

2014

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<http://hdl.handle.net/10026.1/3703>

European Journal of Oncology Pharmacy

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Studies on the stability and compatibility of cytotoxic drug infusions with the Tevadaptor device

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Abstract

Introduction: The role of closed-system drug transfer devices (CSDTD) in the preparation of cytotoxic infusions has attracted considerable interest in recent years. The use of such devices can subject drug infusions to contact with the materials used to construct the CSDTD, with potential implications for compatibility and stability of the drug. This study investigated the stability and compatibility of 11 frequently used cytotoxic drug infusions with the Tevadaptor device.

Methods: Test infusions of 11 cytotoxic drugs at clinically – relevant concentrations were prepared in either prefilled syringes (5) or infusion bags (6) and were stored under controlled conditions. The syringes and bags were divided into two groups; one group fitted with the Tevadaptor device (test), and a second group with no device fitted (controls). At predetermined times each infusion was sampled and subjected to testing for chemical and physical stability against defined acceptance criteria.

Results: In each case there was no difference between test and control groups in chemical or physical test data. The addition of the CSDTD did not influence the infusion stability.

Conclusion: The 11 cytotoxic drug infusions tested were compatible with the Tevadaptor device and infusion stability was not affected.

Keywords: Cytotoxic drugs, closed-system transfer device, stability, compatibility

Introduction

With continuing concerns about the risk of occupational staff exposure to cytotoxic drugs government agencies and special interest groups such as NIOSH and ISOPP have published guidelines [1, 2] on safe handling of these agents. The guidelines recommend use of containment devices such as biological safety cabinets or pharmaceutical isolators; and personal protective equipment such as nitrile gloves, chemo gowns and masks. In an attempt to provide further protection to the operator and the work environment, closed-system drug transfer devices (CSDTD) have been introduced to reduce the generation of aerosols during drug manipulations in hospital pharmacies. Several studies [3, 4] have been published showing the effectiveness of the CSDTDs in reducing work surface contamination with anticancer drugs and also in eliminating the risk of needle stick injuries to operators.

The use of a CSDTD places a new set of materials into contact with the cytotoxic drug infusion. This could influence the physical and chemical stability of the drug infusion and potentially leach compounds from the materials used in manufacture into the drug infusion. To ensure that safety and efficacy are maintained when using these devices it is essential that infusion stability and compatibility is established when a CSDTD is fitted.

The Tevadaptor is a CSDTD and comprises several components; a Vial Adaptor enables connection with drug vials. It contains the Toxi-Guard dual activated carbon and 0.2 micron membrane designed to allow sterile air to enter the vial and to trap drug vapours that may exit from it. The Syringe Adaptor fits standard Luer lock syringes and docks to the Vial Adaptor for syringe filling and to administration connecting sets for needle-free, closed-system administration to the patient. A Spike Port Adaptor

connects to IV infusion bags and also docks to connecting sets for infusion administration. For pre-prepared infusions, the Syringe Adaptor (prefilled syringes) and the Spike Port Adaptor (infusion bags) could be in prolonged contact with cytotoxic infusions.

This study evaluated the compatibility of the Tevadaptor device with the following commonly used cytotoxic infusion: Carboplatin, cisplatin, etoposide, fludarabine, gemcitabine, irinotecan, and oxaliplatin; in infusion bags with Tevadaptor Spike Port Adaptor fitted.

Doxorubicin, epirubicin, flououracil and methotrexate; in prefilled syringes with Tevadaptor Syringe Adaptor fitted.

Test infusions with the CSDTD fitted, and Controls with no device fitted, were incubated under controlled conditions and sampled at various time intervals. The infusion concentrations were selected to be representative of typical clinical practice. Chemical testing included drug assay using stability-indicating HPLC assay and UV-visible spectroscopy to test for leaching of components into the infusion. Physical tests included sub-visual particulate testing, visual inspection, pH monitoring and gravimetric determination of moisture loss/gain. For each infusion the physical and chemical test data for the bags and syringes fitted with the CSDTD fitted (Test) were compared with data obtained for the Controls with no device fitted.

Methods and experimental

Cytotoxic drugs were obtained as proprietary preparations from Teva UK, with the exceptions of epirubicin 2 mg/mL (Fresenius Kabi) and 5-fluorouracil 25 mg/mL (Hospira). All drugs were used within the manufacturers' expiry date. Luer-lock polypropylene syringes (50 mL) were obtained from

Becton Dickinson and 250 mL infusions of 5% dextrose and 0.9% sodium chloride, in polyolefin bags, were obtained from Baxter Healthcare.

