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Original Research

Assessment of environmental viral contamination of liquids prepared in a closed system drug transfer device

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Abstract

Background: Closed system transfer devices (CSTDs) enable preparation and transfer of drugs into syringes and infusion bags, while protecting healthcare professionals from exposure to hazardous drugs. Drug products contaminated by bacteria or viruses harbor a clinical risk to patients. Therefore, CSTDs must also prevent environmental contamination of the compounded liquid. Some CSTDs require priming of syringes with environmental air and introduction of this air into the drug vial for pressure equalization during liquid withdrawal. We examined whether this methodology puts the vial contents at risk for contamination by the human coronavirus OC43 (HCoV-OC43). **Methods:** A CSTD requiring syringe priming was used to transfer liquids between a sterile vial containing saline, a sterile syringe, and, in some cases, an intravenous (IV) bag inside a sealed glove box contaminated by HCoV-OC43 aerosols. Viral contamination of the transferred liquids after a single transfer into a syringe, or after 3 transfers (from the vial into the syringe then from the syringe into the IV bag, and from the IV bag back into the syringe), was assessed by detecting the presence of HCoV-OC43 RNA using quantitative real-time polymerase chain reaction. **Results:** Liquid transferred in a sterile environment using the CSTD was not contaminated but liquid transferred once from the vial into a syringe in a coronavirus-contaminated environment showed cycle threshold (Ct) values corresponding to 3.8-9.4 plaque forming units (PFU)/ml in all 9 replicates tested. Liquid transferred three times in a coronavirus-contaminated environment showed Ct values corresponding to 2.5-4 PFU/ml, but in 3 of the 9 replicates tested Ct values were not detected. **Conclusions:** Liquids contained by CSTDs are susceptible to HCoV-OC43 contamination when the CSTD used requires aspiration of environmental air into a syringe.

Keywords: closed systems; coronaviridae; antineoplastic agents handling; environmental pollution

INTRODUCTION

A closed system transfer device (CSTD) has been defined by the National Institute for Occupational Safety and Health (NIOSH) as "a drug transfer device that mechanically prohibits the transfer of environmental contaminants into the system and the escape of the hazardous drug or vapor concentrations outside the system".[1] CSTDs enable reconstitution of drug powders and transfer of drug liquids into syringes, flexible bottles and infusion bags, while maintaining product sterility and protecting healthcare professionals from exposure to hazardous drugs.[1-3] The performance of CSTDs in the context of drug containment and prevention of exposure of healthcare personnel to antineoplastic drugs and antibiotics has been studied extensively.[4-11]

Drug products contaminated by bacteria or viruses harbor a clinical risk to patients.[12-16] Therefore, in addition to protecting healthcare workers from exposure, CSTDs must prevent environmental contamination of the compounded liquid. CSTD systems have been shown to prevent contamination by Gram-positive and Gram-negative bacteria, yeast, and mold.[17,18] Vials punctured with a CSTD under ISO class 5 conditions demonstrated a low frequency of microbial contamination.[19]

The combination of device structure and method of operation may affect the ability of a CSTD to prevent entrance of contaminants from the environment. In general, an active mechanism or appropriate barrier is necessary to prevent ingress of microorganisms. Although a 0.2 µm membrane is a sufficient barrier for bacteria, virus particles may be small enough to pass through such a membrane, possibly necessitating an additional layer of protection. Detection of viral contamination is often more difficult than detection of other microbial contaminants,[20] and information on prevention of viral contamination by CSTDs is scarce. However, the ability of one CSTD to protect liquids from viral contamination was explored in one study.[21] This particular CSTD contains an activated carbon matrix in addition to a 0.2 µm membrane, which may contribute to viral ingress prevention.

