7, 8, 9, 10, 12 and 14 days at 2–8 and 25°C.
- Paclitaxel (0.3 and 1.2 mg/mL) in low-density polyethylene containers: $t = 0$, 3, 7, 10, 12, 14, 16, 18, and 20 days at 5°C and: $t = 0$, 1, 3, 5, 7, 9 and 11 days at 25°C.

Physical stability of infusions

The physical stability of paclitaxel was assessed using the following methods.

pH measurement. A combinational glass electrode and a Good-Laboratory-Practice pH meter (Hanna pH 302 series) were first calibrated using standard reference solutions of pH 4.0 and 7.0, and then used to measure the pH of infusions. Each pH was recorded as mean value of three infusions.

Weight loss. The infusion bags were weighed before and after sampling on a calibrated six-figure analytical balance (A&D Ltd, model AD-1131) and the percent weight increase or decrease on incubation calculated. Change in weight was recorded and expressed as mean moisture loss of three infusions.

Visual inspection. This was assessed under standard laboratory lighting. Each infusion was examined for any change in colour, clarity or for the presence of particulate matter.

Subvisual particulates. Subvisual particle counts of infusion at 10 and 25 μm were conducted at predetermined time intervals in accordance with the method described in the British Pharmacopoeia (2000) using a Pacific Scientific light-scatter instrument. This was calibrated using certificated diameter latex spheres supplied by Pacific Scientific Ltd.

Acceptance criteria: physical stability. The physical stability of all paclitaxel infusions was assessed according to the following acceptance criteria. Samples passed pH testing if the value obtained was within $+0.5$ pH unit of the initial pH value at $t=0$. Weight loss can indicate loss of moisture from the container, which can potentially mask a low assay result. The acceptance limit for weight variation was set at $\pm 3\%$ w/w of the initial infusion weight.

Chemical stability of infusions using HPLC

Paclitaxel concentrations were analysed using a validated stability-indicating reverse-phase HPLC method. The HPLC system consisted of a quaternary gradient pump (Jasco PU-2089 plus), an in-line degasser, autosampler (Jasco AS-2057 plus), and photodiode array detector (Jasco MD-2010 plus). Separation and quantitative analysis of paclitaxel was achieved on a 5-μm Phenomenex C_8 column (250×4.6 mm) with the mobile phase flowing at a rate of 1.5 mL/min and a detection wavelength of 227 nm. The acquisition run-time for each analysis was 15 minutes. Mobile phase composition for analysis contained 50% 20 mM ammonium acetate, pH 5.0:40% acetonitrile:10% methanol. Samples were diluted with water and injected in duplicate, followed by an injection of the freshly-prepared external standard using the 'bracketing' technique.

The assay was fully validated for linearity of analytical response, precision of system, precision of method, and stability-indication.

A typical chromatogram obtained by injecting a solution of paclitaxel (60 μg/mL) is shown in Figure 1.

Validation of LC assay

Calibration curve (linearity of analytical response). A six-point calibration curve of paclitaxel, over the range 15–90 μg/mL, was constructed with triplicate injections at each concentration. A plot of the mean peak height obtained for each concentration against the respective paclitaxel concentration was subjected to linear least-square regression analysis and was found to be linear over the range tested with a regression coefficient of 0.9997.

Precision of the method. *Intra-day precision:* Eight paclitaxel standard solutions (60 μg/mL) were prepared and each injected onto the LC system in duplicate. From the mean of each duplicate, the CV was calculated ($n=8$) as 1.9%.

Inter-day precision: Paclitaxel solution (60 μg/mL) was prepared on each successive day for 7 days, and injected onto the LC system in duplicate. From the mean of each duplicate, the CV was calculated ($n=7$) as 1.6%.

