Analysis of Extractable/Leachable Compounds From Plastic Intravenous Bag Sets Using GC/MSD Systems

Application Note

Pharmaceuticals

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Abstract

Two Agilent 5977A Series GC/MSD Systems were used for the analysis of extractable and leachable compounds in plastic IV bag sets. Two types of IV bags were investigated: 150-mL dextrose bag (expired) and 1-L sodium chloride bag (warmed). Potentially toxic additives, such as phthalate plasticizers, were shown to have migrated from the IV bag to its infusion solution using the complementation of headspace sampling and liquid injection techniques. High temperature analysis was accomplished using the 7697A Headspace and a 7890A GC coupled with a 5977A MSD. Solvent extracts were analyzed using the MMI 7890A GC coupled with a 5977A MSD. Single ion monitoring (SIM) was used to confirm compound migration.

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Introduction

Pharmaceutical packaging materials offer several advantages, but the use of these materials can involve risk of drug contamination from the package. Pharmaceutical products are manufactured, stored, and administered with the use of polymeric components. These polymeric components allow for product freshness, efficient transportation, extended storage time, and low price. Interaction between the package and the product can affect the quality of the drug. Packaging materials contain additives (extractables) that have the potential to migrate out and accumulate (as leachables) into the drug products. In extractables analysis, the packaging material is exposed to strong conditions (high temperatures and appropriate solvents) to simulate the worst-case leachable profile. In leachables analysis, the drug product is analyzed at normal conditions to observe actual compound migration. Typical sources of extractables and leachables are plastic and elastomeric components, ink and adhesives from labels, and degradation products (from processing, storage, and sterilization). A careful assessment of the potential risk is necessary to protect consumers against harmful migration of by-products from the packaging production.

Regulators grow increasingly concerned with the manufacturing of parenteral and ophthalmic drug products (PODP) and their container closure system (CCS). Leachables found in the drug product can affect the safety, quality, and efficacy of the product. The U.S. Food and Drug Administration (FDA) has formally and comprehensively addressed extractables and leachables after finding patient sensitivity induced by leachables. The Product Quality Research Institute (PQRI) also provided assessment, regulatory guidance, and safety thresholds in the area of extractables and leachables. The United States Pharmacopeia (USP) provided general information on the design and analysis of extractables (USP <1663>) and leachables (USP <1664>) assessment associated with the pharmaceutical packaging/delivery systems. USP <1663> and <1664> do not contain mandatory requirements regarding the analysis of extractable and leachable compounds in packaging material, only general guidelines. The International Organization for Standardization (ISO <10993>) also provides optional testing for the biological evaluation of medical devices.

Extractables on IV bag sets is of interest because the package type has the highest degree of concern associated with the route of administration and a high likelihood of interaction between the package and the drug component. Plastic IV bags and tubing are commonly made of polyvinyl chloride (PVC) to ensure resistance to breakage during storage and shipping. PVC is a hard, brittle, and inflexible substance, so plasticizers (predominantly phthalates) are added to impart flexibility. However, the use of the flexible PVC bags has developed concern with the leaching of harmful plasticizers into intravenous solutions.

PVC-based medical devices contain an average of 20–40 % bis(2-ethylhexyl)phthalate (DEHP), a plasticizer with the potential to leach into contact solution when warmed or agitated [1]. DEHP is lipid-soluble compound, and a suspected carcinogen and hepatotoxin [2]. DEHP is hydrophobic, with minimal to no detection in water, 0.9 % sodium chloride (NaCl), or 5 % dextrose solution [3]. Certain drug formulations, such as cyclosporine and blood have the highest risk of exacerbating leaching of DEHP when prepared in IV solution [4-6]. The IV form of cyclosporine contains large amount of Kolliphor (polyoxyethylated castor oil), a nonionic surfactant that can cause the stripping of DEHP [4,7]. Therefore, Kolliphor-NaCl solution with IV bags were investigated in this study.

Volatile and semivolatile extractable and leachable compounds were investigated in two different IV bag sets using two sample introduction techniques with GC/MS analysis (Figure 1). Extractable compounds in IV bags and tubing were investigated at high temperatures (headspace GC/MS) and solvent extraction (MMI GC/MS). Low level leachable compounds in infusion solutions were identified using large volume injection for sensitivity and made possible using MMI in solvent vent mode. An expired 150-mL dextrose IV bag, heated 1-L NaCl IV bag, and IV tubing were used for the analysis of extractables/leachables in injections and injectable suspensions. Kolliphor was added to NaCl solution to model infusion solution used in medical facilities. Compound migration was investigated in IV bag and their infusion solution using Scan and SIM analysis.

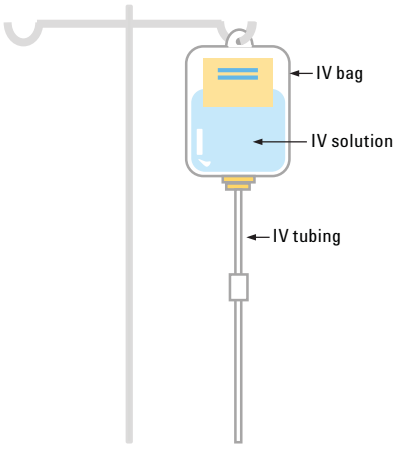

Figure 1. Schematic diagram of an intravenous bag set.

Experimental

Materials and instrumentation

IV bag sets were analyzed at high temperatures using the 7697 Headspace Sampler and a 7890A GC coupled with a 5977A MSD (Headspace GC/MS). Solvent extracts of IV bag set were analyzed using large volume liquid injection with the Multimode Inlet 7890A GC coupled with a 5977A MSD (MMI GC/MS). The 150-mL 5% dextrose IV bag, 1-L 0.9% NaCl IV bag, and IV tubing were acquired from major manufacturers. Dextrose IV bag had been expired for 8 years. NaCl IV bag had been warmed for 58 days at 100 °F. IV tubing had been expired for 3 years. Dichloromethane (650463), hexane (34859), and Kolliphor EL (C5135) were purchased from Sigma-Aldrich.

Analysis of IV bag set using headspace GC/MS

Sample preparation

Plastic IV bags were rinsed with water to remove any residue. IV bags and tubing were analyzed in separate 10-mL headspace vials containing 0.40 g of 1.0-cm^2 plastic IV bag or 0.2 g of 1.0-cm tubing. Infusion solutions (3–5 mL) were concentrated by evaporation at room temperature prior to headspace analysis. All vials were purged with nitrogen and sealed with a high performance PTFE crimp cap before headspace GC/MS analysis.