CSTDs consist of multiple components, the design of which varies depending on the brand/manufacturer. Each brand has a unique fluid path structure, a specific mechanism for pressure equalization among the components, and its associated instructions for use. Several different mechanisms are employed among CSTD brands to ensure that only sterile air enters the system. Some devices are supplied with a flexible compartment containing sterile air; others have anti-bacterial and/or anti-viral membranes through which sterile air can enter the system for pressure equalization. Another type of device sometimes requires direct introduction of environmental air, relying on the sterility of the preparation environment. Once

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such CSTD is PhaSeal™ Optima (BD, Franklin Lakes, NJ, USA). The PhaSeal™ system is generally considered an airtight, leakproof system with a physical barrier that mechanically prohibits the transfer of environmental contaminants into the system and the escape of drug or vapor concentrations outside the system using a membrane-to-membrane technology.[22] It also prevented microbial entry within an ISO Class 5 environment using a proper aseptic technique. However, when the first preparation step is withdrawal of liquid from a vial, the structure and pressure equalization mechanism of the device require aspiration of air from the environment into a syringe prior to connecting a syringe adapter and subsequent inflation of the vial adapter balloon. No sterilizing membrane is present in the pathway through which air enters the system. This may present a contamination risk when the preparation environment is not sterile; for example, when drug doses are prepared outside of clean rooms or during temporary failure of clean room systems.

In this study we examined the ability of the PhaSeal™ Optima CSTD to prevent environmental contamination of liquids by human coronavirus OC43 (HCoV-OC43).

METHODS

Testing environment

PhaSeal™ Optima CSTDs were tested inside a sealed glove box (approximately 35 liters), which was placed in a class II biological safety laminar cabinet.

The glove box interior was aerosolized using an Air Pro nebulizer (Medic Spa, China). The aerosol droplets were 1-5 µm in size. For an uncontaminated negative control environment, the nebulizer was loaded with 1 ml of sterile Modified Eagle's Medium supplemented with 2 mM L-alanyl-L-glutamine, 1% penicillin-streptomycin and 2% fetal bovine serum (Biological Industries, Beit HaEmek, Israel).

The test environment was established by first loading a 1-ml solution containing 5 x 10^6 plaque forming units (PFU)/ml of HCoV-OC43, serving as positive control for the level of environment contamination by the virus. Next, the box was continuously aerosolized with additional 6 ml of the virus solution while the CSTDs were handled.

The air inside the glove box was sampled using an ACD-200 Bobcat dry filler air sampler (InnovaPrep, Drexel, MO, USA) at three different time points: 1) before initiating the liquid sampling procedure of the CSTD in the negative control environment; 2) before initiating the liquid sampling procedure of the CSTDs in the contaminated environment (positive control); and 3) and immediately after handling of the last CSTD in the contaminated environment had been completed (second positive control).

Prior to each air sampling, a new sterile air filter was installed in the air sampler, the nebulizer was turned off, and the air was sampled for 2 minutes at 100 L/min.

The Bobcat air filters were extracted using the Rapid Filter Elution Kit with PBS (InnovaPrep).

CSTD test conditions

A total of 7 sets of PhaSeal™ Optima components were tested under various conditions. Three sets included an infusion adapter, protector, and injector, while 4 sets included a protector and injector only. On the day before the experiment, in an aseptic manner inside a laminar flow cabinet, the septa of 7 IV bags containing 50 ml of sterile saline solution (Baxter International, Deerfield, IL, USA), and the stoppers of 7 sterile empty 30-ml glass vials (Ks-Tek, Shenzhen, China), were sterilized with 70% alcohol pads (Redditch Medical, Redditch, Worcestershire, UK). Then, 20 ml of saline solution were transferred from each IV bag into 1 vial, using a sterile set of Luer lock syringe and needle (BD). The 7 vials and 7 IV bags were kept inside the laminar flow cabinet until the experiment.

Prior to each test, the external surfaces of sealed primary packaging of all the required PhaSeal™ Optima CSTD components were sterilized with 70% ethanol (Hylabs, Israel) and placed in the laminar flow cabinet. Next, the components of each set were placed inside the sealed glove box and subsequently unwrapped and assembled. Component assembly of each set was performed using the required PhaSeal™ components of the relevant sample group and conditions, as described below:

Negative control: One set of CSTD components (protector and injector only) was handled in a non-contaminated environment (i.e., the glove box was aerosolized with sterile complete medium). The vial septum was disinfected with 70% isopropanol prep pads (Aplicare, Meriden, CT, USA) prior to connecting the vial protector. The CSTD protector and injector were handled according to the BD PhaSeal™ Optima System Procedures manual, section 1.4.[23] Priming of the vial was performed by aspirating 20 ml of air into a syringe within the glove box, attaching the injector to the syringe, and then pushing the air from the syringe into the vial containing 20 ml sterile saline solution via the vial protector. Next, the vial was incubated in the box for 1 min, and then 20 ml of saline solution was withdrawn from the vial into the same syringe (Figure 1).