Stability indicating study. A stability indicating study was performed using forced degradation, in order to determine whether paclitaxel could be distinguished in terms of retention time from any degradation products. Table 1 reveals the effect of forcibly degrading paclitaxel by alkaline, acidic and oxidative conditions and by heating at 55°C. Paclitaxel (60 μg/mL) stored in the refrigerator was used as a control sample for comparison purposes. The assay of paclitaxel in the control sample was 61.65 μg/mL. On exposure to each of the following treatments – oxidative degradation, elevated temperature of 55°C and acid hydrolysis – paclitaxel assay was 57.89, 61.09 and 30.53 μg/mL, respectively. In all cases, there was a distinct separation between

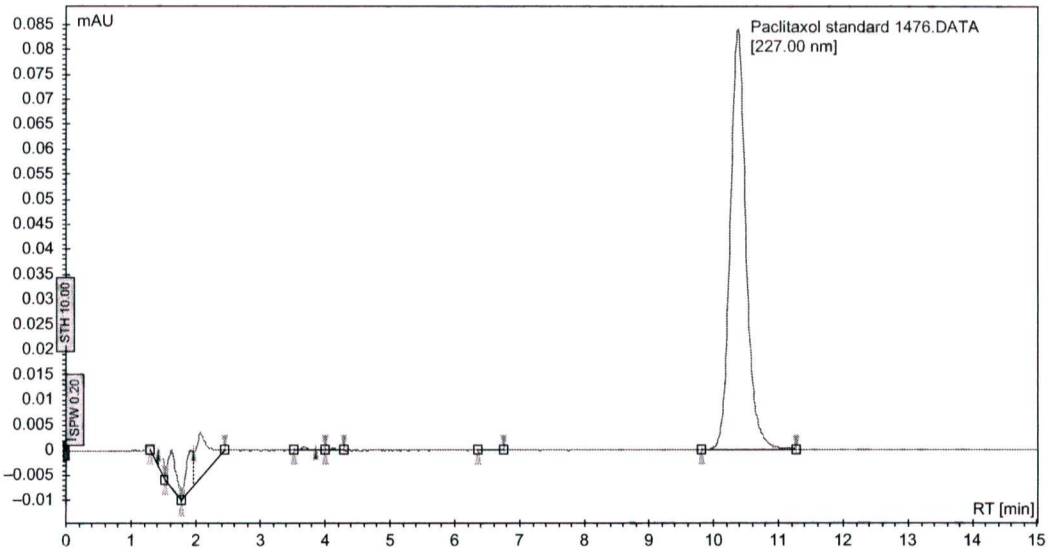

Figure 1. Typical LC chromatogram of paclitaxel (60 μg/mL) solution.

the drug and degradation product peak. Peak purity of the paclitaxel analyte peak was confirmed (> 0.97) by diode-array spectroscopy. A cloudy gel was observed in paclitaxel solution subjected to alkaline hydrolysis. The dispersion was filtered using a 0.2-μm filter, and the filtrate analysed for paclitaxel by LC. Results indicated absence of drug peak implying complete loss of the drug.

Assay validation: summary

The LC assay developed for paclitaxel was stability – indicating for non-specific degradation of the parent drug, gave a linear analytical response and acceptable precision.

Accuracy of the method was determined 'in-use' by routine QC samples (blinded to operator) and was within the range 98.6–101.2% ($n = 27$).

The assay was accepted as fit for purpose.

Table 1. Effect of oxidative degradation, alkaline hydrolysis, acid hydrolysis and elevated temperature (55°C) on paclitaxel stability

Treatment	Retention time (min)	Quantity (μg/mL)
Control	11.37	61.65
Oxidative degradation	11.36	57.89
Alkaline hydrolysis	–	–
Heat (55°C)	11.35	61.09
Acid hydrolysis	11.36	30.53

Acceptance criteria: chemical stability

The assay of drug concentration was accepted where the concentration of paclitaxel remaining at each time point was ≥95.0% of the initial concentration measured by HPLC.

Results

The physical and chemical stability of paclitaxel was determined at intervals over a period of up to 30 days. The stability data for paclitaxel 0.3 mg/mL infusions at 2–8 and 25°C are presented in Tables 2 and 3, respectively, and for the 1.2 mg/mL infusions at 2–8 and 25°C in Tables 4 and 5, respectively.

