Drug Compatibility with a New Generation of VISIV Polyolefin Infusion Solution Containers

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ABSTRACT

A new generation of VISIV polyolefin intravenous solution containers, made of a new and different proprietary polymer, were evaluated for sorption and leaching potential with a cadre of drugs known to exhibit those phenomena with polyvinylchloride containers. Sorption potential was evaluated for amiodarone hydrochloride, carmustine, regular human insulin, lorazepam, nitroglycerin, sufentanil citrate, and thiopental sodium. Leaching potential was evaluated for tacrolimus and teniposide as well as the vehicles of docetaxel and paclitaxel. Representative concentrations of the drugs in infusion solutions or undiluted were placed into the new generation of VISIV containers and left in contact for up to 24 hours at room temperature. High performance liquid chromatography was used to determine drug concentrations and the presence of plasticizer or other plastic components, if any. Only regular human insulin exhibited any substantial loss of concentration in the polyolefin containers that could be attributed to sorption. Other drugs' concentrations were consistent with their stabilities over the test periods. No evidence of leaching of plasticizer or other plastic components was observed.

INTRODUCTION

The loss of drug concentration due to adsorption onto surfaces or absorption into polymer matrices, or leaching of plasticizer from plastic containers and tubing has been documented for a number of parenteral drugs making them incompatible with these plastic containers and administration sets.[1] A new generation of VISIV (Hospira, Inc., Lake Forest, Illinois) polyolefin infusion solution containers have recently been released using a new and improved proprietary polymer from the original version. Although a previous study[2] documented the compatibility of the earlier VISIV containers, the compatibility of drugs that have been documented to be problematic due to sorption or to leaching must also be determined for the new generation of VISIV containers manufactured from this new and different proprietary polymer.

The objective of this study was to determine the compatibility of the new VISIV polyolefin infusion solution containers that were made from the new and different proprietary polymer with seven drugs that have exhibited sorption to polyvinylchloride (PVC) containers and sets and an additional four drugs that have exhibited leaching of plasticizer or other polymer matrix components from PVC containers and sets.

METHODS

Materials

The dextrose 5% (Lot 44-120-JT-02; Hospira, Inc.) and sodium chloride 0.9% (Lot 54-063-JT; Hospira, Inc.) injections for use in this study were obtained commercially. For the sorption portion of the study, finished pharmaceutical dosage forms of amiodarone hydrochloride (Lot 1053008; Bedford Laboratories, Bedford, Ohio), carmustine (Lot 895803A; Bristol-Myers Squibb, Princeton, New Jersey), regular human insulin (Lot SZF0177; Novo Nordisk, Princeton, New Jersey), lorazepam (Lot 3922000; Hospira, Inc.), nitroglycerin (Lot 5116; American Regent Laboratories, Inc.), sufentanil citrate (Lot 101276; Akorn, Inc., Buffalo Grove, Illinois), and thiopental sodium (Lot 40-477-DK; Hospira, Inc.) were obtained commercially. For the leaching portion of the study, diethylhexyl phthalate (DEHP) plasticizer reference standard (Lot VJ0988; Spectrum Chemical, Gardena, California) was obtained commercially. Because the potential for leaching plasticizer is associated with the surfactants present in formulations (rather than the drug molecules themselves), drug-free vehicles representing docetaxel, paclitaxel, tacrolimus, and teniposide drug-free vehicles were evaluated for leaching of plastic components (Table 1). Acetonitrile, methanol, and other mobile phase components were suitable for high-performance liquid chromatographic (HPLC) analysis. The water used was also HPLC grade (Barnstead Nanopure; Barnstead International, Dubuque, Iowa) and was prepared immediately before use. Prototype VISIV polyolefin plastic containers made of the new proprietary polymer for evaluation in this study were provided by Hospira, Inc.