Headspace GC/MS system parameters

IV bags and tubing were investigated at temperatures of 85, 100, 150, 200, 250, and 275 °C. Headspace, GC, and MSD system parameters were similar (Table 2), with variations in the headspace oven, loop, and transfer line temperatures, as shown in Table 1.

Table 1. Headspace GC/MS Parameters for the Different Temperature Studies

Headspace temperatures (°C)						
Oven	85	100	150	200	250	275
Loop	85	100	150	200	250	275
Transfer line	100	120	170	220	270	285

Table 2. Instrument Parameters using Headspace GC/MS at 275 °C

Headspace	Agilent 7697A
Vial pressurization gas	Helium
Loop size	1.0 mL
Vial standby flow	50 mL/min
Transfer line	0.53-mm id deactivated fused silica
HS oven temperature[a]	275 °C
HS loop temperature[a]	275 °C
HS transfer line temperature[a]	285 °C
Vial equilibration time	25 minutes, level 2 shake
GC run time	80 minutes
Vials	10 mL, PTFE/silicone septum
Vial fill mode	Flow to pressure
Vial fill pressure	15 psi
Loop fill mode	Custom
Loop ramp rate	20 psi/min
Loop final pressure	1.5 psi
Loop equilibration time	0.05 minutes
Carrier control mode	GC carrier control
Extraction mode	Single
Vent after extraction	ON
Post injection purge	100 mL/min for 1 minute
GC	**Agilent 7890A**
Injection port	Split/Splitless
Liner	0.75-mm ultra-inert, straight, tapered (p/n 5190-4048)
Inlet temperature[b]	280 °C
Inlet flow	Constant flow, 1.3 mL/min
Split ratio	15:1
Carrier gas	Helium
Oven program	35 °C (3 minutes) to 350 °C (3 minutes) at 5 °C/min
Columns	HP-5ms UI, 30 m × 0.25 mm, 0.5 µm (p/n 190915-133UI)
MSD	**Agilent 5977A**
Transfer line	280 °C
MS source	280 °C
MS Quad	175 °C
Tune	atune.u
Scan	15 to 700 amu, 2.5 scans/sec
Threshold	0
Gain factor	1.0
Software	Agilent MassHunter B.07.01

[a] Varies depending on temperature used for extractables studies (Table 1)

[b] 100 °C and 120 °C was used for HS oven temperatures at 85 °C and 100 °C, respectively

Analysis of solvent extracts in IV bag set

MMI GC/MSD system parameters

Ten microliters of extract was injected using large volume liquid injection. The solvent elimination wizard was used to develop starting parameters for DCM and hexane extracts in solvent vent mode. Similar GC and MSD parameters were used and listed in Table 3 unless specified. DCM and hexane extracts were investigated at solvent vent times ranging from 0.6 to 2.0 minutes and 0.15 to 0.30 minutes, respectively. Initial hold time in the MMI was altered to match the solvent vent times.

Table 3. Instrument Parameters for MMI GC/MS of DCM Extract

GC	Agilent 7890A
Injection port	Multimode Inlet (MMI), CO_2 cooling
Mode	Solvent vent
Inlet program*	–5 °C (0.7 minutes) to 325 °C (5 minutes) at 600 °C/min
Liner	4-mm id ultra inert (p/n 5190-3162)
Inlet vent	100 mL/min (5 psi) for 0.7 minutes
Carrier gas	Helium
Purge flow to split vent	60 mL/min at 3.15 minutes
Oven program	50 °C (3 minutes) to 340 °C (5 minutes) at 6 °C/min
Columns	Agilent HP-5ms UI, 30 m × 250 µm, 0.25 µm (p/n 190915-433UI)
MSD	**Agilent 5977A**
Transfer line	280 °C
MS Source	300 °C
MS Quad	175 °C
Tune	atune.u
Scan	29 to 700 amu, 2.2 scans/s
Threshold	150
Gain Factor	1.0
Software	Agilent MassHunter B.07.00

*Initial temperature and initial hold time differ depending on solvent extract

Solvent extraction of IV bags
0.4 g of IV bags cut into 1-cm^2 pieces were extracted with 5.0 mL solvent (DCM or hexane) in a 12-mL amber vial. IV bags in solvent were sonicated for 5–8 hours and allowed to sit at room temperature for 8 days. The organic layer was analyzed using MMI GC/MS.

Solvent extraction of infusion solutions
Five mL of dextrose (or NaCl) solution were extracted with 5.0 mL of solvent (DCM or hexane) in a 12-mL amber vial by sonication for 5–8 hours and allowed to sit at room temperature for 24 hours. The organic layer was analyzed using MMI GC/MS.

Solvent extraction of Kolliphor-NaCl solutions
0.3 g of 1-L IV bags cut into 1-cm^2 pieces were immersed in a 12-mL amber vial containing 500 µL of Kolliphor EL with 10 mL 0.9 % NaCl solution. Five milliliters of Kolliphor-NaCl solution were extracted with 5.0 mL of solvent (DCM or hexane) by sonication for 5 hours and allowed to sit at room temperature for 24 hours. The organic layer was analyzed using MMI GC/MS

Compound identification
Compounds were characterized using MSD Chemstation Data Analysis F.01.01, MassHunter Unknowns Analysis B.07.00, and AMDIS 2.72. Mass spectra of all compounds were matched with the NIST Library 2.2. Compound with a mass spectral match of $\geq$ 80 were considered, and the top match was used in the investigation.

Results and Discussion

The complementation of the headspace GC/MS and MMI GC/MS allows for the comprehensive analysis of extractable and leachable compounds in IV bag sets. The headspace sampler simplifies the analysis of extractable compounds in packaging material using high sample equilibration temperatures, while the MMI in solvent vent mode allows for large volume injection for the analysis of low level leachables in the drug product. The advantage of using headspace sampling is the closed controlled vial environment combined with minimal sample preparation. Headspace vials allow for maintained sample integrity under an inert atmosphere if desired, contained hazardous chemicals, limited cross contamination, and simplified cleanup.

