

Spill and Leakage Using a Drug Preparation System Based on Double-Filter Technology

OLLE NYGREN^{1*}, EVA OLOFSSON² and LENNART JOHANSSON³

¹Department of Chemistry, Umeå University, SE-901 87 Umeå, Sweden; ²Hospital Pharmacy, University Hospital of Northern Sweden, SE-901 85 Umeå, Sweden; ³Department of Radio Physics, University Hospital of Northern Sweden, SE-901 85 Umeå, Sweden

Received 21 May 2007; in final form 29 November 2007

Occupational exposure to cytotoxic drugs has frequently been reported during recent years. Various drug-handling systems have been applied to reduce the spill and leakage that cause this exposure. Some of these systems have also been tested for spill and leakage using independent test methods. In this paper, a new drug-handling system has been tested for spill and leakage during drug preparation. The handling system, Tevadaptor™, was tested using a modification of an independent test method, the Technetium test method, based on the use of Technetium m-99 as tracer substance. The test results showed that the spill was <100 nl for all 75 preparations and was <1 nl for 70 of the preparations. This is comparable with other tested drug-handling system, e.g. isolators, PhaSeal™. The test shows that the Tevadaptor drug-handling system has similar performance as drug-handling systems regarded as closed systems.

Keywords: drug emission; drug handling; occupational exposure; test methods for preparation systems

INTRODUCTION

Cytotoxic drugs are biological active compounds that may give undesired health effects upon exposure. Consequently, in most countries there are regulations for handling cytotoxic drugs. However, despite handling regulations, numerous studies have shown that medical staff handling cytotoxic drugs may be exposed to these drugs (Nygren and Lundgren, 1997; DesRoches, 2003; Turci *et al.*, 2003). Various systems have been developed for safe drug handling in order to reduce the exposure (Donner, 1978; Cazin and Gosselin, 1999; Sessink *et al.*, 1999; Connor *et al.*, 2002; Nygren *et al.*, 2002). Some of these systems use a particle filter to clean air going in or out of the system during preparation (Nygren *et al.*, 2002). Other systems are physically closed with an expansion enclosure to handle air pressure differences during preparation (Sessink *et al.*, 1999; Connor *et al.*, 2002; Nygren *et al.*, 2002). In yet other systems, the preparation is carried out in a horizontal laminar air flow hood (Donner, 1978), or the preparation is carried out in a confined compartment with separate ventilation with positive or negative pressure (Cazin and Gosselin, 1999). These latter devices are called

isolators and are equipped with a sealed half suit (a hood, jacket and gloves in one piece) and/or with sleeves with fixed gloves. The isolator has a separate ventilated pass-through compartment (a sluice) for entering and exiting goods. Several of these systems have been tested using independent methods and shown to give reduced spill and leakage and thus minimize possible exposure.

In this paper, the results from a test of a newly developed drug-handling system are presented. The system is based on a double-filter technology that cleans air passing the filter system in both directions from particles and vapours. The test was carried out utilizing an independent method developed for testing spill and leakage from drug-handling systems (Nygren *et al.*, 2005).

METHODS

Drug preparation system

The tested system is manufactured by Teva Pharmaceutical Industries Ltd (Israel) and is called Tevadaptor™. The Tevadaptor unit comprises two parts: one part is fixed on the syringe and one part on the drug vial (see Fig. 1). The two parts are connected by pressing the parts together until a snap lock connects and locks the coupling. In this position, there

*Author to whom correspondence should be addressed.
Tel: +46-907-865-483; fax: +46-907-867-655;
e-mail: olle.nygren@chem.umu.se