Sample Preparation and Handling

Sample solutions of each test admixture described in Tables 2 and 3 were prepared and were transferred into three of the new VISIV polyolefin containers made of the new polymer through the access port along with a control solution in a glass container. The test samples were stored at ambient laboratory temperature of about 23°C exposed to fluorescent light while laying flat on laboratory counters to assure maximum

Table 1. Components for Drug-Free Vehicle Evaluated for Diethylhexyl Phthalate Leaching.

Component	Manufacturer	Lot Number
Polysorbate 80	Spectrum Chemical[a]	VI0841
Cremophor EL	Sigma Chemicals[b]	037K0213
Ethanol	Spectrum Chemical[a]	VI1016
Benzyl alcohol	Spectrum Chemical[a]	WE0332
N,N-Dimethylacetamide	Spectrum Chemical[a]	ND0084

[a]Gardenia, California
[b]St. Louis, Missouri

Table 2. Drug Solutions Evaluated for Sorption.[a]

Amiodarone Hydrochloride 1 mg/mL
Carmustine 1 mg/mL[b]
Insulin 0.1 unit/mL[c]
Lorazepam 0.2 mg/mL
Nitroglycerin 0.4 mg/mL
Sufentanil citrate 0.005 mg/mL
Thiopental sodium 0.01 mg/mL

[a]All drug solutions were prepared in 5% dextrose injection and evaluated over 24 hours contact time in the new VISIV polyolefin bags, except where noted otherwise.
[b]Evaluated for only 6 hours due to inherent drug instability.
[c]Prepared in 0.9% sodium chloride injection.

Table 3. Drug Solutions Evaluated for Leaching of Plastic Components.

Docetaxel vehicle equivalent to 0.74 mg/mL
Paclitaxel vehicle equivalent to 1.2 mg/mL
Tacrolimus vehicle equivalent to 0.02 mg/mL
Teniposide vehicle equivalent to 0.1 mg/mL

surface contact of the liquid contents. Samples for analysis were taken from the access port using a needle and syringe initially and after storage for 24 hours for all drugs except for carmustine. Due to its limited stability, the carmustine storage was evaluated for only 6 hours.

HPLC Analysis

Each test solution was evaluated using HPLC. The Hewlett-Packard Series 1100 (Agilent Technologies, Palo Alto, California) consisting of a multisolvent delivery pump, autosampler, and photodiode array detector was used for analysis of the drugs. The system was controlled and integrated by a personal computer with chromatography management software (HPLC ChemStation Version A.09.03; Agilent Technologies). The specific parameters of each of the analytical methods for the drugs evaluated in the sorption portion of the study are cited in Table 4. These methods were demonstrated to be stability indicating by accelerated degradation of the drug exposed to heat, 0.1 N hydrochloric acid, 0.1 N sodium hydroxide, and 3% hydrogen peroxide to intentionally degrade the subject drugs. The decomposition product peaks for each of the drugs did not interfere with the peaks of the respective intact drugs.

The initial concentrations of the drugs were defined as 100%, and subsequent sample concentrations were expressed as percentage of the initial concentration. Compatibility was defined as not less than 90% of the initial drug concentration remaining in the admixtures.

The analyses for leached plastic components were performed using an HPLC analytical method based on that of Waugh et al,[3] with minor modifications to assure DEHP separation from the peaks of the drug product components. The liquid chromatograph

Table 4. High-Performance Liquid Chromatographic Analytical Methods for Analysis of Drug Concentrations.

