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Chemfort™ Contains Real Drug Vapors for Up to 28 Days

Introduction

Chemfort™ is a Closed System Drug Transfer Device (CSTD) designed to prevent the escape of hazardous drug vapors into the environment during drug reconstitution and administration. The design and mechanism of function vary among CSTD manufacturers. CSTDs fall into one of two categories with regard to their mechanism for pressure equalization: physical barrier or air-cleaning. Physical barrier CSTDs include some form of expandable and collapsible air chamber, while air-cleaning type CSTDs allow air to enter and exit the system, but prevent the escape of hazardous drugs and the ingress of microbial contamination. Chemfort™ belongs to the air-cleaning family of CSTDs.

The Chemfort™ Vial Adaptor (VA) automatically equalizes the internal pressure within the vial, thereby saving time and preventing potential errors. As illustrated in Figure 1A, the VA spike contains two channels, one serving as the air pathway and the other as the liquid pathway. Air is released from the system through the air-cleaning Toxi-Guard® component (Figure 1B), comprising a hydrophobic/oleophobic 0.2 µm membrane (Versapor®, Pall, USA) and a 100% activated carbon matrix (Flexzorb™, Chemviron, UK). The membrane acts as a barrier to prevent microorganisms and particles from entering into the vial and aerosols and liquids from being released into the environment. The carbon matrix is highly efficient in the adsorption of drug vapors.

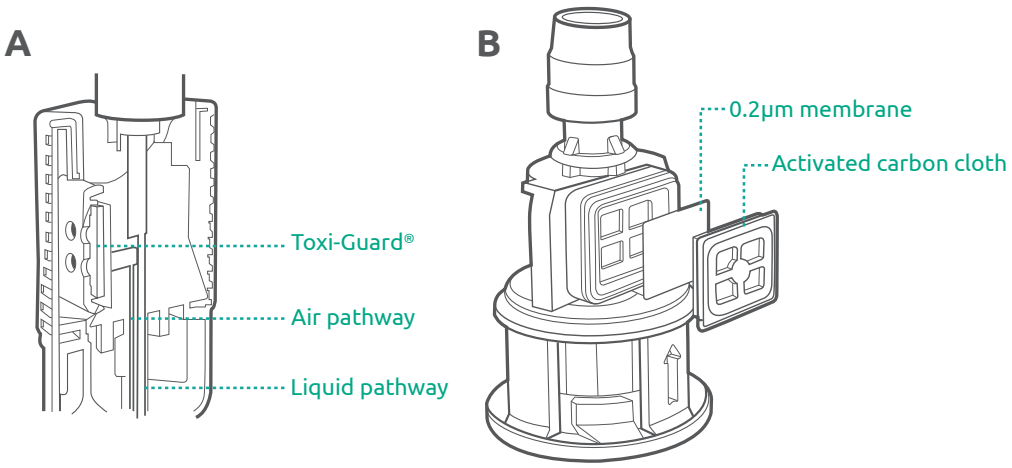

Figure 1. A. Cross section of the Chemfort™ Vial Adaptor.
B. Toxi-Guard® component of the Chemfort™ Vial Adaptor

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In a recent study, Levin and Sessink examined the efficacy of the Chemfort™ Vial Adaptor in preventing the escape of drug vapors.[1] Cyclophosphamide (CP) and 5-fluorouracil (5-FU) were the chemotherapy drugs tested, as they are frequently used and may evaporate at room temperature. Given that the quantity of drug vapors generated under normal use is extremely low (typically below analytical limits of detection), a model system was developed to establish extreme laboratory conditions, in which drug vapors are generated to a much larger extent than in typical working environments in hospitals and pharmacies. These extreme conditions included heating the vials to 50°C and introducing a constant flow of nitrogen into the vials in order to enhance the generation of drug aerosols and vapors. Vapors released from the Chemfort™ VA were trapped within a closed test chamber, collected, and then analyzed by liquid chromatography with tandem mass spectrometry (LC/MS/MS). The study demonstrated that no release of these drugs was detected even after 3 years of simulated aging of the VA, and 7 days of exposure to drug vapors.