PVC additives and plasticizers were identified in plastic IV bags and tubing using headspace GC/MS (Tables 4-6, Figures 2-4). DEHP, benzophenone, palmitic acid, stearic acid and acetophenone were examples of plasticizers identified in IV tubing. DEHP, butylated hydroxytoluene (BHT), and acetophenone were identified in 150-mL IV bag. BHT and Metilox were identified in 1-L IV bag. Benzophenone is a carcinogenic UV stabilizer [8,9]. Acetophenone is a resin used in coating, ink, and adhesives [11]. Palmitic acid and stearic acid are lubricants [12]. Metilox is an antioxidant used in PVC [13]. Leached compounds were not observed in the dextrose solution using headspace analysis at temperatures investigated (85 and 100 °C). If present, they are present at concentrations below levels that can be reached with headspace sampling.

Table 4. Extractable Compounds Identified in IV Tubing Using Headspace GC/MS at 250 °C.

RT (min)	Compounds identified	Origin
3.82	Benzene (1)	Residual solvents
6.37	Toluene (2)	Residual solvents
13.47	Acetophenone (3)	Resin in coating, ink, and adhesives
15.90	Naphthalene (4)	Residual solvents
17.97	Naphthalene, 2-methyl- (5)	Residual solvents
18.27	Phthalic anhydride (6)	Plasticizer
19.41	Biphenyl (7)	Intermediate
22.73	2,2,4-Trimethyl-1,3-pentanediol diisobutyrate (8)	Plasticizer
23.35	Benzophenone (9)	UV stabilizer
24.37	Benzoic acid, 2-ethylhexyl ester (10)	UV stabilizer
27.47	Palmitic acid (11)	Slip agent, lubricant
29.84	Stearic acid (12)	Slip agent, lubricant
34.03	*Bis*(2-ethylhexyl) phthalate (DEHP) (13)	Plasticizer
36.38	*Bis*(2-ethylhexyl) isophthalic acid (14)	Plasticizer

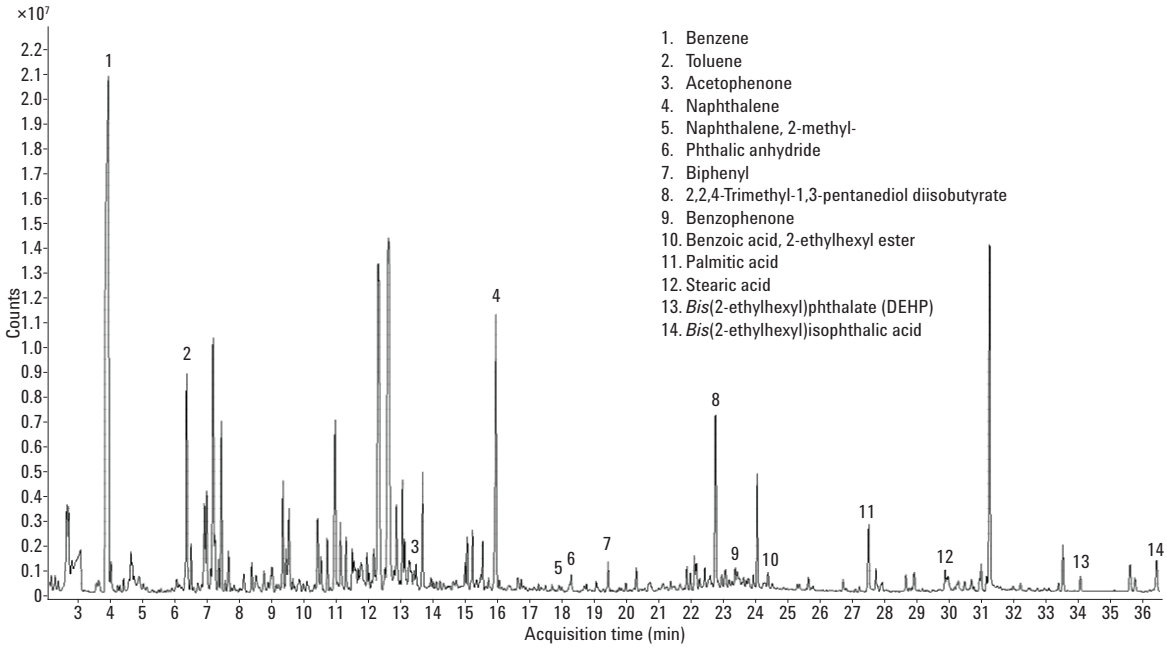

Figure 2. Extractables analysis of IV tubing using headspace GC/MS at 250 °C.

Table 5. Extractable Compounds Identified in 150-mL IV Bag by Headspace GC/MS at 275 °C

RT (min)	Compounds	Origin
6.81	Toluene (1)	Residual solvent
11.08	Styrene (2)	Residual solvent
17.05	Acetophenone (3)	Resin in coating, ink, and adhesives
22.00	Benzothiazole (4)	Vulcanization of rubber
29.68	Butylated hydroxytoluene (BHT) (5)	Antioxidant
31.68	2,2,4-Trimethyl-1,3-pentanediol diisobutyrate (6)	Plasticizer
34.24	2-Ethylhexyl ester benzoic acid (7)	Plasticizer
39.44	Dibutyl phthalate (8)	Plasticizer
49.54	*Bis*(2-ethylhexyl) phthalate (DEHP) (9)	Plasticizer

