Analysis of Extractable/Leachable Compounds from Generic Liquid Drug Formulations Using GC/MSD Systems

Application Note

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Abstract

Pharmaceutical liquid formulations are commonly stored in plastic containers at all risk categories. A pharmaceutical suspension was used as model for investigating compound migration from packaging material. Two Agilent 5977A Series GC/MSD Systems were used. Fatty acid plasticizers were identified using the 7697A Headspace Sampler and a 7890A GC coupled with a 5977A MSD. Phthalate plasticizers were found using the MMI 7890A GC coupled with a 5977A MSD. Single ion monitoring (SIM) confirmed the identification of these plasticizers.

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Introduction

Pharmaceutical liquid products are stored in a variety of packaging materials ranging from low to high risk categories. Liquid drug products represent a broad range of dosage forms (aerosols, solution, suspensions, ointments, gels, and sprays). Drug products in liquid form have a significant potential of leaching compounds from the packaging material due to the close contact. The U.S. Food and Drug Administration (FDA) has ranked liquid drug formulations in several risk categories depending on the route of administration and the likelihood of interaction between the drug product and the packaging material (Table 1). Inhalation and injection solutions are recognized as the highest risk because the drug product is in contact with multiple/complex components in the medical device with immediate drug delivery. For instance, a prefilled syringe contains drug suspension that is in contact with the rubber plunger, plastic barrel, and the metal needle with direct injection into the bloodstream.

Guidance and assessments have been provided for the analysis of extractables and leachables testing in medical devices. The FDA 21 CFR 211.94(a) states that "Drug product containers and closure shall not be reactive, additive, or absorptive so as to later the safety, identity, strength, quality, or purity of the drug beyond the official or established requirements". The Product Quality Research Institute (PQRI) has developed regulatory guidance in the area of extractables and leachables, which is also recognized by the FDA. Guidance is also provided in USP<87>, USP<88>, USP<661>, EP 3.1, EP 3.2, ISO10993, and ICHQ6A for the evaluation of materials for drug packaging. USP<1663> and USP<1664> provide framework and assessments of extractables and leachables associated with pharmaceutical packaging/delivery systems, respectively. These assessments do not establish criteria or specific guidelines, only information and discussion on analysis of particular delivery systems.

Extractables and leachables studies using gas chromatography-mass spectrometry (GC/MS) are designed to detect volatile and some semivolatile compounds from medical devices and closure systems. The sources of extractables are raw materials, additives, stabilizers, accelerants, and breakdown/degradation products that provide protective and physical properties to packaging material. Extractables testing involves exposing the packaging component to appropriate solvent, high temperatures, or an extended period of time to simulate a leachable profile in the worst-case scenario. Leachables studies are conducted on the actual drug product under normal usage or accelerated storage conditions. Leachable compounds are typically a subset of extractables because of the direct contact with the packaging material. New leachables may also form from the interaction between the drug product and the packaging material.

Table 1. Risk Associated with Various Pack Types Based on the Degree of Concern Based on Route and the Likelihood of Interaction with the Drug Product

Degree of concern associated with route of administration	**Likelihood of interaction between packaging component and dosage form**		
	High	**Medium**	**Low**
Highest	Inhalation aerosols and solution Injections and injectable suspensions	Sterile powders Injection powders Inhalation powders	
High	Ophthalmic solutions and suspensions Transdermal ointments and patches Nasal aerosols and sprays		
Low	Topical solutions and suspensions Topical and lingual aerosols Oral solutions and suspensions	Topical powders Oral powders	Oral tablets Oral hard capsules Oral soft gelatin capsules

Adapted from Guidance for Industry; Container Closure Systems for Packaging Human Drug and Biologics, US Department of Health and Human Services, Food and Drug Administration, Rockville, MD, May 1999.

In this application note, a pharmaceutical liquid formulation was investigated for leachable compounds using the complementation of two GC/MS systems. Volatile and semivolatile organic compounds were identified using high temperature headspace sampling and large volume liquid injection techniques. Leachable compounds were chosen for further investigation based on toxicological information on extractables, peak intensity, migration potential, and polymer functional additives. Single ion monitoring (SIM) was used to further confirm the identification of leachable compounds.