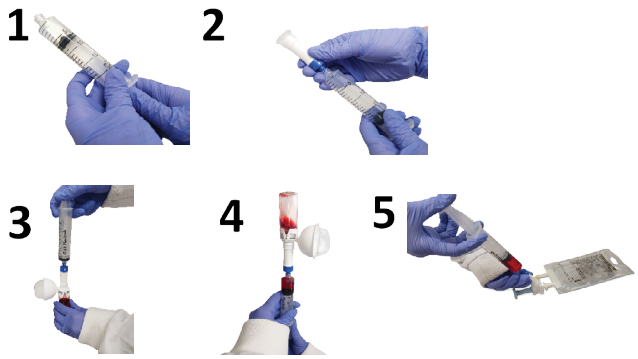

Figure 1. Steps performed using PhaSeal™ Optima inside the glove box. This procedure mimics actual dose preparation for bolus or IV administration in clinics and hospitals. 1. Prime syringe with air; 2. connect injector to syringe; 3. connect injector to protector and inject air to inflate protector balloon; 4. invert vial and withdraw dose into syringe; following disconnection from protector, either administer syringe as bolus or 5. connect injector to infusion adapter and dilute dose in IV bag.

Single transfer: Three CSTD sets (Groups 1-3) were handled in an environment continuously aerosolized with 5 x 10^6 PFU/ml HCoV-OC43. The vial septum was disinfected with 70% isopropanol prep pads (Aplicare, Meriden, CT, USA) prior to connecting the vial protector. The CSTD protector and injector were handled according to the BD PhaSeal™ Optima System Procedures manual, section 1.4.[23] The vial was primed by aspirating 20 ml of air into a syringe within the glove box, attaching the injector to the syringe, and then pushing the air from the syringe into the vial containing 20 ml of sterile saline solution via the vial protector. Next, the vial was incubated in the box for 1 min, and then 20 ml of saline solution was withdrawn from the vial back into the same syringe.

Three transfers: Three CSTD sets (Groups 4-6) were handled in an environment continuously aerosolized with 5 x 10^6 PFU/ml HCoV-OC43. The vial septum was disinfected with 70% isopropanol prep pads (Aplicare, Meriden, CT, USA) prior to connecting the vial protector. The infusion adapter was connected to an IV bag containing 30 ml of sterile saline. The CSTD protector, injector, and infusion adapter ports were handled according to the BD PhaSeal™ Optima System Procedures manual, sections 1.4 and 1.6.[23] The vial was primed by aspirating 20 ml of air into a syringe within the glove box, attaching the injector to the syringe, and then pushing the air from the syringe into the vial containing 20 ml of sterile saline solution via the vial protector. Next, the vial was incubated in the box for 1 min, and then the 20 ml of saline solution was withdrawn from the vial back into the same syringe and transferred from the syringe into the IV bag via the infusion adapter. The IV bag was mixed well and then 20 ml of saline solution was aspirated from the bag into the syringe.

After each test was completed, the syringe unit was removed from the glove box into the laminar flow cabinet, and its outer surface was thoroughly disinfected by spraying 70% ethanol. The injector of each set was then removed from the syringe, and the saline solution (20 ml) was discharged from the syringe into a sterile pre-labeled tube, which was capped and kept on ice until nucleic acid extraction.

Viral RNA extraction

After sampling, viral RNA was extracted from each sample using the MagCore viral nucleic acid extraction kit (RBC Bioscience, New Taipei City, Taiwan) according to the manufacturer's instructions by mixing 250 µl from each sample with lysis buffer, proteinase K, and carrier RNA, all from the MagCore viral nucleic acid extraction kit. For each sample, RNA extraction was performed in triplicates. Following RNA purification, 30 µl from each triplicate from the same sample were combined into one tube to generate a total of 7 90-µl RNA samples (one for each CSTD tested). The 7 pooled samples were used for synthesizing complementary DNA (cDNA) to serve as templates for quantitative real-time polymerase chain reaction (qPCR).

