

Antineoplastic Drug Compatibility with the ChemoClave™ System

INTRODUCTION

Antineoplastic drugs are used in the therapeutic treatment of many cancers. Although a number of cytotoxic agents can be administered orally, most chemotherapy is delivered intravenously. Traditional IV equipment, including tubing and plastic components, can be affected or degraded by exposure to some antineoplastic agents, damaging the plastic and causing the release of chemicals into the fluid path that can ultimately be delivered to the patient.

Furthermore, the health risks posed by direct exposure to these agents for both patients and healthcare workers has prompted organizations such as the National Institute for Occupational Safety and Health (NIOSH) and the United States Pharmacopeia (USP<797>) to recommend the use of specialized IV equipment called closed system transfer devices (CSTD) to reduce patient and clinician exposure to these hazardous drugs.^{1,2}

This paper describes the ways in which certain drugs interact with specific preparation and administration devices. It also describes the compatibility validation process used by ICU Medical to prove that the ChemoClave™ CSTD system meets standards required for hazardous drug preparation and administration.

PLASTIC INTEGRITY FOLLOWING DRUG INTERACTION

Solid plastic components used in the manufacture of intravenous sets and preparation devices can be damaged by interaction with solvent agents such as alcohol. Antineoplastic drugs such as the etoposide and paclitaxol classes contain undiluted organic solvents at 33 and 50 percent respectively.^{3,4} Plastic devices made of acrylic or ABS (a polymer composed of acrylonitrile, butadiene, and styrene) have been reported to crack and leak when exposed to these agents.⁵ The degree of damage caused to ABS or acrylic by etoposide and paclitaxol agents is dependent on several factors, including the design of the component and how much stress is applied into the part. Cracks can occur in the component as the solvent acts as a stress reliever, and can potentially result in drug leakage.

CHEMICAL LEACHING AND SORPTION

In the United States, one fourth of all plastic medical products are made of polyvinyl chloride (PVC), including most IV bags and tubing.⁶ The chemical composition of PVC resins produces a brittle plastic. Therefore, many PVC components contain diethylhexyl phthalate (DEHP), a plasticizer that lends flexibility, strength, and optical clarity to the plastic. The PVC used in medical devices often contains a relatively high percentage (20–40 percent) of DEHP, which has been identified by the United States Environmental Protection Agency as a probable human carcinogen.⁷

Because DEHP is not chemically bound to PVC, it can migrate or leach from the medical device into lipid emulsions.^{8,9,10} In the case of intravenous infusion of antineoplastic agents, chemicals can leach from IV tubing and bags when exposed to antineoplastic drugs. Data collected for the presence of DEHP show that levels increase with time and concentration when dilutions are prepared in PVC containers.

ChemoClave Closed System Transfer Device



All ChemoClave components are non-DEHP and have been proven to resist sorption and support drug stability.

Consequently, the use of plasticized PVC containers and administration sets that contain DEHP is not recommended. None of the components in ICU Medical's ChemoClave product line contain DEHP.

Drug sorption describes the process by which drug components stick to or are absorbed into the plastic devices.¹¹ Drug sorption impacts the agent's chemical makeup and can result in a loss of stability when antineoplastic drugs are exposed to the plastic for long periods of time or infused through lengthy expanses of tubing. Careful selection of plastics used to manufacture infusion devices can improve resistance to drug sorption and the devices' ability to support drug stability. The plastics that are used to manufacture ICU Medical's ChemoClave product line are chosen for their resistance to drug sorption and their ability to support drug stability.

ICU MEDICAL PRODUCT EVALUATION

Recognizing the potential for plastic components to negatively impact the intended use of antineoplastic therapies, ICU Medical developed a stringent compatibility protocol for testing plastic components.

ANTINEOPLASTIC COMPATIBILITY PROTOCOL

To evaluate the interaction between the ChemoClave product line and the series of antineoplastic drugs that are known to react with plastics, protocols were developed at STUDIO AMBIENTE S.r.l. (VR) in Italy that were derived from investigational work in which the researchers studied worst case exposure and storage procedures for a number of preparation and storage methods.

METHOD

Specific drugs were researched and selected to represent various therapeutic classes and chemical compositions. The Spiros®, Genie®, and vial access devices, which are components of the ChemoClave system, were each exposed to the twelve selected antineoplastic drugs in their undiluted form. Drugs were diluted to three times their therapeutic value for testing with IV sets to represent the worst case exposure for the administration equipment. Three separate tests were completed, including a functional integrity test, a drug stability test, and a plastic migration test, to verify drug compatibility with the chemotherapy devices.