Parameter	Amiodarone Hydrochloride	Carmustine	Insulin
Chromatograph	HP 1100	HP 1100	HP 1100
Column	Bondapak C18 (300 × 3.9 mm, 10 mcm)	Phenomenex Luna C18 (250 × 3.0 mm, 5 mcm)	Agilent Zorbax RX-C8 (250 × 4.6 mm, 5 mcm)
Mobile phase	Methanol/water/NH_4OH (94:4:2)	10 mM KH_2PO_4 (pH 6.0) and CH_3CN (55:45)	A. Acetonitrile 5% + 0.1% trifluoroacetic acid B. Acetonitrile 50% + 0.1% trifluoroacetic acid[a]
Flow rate	1.0 mL/minute	1.2 mL/minute	1.5 mL/minute
Detection	254 nm	216 nm	202 nm
Injection volume	10 mcL	5 mcL	90 mcL
Run time	15 minutes	12 minutes	10 minutes
Retention times			
Drug	6.4 minutes	3.6 minutes	8.5 minutes
Decomposition products	Multiple 1.7 -3.3, 5.1, 5.6 minutes	Multiple 0.8-2.3, 6.5, 10.9, 19.9 minutes	7.8, 8.0, 8.9, 9.1, 9.2, 9.4 minutes[b]
Standard curve			
Range	0.25 to 1.25 mg/mL	0.25 to 1.25 mg/mL	0.025 to 0.125 units/mL
Linearity	0.9994	1.0	1.0
Sample dilution	Undiluted	Undiluted	Undiluted
RSD[c] (n = 9)	0.14% at 1000 mcg/mL	0.23% at 1000 mcg/mL	1.36% at 0.1 unit/mL

[a]30% mobile phase B 0 minutes to 3 minutes, 90% mobile phase B 6 minutes to 9 minutes, 30% mobile phase B 9.1 minutes
[b]Metacresol preservative eluted at 9.7 minutes.
[c]Relative standard deviation
[d]Benzyl alcohol eluted at 3.3 minutes.

Table 4. (Continued)

Parameter	Lorazepam	Nitroglycerin	Sufentanil Citrate	Thiopental Sodium
Chromatograph	Hewlett-Packard P 1100	Hewlett-Packard P 1100	Hewlett-Packard P 1100	Hewlett-Packard P 1100
Column	Phenomenex Luna C18 (250 × 3.0 mm, 5 mcm)	Phenomenex Luna C18 (250 × 3.0 mm, 5 mcm)	Phenomenex Gemini C18 (150 × 4.6 mm, 5 mcm)	Agilent Zorbax SB-Phenyl (250 × 4.6 mm, 5 mcm)
Mobile phase	57% Methanol in 50 mM $(NH_4)H_2PO_4$ adjusted to pH 6.5 with NH_4OH	Methanol/water (60:40)	Ammonium acetate 4 g, water 400 mL, methanol 400 mL, CH_3CN 200 mL, to pH 6.6 with acetic acid	Ammonium acetate 4 g, water 400 mL, methanol 400 mL, CH_3CN 320 mL
Flow rate	0.7 mL/minute	0.8 mL/minute	1.5 mL/minute	1.0 mL/minute
Detection	254 nm	216 nm	222 nm	290 nm
Injection volume	5 mcL	15 mcL	70 mcL	5 mcL
Run time	15 minutes	12 minutes	7 minutes	10 minutes
Retention times				
Drug	9.6 minutes	4.5 minutes	5.4 minutes	5.1 minutes
Decomposition products	1.7, 2.0, 4.0, 6.0, 6.3, 7.1, 8.5 minutes	Multiple 1.1 to 2.4, 2.9, 3.2, 6.7, 7.2 minutes	Multiple 1.1 to 2.5, 2.7, 3.0, 3.2, 3.4, 3.6, 4.2 minutes	2.3, 2.7, 3.0, 3.2, 3.6, 3.8 minutes
Standard curve				
Range	50 to 250 mcg/mL	100 to 500 mcg/mL	0.86 to 6.25 mcg/mL	2.5 to 12.5 mcg/mL
Linearity	0.9986	1.0	0.9999	0.9999
Sample dilution	Undiluted	Undiluted	Undiluted	Undiluted
RSD[b] (n = 9)	1.08% at 200 mcg/mL	0.06% at 400 mcg/mL	0.21% at 5 mcg/mL	0.27% at 10 mcg/mL

Table 5. Drug Content Remaining in Test Solutions after 24-hour Contact Periods with the New VISIV Polyolefin Containers.

