Stability and compatibility of four cytotoxic drug infusions in the Graseby 9000 ambulatory pump

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Published in:
Journal of Oncology Pharmacy Practice

Publication date:
1998

Stability of three cytotoxic drug infusions in the Graseby 9000 ambulatory infusion pump

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Objective. The purpose of this study was to determine the stability of three cytotoxic infusions in the Graseby 9000 ambulatory pump (Graseby Medical, Watford, UK) under both refrigerated storage and in-use conditions. The infusions studied were: (a) doxorubicin (2 mg/mL) plus vincristine (0.2 mg/mL) and (b) ifosfamide (20 mg/mL) plus mesna (20 mg/mL) and etoposide (0.5 mg/mL). In each case, the diluent was water for injection.

Methods. Graseby 9000 medication cassettes, each containing one of three infusions studied, were incubated at either 8°C or 37°C to represent refrigerated storage or 'in-use' temperatures, respectively. Samples were withdrawn for chemical and physical analysis at various intervals. Chemical stability was determined using validated, stability-indicating high performance liquid chromatography methods. The assessment of physical stability included pH, appearance, moisture loss from cassettes, subvisual particulate counts, and leaching of diethylhexylphthalate (DEHP) plasticiser from the medication cassettes.

Results. Both the doxorubicin plus vincristine and the ifosfamide plus mesna infusions were physically and chemically stable in Graseby 9000 medication cassettes for 14 days at 8°C and for 7 days at 37°C. The etoposide infusion caused significant leaching of DEHP plasticiser from the Graseby cassette; in addition, one of the infusion cassettes stored at 8°C exhibited precipitation of etoposide by day 10.

Conclusion. Infusions of doxorubicin (2 mg/mL) plus vincristine (0.2 mg/mL) and ifosfamide (20 mg/mL) plus mesna (20 mg/mL) demonstrated acceptable stability in the Graseby 9000 device under refrigerated storage and ambulatory infusion conditions. Precipitation under refrigerated storage and significant leaching of DEHP would preclude the combination of etoposide infusion (0.5 mg/mL) and the Graseby 9000 pump for ambulatory administration.

Key Words: Doxorubicin; vincristine; ifosfamide; mesna; etoposide; stability.

The administration of cytotoxic drugs in continuous infusion schedules has been shown to modify drug-related toxicity and, in some cases, to improve the therapeutic index. The cytotoxic agents for which further studies on continuous infusion schedules may be appropriate include etoposide,[1] doxorubicin, vincristine,[2] and the oxazophosphorine drug ifosfamide.[3]

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Combining the concept of continuous infusion with the use of portable infusion devices has facilitated the ambulatory infusion of cancer chemotherapy on an outpatient or domiciliary basis. The Graseby 9000 infusion pump (Graseby Medical, Watford, UK) is an electronic device with sophisticated safety/alarm systems and polyvinyl chloride (PVC) medication reservoirs that are protected by a rigid cassette. In a comparative study,[4] this device was found to be highly suited to the ambulatory infusion of chemotherapy.

It is advantageous for pharmacy aseptic units that are involved in the preparation of prefilled pump cassettes to be able to prepare the infusions in advance and store them under refrigerated conditions (2–8°C) when

appropriate. In addition, patients who require several cassettes to complete a course of treatment may need to store the cassettes under refrigeration until they are used. During use, infusion pumps are often worn under the patient's clothing, and drug infusions are exposed to temperatures approaching body heat (37°C). Consequently, it is necessary to demonstrate the physical and chemical stability of drug infusions under both storage conditions (2–8°C) and in-use conditions (37°C).[5] Microbiological "stability" (the maintenance of asepsis) is also important, but this stability is normally assured by process validation and the application of quality assurance procedures.

In this study, the stability of three infusions at clinically relevant drug concentrations was determined in Graseby 9000 medication cassettes under storage and in-use conditions. Etoposide was studied as a single agent, vincristine and doxorubicin were admixed together, and an infusion of ifosfamide also contained the urothelial protective agent, mesna. The chemical stability of infusions was determined using validated stability-indicating high performance liquid chromatography (HPLC) assays. Physical stability was assessed on the basis of appearance, subvisual particulates, pH, moisture loss (as weight loss), and also by the leaching of diethylhexylphthalate (DEHP) plasticiser from the medication cassette into the infusions.