In a number of independent drug stability studies, reconstituted drug was demonstrated to be stable for over 7 days. For example, in the case of CP stored at 2-8°C, the decomposition of the active agent was less than 1% on the 7th day and under 1.11% on the 14th day.[2] Another study found that CP dissolved in dimethyl sulfoxide (DMSO) and stored at 4°C remained 100% stable even after 3 months.[3] Hence, a key question is whether efficacy of the Chemfort™ VA can be extended beyond 7 days of exposure to drug vapors.

Objective

In this study, the aim was to determine whether the Chemfort™ Vial Adaptor remains effective in preventing the release of hazardous drug vapors, when connected to a drug vial for 28 days.

Methods

The study was performed at Nextar Chempharma Solutions Ltd (Ness Ziona, Israel). Test conditions were similar to those used in the study of Levin and Sessink.[1] Cyclophosphamide (CP, Figure 2), one of the anti-neoplastic drugs in the list of hazardous compounds published by NIOSH,[4] was chosen as the representative drug, since among these compounds it has one of the highest vapor pressures and Henry's constants.[5] Thus, compared to other commonly used anti-neoplastic drugs, it is either as or more likely to generate vapors.

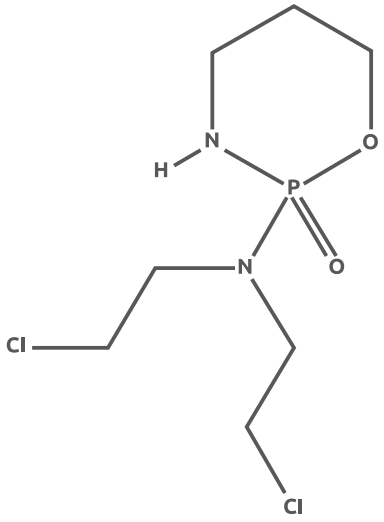

Figure 2. Chemical structure of cyclophosphamide ($C_7H_{15}Cl_2N_2O_2P$). Adapted from https://pubchem.ncbi.nlm.nih.gov/compound/Cyclophosphamide

To mimic the performance of Chemfort™ VAs at the end of their 3-year shelf life, accelerated aging was performed by storing the Chemfort™ VAs at 55°C for 135 days (as instructed in the Standard Guide for Accelerated Aging of Sterile Medical Device Packages[6]). In total, eight CP vials and one blank vial (i.e., a vial containing only water) were tested. A Chemfort™ VA was connected to each vial, and CP was reconstituted according to the drug instructions for use.

Following reconstitution, four vial handlings were tested: (1) Five vials containing CP, connected to Chemfort™ VAs with intact Toxi-Guard® components, and incubated at 30°C for 28 days; (2) two vials containing CP, connected to Chemfort™ VAs with intact Toxi-Guard® components, without incubation; (3) one vial containing CP, connected to Chemfort™ VA without the activated carbon layer of the Toxi-Guard® (positive control); and (4) one vial containing water, connected to Chemfort™ VA with a Toxi-Guard®, and incubated at 30°C for 28 days (negative control).

The experimental setup is illustrated in Figure 3. Following vial handling, each vial was transferred in turn to a closed test chamber. The test chamber was placed in an oven heated to 50°C and connected to a 10 ml vapor trap (chilled to -50°C) located outside the oven (Figure 3). A constant flow of nitrogen gas into the liquid pathway of the vials was maintained at a rate of 250 ml/min for 5 hours (total volume: 75 L). Vapors released from the Chemfort™ VA were trapped in the vapor trap and then recovered by dissolving in 1:1 methanol:water.