Experimental

Materials and instrumentation

Two types of analysis were performed for the identification of leachable compounds in aqueous drug formulation. Components in the drug suspension were analyzed at high temperatures using the 7697A Headspace Sampler and a 7890A GC coupled with a 5977A MSD (Headspace GC/MS). Solvent extracts of drug components were analyzed using the 7693A Automatic Liquid Sampler and a 7890A GC coupled with a 5977A MSD (ALS GC/MS). The ALS GC/MS is equipped with a multimode inlet (MMI) operated in solvent vent mode. The liquid drug formulation used in this work was acquired from a generic pharmaceutical company for extractables and leachables testing. Dichloromethane (DCM) (650463) was purchased from Sigma-Aldrich.

Headspace GC/MS analysis

The drug suspension was centrifuged at 3,000 rpm for 20 minutes. Solid and supernatant (liquid) components were transferred into separate 10-mL headspace vials and allowed to concentrate by evaporation at room temperature. Both components were purged with nitrogen and sealed with a high-performance PTFE crimp cap before investigation at headspace equilibration temperature of 250 °C (Table 2).

Table 2. Instrument Parameters for Headspace GC/MS Analysis

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	250 °C
HS loop temperature	250 °C
HS transfer line temperature	270 °C
Vial equilibration time	25 minutes, level 2 shake
GC run time	64 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	280 °C
Inlet flow	Constant flow, 1.3 mL/min
Split ratio	8:1
Carrier gas	Helium
Oven program	35 °C (3 min) to 280 °C (3 min) at 8 °C/min
Columns	Agilent J&W HP-5ms UI, 30 m × 0.25 mm, 0.5 µm (p/n 19091S-133UI)
MSD	**Agilent 5977A**
Transfer line	280 °C
MS source	280 °C
MS quad	180 °C
Tune	atune.u
Scan	15 to 600 amu, 2.5 scans/sec
Threshold	0
Gain factor	1.0
Software	Agilent MassHunter B.07.01

ALS GC/MS analysis

Five microliters of drug suspension were extracted with 5.0 mL of DCM by sonication for 5–8 hours in a 12-mL amber vial and allowed to sit for 24 hours. The organic layer was transferred to a glass insert inside an autosampler vial for analysis. Ten microliters of extract was injected using the MMI operated in solvent vent mode. The solvent elimination wizard was used to develop starting MMI parameters specific to the analysis of DCM extracts (Table 3).

Table 3. Instrument Parameters for Analysis Using the ALS GC/MS

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	2 mm id ultra inert, dimpled (p/n 5190-4006)
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 J&W HP-5ms UI, 30m × 250 µm, 0.25 µm (p/n 19091S-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/sec
Threshold	150
Gain factor	1.0
Software	Agilent MassHunter B.07.00

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

Compound identification

Compounds were characterized using the 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. Compounds with a mass spectral match of ≥ 80 were considered, and the top match was used in the investigation.

Results and Discussion

The focus of this investigation centered on studying the migration of additives with characteristics of a high-density polyethylene (HDPE) or polypropylene (PP) packaging material. The drug suspension was analyzed for Irganox 1010, Irgafos 168, palmitic acid, stearic acid, butylated hydroxy-toluene (BHT), hexadecane, and 2,4-di-*tert*-butylphenol. Irganox 1010, BHT, Irgafos 168, and 2,4-di-*tert*-butyphenol are antioxidants added to HDPE to provide protection during processing and stability from long term heating (molding) [1]. Stearic acid and palmitic acid provide mechanical properties to HDPE or PP [2,3], while hexadecane is a solvent used in the production of ink for printing [4]. Stearic acid, palmitic acid, and hexadecane were identified in this investigation. Irganox 1010 would be more suitable for analysis by LC/MS due to its high molecular weight. BHT, Irgafos 168, and 2,4-di-*tert*-butylphenol were not observed in the drug suspension, however these additives were identified in extractable studies of plastic materials using the same procedures. Several other additives in HDPE material [5] were identified in this investigation.