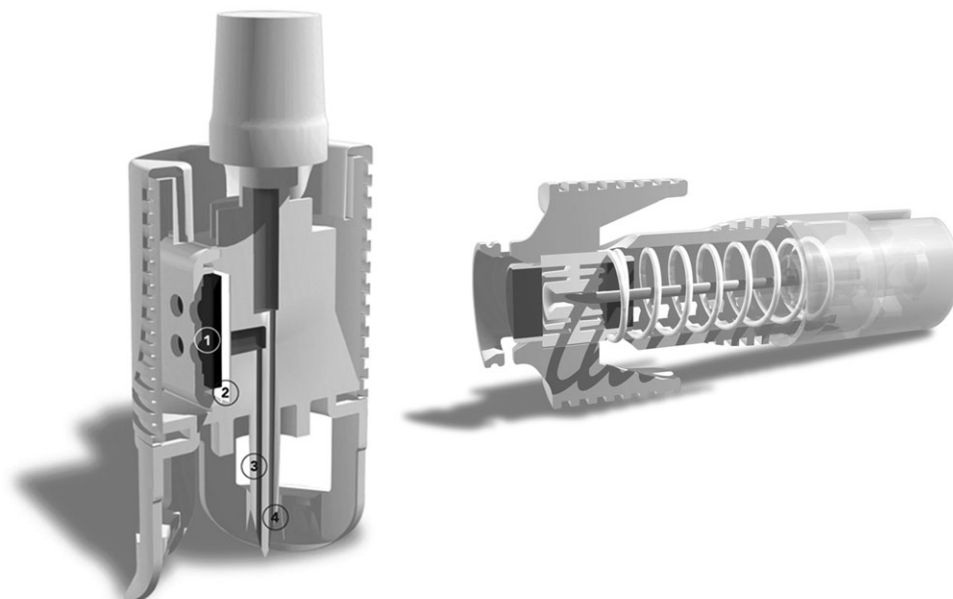


Fig. 1. Cross-cut of the Tevadaptor™ system. Left picture is the part that is attached to the vial with the following: (1) ToxiGuard® active carbon filter, (2) hydrophobic filter (0.2 μm), (3) air path and (4) liquid path. Right picture is the part that is attached to the syringe.

is an open connection between the syringe and the vial. Liquid can then be transferred from or to the syringe and the air pressure in the vial is equalized by air moving in or out of the system through a port with a double-filter seal with one high efficiency particulate air filter that collects aerosols and one charcoal filter that captures vaporous compounds. This double-filter seal is expected both to prevent contamination of the drug from compounds entering the vial from the outside and to prevent drug compound being expelled from the vial and contaminate the environment on the outside of the vial.

Test procedure and materials

A slight modification of the Technetium test method developed by Nygren *et al.* (2005) was used in this test. Test vials (10 ml) were spiked with 1 ml Technetium m-99 ($^{99\text{m}}\text{Tc}$) as sodium pertechnetate in saline and sealed with septum stoppers at the University Hospital of Northern Sweden. $^{99\text{m}}\text{Tc}$ emits photons with an energy of 140 keV and has a half-life of 6 h. The initial activity in the vials (~ 10 to 100 MBq) was measured. Eight pharmacists at the Hospital Pharmacy with various experience of drug preparation in biological safety cabinet (BSC) participated in this test. They made, all together, 75 test preparations using the Tevadaptor drug preparation system. The preparations were carried out in a BSC at the Department of Nuclear Medicine of the University Hospital of Northern Sweden. In the test preparation procedure, 9 ml saline was added to a vial, spiked with $^{99\text{m}}\text{Tc}$, using a disposal syringe and the Teva-

daptor system, followed by mixing and withdrawal of 6 ml solution back to the syringe. The syringe was then disconnected from the vial and connected to an infusion bag using a connection device for the Tevadaptor and the content was injected into the bag. After the injection, the syringe was disconnected from the infusion bag. Bench covers (45 \times 75 Foliodrape, Hartmann, Heidenheim, Germany) were cut into two equally sized parts (450 \times 375 mm) and one of these parts was used for each preparation. The test persons used one pair of disposal gloves for each preparation. The bench cover and the gloves were collected after each preparation and placed together in a screw-capped scintillation jar.