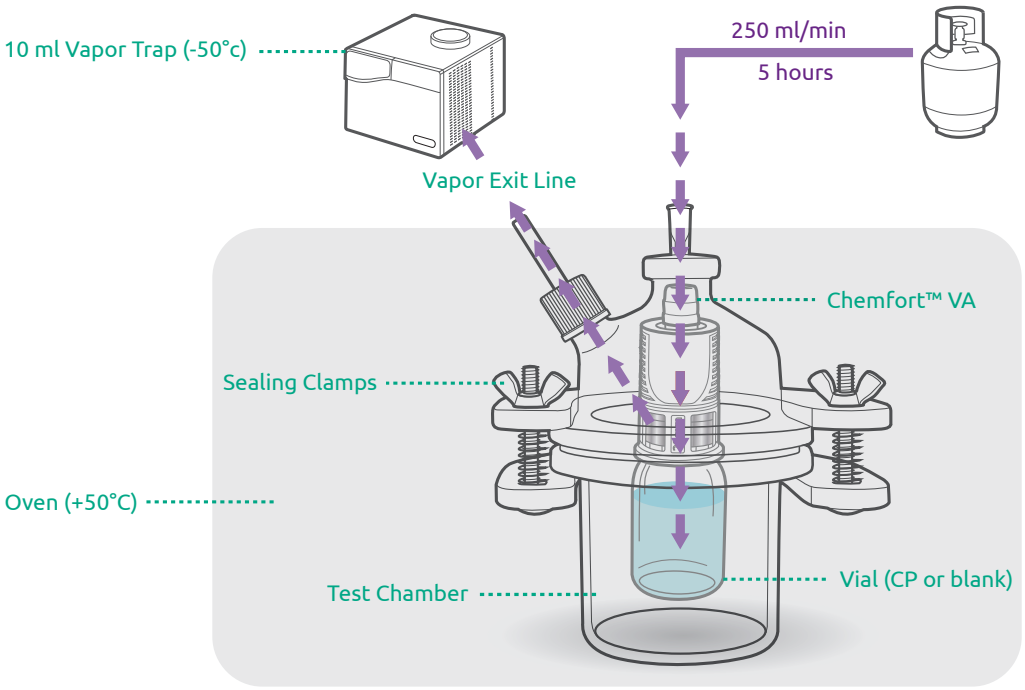

Figure 3. Schematic of experimental setup. Components are out of scale. Adapted from Levin and Sessink, 2012.[1]

Detection and quantification of CP was performed after the vapor trapping procedure, using a validated LC/MS/MS method. The limit of quantitation (LOQ) of the LC/MS/MS method for CP was determined to be 0.1 ng/ml, which represents a LOQ of 1 ng of recovered drug after compensating for the volume of diluent used to recover drug from the test chamber, outside of drug vial, VA and tubing (10 ml). The limit of detection (LOD), estimated based on the signal to noise ratio, was 0.02 ng/ml or 0.2 ng of recovered drug. Thus, if no CP peak was observed in LC/MS/MS, this indicated a CP concentration of less than 0.02 ng/ml.

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Results

Study results are summarized in Table 1.

Table 1. Study results. CP: cyclophosphamide; H_2O: water; + : incubated for 28 days at 30°C; - : No incubation; ND: Not detected (<0.2 ng)

Vial Number	Vial Content	Toxi-Guard®	Incubation	CP Detected (ng)
1	CP	Intact	+	ND
2				ND
3				ND
4				ND
5				ND
6	CP	Intact	-	ND
7				ND
8 (positive control)*	CP	Lacking activated carbon layer	-	110.3
9 (negative control)	H_2O	Intact	+	ND

* To prevent loss of drug and external contamination prior to vapor trapping, the positive control vial and VA assembly, which lacked an activated carbon layer in its Toxi-Guard®, was not incubated.

For the 7 vials containing CP and connected to a VA with an intact Toxi-Guard®, with (n = 5) or without (n=2) incubation, no CP was detected. In the positive control vial (containing CP, and where the activated carbon layer was removed from the Toxi-Guard® of the Chemfort® VA), a CP concentration of 11.03 ng/ml was detected using the LC/MS/MS method, corresponding to an absolute quantity of 110.3 ng CP. This result shows that the test method is valid and that the activated carbon layer plays an important role in preventing drug vapor escape. As expected, in the negative control vial (containing water only, and where the Toxi-Guard® was intact), no CP was detected.

Conclusions

This study demonstrates no release of cyclophosphamide vapors when the Chemfort® Vial Adaptor remained connected to the drug vial for 28 days from reconstitution, even when extreme conditions were employed to encourage the production of vapors, and even when the Chemfort® Vial Adaptor was at the end of its simulated 3-year shelf life.

References

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