Plasticizers, flavor, fragrance, pharmaceutical compounds, and their precursors were identified in the liquid drug formulation using GC/MS analysis by headspace and large volume liquid injection. A summary of all compounds identified using both GC/MS systems are listed in Table 4. Pharmaceutical, flavor, and fragrance compounds are common ingredients in drug products. Plasticizers were further pursued in this investigation since these compounds are highly related to leachables migration from the packaging material.

Table 4. Compounds Detected in Drug Suspension Using Headspace and ALS GC/MS

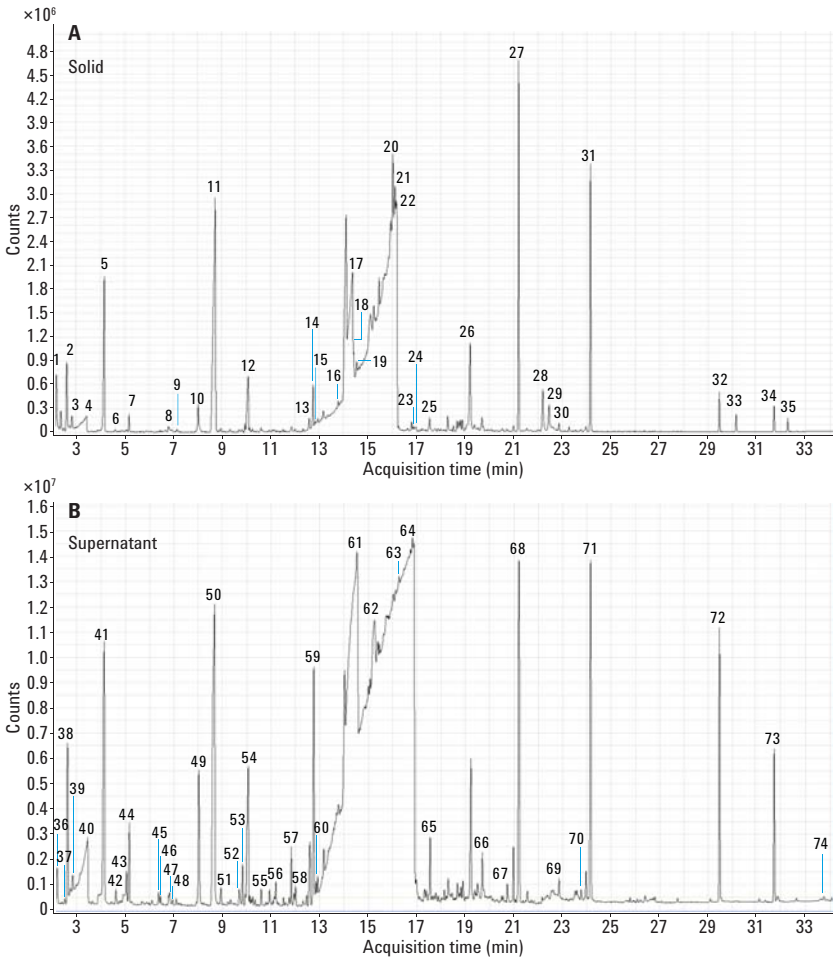
Compound	GC/MS	Common uses
(R)-(+)-1-Benzylglycerol	HS (S)	
1,2,3-Propanetriol, 1-acetate	ALS and HS	
1,2-Benzenediol, O-(2-furoyl)-O'-(pentafluoropropionyl)-	ALS	
1,2-Cyclopentanedione, 3-methyl-	HS (S)	
1,2-Epoxy-3-propyl acetate	HS (L)	
1,2-Ethanediamine, N,N'-dimethyl-N,N'-bis(phenylmethyl)-	ALS	
1-Dodecanamine, N,N-dimethyl-	ALS	
1-Dodecanol	ALS and HS (L)	Plasticizer
1-Dodecene	ALS	
1-Hexadecanol	HS (L)	
1-Hydroxy-2-butanone	HS (L)	Flavor
1-Tetradecanamine, N,N-dimethyl-	ALS and HS	Plasticizer
1-Tridecanamine, N,N-dimethyl-	HS (L)	
1-Undecanamine, N,N-dimethyl-	ALS	
2(3H)-Furanone, 3-acetyldihydro-3-methyl-	HS (S)	
2-(4-Aminophenyl)-4,6-diphenylpyrimidine	ALS	
2,3-Butanedione	HS	Flavor
2,3-Hexanedione	HS (L)	Flavor
2,3-Pentanedione	HS	Flavor or fragrance
2,4,7,9-Tetramethyl-5-decyn-4,7-diol	ALS	Plasticizer
2,5-Furandione, 3,4-dimethyl-	HS (S)	
2,5-Furandione, 3-methyl-	ALS	
2,5-Furandione, dihydro-3-methylene-	ALS	
2-Cyclopenten-1-one, 2-methyl-	HS (L)	
2-Cyclopenten-1-one, 3,4-dimethyl-	HS (L)	Flavor or fragrance
2-Cyclopenten-1-one, 3-ethyl-2-hydroxy-	HS (S)	Fragrance
2-Cyclopenten-1-one, 3-methyl-	HS (L)	Flavor or fragrance
2-Dodecene, (Z)-	ALS	Fragrance
2-Furanmethanol	HS	Plasticizer
2-Furanmethanol, acetate	HS (L)	Flavor or fragrance
2-Furanmethanol, tetrahydro-	HS (S)	Plasticizer
2-Furanone, 2,5-dihydro-3,5-dimethyl	HS (L)	Flavor or fragrance
2-Propanone, 1-(acetyloxy)-	HS (L)	
2-Propanone, 1-hydroxy-	HS	Plasticizer
2-Propen-1-ol	HS	Precursor to plasticizer
3-(N-Benzyl-N-methylamino)-1,2-propanediol	HS	
3-Chloropropionic acid, tetradecyl ester	ALS	
Acetic acid	HS	Monomer
Acetoin	HS (L)	Flavor or fragrance
Adipate, di(2-ethylhexyl)	ALS	Plasticizer
Benzamphetamine	ALS	
Benzenemethanamine, N,N-dimethyl-	ALS and HS (L)	Catalyst
Benzoic acid	ALS	Plasticizer
Benzyl alcohol	ALS and HS	Precursor to plasticizer

