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Prevention of Hazardous Drug Vapor Release by the Chemfort® Vial Adaptor

Figure 1. Chemfort® Vial Adaptor | TOXIGUARD®'s Charcoal drug adsorbing matrix | TOXIGUARD®'s 0.2 hydrophobic and oleophobic membrane

TOXIGUARD®

Summary

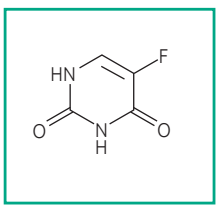
Chemfort® is a Closed System Transfer Device (CSTD) designed to prevent the escape of hazardous drug in liquid, vapor, or aerosol form into the environment during drug reconstitution and administration. Drug containment in the Chemfort® Vial Adaptor is accomplished by the TOXIGUARD® drug-binding mechanical barrier, which contains a 100% activated carbon[1] matrix and 0.2 µm hydrophobic and oleophobic membrane (Figure 1). The activated carbon matrix is highly efficient in adsorption of drug vapors, actively pulling and physically locking hazardous drug molecules within its pore structure. The carbon matrix exhibits dual action by also deactivating and locking out microbial contaminants, preventing their entry into the drug vial. The 0.2 µm membrane is a sterile barrier preventing microorganisms and particles from entering the system and, due to its hydrophobic and oleophobic properties, preventing aerosols and liquids from being released from the system.

Together, they serve as an effective sterile, particulate and toxic drug barrier. The TOXIGUARD® system ensures that the Chemfort® air path only allows air free of bacteria and particles to enter the drug vial during drug reconstitution and preparation. It also ensures that the air exiting the drug vial is free of hazardous drug vapor.

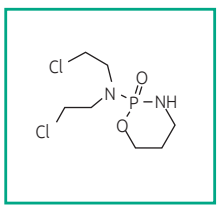
Several studies were performed, challenging the efficacy of the Chemfort® Vial Adaptor to prevent the escape of drug vapors.[2,3] A model system was designed to induce drug vapors within the drug vial. Since under normal usage conditions, the drug vapors that are generated are minimal, extreme conditions were employed to significantly increase vapor quantity. Vapors released from the Chemfort® Vial Adaptor were trapped within a closed test chamber. The trapped drug was collected and then analyzed by highly sensitive LC/MS/MS methods.
The Chemfort® Vial Adaptor was challenged with three commonly used antineoplastic drugs: cyclophosphamide, 5-fluorouracil and doxorubicin (Figure 2). The Chemfort® Vial Adaptor was further challenged at the end of its 3 year shelf life and after 7 days exposure to cyclophosphamide, prior to testing. With cyclophosphamide and 5-fluorouracil, vapors were consistently detected in control samples in which the activated carbon component of the TOXIGUARD® system had been removed from the Chemfort® Vial Adaptor. In test samples containing an intact TOXIGUARD® system, **no drug vapors were detected**. With doxorubicin no drug vapors were detected in either the positive control or test sample.

These results support the validity of the Chemfort® Vial Adaptor to prevent release of hazardous drug vapors for its entire 3 year shelf life and 7 day usage period.

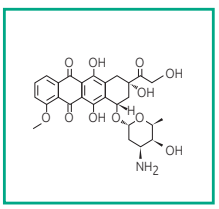
Figure 2. Chemical structures of the antineoplastic drugs used for challenging the Chemfort® Vial Adaptor and the TOXIGUARD® system. Figure shows the range of the drugs tested in terms of their size (molecular weight) and structural complexity.