Complementary DNA preparation and quantitative PCR

Complementary DNA was synthesized from each extracted RNA pool using the Hy RT PCR Kit (Hylabs). Briefly, 12.4 µl from each RNA pool were used for the test samples and for controls with no reverse transcriptase (-RT). The cDNA and -RT samples were each diluted 1:2 in nuclease-free water. Five microliters of the diluted cDNA sample were then used as template for qPCR in a mix containing specific primers for HCoV-OC43 (forward: 5'-ATTGTCG ATCGGG ACCCAAG-3'; reverse: 5'-TGTGCGCGAAGTAGATCTGG-3') and platinum SYBR Green qPCR SuperMix-UDG (Invitrogen, Waltham, MA, USA). The specificity of the qPCR was demonstrated by using *influenza A* virus H1N1 with the HCoV-OC43 primers as described in a previous publication.[21]

Determination of contamination values using HCoV-OC43 standard curve

An HCoV-OC43 stock solution at a concentration of 5 x 10^6 PFU/ml was used for generating a standard curve. Six 10-fold dilutions were prepared to obtain the different standard curve samples, ranging from 5 to 5 x 10^5 PFU/ml. RNA was extracted from each dilution sample and analyzed by qPCR as described above for the samples obtained from the CSTD devices. The cycle threshold (Ct) value for each dilution sample was determined and plotted against the PFU/ml value.

Statistical Analysis

Data analysis was performed using the CFX Manager 2.1 software package (Bio-Rad, CA, USA). Data were analyzed using descriptive statistics. Continuous variables were summarized as mean and standard deviation.

RESULTS

The HCoV-OC43 standard curve is shown in Figure 2. The quantifiable range for detected extracted viral RNA was 5 x 10^5 to 5 PFU/ml. The slope obtained for the HCoV-OC43 standard curve was -3.555, and the Y intercept was 38.978. Therefore, the equation for calculating the value for X (i.e., the original PFU/ml in each saline/air sample) was:

$X_{[PFU/ml]} = 10^{[(y-38.978)/-3.555]}$, where Y is the obtained Ct value per sample.

As expected, no Ct value was obtained for the standard curve negative control. The lowest concentration of viral RNA proven to be quantifiable was 5 PFU/ml, which corresponded to a Ct value of 36.58. Thus, any Ct value ≤36.58 can be considered quantitative, whereas detected Ct values >36.58 correspond to unquantifiable traces of viral RNA.

As shown in Table 1, when the glove box was aerosolized with sterile medium (negative control), no viral RNA was detected in the air. When the glove box was aerosolized with the HCoV-OC43 stock solution, the mean Ct values of viral RNA in air samples collected prior to handling the PhaSeal™ Optima sets and at the end of the experiments were 22.19 ± 0.07 (52653 PFU/ml) and 21.47 ± 0.05 (84119 PFU/mL), respectively (Table 1).

The qPCR results of the test samples (Table 2) showed that the liquid transferred in a sterile environment using the PhaSeal™ Optima set was not contaminated by HCoV-OC43. Liquid transferred once from the vial into the syringe using the

Table 1. qPCR Ct results of air samples filters

Filter sample	Ct value			
	Replicate Ct values			Mean Ct ± SD (PFU/ml)
	1	2	3	
Negative control	ND	ND	ND	ND
Positive control	22.14	22.27	22.17	22.19 **± 0·07** (52653)
Endpoint	21.46	21.52	21.43	21.47 **± 0.05 (84119)**

Negative control: filter of air sampled from box aerosolized with sterile medium
Positive control: filter of air sampled from box aerosolized with HCoV-OC43 stock solution
Endpoint: filter of air sampled from box aerosolized with HCoV-OC43 stock after the test of CSTDs was complete
Ct=cycle threshold, ND=not detected, PFU=plaque forming units, SD=standard deviation

Table 2. Detection of HCoV-OC43 RNA in samples obtained using PhaSeal™ Optima set under various conditions