MATERIALS AND METHODS

Ifosfamide in 2-g vials (batch 023087) and mesna (1 g) in 10-mL vials (batch 032184) were obtained from Asta Medica (Cambridge, UK). Doxorubicin (50 mg) in 25-mL vials (batch 70454C) was obtained from Pharmacia and Upjohn (Milton Keynes, UK). Etoposide (100 mg) in 5-mL vials (batch 4C2546) was obtained from Bristol Myers Squibb (Slough, UK), and vincristine in 2-mg vials (batch 6027076) was obtained from Faulding (Leamington, UK). Water was obtained in 100-mL vials for injections BP (batch 303031) from the Sterile Production Unit (Torbay Hospital, Torquay, UK).

Reference standards of etoposide (Bristol Myers Squibb) and ifosfamide plus mesna (Asta Medica) were obtained as gifts. Doxorubicin (>98% thin-layer chromatography) and vincristine (>98% HPLC) were obtained from Sigma (Poole, UK).

Medication cassettes with a capacity of 100 mL (batch C/212) were obtained from Graseby Medical.

All other chemicals and solvents were of HPLC grade (BDH, Poole, UK).

Preparation of cytotoxic drug infusions

All infusions were prepared in a type II isolator, resulting in a European Grade A environment. The isolator was located in a clean room, which provided a European Grade B background environment. Infusions were prepared by trained, validated personnel in accordance with standard operating procedures that had been approved by the UK Medicines Control Agency.

Graseby 9000 series medication cassettes (100 mL volume) containing 100 mL of the following infusions were prepared: (a) Doxorubicin (2 mg/mL) plus vincristine (0.2 mg/mL) in water for injections; (b) Ifosfamide (20 mg/mL) plus mesna (20 mg/mL) in water for injections; and (c) Etoposide (0.5 mg/mL) in water for injections.

Incubation of test infusions

Duplicate cassettes of each infusion were then incubated at each of the study temperatures (8°C and 37°C) using an externally monitored refrigerator (LEC pharmaceutical refrigerator, LEC, Bognor Regis, UK) or incubator (Sanyo fan-assisted programmable incubator, supplied by Fisons Scientific, Loughborough, UK). All cassettes were wrapped in a single polythene bag and protected from light. Samples were taken for analysis at the following time points: 8°C: 0, 1, 3, 5, 7, 10, and 14 days; 37°C: 0, 1, 3, 5, and 7 days.

Determination of chemical stability

HPLC methods were developed and validated for each test drug. The HPLC methods are summarised in Table 1, and the corresponding validation data are presented in Table 2.

The HPLC system comprised an isocratic pump, variable wavelength detector and Rheodyne loop valve (all supplied by Jasco UK, Essex, UK) that were coupled for validation purposes in series with a diode-array detector for peak purity determination (Perkin Elmer, Beaconsfield, UK). All HPLC assays were conducted using an external standard; duplicate test injections were bracketed by injections of standard solutions.

Determination of physical stability

Visual appearance. This was conducted under standard laboratory lighting and also under polarised light with an Allen Lamp.

pH measurement. pH was determined using a glass electrode and a Denver Instruments digital pH meter (Norfolk, UK). The pH meter was calibrated using standard reference solutions at pH 4, 7, and 10 (BDH Ltd, Poole, UK).

