OnGuard™

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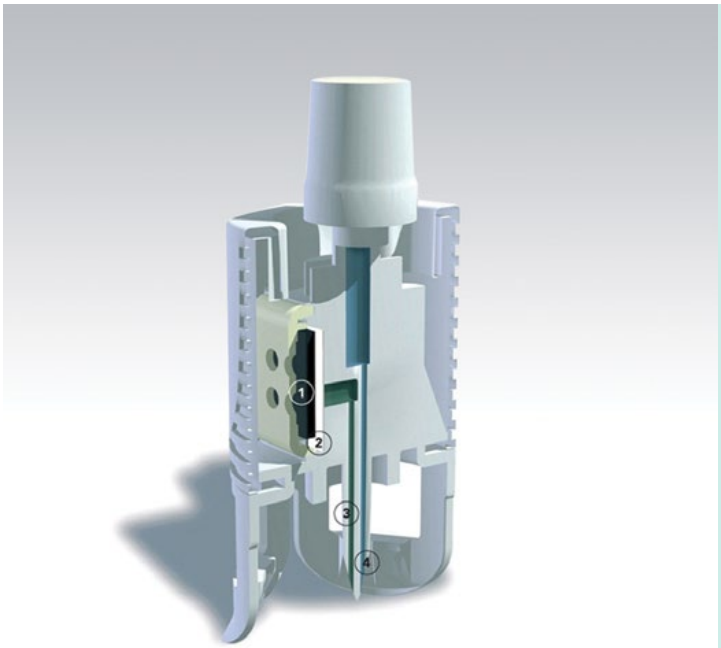

Prevention of Hazardous Drug Vapor Release by the Tevadaptor® Vial Adaptor

Figure 1. Cross-cut of the Tevadaptor® Vial Adaptor. (1) TOXI-GUARD® active carbon matrix, (2) 0.2 µm hydrophobic membrane, (3) air path and (4) liquid path.

Summary

Tevadaptor® 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. Drug containment in the Tevadaptor® Vial Adaptor is accomplished by the TOXI-GUARD® system, which contains a 100% activated carbon[1] drug binding matrix and 0.2 micron hydrophobic membrane (see Figure 1). The activated carbon matrix is highly efficient in adsorption of drug vapors. The 0.2 micron membrane is a sterile barrier preventing microorganisms and particles from entering the system and, due to its hydrophobic properties, preventing aerosols and liquids from being released from the system. Together, they serve as an effective sterile, particulate and toxic drug vapor barrier. The TOXI-GUARD® System ensures that the Tevadaptor® air pathway only allows sterile air to enter or exit the drug vial during drug reconstitution and preparation.

Studies were performed, challenging the efficacy of the Tevadaptor® to prevent the escape of drug vapors. 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 Tevadaptor® were trapped within a closed test chamber. The trapped drug was collected and then analyzed by highly sensitive LC/MS/MS methods.

The Tevadapor® was challenged with six commonly used antineoplastic drugs: Etoposide, Doxorubicin-HCl, Carboplatin, Cyclophosphamide, 5-Fluorouracil and Paclitaxel (Figure 2). With Etoposide, Doxorubicin-HCl, Carboplatin, Cyclophosphamide and 5-Fluorouracil, vapors were consistently detected in control samples in which the TOXI-GUARD® system had been removed from the Tevadaptor®. In test samples containing an intact TOXI-GUARD® system, no drug vapors were detected. With Paclitaxel no drug vapors were detected in either the positive control or test sample. These results support the validity of the Tevadaptor® Vial Adaptor to prevent release of hazardous drug vapors.