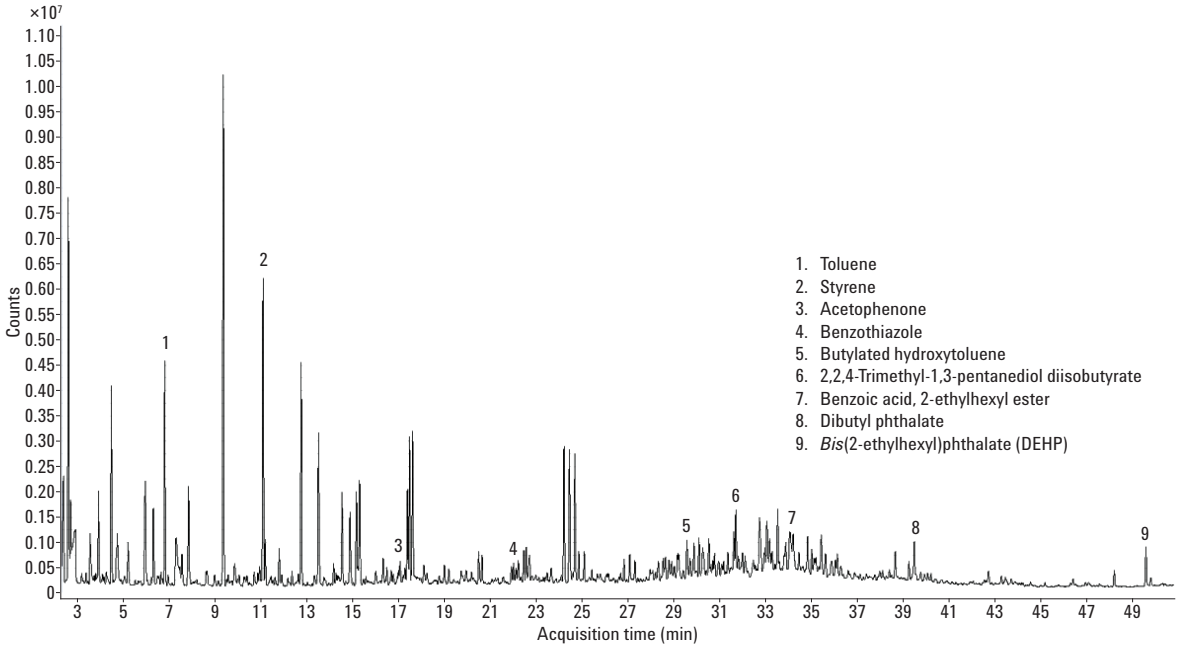

Figure 3. Extractables analysis of 150-mL IV bag using headspace GC/MS at 275 °C.

Table 6. Extractable Compounds Identified in 1-L IV Bag Using Headspace GC/MS at 250 °C

RT (min)	Compounds	Origin
16.96	Acetophenone (1)	Resin found in ink, coating, and adhesives
26.82	Diphenyl ether (2)	Residual solvent
28.50	2,6-di-*tert*-butyl-1,4-benzoquinone (3)	Plasticizer
29.59	Butylated hydroxytoluene (BHT) (4)	Antioxidant
31.51	Diethyl phthalate (5)	Plasticizer
31.59	2,2,4-Trimethyl-1,3-pentanediol diisobutyrate (6)	Plasticizer
34.15	2-Ethylhexyl ester benzoic acid (7)	Plasticizer
35.42	3,5-di-*tert*-Butyl-4-hydroxybenzaldehyde (8)	Residual solvent
37.47	Diisobutyl phthalate (9)	Plasticizer
38.97	Metilox (10)	Plasticizer
39.34	Dibutyl phthalate (11)	Plasticizer

Metilox: 3,5-*Bis*(1,1-dimethylethyl)-4-hydroxy-methyl ester benzenepropanoic acid

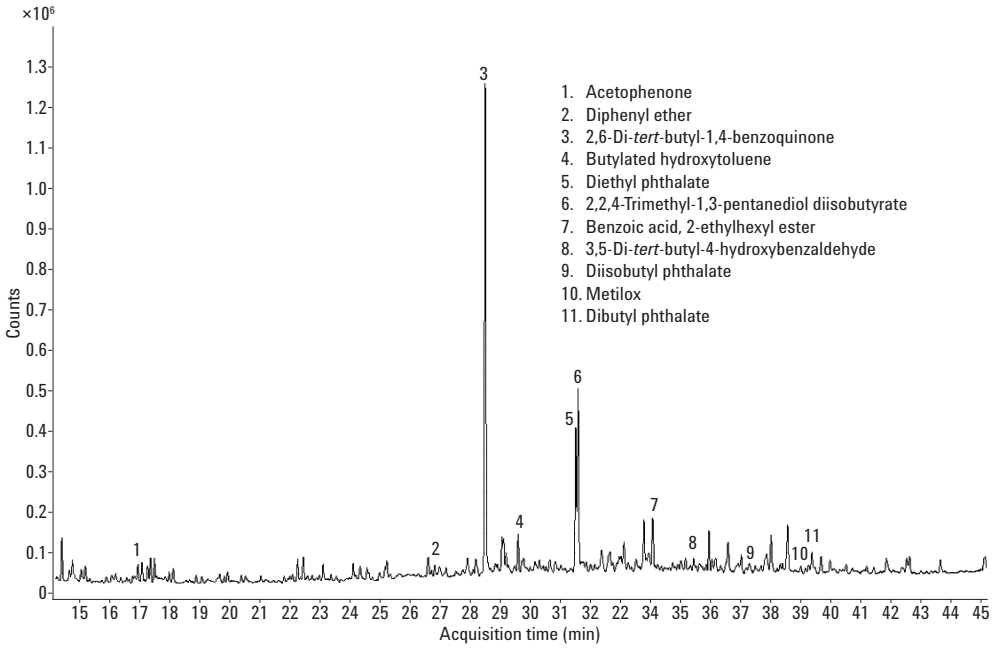

Figure 4. Extractables analysis of 1-L IV bag using headspace GC/MS at 250 °C.

The MMI in solvent vent mode allows for the analysis of low level extractable/leachable compounds and liquid extracts in IV bag systems. Leachables are typically present in low levels, which makes the capability of using large volume injection very advantageous.

An expired dextrose IV bag set was investigated for potential migration of plasticizers due to extended storage using MMI GC/MS. DEHP and DEHA were identified in DCM and hexane extracts of dextrose solution and IV bag (Tables 7-8, Figures 5-6). SIM data confirmed potential migration of DEHP and DEHA (Figure 5C).

Table 7. Extractables/Leachables Identification in DCM Extracts of Dextrose IV Bags Using MMI GC/MS

RT (min)	IV bags	Dextrose solution	Toxicity
20.58	Hexadecane (1)		
20.89	Butylated hydroxytoluene (2)		
22.58	2,2,4-Trimethyl-1,3-pentanediol diisobutyrate (3)		
23.38	Benzophenone (4)		Carcinogen
27.50	Isobutyl nonyl phthalate (5)		
28.26	7,9-Di-*tert*-butyl-1-oxaspiro(4,5)deca-6,9-diene-2,8-dione (6)		
29.19	2-Mercaptobenzothiazole (7)		
29.22	Palmitic acid (8)		
30.23	Isopropyl palmitate (9)		
32.72	Palmitic acid, butyl ester (10)		
34.58	2-Ethylhexyl trans-4-methoxycinnamate (11)		
34.91	Benzyl butyl phthalate (12)		
35.58	DEHA (13)	DEHA (13)	Carcinogen
36.81	Di(oct-3-yl) phthalate (14)		
37.50	DEHP (15)	DEHP (15)	Endocrine disruptor
47.15	Irgafos 168 (16)		
48.81	*Tris*(2,4-di-*tert*-butylphenyl) phosphate (17)		