Test (+CSDTD) and Control (-CSDTD) infusions were prepared in duplicate for each drug included in the study. All test and control infusions were prepared by an experienced technician in a pharmaceutical isolator providing an EU Class A environment, and in accordance with the principles of good pharmaceutical manufacturing practice. Test syringes and infusion bags were fitted with the Tevadaptor Syringe Adaptor System or the Spike Port Adaptor, respectively. Control syringes were sealed with a conventional blind hub. Infusion concentrations, containers, diluents are shown in Table 1, together with storage conditions and sample times. Sampling times, and the duration of each stability/compatibility study was based on the authors' previous experience. Infusion samples were obtained from Control syringes and bags by removing the blind hub and dispensing or withdrawing infusion via the additive port with a syringe and needle, respectively. In the case of Test syringes a Luer Lock Adaptor was fitted to the Syringe Adaptor enabling the infusion to be dispensed from the syringe, and for infusions the samples were drawn from the Spike Port Adaptor after releasing the clamp. In each case this replicates the fluid-path experienced by infusions during clinical use.

At each sample time, the samples of both test and control infusions were subjected to the schedule of analysis described briefly below:

Drug assay by stability-indicating HPLC

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). Data were analysed with EZChrom Elite software (scientific software), version 3.1.7. Samples were injected in duplicate, bracketed with injections of the appropriate external standard. HPLC methods were fully validated (linearity of response, intra- and inter-day precision, stability-indicating ability using

forced degradation studies where drugs were subjected to acid, base and oxidative stress at elevated temperature).

Acceptance criteria: Drug assay; assay value at each time point is within 95–105% of initial (t_0) value.

Specific details of each method and main validation data are outlined below:

Carboplatin, cisplatin and oxaliplatin: 250 × 4.6 mm Spherisorb CN 5µm column, mobile phase of 0.005 M phosphate buffer pH 6.5 at 1 mL/min. Detection UV 205 nm.

Validation (carboplatin): Linear range 0.5-100 µg/mL, $R^2=0.999$. Intra-day and inter-day precision CV = 0.33% and 1.18%, respectively. Stability-indicating.

Validation (cisplatin): Linear range 0.5-100 µg/mL, $R^2=0.999$. Intra-day and inter-day precision CV = 1.3% and 1.7%, respectively. Stability-indicating.

Validation (oxaliplatin): Linear range 0.5-100 µg/mL, $R^2=0.999$. Intra-day and inter-day precision CV = 0.4% and 1.6%, respectively. Stability-indicating.

Doxorubicin, epirubicin: 250 × 4.6 mm Varian C18, 5 µm column, mobile phase of 0.005 M phosphate buffer pH 5:methanol:acetonitrile (40:30:30) with 0.6 g/L sodium dodecyl sulphate at 1 mL/min. Detection UV 232 nm.

Validation (doxorubicin): Linear range 0.01-10 µg/mL, $R^2=0.999$. Intra-day and inter-day precision CV = 1.1% and 1.3%, respectively. Stability-indicating.

Validation (epirubicin): Linear range 0.01-10 µg/mL, $R^2=0.999$. Intra-day and inter-day precision CV = 0.8% and 1.4%, respectively. Stability-indicating.

Etoposide: 250 × 4.6 mm Techsphere CN 5 µm column, mobile phase of water:acetonitrile (70:30) with 2.0 g/L sodium acetate at 1.5 mL/min. Detection UV at 285 nm.

Validation: Linear range 0.05-50 µg/mL, $R^2=0.998$. Intra-day and inter-day precision CV = 1.6% and 1.5%, respectively. Stability-indicating.