Drug Name	Initial (mg/mL)	24 hours (% Remaining)
Amiodarone Hydrochloride	0.969 ± 0.004	92.9 ± 0.5
Carmustine	0.991 ± 0.078	91.3 ± 1.2[a]
Regular Human Insulin	0.105 ± 0.0.003[b]	55.6 ± 1.8
Lorazepam	0.196 ± 0.003	100.2 ± 0.3
Nitroglycerin	0.396 ± 0.002	99.3 ± 0.1
Sufentanil citrate	5.00 ± 0.02[c]	98.4 ± 0.5
Thiopental sodium	10.8 ± 0.0[c]	95.0 ± 0.6

[a]Tested at 6 hours.
[b]Unit/mL
[c]Micrograms/mL

was also a Hewlett-Packard Series 1100 (Agilent Technologies). A Phenomenex Luna C18 reverse-phase analytical column (Phenomenex, Torrance California) was used, along with a guard column of the same material. The mobile phase consisted of methanol, water, and glacial acetic acid (1800:198:2). The flow rate was 1.4 mL/min and the run time was 20 minutes. Sample injection volume was 10 microliters for each of the drugs. Detection was performed at 225 nm. The retention time for DEHP under these analytical conditions was about 7.5 minutes. The surfactant peaks did not interfere with the DEHP peak. The standard curve was over the range of 6.2 to 310 mcg/mL. The correlation coefficient was greater than 0.9999. The limits of quantitation and detection were 5.32 and 1.56 ng, respectively. The relative standard deviation from nine injections of DEHP for each drug admixture was 0.2% or less. Absence of detectable plastic components such as DEHP plasticizer was defined as compatibility.

RESULTS AND DISCUSSION

Of the seven drugs tested that exhibited sorption to PVC, only insulin demonstrated a substantial loss in the new VISIV polyolefin containers (Table 5). About 45% of the insulin was lost after 24 hours. A control solution in a glass container exhibited a similar loss of insulin.

Carmustine exhibited about 10% loss in 6 hours, which is consistent with previous reports of the drug's chemical instability,[4-6] indicating that the new VISIV polyolefin container does not accelerate carmustine decomposition or result in sorption. In addition, a control solution in a glass container exhibited a similar loss of carmustine.

Thiopental sodium concentration in the test samples declined about 5% in 24 hours, which is nearly identical to the loss that occurred in the thiopental sodium control solution in a glass bottle in the same time period. This result again indicates that the new VISIV container does not accelerate thiopental sodium decomposition or result in sorption.

In this study of the new VISIV polyolefin containers, none of the surfactant-containing vehicles for drugs that are known to leach plastic components, such as DEHP plasticizer from PVC

equipment,[1,3,7,8] exhibited any leached components in the new polyolefin containers. This is consistent with previous research involving similar non-PVC devices and equipment.[2,8-11]

In 1968, Weisenfeld et al[12] reported substantial loss of insulin to infusion solution containers and administration sets. At least 35 additional published articles and research studies[1] have also addressed this sorptive loss of insulin. The previous studies that have reported insulin adsorption to surfaces have reported losses as high as 80%, but losses are more commonly cited as around 30% to 40% in a variety of glass and plastic container types.[1] The current result indicates that insulin sorptive loss also occurs to the new VISIV polyolefin containers to an extent that is consistent with previous studies of a variety of container types as well as the former VISIV polyolefin container.[2,8-11]

For drugs that are formulated using surfactants, the surfactants have been found to leach the plasticizer DEHP from PVC containers and administration sets.[3,4,7,8] The problem of plastic component leaching has extended to other types of plastic bags as well.[9] However, no plasticizer leaching was found using the new VISIV polyolefin containers.

CONCLUSION

Of the drugs tested, only insulin exhibited sorption to the new VISIV polyolefin containers. No leaching of plastic components such as plasticizer from the container was found with the vehicles of any of the surfactant-containing drugs.

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