BHT: Butylated hydroxytoluene
DEHA: *Bis*(2-ethylhexyl) ester hexanedioic acid
DEHP: *Bis*(2-ethylhexyl) phthalate
Irgafos 168: *Tris*(2,4-di-tert-butylphenyl) phosphite

Table 8. Extractables/Leachables Identification in Hexane Extracts of Dextrose IV Bags Using MMI GC/MS

RT (min)	IV bag	Dextrose solution	Toxicity concerns
25.34	Hexadecane (1)		
27.39	7,9-Di-*tert*-butyl-1-oxaspiro(4,5)deca-6,9-diene-2,8-dione (2)		
28.09	Dibutyl phthalate (3)		
34.51	DEHA (4)	DEHA (4)	Carcinogenic
36.47	DEHP (5)	DEHP (5)	Endocrine disruptor
48.07	*Tris*(2,4-di-*tert*-butylphenyl) phosphate (6)		

DEHA: *Bis*(2-ethylhexyl) ester hexanedioic acid
DEHP: *Bis*(2-ethylhexyl) phthalate

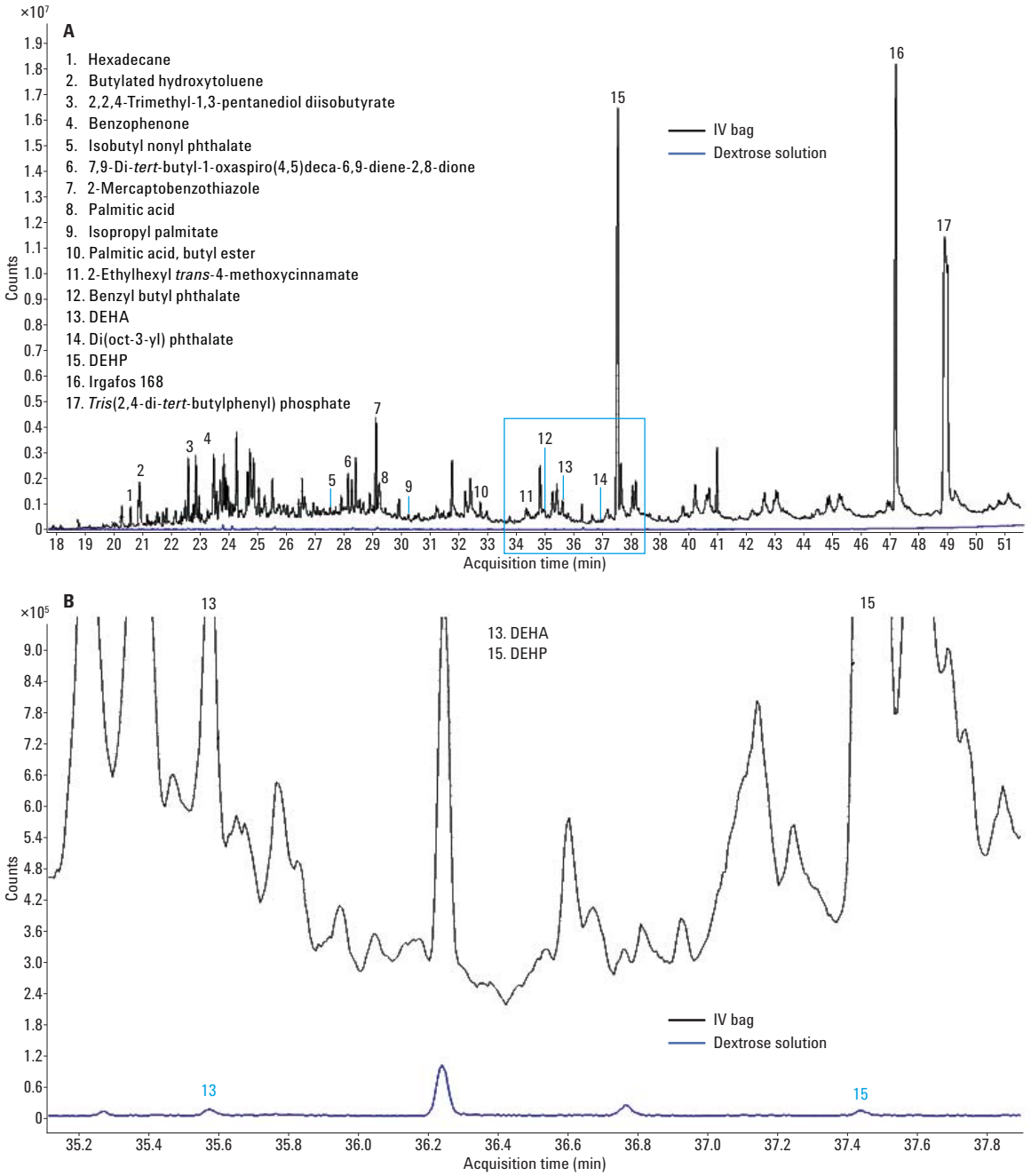

Figure 5. Extractables/Leachables analysis of dextrose IV bag by DCM extraction using MMI GC/MS. Extractables identified in 150-mL IV bag (A) with boxed region enlarged in (B). Leachables identified in dextrose solution (B) SIM analysis of DEHA and DEHP (C, on next page).