Table 1: Cytotoxic infusions included in study, container type, storage conditions and sampling schedule

Infusion and container	Storage conditions	Sampling times (days)
Carboplatin 2 mg/mL in 5% dextrose. 250 mL Polyolefin bag	2–8°C, protected from light	0, 7, 14, 28, 56, 84
Cisplatin 0.5 mg/mL in 0.9% NaCl. 250 mL Polyolefin bag	2–8°C, protected from light	0, 7, 14, 28
Doxorubicin 2 mg/mL undiluted. 50 mL Polypropylene syringe	2–8°C, protected from light	0, 7, 14, 28, 56, 84
Epirubicin 2 mg/mL undiluted. 50 mL Polypropylene syringe	2–8°C, protected from light	0, 7, 14, 28, 56, 84
Etoposide 0.25 mg/mL in 0.9% NaCl. 250 mL Polyolefin bag	20°C, protected from light	0, 2, 3, 5
Fludarabine 0.15 mg/mL in 0.9% NaCl. 250 mL Polyolefin bag	2–8°C, protected from light	0, 3, 7, 10, 14
5-Fluorouracil 25 mg/mL. Undiluted. 50 mL Polypropylene syringe	2–8°C, protected from light	0, 7, 14, 28, 56, 84
Gemcitabine 9 mg/mL in 0.9%NaCl. 250 mL Polyolefin bag	2–8°C, protected from light	0, 7, 14, 28, 56, 84
Irinotecan 1 mg/mL in 0.9%NaCl. 250 mL Polyolefin bag	2–8°C, protected from light	0, 7, 14, 28, 56, 84
Methotrexate 25 mg/mL. Undiluted. 50 mL Polypropylene syringe	2–8°C, protected from light	0, 7, 14, 28, 56, 84
Oxaliplatin 1.5 mg/mL in 5% dextrose. 250 mL Polyolefin bag	2–8°C, protected from light	0, 7, 14, 28, 56, 84

Fludarabine: 250 × 4.6 mm Techsphere ODS 5 µm column, mobile phase of 0.005 M phosphate buffer pH 6.5:methanol (85:15) at 1 mL/min. Detection UV 250 nm.

Validation: Linear range 0.1-50 µg/mL, $R^2 = 0.999$. Intra-day and inter-day precision CV = 0.3% and 1.1%, respectively. Stability-indicating.

5-Fluorouracil: 250 × 4.6 mm Luna C18 5 µm column, mobile phase of water:methanol (98:2) at 1 mL/min. Detection UV at 266 nm.

Validation: Linear range 1-100 µg/mL, $R^2 = 0.999$. Intra-day and inter-day precision CV = 1.7% and 2.0%, respectively. Stability-indicating.

Gemcitabine: 150 × 4.6 mm Gemini C18 5 µm column, mobile phase of water:methanol (95:5) with 4.1 g/L sodium acetate at 1 mL/min. Detection UV at 269 nm.

Validation: Linear range 0.1-100 µg/mL, $R^2 = 0.999$. Intra-day and inter-day precision CV = 0.8% and 1.7%, respectively. Stability-indicating.

Irinotecan: 250 × 4.6 mm Techsphere ODS 5 µm column, mobile phase of 0.01 M KH_2PO_4 :methanol:acetonitrile:isopropanol (47:26:25:2) with 1.22 g/L sodium-1-decanesulfonate at 1.2 mL/min. Detection UV at 254 nm.

Validation: Linear range 1-100 µg/mL, $R^2 = 0.998$. Intra-day and inter-day precision CV = 0.9% and 1.9%, respectively. Stability-indicating.

Methotrexate: 250 × 4.6 mm Techsphere ODS 5 µm column, mobile phase of 0.005 M citrate-phosphate buffer, pH 6.0:acetonitrile:methanol (85:10:5) at 1 mL/min. Detection UV at 270 nm.

Validation: Linear range 1-100 µg/mL, $R^2 = 0.999$. Intra-day and inter-day precision CV = 1.4% and 1.5%, respectively. Stability-indicating.

pH measurement

A combination glass electrode and a GLP-compliant pH meter (Hanna pH 302 series) were first calibrated using standard reference solutions of pH 4.0, 7.0 and 10.0 before determination of infusion pH.

Acceptance criteria: any pH change is within ± 0.5 units of initial (t_0) value.

Weight change

Infusion bags and syringes were weighed before and after sampling on a calibrated analytical balance (KERN KB 10000-1) and the percentage weight increase/decrease on storage was calculated. Change in weight represents transfer of water vapour through the walls of the infusion container.

Acceptance criteria: Maximum weight change over a given storage interval is $< 2\%$ w/w. This test ensures that any water loss through the container walls does not mask drug loss due to degradation.