Group	Environment	Number of transfers	Ct value			
			Replicate number			Mean Ct ± SD (PFU/ml)
			1	2	3	
Negative control	Sterile	1	ND	ND	ND	0
1	Contaminated	1	36.86	36.25	37.67	36.93 ± 0.71 (3.8)
2	Contaminated	1	36.09	34.72	35.73	35.51 ± 0.71 (9.4)
3	Contaminated	1	37.60	36.72	36.48	36.93 ± 0.59 (3.8)
4	Contaminated	3	36.06	36.71	37.79	36.85 ± 0.87 (4)
5	Contaminated	3	ND	37.54	ND	37.54 (2.5)
6	Contaminated	3	38.06	36.05	ND	37.06 ± 1.42 (3.5)

The negative control group was handled in a glove box aerosolized with sterile medium. Groups 1-6 were handled in a glove box aerosolized with HCoV-OC43.
Ct=cycle threshold, ND=not detected, PFU=plaque forming units, SD=standard deviation

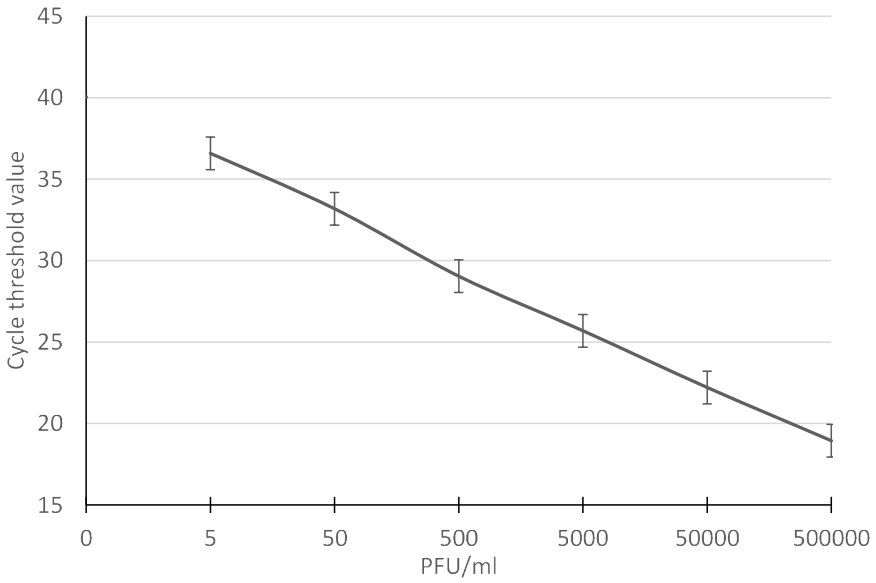

Figure 2. HCoV-OC43 standard curve

PhaSeal™ Optima in a coronavirus-contaminated environment showed Ct values corresponding to 3.8-9.4 PFU/ml (Groups 1-3, Table 2), where Ct values for 5 out of 9 replicates corresponded to quantifiable concentrations of viral RNA (≥5 PFU/ml). Concentrations <5 PFU/ml are extrapolated and not within the quantitative range of the standard curve. Liquid transferred three times (i.e., from the vial into the syringe, then from the syringe into the IV bag and from the IV bag back

into the syringe) in a coronavirus-contaminated environment showed Ct values corresponding to 2.5-4 PFU/ml (Groups 4-6, Table 2). Two out of the 9 replicates contained quantifiable concentrations of viral RNA, while 4 replicates contained non-quantifiable traces. In 3 of the 9 replicates Ct values were not detected. At least one technical replicate of each experimental group showed viral contamination.

DISCUSSION

This study showed that HCoV-OC43 present in the outer environment can contaminate the contents of the BD PhaSeal™ Optima CSTD when liquids are transferred according to the BD PhaSeal™ Optima System Clinical Procedures manual.[23] This may be attributed to the vial priming procedure required prior to withdrawing liquid from the vial. While this step is necessary to allow pressure equalization during the subsequent liquid withdrawal from the vial into the syringe, it involves aspirating potentially nonsterile air directly from the environment into a syringe and subsequent introduction of this air into the vial protector expansion chamber, without passing it through a sterilizing membrane.