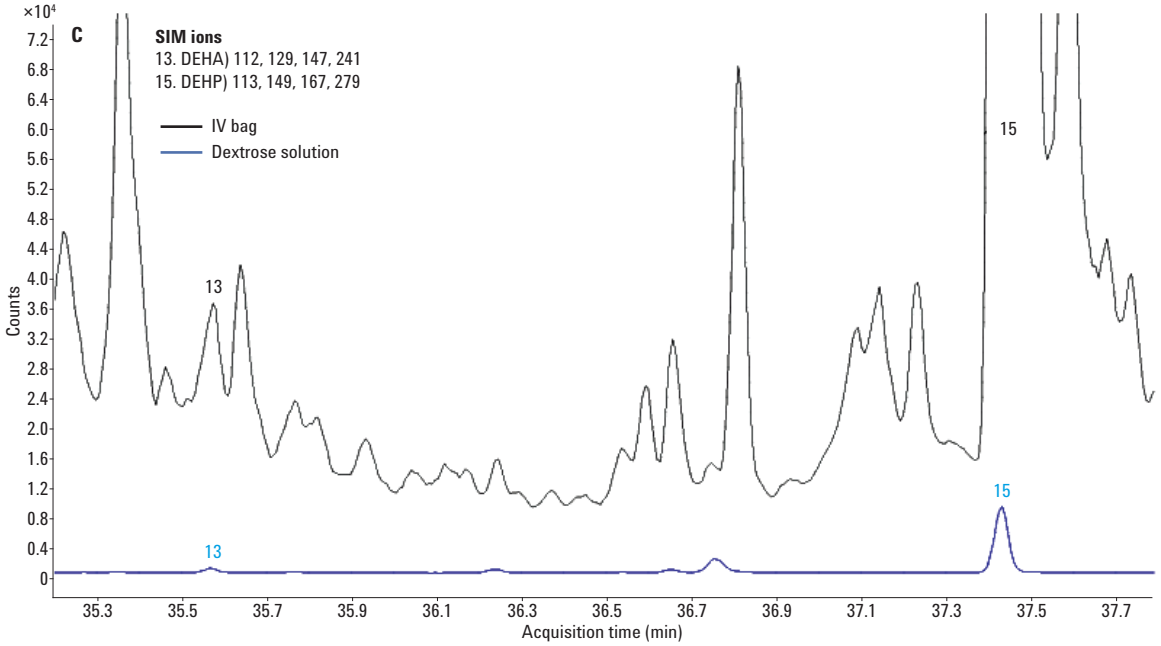

Figure 5C. Extractables/Leachables analysis of dextrose IV bag by DCM extraction using MMI GC/MS. SIM analysis of DEHA and DEHP.

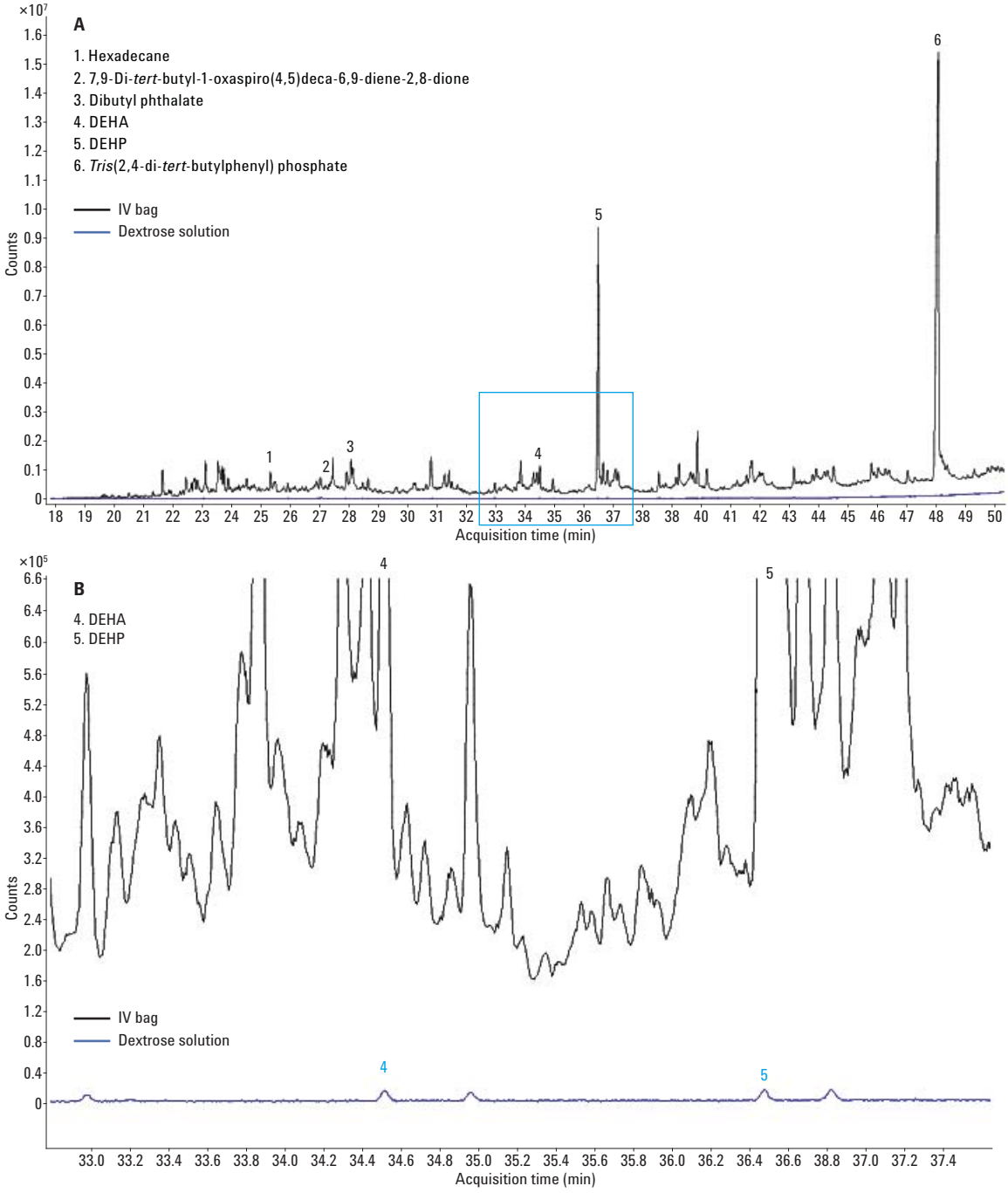

Figure 6. Extractables/Leachables analysis of dextrose IV bag by hexane extraction using MMI GC/MS. Extractables identified in 150-mL IV bag (A) with boxed region enlarged in (B). Leachables identified in dextrose solution (B).

NaCl and Kolliphor-NaCl IV bags were investigated for potential compound migration due to heat using MMI GC/MS. Plasticizers were identified in DCM and hexane extracts of IV bag and NaCl solutions (Tables 9-10, Figures 7-8). Dibutyl phthalate was identified in NaCl solution and the IV bag. Kolliphor-NaCl solution enhanced leaching of plasticizer 2,2,4-trimethyl-1,3-pentanediol diisobutyrate. Similar phthalate plasticizers were identified at the same retention time and will require GC/QTOF for identification because of their similar fragmentation patterns. For example, DCM extract of NaCl IV bag set at 27.01 minutes could be diisobutyl phthalate or 6-ethyl-2-octyl butyl phthalate.