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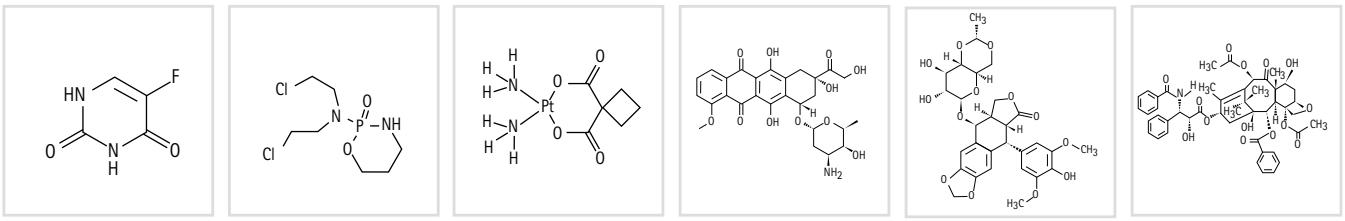
Figure 2. Chemical structures of the anti-neoplastic drugs used for challenging the Tevadaptor® Vial Adaptor and the TOXI-GUARD® System. Figure shows the wide range of the drugs tested in terms of their size (molecular weight) and structural complexity.



5-Fluorouracil	Cyclophosphamide	Carboplatin	Doxorubicin-HCl	Etoposide	Paclitaxel
$C_4H_3FN_2O_2$	$C_7H_{15}Cl_2N_2O_2P$	$C_6H_{12}N_2O_4Pt^{-2}$	$C_{27}H_{29}NO_{11}$	$C_{29}H_{32}O_{13}$	$C_{47}H_{51}NO_{14}$
130 Daltons	261 Daltons	371 Daltons	544 Daltons	589 Daltons	854 Daltons

Introduction

The Tevadaptor® Vial Adaptor is a Closed System Transfer Device (CSTD) that is designed to equalize 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 pathway (see Figure 1, item 3) and the second channel as the liquid pathway (see Figure 1, item 4). The TOXI-GUARD® System has a sterile 0.2 micron hydrophobic membrane (Figure 1, item 2) on the interior side of the air channel and a sterile 100% activated carbon[1] drug binding matrix on its exterior side (Figure 1, item 1). The hydrophobic membrane blocks passage of aqueous liquids and vapors 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 3). This matrix is highly efficient at adsorbing organically active molecules that may pass through the 0.2 micron filter, preventing their release into the environment.

Figure 3. Activated Carbon Cloth Matrix (Zorflex®) in the TOXI-GUARD® system. Left panel, unmagnified picture. Right panel, magnified picture of the active carbon cloth, showing the tight weave of the carbon cloth matrix.

About Zorflex® 100% Activated Carbon Cloth: 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 Zorflex® 100% activated carbon cloth is manufactured by Chemviron Carbon. Their special manufacturing process results in the cloth having a uniform 2 nm micro-porous matrix, with an extremely large surface area. 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 (1 cubic centimeter of air per second per square centimeter cloth). 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, results in the carbon cloth having very rapid adsorption kinetics. This makes the 100% active carbon cloth matrix highly efficient at adsorbing both liquids and gasses[1].

Test Method

The efficacy of TOXI-GUARD® 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 Tevadaptor® Vial Adaptor fluid pathway. Vapors released from the Tevadaptor® 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 Tevadaptor® Vial Adaptors in which the TOXI-GUARD® system had been removed. 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.

Test Results

Study parameters and results are listed in Table 1. Testing was performed at two reference laboratories, Analyst (Rehovot, Israel) and Nextar (Rehovot, Israel). The limit of quantitation (LOQ) in the LC/MS/MS systems ranged between 0.05-1 ng/ml, which represents a LOQ of 0.5-10 ng of recovered drug after compensating for the volume of diluent used to recover drug from the closed vapor trap chamber. Representative chromatograms from both labs are shown in Figures 4 and 5, respectively. Drug vaporization at Analyst was performed using 90 L nitrogen gas at a 50°C drug incubation temperature and at Nextar using 60 L nitrogen gas and 60°C temperature. With Cyclophosphamide (both labs), Carboplatin, Etoposide, Doxorubicin and 5-Flourouracil, drug was consistently recovered in the positive control samples which had Tevadaptor® Vial Adaptors **without** the TOXI-GUARD® system, and not found in the test samples which had Tevadaptor® Vial Adaptors **with** the TOXI-GUARD® System. With Paclitaxel, even under the extreme conditions that were employed, no drug was recovered in either the positive control or test sample.