Paclitaxel 0.3 mg/mL in 0.9% sodium chloride remained stable for 13, 16 and 13 days at 2–8°C in polyolefin, low-density polyethylene and glass containers, respectively; in 5% glucose for 13, 18, and 20 days, respectively. At 25°C, paclitaxel 0.3 mg/mL remained stable for 3 days in all diluent/container combinations with the exception of 5% glucose in glass, where stability lasted 7 days. Paclitaxel 1.2 mg/mL in 0.9% sodium chloride remained stable for 9, 12, and 8 days at 2–8°C in polyolefin, low-density polyethylene and glass containers, respectively; in 5% glucose for 10, 12, and 10 days, respectively. At 25°C, paclitaxel 1.2 mg/mL remained stable for 3 days in all diluent/container combinations with the exception of glass, where stability of 5 days was obtained in

Table 2. Physical and chemical stability of paclitaxel 0.3 mg/mL in 0.9% sodium chloride or 5% glucose in polyolefin, low-density polyethylene and glass containers at 2–8°C

Time (days)	pH	Moisture loss (%)	Subvisual particles/mL		Visual appearance	% Concentration ± SD paclitaxel remaining
			10 μM	25 μM		
0.3 mg/mL Paclitaxel in 0.9% sodium chloride in polyolefin bags						
0	3.77	–	25	0	Pass	0.296 mg/mL = 100%
3	3.95	0	57	0.22	Pass	99.54 ± 1.7
7	3.75	0	80	0.17	Pass	98.09 ± 1.0
10	3.75	0.14	148	0.77	Pass	98.09 ± 0.9
13	3.66	0.29	628	11.11	Pass	97.64 ± 0.3
15	3.97	0	3417	94.3	Fail	–
0.3 mg/mL Paclitaxel in 5% glucose in polyolefin bags						
0	3.94	–	18	0.33	Pass	0.292 mg/mL = 100%
3	4.09	0.12	68	0.61	Pass	97.32 ± 0.2
7	3.86	0	106	0.66	Pass	98.53 ± 1.2
10	3.92	0	121	0	Pass	98.44 ± 1.4
13	3.69	0	181	1.33	Pass	97.99 ± 1.8
15	4.06	0	367	5	Fail	–
0.3 mg/mL Paclitaxel in 0.9% sodium chloride in low-density polyethylene containers						
0	3.66	–	44.22	0	Pass	0.292 mg/mL = 100%
3	3.56	0.06	73.33	0.33	Pass	100.66 ± 0.97
7	3.56	0.06	33.33	0.22	Pass	99.74 ± 1.25
10	3.69	0.13	25.22	0.22	Pass	99.27 ± 0.91
12	3.58	0.06	31.66	0.33	Pass	97.22 ± 0.42
14	3.55	0	26.66	0.11	Pass	99.29 ± 0.84
16	3.59	0	24.77	0.11	Pass	100.69 ± 1.35
18	3.56	0	51.44	0.11	Fail	101.15 ± 0.12
0.3 mg/mL Paclitaxel in 5% glucose in low-density polyethylene containers						
0	3.89	–	43.11	0.22	Pass	0.310 mg/mL = 100%
3	3.58	0	55.89	0	Pass	100.36 ± 0.97
7	3.69	0	24.66	0	Pass	99.75 ± 0.51
10	3.78	0.13	47.88	0.33	Pass	99.70 ± 1.84
12	3.87	0	27.77	0.33	Pass	98.19 ± 0.44
14	3.81	0	24.66	0.33	Pass	100.43 ± 0.88
16	3.84	0	42.88	0.22	Pass	100.41 ± 0.98
18	3.81	0	40.88	0	Pass	10.31 ± 0.35
20	3.80	0	–	–	Fail	–
0.3 mg/mL Paclitaxel in 0.9% sodium chloride in glass containers						
0	3.71	–	90	0.33	Pass	0.289 mg/mL = 100%
3	3.95	0	97	0.5	Pass	98.09 ± 0.4

Table 2 (*Continued*)