Sub-visual particulates

Sub-visual particle counts of infusions were conducted at predetermined time intervals in accordance with the Pharmacopoeial method using an LS-200/LiQuilaz AZ-E20 particle size analyser with APSS-view software, version 3.4 (Particle Measuring System Europe, UK). This was calibrated using certificated diameter latex spheres supplied by Particle Measurement Technique Ltd. The number of particles/mL at 10 and 25 µm were recorded for duplicate samples and the mean count of each was calculated. This analysis was used to detect particle growth in infusions, Pharmacopoeial standards were not applicable and, in view of the limited number of counts performed for each sample ($n = 3$), the counts obtained were considered to be semi-quantitatively only.

Acceptance criteria: < 5 -fold increase in sub-visual particulate count/mL of both 10 and 25 µm diameter particles.

Visual inspection

Infusions were examined under ambient light against both white and black backgrounds for any change in colour, clarity or for the presence of particulate matter.

Acceptance criteria: no change in colour or clarity with respect to the initial (t_0) sample.

UV-visible scan

Infusions were diluted 1 to 10 with water and test infusions (+CSDTD) were scanned against a reference cell of the control infusion (-CSDTD) over the range 200-600 nm and any deviation from the baseline was recorded.

Acceptance criteria: deviation from baseline is < 0.05 au over entire scan.

Results

Chemical and physical data obtained for all infusions (Test and Control) were within the above acceptance criteria at all sample times in this study. The chemical and physical analysis data for the initial ($t = 0$) and final ($t = x$) sample time points for test and control infusions of each drug are summarized in Table 2. The small variations seen in pH and drug assay between initial and final sample – points was within normal experimental error and was not considered to be of pharmaceutical or clinical significance. Small increases in sub-visual particle counts were observed over time, but these occurred in both test and control infusions and, again, were within the predetermined acceptance criteria. Similarly, the visual appearance, UV-visible spectra and weight-change of infusions were all compliant with acceptance criteria at all sample points.

Discussion

As evidence on the effectiveness of CSDTD devices in reducing cytotoxic contamination continues to emerge [3, 4], the deployment of these devices is likely to increase, albeit at a slow rate because of financial issues. It is essential to demonstrate the containment effect of CSDTDs under actual practice conditions

Table 2: Physical and chemical stability/compatibility data at initial (t = 0) and final sample points for 11 cytotoxic infusions in the presence (Test) and absence (Control) of the Tevadaptor device

Infusion	Test/Control sample time(d)	pH	Sub-visual particles/mL		Appearance/ Wt. change/ UV-visual scan	Drug Assay (% of initial value)
			10 μ	25 μ		
Carboplatin 2 mg/mL	Test 0	4.4	38	1.8	Complies	100 (1.9 mg/mL)
Infusion bag	Test 84	4.4	68	1.1	Complies	98.8
	Control 0	4.4	52	0.8	Complies	100 (1.9 mg/mL)
	Control 84	4.2	87	1.3	Complies	98.3
Cisplatin 0.5 mg/mL	Test 0	5.5	15	0.6	Complies	100 (0.48 mg/mL)
Infusion bag	Test 28	5.9	15	0.4	Complies	103.9
	Control 0	5.5	23	1.0	Complies	100 (0.50 mg/mL)
	Control 28	5.9	9	0.2	Complies	100.8
Doxorubicin 2 mg/mL	Test 0	2.7	27	1.1	Complies	100 (1.96 mg/mL)
Prefilled syringe	Test 84	2.6	36	0.9	Complies	97.3
	Control 0	2.7	35	0.8	Complies	100 (1.89 mg/mL)
	Control 84	2.6	41	1.2	Complies	98.9
Epirubicin 2 mg/mL	Test 0	3.9	39	0.7	Complies	100 (1.95 mg/mL)
Prefilled syringe	Test 84	4.1	62	1.2	Complies	100.8
	Control 0	3.9	26	0.2	Complies	100 (2.0 mg/mL)
	Control 84	4.2	52	0.9	Complies	98.8
Etoposide 0.25 mg/mL	Test 0	3.5	43	0.6	Complies	100 (0.25 mg/mL)
Infusion bag	Test 5	3.4	96	0.8	Complies	99.5
	Control 0	3.4	35	0.2	Complies	100 (0.24 mg/mL)
	Control 5	3.4	61	0.9	Complies	97.2
Fludarabine 0.15 mg/mL	Test 0	6.2	26	2.3	Complies	100 (0.15 mg/mL)
Infusion bag	Test 14	6.3	49	4.5	Complies	103.3
	Control 0	6.3	32	1.9	Complies	100 (0.15 mg/mL)
	Control 14	6.2	58	6.2	Complies	99.3
5-Fluorouracil 25 mg/mL	Test 0	8.9	57	1.0	Complies	100 (26.0 mg/mL)
Prefilled syringe	Test 84	8.9	37	0	Complies	97.6
	Control 0	8.9	32	0.4	Complies	100 (26.2 mg/mL)
	Control 84	8.9	28	0	Complies	96.4
Gemcitabine 9 mg/mL	Test 0	2.7	49	2.1	Complies	100 (8.95 mg/mL)
Infusion bag	Test 84	2.8	63	1.8	Complies	100.7
	Control 0	2.7	33	1.6	Complies	100 (8.81 mg/mL)
	Control 84	2.8	71	2.3	Complies	103.8
Irinotecan 1.0 mg/mL	Test 0	3.7	17	0.6	Complies	100 (0.99 mg/mL)
Infusion bag	Test 84	3.6	39	2.3	Complies	99.4
	Control 0	3.7	23	0.5	Complies	100 (1.01 mg/mL)
	Control 84	3.6	31	1.9	Complies	101.9