5-Fluorouracil
$C_4H_3FN_2O_2$
MW = 130 g/mol



Cyclophosphamide
$C_7H_{15}Cl_2N_2O_2P$
MW = 261.1 g/mol



Doxorubicin
$C_{27}H_{29}NO_{11}$
MW = 543.5 g/mol

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Introduction

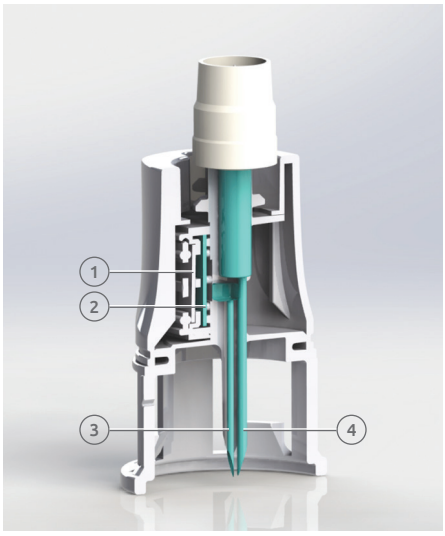
About Flexzorb™

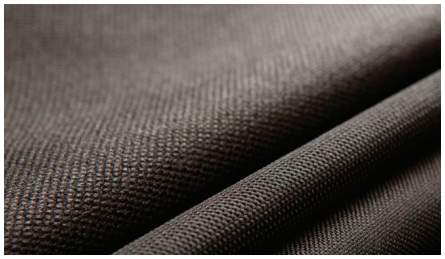
Protection against toxic gases is one of the oldest applications of activated carbon, dating back to its use in World War I for protection against chlorine and other gases. Today it is used for a variety of industrial, military and medical applications. This includes removal of toxic and volatile gases in chemical manufacturing plants, in water purification systems, in industrial and military respirators, as protective clothing against chemical, biological or nuclear agents, and as wound dressings for protection against microbial infection.

The Flexzorb™ 100% activated carbon cloth is manufactured by Chemviron Carbon. Their special manufacturing process results in the cloth having a micro-porous matrix, with an extremely large surface area (1000-2000 m^2/g). The surface area of one gram of activated carbon cloth is over half the size of a football pitch. The microporous structure and cloth weave, gives the cloth a very high air permeability. The large surface area of the cloth, combined with the strong electrostatic forces that are induced in the cloth as part of the manufacturing process, and its high air permeability, result in the carbon cloth having very rapid adsorption kinetics. In addition, the active carbon cloth is suitable for use in applications where there is high humidity as its adsorption capacity is less adversely affected by moisture.[1]

About TOXIGUARD®

The Chemfort® Vial Adaptor equalizes the pressure inside the vial without any need of action or activity by the user, thereby saving time and preventing potential errors. The Vial Adaptor spike contains two channels. One channel serves as the air path (see Figure 3, item 3) and the second channel as the fluid path (see Figure 3, item 4). The TOXIGUARD® system has a sterile 0.2 µm hydrophobic and oleophobic membrane (Figure 3, item 2) on the interior side of the air channel and a 100% activated carbon drug binding matrix on its exterior side (Figure 2, item 1). The hydrophobic membrane blocks passage of liquids out of the air channel, while maintaining high air permeability. The manufacturing process for the activated carbon matrix results in a woven carbon cloth with a highly microporous structure and strong electrostatic forces (Figure 4). This matrix is highly efficient in adsorbing molecules that may pass through the 0.2 µm membrane, preventing their release into the environment.[1] The surface area available for drug adsorption in one TOXIGUARD® is more than 60 m^2, or a quarter of a tennis court.





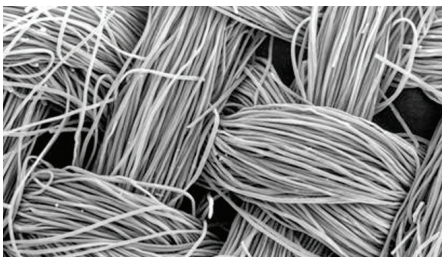


Figure 3. Left. Cross-section of the Chemfort® Vial Adaptor. (1) TOXIGUARD® activated carbon matrix, (2) 0.2 µm hydrophobic and oleophobic membrane, (3) air path and (4) fluid path.

Figure 3. Right. Activated Carbon Cloth Matrix (Flexzorb™) in the TOXIGUARD® system. Top panel, unmagnified picture. Bottom panel, magnified picture of the active carbon cloth, showing the tight weave of the carbon cloth matrix.

Based on Simplivia's in situ testing with a model compound, TOXIGUARD® can adsorb at least 4.2 mg of contaminant from vapor.[4]

The vapor concentrations present in the gas phase above the liquid in a drug vial of commonly used volatile hazardous drugs are shown in Table 1. These values were obtained through calculations, based on Henry's constants,[5] maximum drug solution concentrations, and the ideal gas law.

Considering the highest concentration (339 ng/L for 5-fluorouracil), over 12,000 L of contaminated air would be required to saturate the activated carbon matrix (i.e., in order to force 4.2 mg of hazardous drug compound through the TOXIGUARD®).

The largest known drug vial volume available is 100 ml. Thus, the volume of air passing through the TOXIGUARD® matrix during preparation never exceeds 200 ml. Therefore, the activated carbon matrix will never become saturated with cytotoxic active ingredients during normal use.

While the adsorption capacity provided by the manufacturer of the activated carbon matrix was based on model compounds (as opposed to real hazardous drug compounds) and the calculations presented here are theoretical, they allow for a 60,000-fold safety factor (12,000 L compared to 200 ml).