Table 1. Quantity of Drug Recovered following Vaporization

Drug Tested	System LOQ[1]	Liters N_2 Gas[2]	Quantity Drug Recovered from Outside of the Vial Adaptor	
			Positive Control (TOXI-GUARD® Removed)	Test Sample (TOXI-GUARD® Present)
Cyclophosphamide[3]	10 ng	90	32 ng	Below LOQ[5]
Cyclophosphamide[4]	0.5 ng	60	14 ng	Below LOQ
Carboplatin[3]	10 ng	90	53 ng	Below LOQ
Etoposide[3]	10 ng	90	11,150 ng	Below LOQ
Doxorubicin[3]	10 ng	90	460 ng	Below LOQ
5 Fluorouracil[4]	10 ng	60	147 ng	Below LOQ
Paclitaxel[4]	0.8 ng	60	Below LOQ	Below LOQ

[1] 10 fold the LC/MS/MS Limit of Quantitation

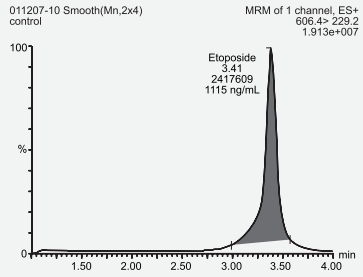
[2] Liters of nitrogen gas used to induce the drug vapors

[3] Third-party lab testing performed at Analyst Research Laboratories, Ltd. Rehovot, Israel Reference reports 2007-001 Et001C

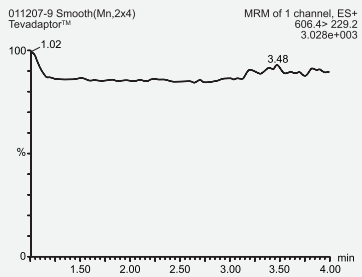
[4] Third party lab testing performed at Nextar Chempharma Solutions, Ltd. Rehovot, Israel Reference reports 5560140RE-02, 5560140RE-03 and 5560140RE-04

[5] LOQ- Limit of Quantitation

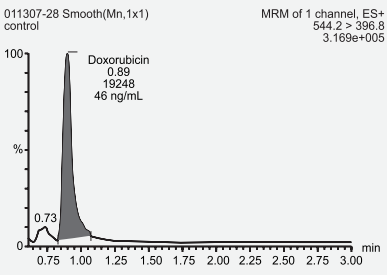
Etoposide Positive Control (without the TOXI-GUARD® System)



Etoposide Test Sample (with the TOXI-GUARD® System)



Doxorubicin Positive Control (without the TOXI-GUARD® System)



Doxorubicin Test Sample (with the TOXI-GUARD® System)

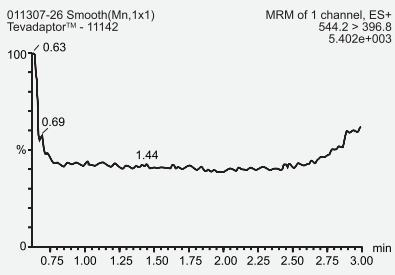
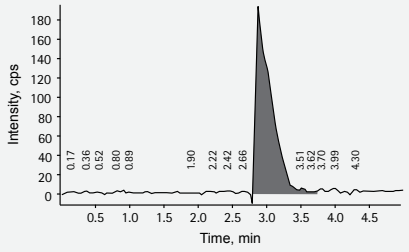


Figure 4. Representative LC/MS/MS chromatograms of Etopside (top panel) and Doxorubicin (bottom panel). Left panels represent drug vapors recovered when the Tevadaptor® Vial Adaptor TOXI-GUARD® system is removed and the right panels represent drug vapors recovered when an intact Tevadaptor® Vial Adaptor TOXI-GUARD® system is in place.

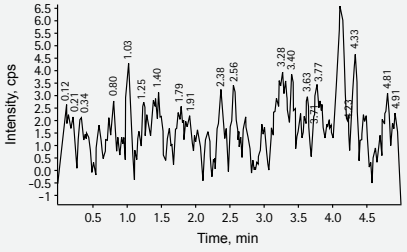
The chromatograms are adjusted according to the height of the major peak detected in the sample. In the Etoposide positive control sample the drug is detected at 3.41 minutes retention time. In the test sample a corresponding peak was not detected, even after 6300 fold amplification of the chromatogram to full (100%) scale. With Doxorubicin the drug peak is clearly detected in the positive control sample; whereas, in the test sample only background noise is seen following 58 fold amplification to full scale.