Compound	GC/MS	Common uses
Benzyl chloride	ALS	Precursor to plasticizer
Butyrolactone	HS	Solvent for flavor or plasticizer
Catechol	HS	Precursor to flavor or fragrance
Dodecanal	HS	Fragrance
Dodecane, 1-chloro-	ALS	
Estradiol	ALS	Pharmaceutical
Formic acid, ethenyl ester	HS (S)	Flavor or fragrance
Furan, 2,2'-methylenebis-	HS (S)	Flavor or fragrance
Furan, 2,3-dihydro-	HS (L)	
Furan, 2-methyl-	HS	Flavor or fragrance
Furfural	HS (S)	Solvent
Glycerin	HS	Pharmaceutical
Glycerol 1,2-diacetate	HS	Flavor or fragrance
Hexadecanal	HS (S)	
Hexadecane	ALS	Plasticizer
Maltol	HS (S)	Flavor or fragrance
N-Methyl-N-benzyltetradecanamine	ALS and HS (L)	
Nonanal	ALS	
Nonanoic acid	ALS	Flavor or fragrance
Octanoic acid	ALS	Fragrance or plasticizer
Oxiranemethanol, (R)-	HS (S)	
Oxiranemethanol, (S)-	HS (L)	
Palmitic acid	ALS	Plasticizer
Palmitic acid, butyl ester	HS (S)	Plasticizer
Phenol, 2,2'-methylenebis[6-(1,1-dimethylethyl)-4-ethyl-	HS (L)	Plasticizer
Phenol, 4-propoxy-	HS (L)	
Phthalate, di(2-propylpentyl)	ALS	Plasticizer
Propanal	HS	Plasticizer
Stearic acid	ALS	Plasticizer
Stearic acid, 2-methylpropyl ester	HS (S)	Plasticizer
Tetradecanal	HS (L)	
Tetrahydrofurfuryl chloride	HS (L)	
Tetrahydropyran Z-10-dodecenoate	HS (S)	
Toluene	HS (L)	Plasticizer