Table 1. Summary of HPLC Methods Used for Assay of Cytotoxic Drug Infusions in Graseby 9000 Cassettes

	Analyte				
	Doxorubicin	Vincristine	Ifosfamide	Mesna	Etoposide
Column dimensions (mm)	250 × 4.0	250 × 4.0	250 × 4.0	150 × 2.0	250 × 4.6
Column packing	Lichrosorb RP8	Lichrosorb RP8	Spherisorb 5CN	Techopak 10	Spherisorb 5CN
Mobile phase	0.01 M NaCl (60%) acetonitrile (40%) to pH 2.25 with perchloric acid	0.1% NH_4 (40%) acetonitrile (60%) to pH 4 with formic acid	0.005 M NH_4SO_4 (70%)+methanol (30%) to pH 3.5 with H_2SO_4	0.005 M tetrabutylammonium hydrogen sulfate + methanol (5%)	0.02 M acetate buffer (pH 4) with 15% acetonitrile
Flow rate (mL/min)	1.0	1.0	1.0	0.5	1.0
Injection vol (μl)	20	20	20	20	50
Detection wavelength (nm)	546	313	205	220	285
Detector range (Aufs)	0.02	0.005	0.01	0.01	0.01
Sample dilution	1 to 100	1 to 100	1 to 1000	1 to 1000	1 to 500

Weight change. Medication cassettes were weighed before and after sampling on a six-figure analytical balance (Ohaus, Florham Park, NJ).

Subvisual particulates. Subvisual particle counts were conducted in accordance with the 1993 BP method[6], using an HIAC 420 particle counter with off-line sampling (Royco, Montclain, Calif). Subvisual counts were determined immediately after infusion preparation and again at the final sampling time. For comparative purposes, a control in pharmaceutical grade glass was prepared for each infusion and immediately subjected to particulate determination.

Determination of plasticiser leaching (as DEHP)

The method described by Tidy[7] was adapted for this study. Briefly, the test sample (1 mL) was mixed with an equal volume of acetic acid solution (1% w/v) and aspirated through a diol solid-phase extraction column (Phase Separations, Clwyd, UK) which had previously been conditioned with acetonitrile. The DEHP was eluted with acetonitrile (1 mL), and the eluate was analysed using the HPLC system described below:

Column: 250 × 4.0 mm stainless steel packed with Spherisorb C8, 5-μm diameter material;

Table 2. Summary of Validation Data for HPLC Methods Used in the Assay of Cytotoxic Drug Infusions in Graseby 9000 Cassettes

	Analyte				
Parameter	Doxorubicin	Vincristine	Ifosfamide	Mesna	Etoposide
Calibration range	5–25 μg/mL	0.5–3.0 μg/mL	5–25 μg/mL	2.5–25 μg/mL	4–12 μg/mL
Calibration/least squares equation	y = 637.6 × − 2.55	y = 2507 × + 50.8	y = 356 × − 8.9	y = 326 × − 9.3	y = 562 × − 8.1
Calibration plot correlation coefficient	r = 0.999	r = 0.999	r = 0.999	r = 0.999	r = 0.998
Calibration number of data points	8	8	8	9	
Precision of method (CV%)	0.65, n = 6*	0.67, n = 6†	0.42, n = 6‡	0.71, n = 5§	1.63, n = 7‖
Interday precision (CV%)	0.91, n = 5*	1.44, n = 5†	2.10, n = 5‡	1.57, n = 5§	2.04, n = 5‖
Stability-indicating?¶	Yes	Yes	Yes	Yes	Yes

**Doxorubicin concentration = 20 μg/mL.*
†Vincristine concentration = 2 μg/mL.
‡Ifosfamide concentration = 20 μg/mL.
§Mesna concentraiton = 20 μg/mL.
‖Etoposide concentration = 10 μg/mL.
¶With respect to forced degradation under acid, alkali, and oxidative conditions. Peak purity was assessed with a diode-array detector.

Table 3. Chemical Stability of Three Cytotoxic Drug/Drug Admixture Infusions in Graseby 9000 Cassettes at (a) 8°C and (b) 37°C

a. Refrigerated conditions (8°C)