Figure 5. Representative LC/MS/MS chromatograms of 5-Fluorouracil (top panel) and Cyclophosphamide (bottom panel). Left panels represent drug vapors recovered when the Tevadaptor® Vial Adaptor TOXI-GUARD® system is removed and the right panels represent drug vapors recovered when an intact Tevadaptor® Vial Adaptor TOXI-GUARD® system is present. Note that the Intensity Scale differs for the Positive Control Samples and the Test Samples. With Fluorouracil, the Positive Control has an Intensity Scale of 0–180 counts per second (cps) as compared to -1 to 6.5 cps for the Test Sample. Magnification of the the Test Sample scale 28 fold over the Positive Control Sample was performed in order to determine if a peak representing recovered drug could be detected over the background noise. No peak was detected. A similar procedure was followed for the Cyclophosphamide. The chromatogram for the test sample had an Intensity scale of 0–22 cps as compared to 0–380 cps for the positive control sample. Even with the 17 fold amplification, no peak representing the drug could be detected over the background noise.

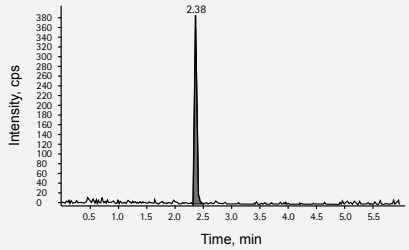
Fluorouracil Positive Control (without the TOXI-GUARD® System)



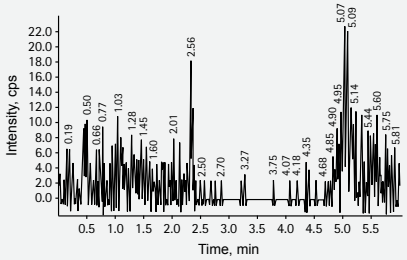
Fluorouracil Test Sample (with the TOXI-GUARD® System)



Cyclophosphamide Positive Control (without the TOXI-GUARD® System)



Cyclophosphamide Test Sample (with the TOXI-GUARD® System)



Study Conclusions

Extreme conditions were employed to challenge the efficacy of the Tevadaptor® Vial Adaptor's TOXI-GUARD® system to trap hazardous drug vapors. Six different anti-neoplastic drugs were utilized in the study. These drugs differed in size, physical properties and chemical formulation. With five of the six antineoplastic drugs tested, drug was recovered from the positive control samples in which the TOXI-GUARD® system was removed from the Tevadaptor® Vial Adaptor. Drug levels recovered in these Positive Control samples ranged between 14 ng to 11,150 ng. In contrast to these levels, in the Test Samples which had an intact Tevadaptor® Vial Adaptor TOXI-GUARD® system, drug levels were consistently below the level of quantitation. **The absence of recovered drug vapor in the test samples confirms the efficacy of the TOXI-GUARD® system present in the Tevadaptor® Vial Adaptor to stop hazardous drug vapors.** With Paclitaxel no drug was detected in either the positive control samples or the test samples. This is most likely due to the excipients present in its formulation (for example Macrogoglycerol ricinoleate) and the overall viscosity of the solution. In contrast to the other drugs tested in this study, this formulation is not volatile, even under the extreme conditions used in the study.

The ability of the TOXI-GUARD® system to prevent vapor release with the different drugs that were tested, attests to the efficacy of the Tevadaptor® Vial Adaptor to meet the challenge of different drug structures and their formulations; whether it be a relatively small molecule such as 5-Fluorouracil or a large complex organic molecule such as Etoposide.

The large difference in the quantities of drug recovered in the positive control samples for the different drugs is reflective of the differences in the nature of their drug formulations and their different tendencies to form drug vapors. However, even with the highly volatile Etoposide, were 11,150 ng of drug was recovered in the vapor trap of the positive control sample, the absence of drug detected with the Test Sample, points to the very high capacity of the TOXI-GUARD® system to prevent escape of hazardous drug vapors.

References

1. Zorflex® Activated Carbon Cloth Product Brochure published by Chemviron Carbon, Cloth Division, United Kingdom http://www.chemvironcarbon.com

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