DEHA and *bis*(2-propylpentyl) phthalate were identified in NaCl and Kolliphor-NaCl solutions, but not in the IV bag. Formation of new leachable compounds is possible due to interactions from the close contact or from heating.

Table 9. Extractables/Leachables Identification in DCM Extracts of NaCl and Kolliphor-NaCl IV Bags Using MMI GC/MS

RT (min)	IV bag	NaCl solution	Kolliphor-NaCl solution
18.27	Diphenyl ether (1)		
20.37	BHT (2)		
22.11	2,2,4-Trimethyl-1,3-pentanediol diisobutyrate (3)		2,2,4-Trimethyl-1,3-pentanediol diisobutyrate (3)
27.01	Diisobutyl phthalate (4)	6-Ethyl-3-octyl butyl phthalate (8)	
28.24	Metilox (5)		
28.56	Dibutyl phthalate (6)	Dibutyl phthalate (6)	Butyl cyclobutyl phthalate (9)
35.12	Triphenyl phosphate (7)		

Metilox: 3,5-*Bis*(1,1-dimethylethyl)-4-hydroxy-methyl ester benzenepropanoic acid
BHT: butylated hydroxytoluene

Table 10. Extractables/Leachables Identification in Hexane Extracts of NaCl and Kolliphor-NaCl IV Bags Using MMI GC/MS

RT (min)	IV bag	NaCl solution	Kolliphor-NaCl solution
20.42	Butylated hydroxytoluene (1)		
22.06	2,2,4-Trimethyl-1,3-pentanediol diisobutyrate (2)		
22.67	Benzophenone (3)		
26.9	Hept-4-yl isobutyl phthalate (4)		
28.14	Metilox (5)		
28.44	Dibutyl phthalate (6)	Butyl cyclobutyl phthalate (8)	Butyl hex-3-yl phthalate (11)
34.89		DEHA (9)	DEHA (9)
35.12	Triphenyl phosphate (7)		
36.86		*Bis*(2-propylpentyl) phthalate (10)	*Bis*(2-propylpentyl) phthalate (10)

Metilox = 3,5-*Bis*(1,1-dimethylethyl)-4-hydroxy-methyl ester benzenepropanoic acid
DEHA = *Bis*(2-ethylhexyl) ester hexanedioic acid
BHT = Butylated hydroxytoluene

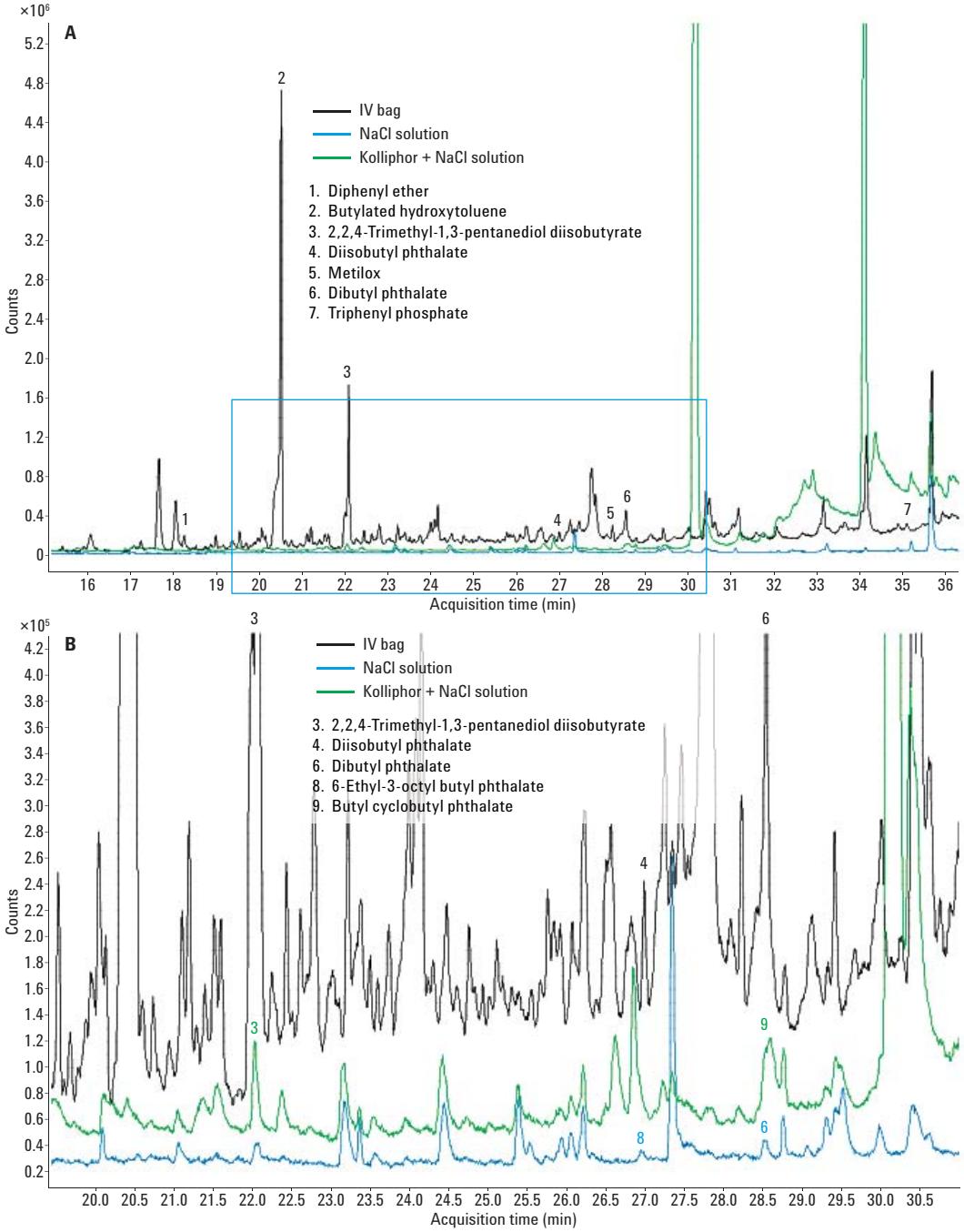

Figure 7. Extractables/Leachables analysis of NaCl and Kolliphor-NaCl IV bags by DCM extraction using MMI GC/MS. Extractables identified in 1-L IV bag (A) with box region enlarged in (B). Leachables identified in NaCl (blue), and Kolliphor-NaCl (green) solutions (B).