L = liquid supernatant only; S = solid component only; HS = Headspace (both components); ALS = Automatic liquid sampler

Plasticizers identified using high temperature headspace analysis were 2-furanmethanol (flexibility), 1-hydroxy-2-propanone (sealant and coating), tetrahydro-2-furanmethanol (flexibility), butyl ester palmitic acid (resin), 2-methylpropyl ester stearic acid (resin), 2,2'-methylenebis[6-(1,1-dimethylethyl)-4-ethyl-phenol] (antioxidant), 1-dodecanol (coating), and N,N-dimethyl-1-tetradecanamine (detergent) (Figure 1, Table 5) [6-13].

SIM analysis confirmed the identification of butyl ester palmitic acid and 2-methylpropyl ester stearic acid (Figure 2). Palmitic acid and stearic acid are also possible leachable plasticizers [14] since they exhibit similar ions, peak intensity, and retention time as butyl ester palmitic acid and 2-methylpropyl ester stearic acid, respectively.



1,36.	2-Propen-1-ol
2, 38.	2,3-Butanedione
3, 39.	Furan, 2-methyl-
4,40.	Acetic acid
5, 41.	2-Propanone, 1-hydroxy-
6, 42.	2,3-Pentanedione
7.	Oxiranemethanol, (R)-
8, 47.	Propanal
9.	Formic acid, ethenyl ester
10.	Furfural
11, 50.	2-Furanmethanol
12, 54.	Butyrolactone
13.	1,2-Cyclopentanedione, 3-methyl-
14, 59.	Benzyl alcohol
15.	2,5-Furandione, 3,4-dimethyl-
16.	Furan, 2,2'-methylenebis-
17, 23, 64.	1,2,3-Propanetriol, 1-acetate
18.	Maltol
19.	2-Cyclopenten-1-one, 3-ethyl-2-hydroxy-
20.	Tetrahydropyran Z-10-dodecenoate
21, 63.	Catechol
22, 61.	Glycerin
24, 62.	Glycerol 1,2-diacetate
25.	2(3H)-Furanone, 3-acetyldihydro-3-methyl-
26, 66.	Dodecanal
27, 31, 71.	1-Tetradecanamine, N,N-dimethyl-
28.	(R)-(+)-1-Benzylglycerol
29.	2-Furanmethanol, tetrahydro-
30.	Hexadecanal
32, 34, 72.	3-(N-Benzyl-N-methylamino)-1,2-propanediol
33.	Palmitic acid, butyl ester
35.	Stearic acid, 2-methylpropyl ester
37.	Furan, 2,3-dihydro-
43.	Acetoin
44.	Oxiranemethanol, (S)-
45.	Toluene
46.	1-Hydroxy-2-butanone
48.	2,3-Hexanedione
49.	Tetrahydrofurfuryl chloride
51.	2-Propanone, 1-(acetyloxy)-
52.	1,2-Epoxy-3-propyl acetate
53.	2-Cyclopenten-1-one, 2-methyl-
55.	2-Cyclopenten-1-one, 3,4-dimethyl-
56.	2-Cyclopenten-1-one, 3-methyl-
57.	2-Furanmethanol, acetate
58.	2-Furanone, 2,5-dihydro-3,5-dimethyl
60.	Benzenemethanamine, N,N-dimethyl-
65.	Phenol, 4-propoxy-
67.	1-Dodecanol
68.	1-Tridecanamine, N,N-dimethyl-
69.	Tetradecanal
70.	1-Hexadecanol
73.	N-Methyl-N-benzyltetradecanamine
74.	Phenol, 2,2'-methylenebis[6-(1,1-dimethylethyl)-4-ethyl-

Figure 1. Headspace GC/MS analysis of solid (A) and liquid (B) components in drug suspension.