The activity in the samples was measured at the Department of Radio Physics, University Hospital of Northern Sweden. The samples were taken to the measurement laboratory immediately after the samples had been collected. Due to the short half-life of $^{99\text{m}}\text{Tc}$, it is important to begin the measurements as soon as possible after the samples have been collected to obtain and maintain a low detection limit. The measurements began within 1 h after the sampling was completed. A $\text{O} 3'' \times 2''$ NaI(Tl) scintillation detector (Saint-Gobain, Paris, France) connected to a personal computer equipped with a multichannel analyser (Ortec, Oak Ridge, TN, USA) was used to measure the activity. A measuring cell was made by building an enclosed compartment using lead bars. The activity in the samples was measured for 120 s. The blank activity was measured for at least 1000 s (to obtain stable values due to the low level

of the background radiation). The blanks consisted of an unused bench cover and pair of gloves in the same type of jar as the samples. The detector was calibrated using a known activity amount of ^{99m}Tc measured in the same geometry. All calculations were made using spreadsheet software (MS Excel) on a personal computer. The detection limit for this method is 2 Bq defined as three standard deviations of the background. This corresponds to ~ 0.5 nl. However, considering uncertainties due to possible variations in the geometry of a sample for which there is no activity detected, the detection limit was set to 1 nl.

RESULTS AND DISCUSSION

Table 1 shows the results of the test. Since the test comprised 75 preparations, seven of the test persons performed 10 preparations, while the eighth test person only performed 5 preparations. In the samples from two preparations, the spill was found to be >10 nl and between 5 and 10 nl in the samples from three other preparations. For the remaining 70 preparations, the spill was found to be <1 nl for each preparation. The median, average (\pm standard deviation) and total spill from all 75 preparations were <1 nl, 1.6 (± 6.5) nl and 122.1 nl, respectively. In these statistical calculations, half the detection limit (0.5 nl) was used for all values below the detection limit (Miller and Miller, 1986). The highest spill during a single preparation was 53.8 nl. No visible spill was discovered during the 75 test preparations.

A similar study with other drug preparation systems has been published (Nygren *et al.*, 2002). Each of 10 subjects performed six similar preparations as in this study and the spill on bench cover and gloves from each preparation was measured. Using an open system (milking technique), the average spill for all test subjects was 56 μl as compared with the closed system (PhaSealTM) showing an average leakage for all test subjects of 9 nl, which is similar to the average level of spill that occurred with the Tevadaptor.

Isolators are another example of closed systems used for drug preparations (Cazin and Gosselin,

1999). They are frequently used in France and the UK. An isolator is an enclosed compartment ventilated by positive air pressure with filtered air without recirculation. An isolator has a pass-through chamber with separate ventilation for cleaning and sterilizing goods to be entered or exited the isolator. A test with isolators showed spill of cyclophosphamide (CP) from below detection limit to 6.55 ng cm^{-2} inside the isolator and from below the detection limit to 0.22 ng cm^{-2} outside of the isolator (Crauste-Manciet *et al.*, 2005). Assuming that the CP concentration in the spill liquid corresponds to a concentrated dissolved drug, e.g. a 500-mg CP vial dissolved with 10 ml of saline, this will give a concentration of 50 mg cm^{-3} . Recalculating the result with this assumption to spill volumes will give at hand a maximum spill volume of <1 nl, which is slightly lower or in the similar range as the spill volumes obtained with other closed systems (Sessink *et al.*, 1999; Nygren *et al.*, 2002) and the Tevadaptor in this test.

The Swedish Pharmacy (Apoteket AB) Internal Quality Manual prescribes a limit value of 100 nl for total spill volume on bench cover and gloves for one preparation. Internal tests have shown that a level of spill <10 nl can be regularly achieved during normal routine preparations. The Swedish Work Health Authority has in their ordinance on handling cytotoxic drugs (Work Health Authority, 2005) prescribed the precautionary principle, i.e. these drugs can cause severe health effects and the exposure should therefore be kept as low as possible, and a maximum allowed spill level of 1 nl cm^{-2} is recommended.