Sample time (days)	Container number	Assay (as % of initial concentraiton)*		
		Doxorubicin + vincristine	Ifosfamide + mesna	Etoposide
0	1	100.0 + 100.0	100.0 + 100.0	100.0
	2	100.0 + 100.0	100.0 + 100.0	100.0
1	1	100.0 + 98.9	97.8 + 98.6	98.3
	2	99.4 + 99.2	98.3 + 98.4	100.1
3	1	99.6 + 97.7	100.9 + 97.5	98.4
	2	100.1 + 96.4	100.7 + 100.0	101.2
5	1	99.9 + 96.6	98.5 + 97.5	98.4
	2	99.5 + 96.4	98.4 + 97.3	101.8
7	1	99.0 + 96.6	98.9 + 97.4	99.6
	2	100.9 + 97.3	98.6 + 97.6	101.3
10	1	98.1 + 96.6	100.5 + 97.9	41.4†
	2	97.4 + 98.5	97.4 + 100.2	100.9
14	1	96.9 + 96.0	101.5 + 97.9	31.4†
	2	95.9 + 96.5	99.6 + 98.8	96.1

b. In-use conditions (37°C)

Sample time (days)	Container number	Assay (as % of initial concentration)*		
		Doxorubicin + vincristine	Ifosfamide + mesna	Etoposide
0	1	100.0 + 100.0	100.0 + 100.0	100.0
	2	100.0 + 100.0	100.0 + 100.0	100.0
1	1	99.9 + 98.9	99.6 + 98.6	98.6
	2	99.8 + 99.3	97.9 + 96.3	101.0
3	1	99.8 + 100.0	100.7 + 97.9	100.0
	2	99.4 + 98.6	100.3 + 96.7	101.0
5	1	99.9 + 97.7	97.5 + 99.3	100.0
	2	100.0 + 100.3	96.5 + 98.3	101.1
7	1	100.3 + 98.8	97.8 + 91.2	99.3
	2	101.2 + 100.8	97.0 + 90.9	102.1

**Mean of duplicate HPLC assays.*
†Precipitate present on this infusion.

Mobile phase: Acetonitrile (80%), acetic acid (20%);
Flow rate: 1 mL min^{-01};
Injection volume: 20 μL;
Detection: ultraviolet 225 nm at 0.01 absorbance units full scale.

Method validation

Calibration: DEHP concentrations of 2.5–100 μg/mL, $n = 7$. Least squares regression equation: $y = 302(x) - 197$, $r = 0.999$;
Limit of quantitation (LOQ): 2.94 μg/mL;
Precision: coefficient of variation = 2.03%, $n = 6$;
Recovery of DEHP: 78.6%.

The absence of interference from the cytotoxic drugs present in the infusion was also confirmed.

RESULTS

Chemical and physical stability

Data for the chemical stability of the three test infusions at 8°C and 37°C are presented in Table 3, a and b, respectively. Physical stability data for the test infusions at 8°C and 37°C are presented in Table 4, a and b, respectively.

Leaching of plasticiser (as DEHP)

Samples that were taken from the doxorubicin plus vincristine and the ifosfamide plus mesna infusions on day 0 (both temperatures), day 14 (8°C), and day 7 (37°C) produced no DHEP peak (LOQ = 2.94 μg/mL).

Table 4. Physical Stability of Three Cytotoxic Drug/Drug Admixture Infusions in Graseby 9000 Cassettes at (a) 8°C and (b) 37°C

a. Refrigerated conditions (8°C)

Sample time (days)	Test	Infusion		
		Doxorubicin + vincristine	Ifosfamide + mesna	Etoposide
0	pH	4.70	7.70	3.71
	Wt loss (%)	0	0	0
	Appearance	c/r	c/c	c/c
1	pH	4.81	7.65	3.74
	Wt loss (%)	0.02	0.02	0.10
	Appearance	c/r	c/c	c/c
3	pH	4.72	7.55	3.85
	Wt loss (%)	0.03	0.03	0.14
	Appearance	c/r	c/c	c/c
5	pH	4.72	7.50	3.85
	Wt loss (%)	0.03	0.03	0.20
	Appearance	c/r	c/c	c/c
7	pH	4.85	7.52	3.80
	Wt loss (%)	0.04	0.03	0.33
	Appearance	c/r	c/c	c/c
10	pH	4.95	7.50	3.88
	Wt loss (%)	0.04	0.06	0.43
	Appearance	c/r	c/c	ppt§
14	pH	4.90	7.42	3.48
	Wt loss (%)	0.06	0.05	0.60
	Appearance	c/r	c/c	ppt§

b. In-use conditions (37°C)