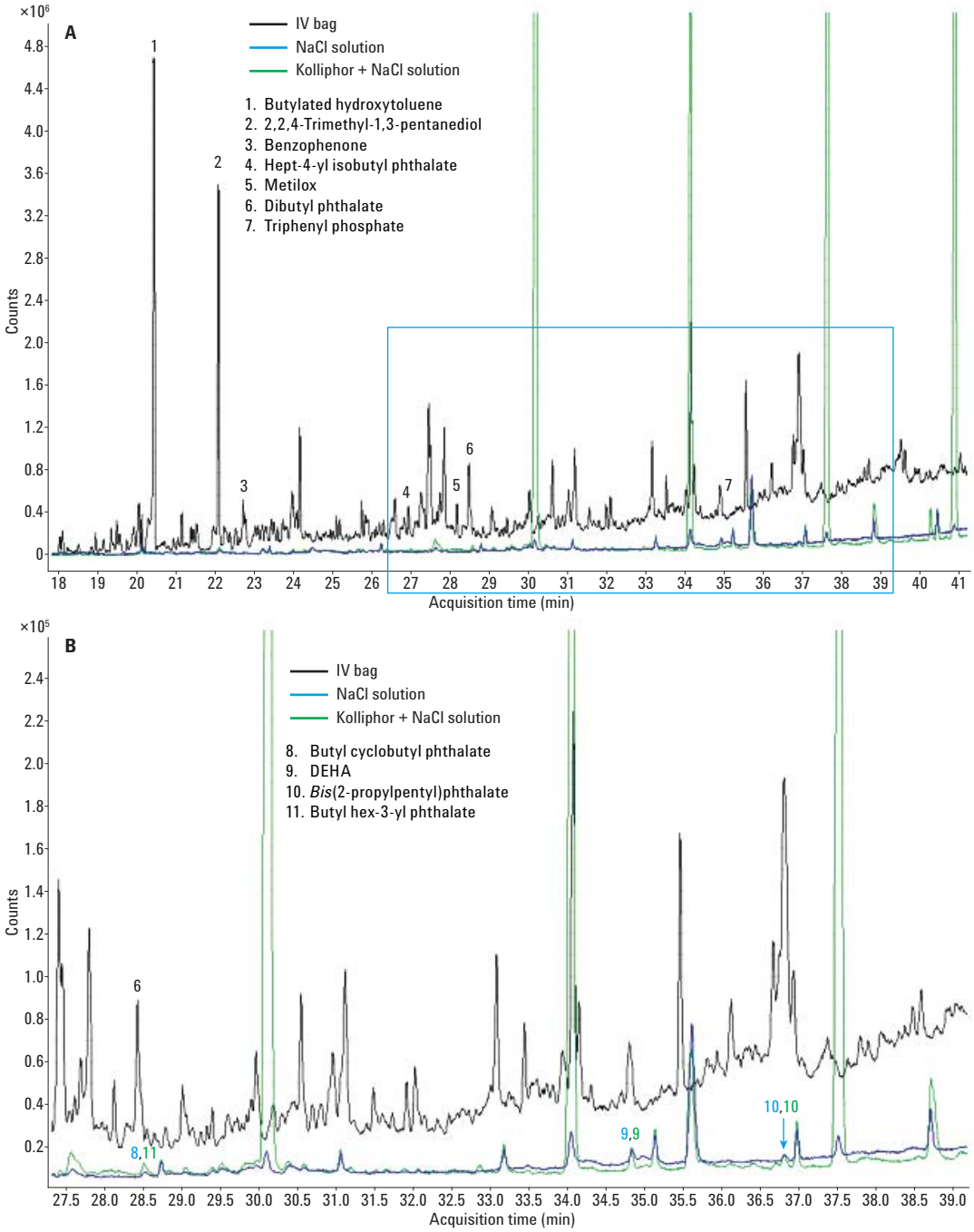

Figure 8. Extractables/Leachables analysis of NaCl and Kolliphor-NaCl IV bags by hexane extraction using MMI GC/MS. Extractables identified in 1-L IV bag (A) with boxed region enlarged in (B). Leachables identified in NaCl and Kolliphor-NaCl solutions (B).

Headspace GC/MS and MMI GC/MS allowed for the comprehensive analysis of plasticizers in IV bag sets used in this investigation. For example, benzothiazole was only identified using headspace GC/MS, while benzophenone, palmitic acid, and Irgafos 168 were only characterized using MMI GC/MS in 150-mL IV bag. Triphenyl phosphate is a plasticizer [15] that was only identified using MMI GC/MS in 1-L IV bag.

The limit of detection, or how low to go, is one of the biggest topics in extractables and leachables analysis. PQRI has provided definitions to help identify the limit of quantification. The Safety Concern Threshold (SCT) of below 0.15 µg/day has been defined as the leachables threshold that would present negligible safety concerns from possible carcinogenic to noncarcinogenic toxic effects. The Analytical Evaluation Threshold (AET), which is based on SCT, states that any leachable and/or extractables identified at or above 5.0 µg/day should be reported for potential toxicological assessment. The manufacturer states that IV bags and tubing are DEHP-free, latex-free, and PVC-free. DEHP was not identified in 1-L IV bag, but an alternative phthalate plasticizer could have been used instead. DEHP was still identified in the dextrose IV bag set, which suggests that the DEHP levels would be below the SCT level of 0.15 µg/day.

This work was largely qualitative. Future studies will look at quantifying leachables. This can be challenging since pure standards may be difficult to find. One potential approach is to use three or four available compounds of similar structure to the compounds under investigation and average the response factors of the standards and apply this to the unknowns.

Conclusion

Headspace GC/MS in combination with MMI GC/MS analysis offers a comprehensive identification of compounds migrating from the pharmaceutical packaging to its drug product. The headspace sampler simplifies preparation for the extractables analysis of packaging material, while the large volume injection capabilities of the MMI allows for the identification of low level leachables. The two GC/MSD systems used in this application note will assist the user to identify plasticizers and other extractable/leachable compounds potentially present in plastic IV bag sets including those labeled DEHP-free.

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