Time (days)	pH	Moisture loss (%)	Subvisual particles/mL		Visual appearance	% Concentration ± SD paclitaxel remaining
			10 μM	25 μM		
7	3.68	0	153	1	Pass	96.34 ± 0.2
10	3.72	0.14	107	0.17	Pass	98.08 ± 0.9
13	3.59	0	140	0.67	Pass	95.86 ± 0.4
15	4.03	0	215	0.7	Fail	96.66 ± 0.2
0.3 mg/mL Paclitaxel in 5% glucose in glass containers						
0	3.83	–	33	0	Pass	0.286 mg/mL = 100%
3	4.16	0.13	16	0	Pass	96.03 ± 1.5
7	3.78	0.13	24	0	Pass	98.30 ± 0.6
10	3.95	0	25	0.33	Pass	95.87 ± 0.4
13	3.69	0	16	0.17	Pass	96.98 ± 1.1
15	4.28	0	46	0.33	Pass	98.25 ± 0.6
20	4.17	0	41	0	Pass	96.18 ± 1.4
30	4.03	0	35	0.33	Pass	84.08 ± 1.1

0.9% sodium chloride, and 7 days in 5% glucose. These timescales are presented in Figure 2.

Discussion

Solutions for parenteral infusion with a nominal content of >100 mL comply with the British Pharmacopoeia (2000) requirements for sub-visual particulates, if the average number of particles present in the units tested does not exceed 25/mL ≥10 μm, and does not exceed 3/mL ≥25 μm diameter. The particulate count data presented in Tables 2–5, show that the infusions would exceed the pharmacopoeial limits for particles of ≥10 μm diameter, but most would pass at the ≥25 μm level. However, in accordance with the marketing authorisation, paclitaxel infusion is administered to the patient via a 0.22 micron in-line filter and, therefore, it may not be realistic to apply pharmacopoeial limits for sub-visual particulate counts of this product. Nonetheless, sub-visual particle counts were monitored in order to predict possible product precipitation under visual observation, and in this role, the technique did exhibit some predictive capability. Products were considered to pass visual observation only on presentation of a clear, colourless solution with no visible precipitate. There was an exception to this criteria on day 9, where the assay result for paclitaxel 1.2 mg/mL in 5% glucose (glass container) at 2–8°C gave a value of 94.62% of initial concentration. This was rounded up to 95% on the basis that reassay on the subsequent day (day 10) gave a result 96.92% of initial concentration.

In each instance, precipitation was the limiting factor for infusion stability, as reported in previous studies.[19,20] Precipitation was at all times accompanied by a sharp reduction in the paclitaxel assay result. Storage temperature was a key factor affecting stability. Infusions stored under refrigeration (2–8°C) (Tables 2 and 4) were stable for a longer period compared to the corresponding infusions stored at room temperature (25°C) (Tables 3 and 5). In addition, under refrigerated storage, the 0.3 mg/mL infusions were more stable than the 1.2 mg/mL for all diluent/container combinations. Changes in infusion pH or significant weight loss were not observed in this study (Tables 2–5). In view of the subtle differences in the cremophor EL quality and the methods used to manufacture paclitaxel, the data presented in this study should be considered specific to paclitaxel (Teva Pharmaceuticals).

Table 3. Physical and chemical stability of paclitaxel 0.3 mg/mL in 0.9% sodium chloride or 5% glucose in polyolefin, low-density polyethylene and glass containers at 25°C