Table 1. Calculated vapor phase concentrations at room temperature inside drug vials for several common antineoplastic drugs

Drug	Gas phase conc. at 25°C (ng/l)
Thiotepa	1.16×10^{2}
Cyclophosphamide	2.78×10^{2}
Cisplatin	8.55×10^{-16}
Carboplatin	2.25×10^{-2}
Carmustine	6.42
Etoposide	1.43×10^{-18}
5-Fluorouracil	3.39×10^{2}

Test Method

The efficacy of TOXIGUARD® system to prevent release of hazardous drug vapors was evaluated by employing a closed test chamber for capture of released drug vapors. Since the quantity of drug vapors that may be generated under normal use conditions is extremely low, and typically below analytical limits of detection, a model system was developed using extreme laboratory conditions to induce and generate drug vapors to a much larger extent than what would be found in typical working environment in hospitals and pharmacies. This entailed heating the drug vial and its solution to elevated temperatures (50-60°C) and having a constant stream of nitrogen gas flow into the vial via the Chemfort® Vial Adaptor fluid path. Vapors released from the Chemfort® Vial Adaptor were trapped and then recovered by dissolving in the appropriate diluent. LC/MS/MS methods developed and validated specifically for each test drug, were employed to detect and quantify the amount of drug recovered. In order to verify that the test conditions resulted in drug vaporization, parallel testing was performed using Chemfort® Vial Adaptors in which the TOXIGUARD® system had been removed (positive control). For each drug tested, the quantity of drug recovered from the sealed test chamber when intact Vial Adaptors were challenged, was compared to the quantity of drug recovered in the Positive Control sample.

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Test Results

Study parameters and results are listed in Table 2. Testing was performed at Nextar (Ness Ziona, Israel). The limit of detection (LOD) in the LC/MS/MS systems ranged between 0.03-0.2 ng/ml, which represents a LOD of 0.3-2 ng of recovered drug after compensating for the volume of diluent used to recover drug from the closed vapor trap chamber (10 ml).
Drug vaporization was performed using 75 L nitrogen gas at a 50ºC drug incubation temperature. With cyclophosphamide and 5-flourouracil, drug was consistently recovered in the positive control samples which had Chemfort® Vial Adaptors without the activated carbon component of the TOXIGUARD® system, and not found in the test samples which had Chemfort® Vial Adaptors with intact TOXIGUARD® systems. This was true for cyclophosphamide even when devices were at the end of their shelf life and when the Vial Adaptors were connnected to the drug vials 7 days prior to testing. With doxorubicin, even under the extreme conditions that were employed, no drug was recovered in either the positive control or test sample.

Table 2. Quantity of Drug Recovered following Vaporization

Drug Tested	Incubation Period	Device Aging	System LOD[1]	Liters N_2 Gas[2]	Quantity Drug Recovered from Outside of the Vial Adaptor	
					Positive Control (Activated Carbon Removed)	Test Sample (TOXIGUARD® Intact)
Cyclophosphamide	None	None	0.3 ng	75	69 ng	not detected
	7 days	3 years				
5 Fluorouracil	None	None	2 ng	75	37 ng	not detected
Doxorubicin	None	None	2 ng	75	not detected	not detected

1. LC/MS/MS limit of detection based on signal to noise ratio
2. Liters of nitrogen gas used to induce the drug vapors

Study Conclusions

Extreme conditions were employed to challenge the efficacy of the Chemfort® Vial Adaptor's TOXIGUARD® system to trap hazardous drug vapors. Three different antineoplastic drugs were utilized in the study. One drug was tested with Vial Adaptors at the end of their 3 year shelf life and the end of their 7 day approved usage period.
These drugs differ in size, physical properties and chemical formulation. Two of the three antineoplastic drugs tested are among the most volatile of hazardous drugs, and with those two, drug was recovered from the positive control samples in which the activated carbon component of the TOXIGUARD® system was removed from the Chemfort® Vial Adaptor. Drug levels recovered in these positive control samples ranged between 37-69 ng. In contrast to these levels, in the test samples which had an intact TOXIGUARD® system, drug levels were consistently below the level of detection.

The absence of recovered drug vapor in the test samples confirms the efficacy of the TOXIGUARD® system present in the Chemfort® Vial Adaptor and, in particular, its activated carbon component, to stop hazardous drug vapor release.

With doxorubicin no drug was detected in either the positive control samples or the test samples. This is most likely due to low vapor pressure as a result of the large size of the molecule.

The ability of the TOXIGUARD® system to prevent vapor release with the different drugs that were tested under extreme conditions attests to the efficacy of the Chemfort® Vial Adaptor to meet the challenge of different drugs for its entire shelf-life and usage period.

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