Sample time (days)	Test	Infusion		
		Doxorubicin + vincristine	Ifosfamide + mesna	Etoposide
0	pH	4.80	7.70	3.80
	Wt loss (%)	0	0	0
	Appearance	c/r	c/c	c/c
1	pH	4.82	6.45	3.73
	Wt loss (%)	0.10	0.09	0.1
	Appearance	c/r	c/c	c/c
3	pH	4.85	5.55	3.74
	Wt loss (%)	0.21	0.21	0.34
	Appearance	c/r	c/c	c/c
5	pH	4.84	5.20	3.75
	Wt loss (%)	0.18	0.26	0.57
	Appearance	c/r	c/c	c/c
7	pH	4.80	5.15	3.70
	Wt loss (%)	0.38	0.18	0.82
	Appearance	c/r	c/c	c/c

Test results are the mean from duplicate samples.
c/r = clear, red solution.
c/c = clear, colourless solution.
Precipitate present in one of two test infusions.

However significant concentrations of DEHP were found in the etoposide infusions: 35 μg/mL after 14 days at 8°C and 90 μg/mL after 7 days at 37°C. On the basis of these results, the experiment with the etoposide infusion was repeated with sampling on days 0, 1, 2, 4, 7, 10, and 14 at both 37°C and 8°C. A control cassette containing 0.9% sodium chloride solution was also incubated at 37°C and sampled at the same times. Data from this experiment are presented graphically in Figure 1.

CONCLUSIONS

Doxorubicin (2 mg/mL) plus vincristine (0.2 mg/mL) infusion

There was no significant loss of either drug over the 14-day incubation at 8°C (Table 3a) or over the 7-day incubation at 37°C (Table 3b); mean assay values were consistently >96% of the original drug concentration. In terms of physical stability, the infusion exhibited no

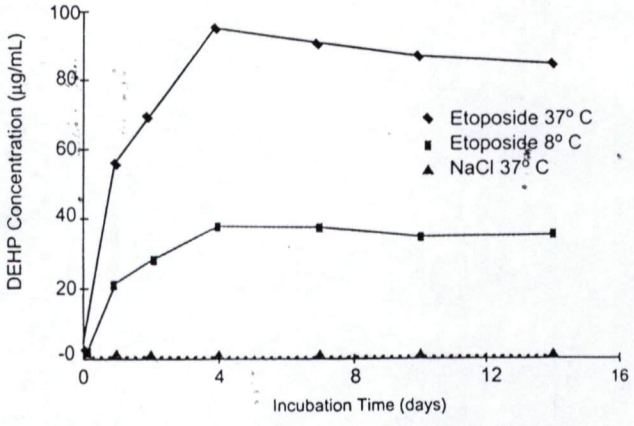

Figure 1. DEHP concentrations in Graseby cassettes containing etoposide infusion.

change in appearance and only a small change in pH at both study temperatures (Table 4, a and b). Weight losses were minimal, indicating that there was little moisture transmission through the container wall of the Graseby medication cassette. Subvisual particulate levels increased slightly during the incubation period (Table 5), but these remained well within the British Pharmacopoeia[6] limits of 1000 > 2 μm and 100 > 5 μm. More recently, the BP has introduced limits for larger particle sizes[8] that may have more clinical relevance. However, the methodology described in this report provides useful information on the physical stability of infusions and on particulate shedding by containers. No DEHP plasticiser was detected in infusions incubated at either temperature, confirming that DEHP concentrations were below the LOQ for the assay (2.94 mg/mL).

This admixture in Graseby 9000 medication cassettes is chemically and physically stable for 14 days at 8°C and 7 days at 37°C when protected from light.