Time (days)	pH	Moisture loss (%)	Subvisual particles/mL		Visual appearance	% Concentration paclitaxel remaining
			10 μM	25 μM		
0.3 mg/mL Paclitaxel in 0.9% sodium chloride in polyolefin bags						
0	3.76	–	27	0.11	Pass	0.298 mg/mL = 100%
3	3.99	0	168	0.22	Pass	95.79 ± 1.1
7			–	–	Fail	–
0.3 mg/mL Paclitaxel in 5% glucose in polyolefin bags						
0	3.94	–	27	0.11	Pass	0.305 mg/mL = 100%
3	4.10	0.12	130	0.44	Pass	98.65 ± 0.3
7			–	–	Fail	–
0.3 mg/mL Paclitaxel in 0.9% sodium chloride in low-density polyethylene containers						
0	3.65	–	53.88	0.33	Pass	0.296 mg/mL = 100%
1	3.58	0	33.77	0.22	Pass	99.15 ± 0.76
3	3.52	0	43.55	0.11	Pass	100.84 ± 0.5
5	3.62	0	24.22	0	Fail	–
0.3 mg/mL Paclitaxel in 5% glucose in low-density polyethylene containers						
0	3.85	–	32.66	0	Pass	0.293 mg/mL = 100%
1	3.80	0	8	0.11	Pass	99.33 ± 0.53
3	3.58	0.06	36.66	0.55	Pass	100.68 ± 1.24
5	3.74	0	11.11	0	Fail	–
0.3 mg/mL Paclitaxel in 0.9% sodium chloride in glass containers						
0	3.75	–	62	0.33	Pass	0.307 mg/mL = 100%
3	3.90	0	88	0.7	Pass	95.66 ± 1.2
7			–	–	Fail	–
0.3 mg/mL Paclitaxel in 5% glucose in glass containers						
0	3.84	–	56	0.5	Pass	0.302 mg/mL = 100%
3	4.16	0.13	11	0	Pass	96.60 ± 0.7
7	3.80	0.26	10	0	Pass	96.93 ± 0.2
10			–	–	Fail	–

Table 4. Physical and chemical stability of paclitaxel 1.2 mg/mL in 0.9% sodium chloride or 5% glucose in polyolefin, low-density polyethylene and glass containers at 2–8°C

Time (days)	pH	Moisture loss (%)	Subvisual particles/mL		Visual appearance	% Concentration paclitaxel remaining
			10 μM	25 μM		
1.2 mg/mL Paclitaxel in 0.9% sodium chloride in polyolefin bags						
0	3.49		68	0.22	Pass	1.24 mg/mL = 100%
3	3.56	0	81	0.66	Pass	99.73 ± 0.4
5	3.56	0	113	0.88	Pass	96.21 ± 0.9
7	3.61	0	150	0.88	Pass	98.64 ± 0.4
8	3.51	0	182	2	Pass	97.01 ± 1.2
9	3.55	0.15	183	1.44	Pass	96.75 ± 0.2
10			–	–	Fail	–
1.2 mg/mL Paclitaxel in 5% glucose in polyolefin bags						
0	3.74		67	0.38	Pass	1.20 mg/mL = 100%
3	3.74	0	72	0.11	Pass	97.31 ± 1.1
5	3.78	0	86	0.33	Pass	98.11 ± 0.4
7	3.75	0	130	0.22	Pass	99.73 ± 1.7
8	3.83	0	88	0.55	Pass	98.12 ± 1.2
9	3.83	0	106	1.44	Pass	97.57 ± 0.8
10	3.72	0	111	1.17	Pass	98.65 ± 1.7
12			–	–	Fail	–
1.2 mg/mL Paclitaxel in 0.9% sodium chloride in low-density polyethylene containers						
0	3.52	–	38.44	0.11	Pass	1.17 mg/mL = 100%
3	3.49	0	52	0.33	Pass	100.62 ± 1.22
7	3.40	0.06	32.88	0.11	Pass	98.74 ± 0.3
10	3.50	0.06	31	0	Pass	97.97 ± 0.61
12	3.53	0.13	23.22	0	Pass	97.04 ± 0.36
14	3.54	0.06	36.44	0.33	Fail	–
1.2 mg/mL Paclitaxel in 5% glucose in low-density polyethylene containers						
0	3.67	–	49.88	0.22	Pass	1.17 mg/mL = 100%
3	3.77	0	31.66	0.11	Pass	98.99 ± 2.5
7	3.72	0.06	24.88	0.11	Pass	99.25 ± 1.33
10	3.83	0.064	30.66	0.33	Pass	98.69 ± 0.96
12	3.76	0	25.33	0	Pass	97.82 ± 0.98
14	3.71	0	34	0	Fail	–
1.2 mg/mL Paclitaxel in 0.9% sodium chloride in glass containers						
0	3.59		77	0	Pass	1.22 mg/mL = 100%
3	3.55	0.13	99	0.5	Pass	95.78 ± 0.5
5	3.57	0	115	0.66	Pass	96.17 ± 1.1
7	3.63	0	175	0.67	Pass	96.17 ± 1.1