Table 5. Compounds Identified in Drug Suspension Using Headspace GC/MS

RT (min)	Solid	RT (min)	Supernatant
2.17	2-Propen-1-ol	2.20	2-Propen-1-ol
2.62	2,3-Butanedione	2.51	Furan, 2,3-dihydro-
2.84	Furan, 2-methyl-	2.62	2,3-Butanedione
3.43	Acetic acid	2.84	Furan, 2-methyl-
3.92	2-Propanone, 1-hydroxy-	3.45	Acetic acid
4.62	2,3-Pentanedione	3.89	2-Propanone, 1-hydroxy-
5.19	Oxiranemethanol, (R)-	4.62	2,3-Pentanedione
6.80	Propanal	5.06	Acetoin
7.15	Formic acid, ethenyl ester	5.17	Oxiranemethanol, (S)-
8.03	Furfural	6.38	Toluene
8.67	2-Furanmethanol	6.45	1-Hydroxy-2-butanone
10.08	Butyrolactone	6.79	Propanal
12.59	1,2-Cyclopentanedione, 3-methyl-	6.82	2,3-Hexanedione
12.75	Benzyl alcohol	7.99	Tetrahydrofurfuryl chloride
12.84	2,5-Furandione, 3,4-dimethyl-	8.65	2-Furanmethanol
13.79	Furan, 2,2'-methylenebis-	8.93	2-Propanone, 1-(acetyloxy)-
14.37-16.81	1,2,3-Propanetriol, 1-acetate	9.69	1,2-Epoxy-3-propyl acetate
14.42	Maltol	9.83	2-Cyclopenten-1-one, 2-methyl-
14.54	2-Cyclopenten-1-one, 3-ethyl-2-hydroxy-	10.06	Butyrolactone
16.04	Tetrahydropyran Z-10-dodecenoate	10.60	2-Cyclopenten-1-one, 3,4-dimethyl-
16.12	Catechol	11.20	2-Cyclopenten-1-one, 3-methyl-
16.20	Glycerin	11.83	2-Furanmethanol, acetate
16.87	Glycerol 1,2-diacetate	12.01	2-Furanone, 2,5-dihydro-3,5-dimethyl
17.54	2(3H)-Furanone, 3-acetyldihydro-3-methyl-	12.76	Benzyl alcohol
19.70	Dodecanal	12.92	Benzenemethanamine, N,N-dimethyl-
21.21-24.16	1-Tetradecanamine, N,N-dimethyl-	14.51	Glycerin
22.16	(R)-(+)-1-Benzylglycerol	15.26	Glycerol 1,2-diacetate
22.46	2-Furanmethanol, tetrahydro-	16.24	Catechol
22.86	Hexadecanal	16.82	1,2,3-Propanetriol, 1-acetate
29.45-31.75	3-(N-Benzyl-N-methylamino)-1,2-propanediol	17.56	Phenol, 4-propoxy-
30.15	Palmitic acid, butyl ester	19.70	Dodecanal
32.30	Stearic acid, 2-methylpropyl ester	20.73	1-Dodecanol
		21.20	1-Tridecanamine, N,N-dimethyl-
		22.86	Tetradecanal
		23.77	1-Hexadecanol
		24.16	1-Tetradecanamine, N,N-dimethyl-
		29.46	3-(N-Benzyl-N-methylamino)-1,2-propanediol
		31.75	N-Methyl-N-benzyltetradecanamine
		33.75	Phenol, 2,2'-methylenebis[6-(1,1-dimethylethyl)-4-ethyl-