Ifosfamide (20 mg/mL) plus mesna (20 mg/mL) infusion

Both ifosfamide and mesna were chemically stable over 14 days at 8°C, with a mean of >98% of the initial drug concentration remaining (Table 3a). At 37°C, the mean ifosfamide concentration remained at >97% of the initial concentration over 7 days, whereas the mean mesna concentration had fallen to 91% of the original concentration by day 7 (Table 3b). The main degradation product of mesna in pharmaceutical infusions is the oxidation product dimesna.[9] This product is produced from mesna *in vivo*, and the majority of the dimer is oxidised back to the urothelial protectant mesna in the bladder.[10] In view of this toxicological information, a limit of 10% for mesna degradation was considered acceptable in this study.

In terms of physical stability, there was no significant weight loss or change in the appearance of the infusion over 14 days at 8°C or 7 days at 37°C (Table 4, a and b). At 8°C, the infusion pH was virtually unchanged over 14 days, whereas the infusion pH fell by ~2.5 U over 7 days at 37°C (Table 4b). This lower pH was attributed to the liberation of hydrogen ions from the oxidation of mesna but was not considered to be pharmaceutically or clinically significant for this infusion.

No DEHP was leached from the Graseby 9000 medication reservoirs by the ifosfamide plus mesna infusion, and although subvisual particulate counts increased slightly during incubation, these remained well inside pharmacopoeial limits.[6]

The ifosfamide (20 mg/mL) and mesna (20 mg/mL) admixture in Graseby 9000 medication cassettes is chemically and physically stable for 14 days at 8°C and 7 days at 37°C when protected from light.

Table 5. Subvisual Particulate Counts in Three Cytotoxic Drug/Drug Admixture Infusions in Graseby 9000 Cassettes at 8°C and 37°C

Temperature (°C)	Sample time (days)	Container number	Sub-visual particles mL^{-1}					
			Doxorubicin + vincristine		Ifosfamide + mesna		Etoposide	
			>2 μm	>5 μm	>2 μm	>5 μm	>2 μm	>5 μm
8	0	1	207	15	274	24	385	28
		2	288	32	186	14	459	45
	14	1	317	27	311	23	ppt*	ppt*
		2	295	45	189	20	406	50
37	0	1	383	29	304	31	436	51
		2	279	25	347	27	491	46
	7	1	370	33	295	35	480	59
		2	344	28	322	26	394	40
Control	—	—	147	17	175	9	321	37

ppt = precipitate in infusion and subvisual particulate count not performed.

Etoposide (0.5 mg/mL) infusion

Although the chemical (Table 3, a and b) and physical (Table 4, a and b, and Table 5) stability of the etoposide infusion was mainly satisfactory, one infusion (cassette 1) stored at 8°C exhibited a white precipitate after 10 days. The low assay results on days 10 and 14 for cassette 1 confirmed that the precipitate was etoposide. The test concentration of 0.5 mg/mL has seen widespread clinical use in the UK but is twice the manufacturer's recommended concentration for etoposide infusions.[11]

Etoposide infusion caused significant leaching of DEHP plasticiser from the PVC reservoir in the Graseby medication cassette (Fig 1). Although there are no specific limits for DEHP levels in this type of infusion, a previous report on DEHP leaching by docetaxel[12] suggests that even the 24-hour levels obtained at both test temperatures for etoposide infusion are unacceptable. Cosolvents and solubilising agents in the etoposide formulation were likely to be the main cause of DEHP leaching from the Graseby cassette.

PVC-based medication reservoirs are not suitable for the storage or administration of the etoposide infusion. Further plasticiser could also be leached from the administration set tubing by this infusion. This problem could be circumvented by the use of nonplasticiser-containing medication reservoirs. However, the precipitation of etoposide from relatively concentrated infusions under refrigerated storage is a major limitation to the domiciliary use of this infusion. These findings suggest that use of the new etoposide phosphate formulation[13] is the only satisfactory option for ambulatory infusion. Further studies should be undertaken to evaluate the stability of this formulation in ambulatory infusion pumps.

The conclusions and expiration periods given for the three infusions in this report are dependent upon the maintenance of asepsis during the preparation, storage, and use of the drug infusions. Therefore, it is essential that aseptic technique is thoroughly validated before extended expiration dates are assigned.

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