Table 4 (*Continued*)

Time (days)	pH	Moisture loss (%)	Subvisual particles/mL		Visual appearance	% Concentration paclitaxel remaining
			10 μM	25 μM		
8	3.52	0	155	0.17	Pass	95.02±1.6
9	3.55	0	244	2.7	Fail	95.02±1.5
1.2 mg/mL Paclitaxel in 5% glucose in glass containers						1.25 mg/mL = 100%
0	3.7		45	0.17	Pass	95.77±0.5
3	3.74	0.13	68	0.33	Pass	95.76±0.5
5	3.80	0	73	0	Pass	96.92±1.1
7	3.83	0	112	2	Pass	95.00±1.7
8	3.72	0	67	0	Pass	94.62±1.1
9	3.82	0	113	1	Pass	96.92±1.1
10	3.73	0	89	0.83	Pass	95.39±2.2
12	3.82	0	114	1	Fail	

The use of glucose 5% w/v diluent, as opposed to sodium chloride 0.9% w/v, afforded a marginal increase in physical stability in some cases (Tables 2–5). A tentative explanation for this may relate to the higher ionic strength in the saline infusions causing more rapid degradation of the cremophor/ethanol miscelles formed with paclitaxel, and a concomitant reduction in drug solubility.

The apparent increase in physical stability afforded by the low-density polyethylene and glass containers may be attributed to the lower sub-visual particulate counts of infusions stored in these containers compared to polyolefin bags (Tables 2–5). This could reduce the 'seeding' effect on unstable solutions of paclitaxel following dilution of the formulation vehicle.

The stability profiles under refrigerated conditions obtained in this study were sufficient to develop dose-banding schemes, where extended stability of standard infusions is essential,[18] and would also be adequate to avoid wastage in cases where treatment is deferred after infusion preparation. In the UK, there is a growing tendency to use 90 mg/m^2× weekly schedules,[13] for which the more stable, lower concentration infusions (0.3 mg/mL) are well suited.

Absence of microbiological contamination is crucial with all aseptically prepared infusions. It is essential, therefore, that extended shelf-lives are only applied to infusions prepared under controlled conditions, which have been microbiologically validated. Refrigerated storage conditions are also recommended, not only for improved physico-chemical stability, but also for the inhibition of microbial growth should ingress inadvertently occur.

Conclusion

Paclitaxel at 0.3 and 1.2 mg/mL in 0.9% sodium chloride or 5% glucose is physically and chemically stable (as defined by the acceptance criteria in the Methods section) in polyolefin, low-density polyethylene and glass containers at 2–8 and 25°C. Stability ranged from 3 to 20 days. Infusions were more stable when stored at 2–8°C, where the lower concentration of paclitaxel (0.3 mg/mL) was also more stable than the higher concentration (1.2 mg/mL) for all diluent/container combinations. Stability data for each concentration/diluent and temperature combination are summarised in Figure 2. This study has demonstrated sufficient stability of infusions prepared from a generic paclitaxel (Teva) to support

Table 5. Physical and chemical stability of paclitaxel 1.2 mg/mL in 0.9% sodium chloride or 5% glucose in polyolefin, low-density polyethylene and glass containers at 25°C