The tested system in this paper cannot physically be regarded as a closed system according to the National Institute for Occupational Safety and Health definition of closed system (NIOSH, 2004) since air can pass in and out of the system during preparation. When the system was used as recommended by the manufacturer, the double-filter system, however, showed similar aerosol and particle capturing performance as other tested closed systems, e.g. isolators and the closed system PhaSeal. The capturing capacity for vapours was not tested since ^{99m}Tc is not

Table 1. Measured spill during drug preparation using the Tevadaptor

Subject no.	Preparations/measured spill (nl)									
	1	2	3	4	5	6	7	8	9	10
1	<1	<1	<1	<1	<1	<1	<1	<1	<1	<1
2	<1	<1	<1	<1	<1	<1	<1	<1	<1	1.3
3	<1	<1	<1	<1	5.5	<1	<1	<1	<1	<1
4	<1	<1	<1	16.6	<1	<1	<1	<1	<1	<1
5	<1	<1	<1	<1	<1	<1	<1	<1	<1	<1
6	<1	<1	<1	<1	<1	<1	<1	<1	<1	<1
7	<1	<1	<1	<1	<1	<1	<1	<1	53.8	<1
8	<1	<1	<1	9.9	<1					

volatile. A test with a volatile organic compound is recommended to test the Tevadaptor system for capturing vapours. Moreover, in this test, only normal handling of the system was tested. No handling mistakes occurred or products with manufacturing defects were used. Consequently, this test do not include possible spill that can be caused by erroneous handling of the system or use of defect products.

Acknowledgements—The manufacturers of the device paid the Hospital Pharmacy at the University Hospital of Northern Sweden for the tests. None of the authors have any financial link with the device or its producers.

REFERENCES

- Cazin J-L, Gosselin P. (1999) Implementing a multiple-isolator unit for centralized preparation of cytotoxic drugs in a cancer center pharmacy. *Pharm World Sci*; 21: 177–83.
- Connor TH, Anderson RW, Sessink PJ *et al.* (2002) Effectiveness of a closed-system device in containing surface contamination with cyclophosphamide and ifosfamide in an i.v. admixture area. *Am J Health Syst Pharm*; 59: 68–72.
- Crauste-Manciet S, Sessink PJM, Ferrari S *et al.* (2005) Environmental contamination with cytotoxic drugs in healthcare using positive air pressure isolators. *Ann Occup Hyg*; 49: 619–28.
- DesRoches P. (2003) Cytotoxic drug handling—monitoring in the occupational health setting. *AAOHN J*; 51: 106–8.
- Donner AL. (1978) Possible risk of working with antineoplastic drugs in horizontal laminar flow hoods (letter). *Am J Hosp Pharm*; 35: 900.
- Miller JC, Miller JN. (1986) *Statistics for analytical chemistry*. Chichester, UK: Ellis Horwood Ltd.
- National Institute for Occupational Safety and Health (NIOSH). (2004) NIOSH alert 2004-165. Preventing occupational exposures to antineoplastic and other hazardous drugs in health care settings. Cincinnati, OH: NIOSH. Available at <http://www.cdc.gov/niosh/docs/2004-165/pdfs/2004-165.pdf>. Accessed 14 May 2007.
- Nygren O, Lundgren C. (1997) Determination of platinum in workroom air and in blood and urine from nursing staff attending patients receiving cisplatin chemotherapy. *Int Arch Occup Environ Health*; 70: 209–14.
- Nygren O, Gustavsson B, Ström L *et al.* (2002) Exposure to anti-cancer drugs during preparation and administration. Investigations of an open and a closed system. *J Environ Monit*; 4: 739–42.
- Nygren O, Gustavsson B, Eriksson R. (2005) A test method for assessment of spill and leakage from drug preparation systems. *Ann Occup Hyg*; 49: 711–8.
- Sessink PJM, Rolf M-AE, Ryden NS. (1999) Evaluation of the PhaSeal hazardous drug containment system. *Hosp Pharm*; 34: 1311–7.
- Turci R, Sottani C, Spagnoli G *et al.* (2003) Biological and environmental monitoring of hospital personnel exposed to antineoplastic agent: a review of analytical methods. *J Chromatogr B*; 789: 169–209.
- Work Health Authority. (2005) Ordinance AFS 2005:5. Cytostatics and other drugs with persistent toxic effects. Stockholm, Sweden: Swedish Work Health Authority.