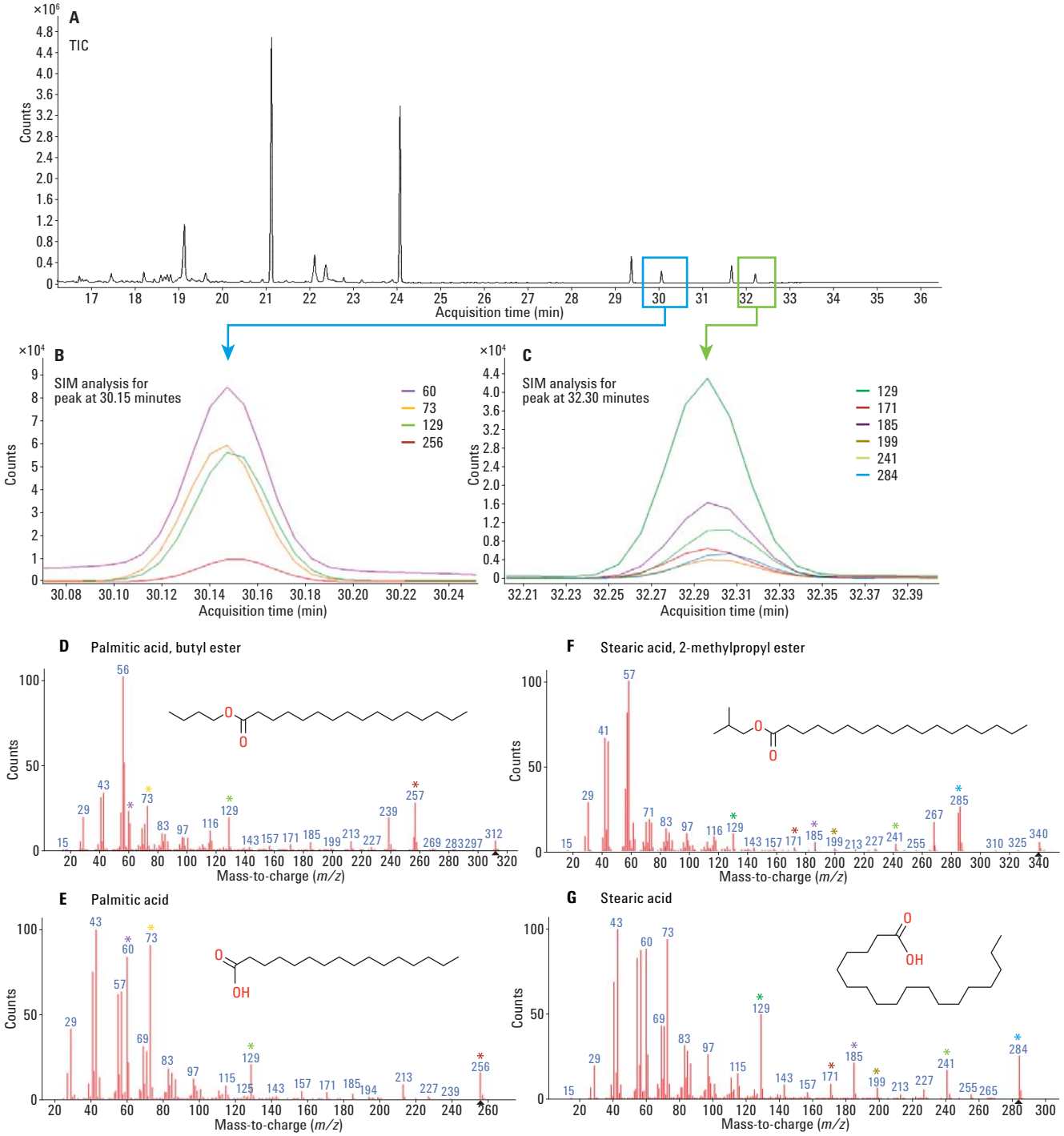
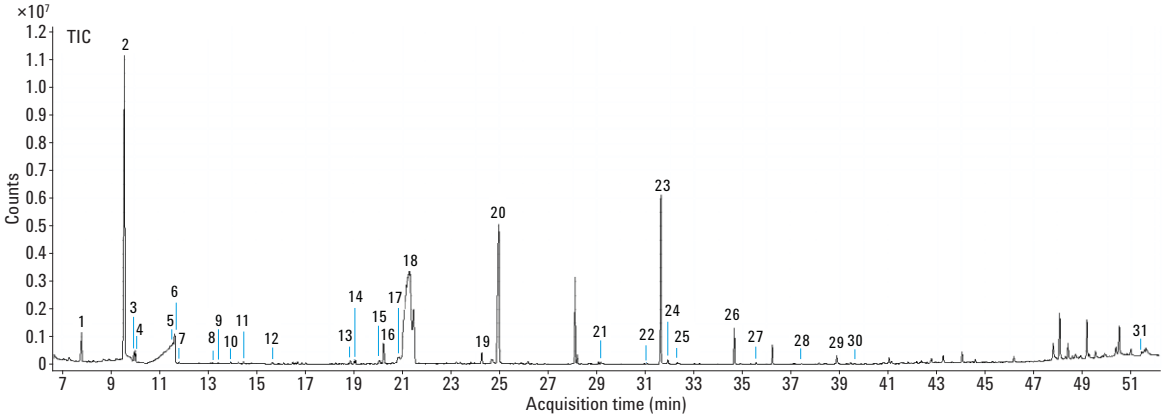