Time (days)	pH	Moisture loss (%)	Subvisual particles/mL		Visual appearance	% Concentration paclitaxel remaining
			10 μM	25 μM		
1.2 mg/mL Paclitaxel in 0.9% sodium chloride in polyolefin bags						
0	3.48		101	0.67	Pass	1.21 mg/mL = 100%
3	3.57	0	46	0.77	Pass	99.20 ± 1.3
5	3.58	0	60	0.89	Fail	96.53 ± 1.7
1.2 mg/mL Paclitaxel in 5% glucose in polyolefin bags						
0	3.71		66	0.22	Pass	1.24 mg/mL = 100%
3	3.74	0	27	0.22	Pass	98.93 ± 1.7
5	3.80	0.13	–	–	Fail	98.11 ± 0.9
1.2 mg/mL Paclitaxel in 0.9% sodium chloride in low-density polyethylene containers						
0	3.49	–	44.88	0.33	Pass	1.20 mg/mL = 100%
1	3.44	0.12	64.11	0.22	Pass	99.04 ± 0.11
3	3.48	0.06	77.22	0.22	Pass	99.54 ± 1.11
5	3.53	0.06	32.11	0	Fail	–
1.2 mg/mL Paclitaxel in 5% glucose in low-density polyethylene containers						
0	3.69	–	26.77	0.11	Pass	1.24 mg/mL = 100%
1	3.61	0.06	59.77	0.22	Pass	100.91 ± 0.93
3	3.75	0	41	0	Pass	101.50 ± 1.37
5	3.82	0.13	16.44	0.22	Fail	–
1.2 mg/mL Paclitaxel in 0.9% sodium chloride in glass containers						
0	3.46		178	1.17	Pass	1.18 mg/mL = 100%
3	3.54	0	126	1.83	Pass	98.81 ± 0.5
5	3.58	0	134	1.33	Pass	97.64 ± 1.1
7			–	–	Fail	–
1.2 mg/mL Paclitaxel in 5% glucose in glass containers						
0	3.73		40	0	Pass	1.17 mg/mL = 100%
3	3.76	0	30	0	Pass	95.54 ± 1.3
5	3.80	0.14	24	0	Pass	97.59 ± 2.1
7	3.76	0	78	0.5	Pass	94.06 ± 1.4
8	3.71	0	63	0	Fail	–

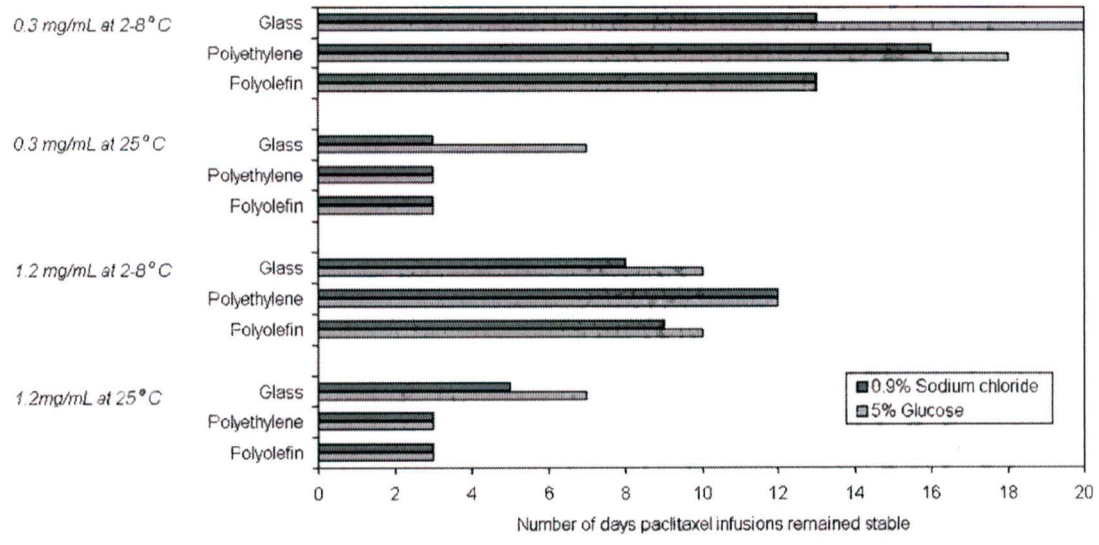

Figure 2. Stability timescales for paclitaxel in fusions showing all concentration/diluent/container-type/storage-temperature combinations.

efficient dose-banding schemes and to reduce infusion wastage in cases of deferred treatment.

REFERENCES

1 Wani M, Taylore HL, Wall ME, Coggon P, McPhail AT. The isolation and structure of Taxol, a novel antileukemic and antitumor agent from *Taxus brevifolia*. *J Am Chem Soc* 1971; 93: 2325–37.