To prepare test samples, each drug was infused through independent test samples, agitated, and then subjected to a storage protocol as noted in the table on the following page. Samples were placed in refrigeration for a specified time period and then stored at room temperature for a specified time period. Devices were visually inspected during the storage period at various times and then leak tested to verify functional integrity.

Following the storage period using cisplatin, etoposide, fluorouracil, and herceptin, the drug was removed from each sample and tested for stability using the High-Performance Liquid Chromatography (HPLC) method. Using gas chromatography with mass detector, the drug samples were then evaluated for plastic migration, including concentrations of phthalate and vinyl chloride. The standard used for phthalate concentration was based on the European Directive 2005/84/EC with an acceptance level of 0.1 percent of mass. The standard used for vinyl chloride concentration was based on the European Pharmacopeia, which requires <1ppm. All results are available in Table 1.

RESULTS

All ICU Medical chemotherapy preparation and delivery devices evaluated per the protocol reached acceptable limits for all phases of testing.

CONCLUSION

Known effects of drug interaction, including cracking of plastic devices, reduced stability due to drug sorption, and leaching of chemicals such as DEHP, can be eliminated with proper product design and validation. Ongoing evaluation of all plastic components developed for use in the chemotherapy product line follows the aforementioned Antineoplastic Compatibility Protocol. In addition, ICU Medical components are non-DEHP and are proven to resist sorption and support drug stability. Complete test reports are kept on file at ICU Medical, San Clemente, CA.^{12,13,14}

Table 1.

Antineoplastic Agent	Spiros Closed Male Luer 120 Days Refrigeration, and 7 Days Room Temperature			Genie Closed Vial Access Device* 30 Days Refrigeration, and 10 Days Room Temperature		
	Functional Failure	Drug Stability 120-Days	Plastic Migration per Device	Functional Failure	Drug Stability 30-Days	Plastic Migration per Device
Bevacizumab	0/10	NT	NT	0/10	NT	NT
Cetuximab	0/10	NT	NT	0/10	NT	NT
Cisplatin	0/10	99.60%	P= .25µg VC= <.08µg	0/10	99.60%	P= .25µg VC= <.08µg
Cyclophosphamide	0/10	NT	NT	0/10	NT	NT
Doxorubicin	0/10	NT	NT	0/10	NT	NT
Etoposide	0/10	99.60%	P= .05µg VC= <.05µg	0/10	99.20%	P= .05µg VC= <.05µg
Flourouracil	0/10	99.60%	P= .58µg VC= <.07µg	0/10	99.20%	P= .58µg VC= <.07µg
Herceptin	0/10	97.30%	P= <5µg VC= <.2µg	0/10	97.30%	P= <5µg VC= <.2µg
Methotrexate	0/10	NT	NT	0/10	NT	NT
Paclitaxol	0/10	NT	NT	0/10	NT	NT
Vincristine	0/10	NT	NT	0/10	NT	NT

Antineoplastic Agent	Vial Access Devices* 30 Days Refrigeration, and 7 Days Room Temperature			Administration Sets* 24 Hours at Room Temperature Diluted to 3x therapeutic level		
	Functional Failure	Drug Stability 30-Days	Plastic Migration p per Device	Functional Failure	Drug Stability 24-Hours	Plastic Migration per Device
Bevacizumab	0/10	NT	NT	0/10	NT	NT
Cetuximab	0/10	NT	NT	0/10	NT	NT
Cisplatin	0/10	99.96%	P= .125µg VC= <.05µg	0/10	99.93%	P= .07µg VC= .07µg
Cyclophosphamide	0/10	NT	NT	0/10	NT	NT
Doxorubicin	0/10	NT	NT	0/10	NT	NT
Etoposide	0/10	99.66%	P= .014µg VC= <.05µg	0/10	99.73%	P= .25µg VC= .09µg
Flourouracil	0/10	99.52%	P= .014µg VC= <.05µg	0/10	99.73%	P= .60µg VC= .05µg
Herceptin	0/10	97.30%	P= <5µg VC= <.2µg	NT	NT	NT
Methotrexate	0/10	NT	NT	0/10	NT	NT
Paclitaxol	0/10	NT	NT	0/10	NT	NT
Vincristine	0/10	NT	NT	0/10	NT	NT

*Includes Clave® Needlefree Connector in Evaluation

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