(Continued)

Table 2: Physical and chemical stability/compatibility data at initial (t = 0) and final sample points for 11 cytotoxic infusions in the presence (Test) and absence (Control) of the Tevadaptor device (Continued)

Methotrexate 25 mg/mL	Test 0	8.4	29	0	Complies	100 (25.1 mg/mL)
Prefilled syringe	Test 84	8.6	53	1.0	Complies	101.5
	Control 0	8.4	30	0	Complies	100 (24.9 mg/mL)
	Control 84	8.7	51	0.7	Complies	101.6
Oxaliplatin 1.5 mg/mL	Test 0	7.1	39	0.2	Complies	100 (1.6 mg/mL)
Infusion bag	Test 84	7.0	38	2.1	Complies	97.4
	Control 0	7.1	28	1.5	Complies	100 (1.6 mg/mL)
	Control 84	7.1	21	1.9	Complies	98.1

Data shown are means of duplicate determinations. 'Complies' indicates compliance with stated acceptance criteria for weight change, visible appearance and UV-visible scans.

in pharmacy cytotoxic units and chemotherapy clinics. The debate on whether a device is a 'fully closed-system' or not would seem of secondary importance to performance of the device in 'real-life'. However, before CSDTDs can be evaluated in the clinical setting, evidence is required to demonstrate that the device does not adversely affect the infusion or drug stability prior to administration to the patient. This study has evaluated the physical and chemical compatibility of the Tevadaptor device with 11 cytotoxic drug infusions with a view to facilitating evaluation of the device in pharmacy and clinical practice.

Tevadaptor Syringe and Spike Port Adaptors were challenged with a range of cytotoxic infusions, including those containing co-solvents to solubilize the drug (etoposide infusion) and infusions of low pH, e.g. gemcitabine and doxorubicin; and high pH, e.g. 5-fluorouracil and methotrexate. The schedule of testing was designed to identify any effect the CSDTD could have on drug stability, on damage to either the device or the container to which it was fitted resulting in the liberation of particulates or increased transfer of moisture (evidenced by weight change), change in pH, or the leaching of components such as pigments into the infusion that would absorb in the UV-visible region. The CSDTD and the containers used were not PVC-based so no specific tests were undertaken for plasticizers. In each case the CSDTD remained in contact with the infusion for the full, normally assigned shelf life under standard storage conditions. Overall, and to ensure rigour, the study design was compliant with the guidelines published in consensus report [5] of a European expert conference on cytotoxic stability.

For all of the infusions tested, and at all sample times, the infusions fitted with the appropriate Tevadaptor device, and the control infusions with no CSDTD fitted, were all within the stated acceptance criteria for each test. Furthermore, there were no significant differences observed between the Test and Control infusions in any of the physical and chemical tests deployed. This study has confirmed that under the normal storage conditions stated, the Tevadaptor Syringe Adaptor and Spike Port Adaptor were compatible with a range of commonly used cytotoxic infusions at typical drug concentrations. The fact that the long shelf

lives assigned to these infusions were not compromised by the CSDTD suggests the device would be appropriate for use in centralized cytotoxic preparation units and for dose-banding schemes where extended stability is required [6]. We recommend that compatibility with drug infusions should be established for all CSDTD devices before they are introduced into clinical practice.

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