2 Rowinsky EK, Cazenave LA, Donehower RC. Taxol-A novel investigational antimicrotubule agent. *J Natl Cancer Inst* 1990; 82: 1247–59.

3 Donehower RC, Rowinsky EK, Grochow LB, Longenecke SM, Ettinger DS. Phase I trial of Taxol in patients with advanced cancer. *Cancer Treat Rep* 1987; 71: 1171–77.

4 Huizing MT, Misser VH, Pieters RC, ten Bokkel Huinink WW, Veenhof CH, Vermorken JB, Pinedo HM, Beijnen JH. Taxanes: a new class of antitumor agents. *Cancer Invest* 1995; 13: 381–404.

5 Lee J, Lee SC, Acharya G, Chang C, Park K. Hydrotropic solubilization of paclitaxel: analysis of chemical structures for hydrotropic property. *Pharm Res* 2003; 20: 1022–30.

6 Mathew AE, Mejillano MR, Nath JP, Himes RH, Stella VJ. Synthesis and evaluation of some water-insoluble prodrugs and derivatives of Taxol with antitumor activity. *J Med Chem* 1992; 35: 145.

7 Panchagnula R. Pharmaceutical aspects of paclitaxel. *Int J Pharm* 1998; 172: 1–15.

8 Rowinsky E, Donehower RC. Taxol: twenty years later, the story unfolds. *J Natl Cancer Inst* 1991; 83: 1778–81.

9 Weiss RB, Donehower RC, Wiernik PH, Hnuma T, Gralla RJ, Trump DL, Baker JR, Van Echo DA, Von Hoff DD, Leyland-Jones B. Hypersensitivity reactions from Taxol. *J Clin Oncol* 1990; 8: 1263–68.

10 Dorr RT. Pharmacology and toxicology of Cremophor EL diluent. *Ann Pharmacother* 1994; 28: 511–14.

11 Mazzo DJ, Nguyen-Huu J-J, Pagniez S, Denis P. Compatibility of docetaxel and paclitaxel in intravenous solutions with polyvinyl chloride infusion materials. *Am J Health-Syst Pharm* 1997; 54: 566–69.

12 Allwood M, Martin H. The extraction of diethylhexylphthalate (DEHP) from polyvinyl chloride components of intravenous infusion containers and administration sets by paclitaxel injection. *Int J Pharm* 1996; 127: 65–71.

13 Summerhayes M, Daniels S eds. *Practical chemotherapy*. Radcliffe Medical Press, 2003: 275.

14 Waugh W, Trissel LA, Stella VJ. Stability, compatibility and plasticizer extraction of Taxol (NSC 125973) injection diluted in infusion solutions and stored in various containers. *Am J Hosp Pharm* 1991; 48: 1520–24.

15 Krammer I, Heuser A. Paclitaxel pharmaceutical and pharmacological issues. *Eur Hosp Pharm* 1995; 1: 37–41.

16 Straubinger RM. Biopharmaceutics of paclitaxel (Taxol): formulation, activity and pharmacokinetics. In Suffness M ed. *Taxol: science and applications*. CRC Press, 1995: 237–54.

17 Adams JD, Flora KP, Goldspiel BR. Taxol: a history of pharmaceutical development and current pharmaceutical concerns. *J Natl Cancer Inst* 1993; 15: 141–47.

18 Plumridge RJ, Sewell GJ. Dose-banding of cytotoxic drugs: a new concept in cancer chemotherapy. *Am J Health-Syst Pharm* 2001; 58: 1760–64.

19 Sautou-Miranda V, Brigas F, Vanheerswynghels S, Chopineau J. Compatibility of paclitaxel in 5% glucose solution with ECOFLAC® low-density polyethylene containers-stability under different storage conditions. *Int J Pharm* 1999; 178: 77–82.

20 Xu Q, Trissel LA, Martinez JF. Stability of paclitaxel in 5% dextrose injection or 0.9% sodium chloride injection at 4, 22, or 32 DGC. *Am J Hosp Pharm* 1994; 51: 3058–60.