To simulate dose preparation for bolus administration in hospitals and clinics, a single liquid transfer between a vial and a syringe was performed using the CSTD. To simulate drug preparation for IV administration in hospitals and clinics, a total of 3 liquid transfers using the CSTD were performed - between a vial and an IV bag via a syringe and back to the syringe. The final transfer was necessary to allow sampling of the IV bag contents and did not constitute part of the simulation.

The average HCoV-OC43 concentration range in PFU/ml was higher following a single transfer (bolus simulation) compared to 3 transfers (IV bag preparation simulation) performed with the CSTD. In fact, in one of the experimental replicates, all 3 technical replicates contained quantifiable viral RNA within the range of the calibration curve. After injection of the liquid aspirated from the vial into an IV bag containing 30 ml of liquid, the viral concentration is diluted, and thus slightly lower amounts of viral nucleic acid were detected in samples that underwent 3 liquid transfers compared to a single transfer. These lower amounts were possibly marginal in terms of the method detection limit (which was not determined in this study), as 3 out of 9 replicates displayed no detection of viral nucleic acid (Table 2). However, at least one technical replicate of each experimental replicate contained viral RNA at levels greater than the negative control. Thus, for every experimental replicate, some traces of viral RNA were detected.

Although the concentration of HCoV-OC43 detected in liquids transferred using the system was relatively low compared to its concentration in the filters of the air samplers, by definition, liquids transferred using CSTDs should be completely sterile,[1] as they are usually used for preparing antineoplastic drugs and monoclonal antibodies for oncologic patients who are often immunocompromised. Viral contamination harbors a greater risk for immunocompromised patients[24] and thus should raise concern.

Another study assessed the risk of viral contamination during liquid transfers using the Chemfort® CSTD (Simplivia Healthcare, Ltd., Kiryat Shmona, Israel).[21] Integral to this CSTD is the Toxi-Guard® system pressure equalization, which comprises a hydrophobic membrane with 0.2 µm pores (Versapor®) and an activated carbon layer (Flexzorb™). Viral traces were observed only in liquids transferred with the Chemfort® CSTD from which both the membrane and activated carbon layer had been removed (positive control), after it was challenged with a viral spray. The intact Chemfort® CSTD systems prevented detectable viral contamination in 100% of repetitions.[21] Of note, vial priming is not necessary with the Chemfort® device, since pressure equalization happens automatically through the Toxi-Guard® during injection and withdrawal. Once the Chemfort® Syringe Adaptor is connected to an empty syringe, all air entering the system passes through the double layer of the Toxi-Guard®.

The particle size of the coronavirus used in this study, HCoV-OC43, is 0.08-0.12 µm in diameter.[25,26] Although humans produce infectious aerosols in a wide range of particle sizes, pathogens predominate in small particles (<5 µm) that are immediately respirable by exposed individuals.[27] As a 0.2 µm membrane, which can prevent bacterial contamination, may not be sufficient to prevent viral contamination, the presence of an additional barrier, such as an activated carbon layer, may help reduce the risk of viral contamination in CSTDs, and potentially offer greater protection to vulnerable oncology patients.

For drugs prepared in controlled environments such as laminar air flow hoods or positive pressure isolators, the risk of microbial contamination is very low, even without the use of a CSTD.[19] In such environments, the vial priming step required by BD PhaSeal™ Optima prior to drug withdrawal poses a much smaller risk of infection to patients. However, in some hospitals, drugs are prepared by nurses in patient wards,[7,28] where the surrounding environment is expected to contain large quantities of microorganisms, including viruses. In such cases, a system requiring vial priming with environmental air potentially increases patients' risk of infection. Furthermore, cleanrooms and other technologies that provide an atmosphere of sterile air, may break down, or fail temporarily. To maintain sterility of drug preparations, even under such circumstances, vial priming with environmental air should be avoided.

While the study attempted to simulate drug preparation for bolus and IV administration in hospitals and clinics, its limitations include the absence of a comparison to other types of CSTDs, which is warranted in future studies.

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AUTHOR CONTRIBUTION: MA's contributions included: formal analysis, investigation, methodology, validation, and writing—review & editing. EASS's and SS's contributions including: conceptualization, methodology, funding acquisition, resources, and writing—review & editing.

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