Figure 2. SIM analysis of plasticizers identified using headspace GC/MS. TIC of drug suspension (A) with SIM of butyl ester palmitic acid analyzed at 30.15 minutes (B) and 2-methylpropyl ester stearic acid analyzed at 32.30 minutes (C). Reference mass spectra for butyl ester palmitic acid (D), palmitic acid (E), 2-methylpropyl ester stearic acid (F), and stearic acid (G) were obtained from the NIST MS Search 2.2. (*) represents ions used for SIM analysis and color-coded to match EIC.

Flavor compound, 2,3-butanedione, was the only compound identified in the drug suspension using the full evaporation headspace sampling technique at 85 and 100 °C. Therefore, the drug solution was separated into solid and liquid components to aid with separation and compound identification. Glycerin shows poor chromatographic performance, with a broad peak from 13 to 17 minutes.

Plasticizers that were identified using ALS GC/MS were 2,4,7,9-Tetramethyl-5-decyn-4,7-diol (adhesives), hexadecane, di(2-ethylhexyl) adipate (DEHA), *n*-palmitic acid, stearic acid, di(2-propylpentyl) phthalate (DPPP), octanoic acid, 1-dodecanol, and N,N-dimethyl-1-tetradecanamine (Figure 3, Table 6) [15-19].



1. 2,5-Furandione, 3-methyl-
2. Benzyl chloride
3. 2,5-Furandione, dihydro-3-methylene-
4. Benzyl alcohol
5. 1,2,3-Propanetriol, 1-acetate
6. Benzenemethanamine, N,N-dimethyl-
7. Nonanal
8. Benzoic acid
9. Octanoic acid
10. 1-Dodecene
11. 2-Dodecene, (Z)-
12. Nonanoic acid
13. 2,4,7,9-Tetramethyl-5-decyn-4,7-diol
14. 1-Dodecanol
15. 1,2-Benzenediol, O-(2-furoyl)-O'-(pentafluoropropionyl)-
16. Dodecane, 1-chloro-
17. 1-Undecanamine, N,N-dimethyl-
18. 1-Dodecanamine, N,N-dimethyl-
19. Dodecane, 1-chloro-
20. 1-Tetradecanamine, N,N-dimethyl-
21. *n*-Palmitic acid
22. Benzamphetamine
23. 1,2-Ethanediamine, N,N'-dimethyl-N,N'-bis(phenylmethyl)-
24. 3-Chloropropionic acid, tetradecyl ester
25. Stearic acid
26. N-Methyl-N-benzyltetradecanamine
27. di(2-ethylhexyl) adipate
28. di(2-propylpentyl) phthalate
29. Estradiol
30. Hexadecane
31. 2-(4-Aminophenyl)-4,6-diphenylpyrimidine

Figure 3. Leachable analysis of drug suspension using ALS GC/MS.

Table 6. Compounds Identified in Drug Suspension Using ALS GC/MS Analysis

RT (min)	Compound
7.81	2,5-Furandione, 3-methyl-
9.58	Benzyl chloride
9.97	2,5-Furandione, dihydro-3-methylene-
10.02	Benzyl alcohol
11.57	1,2,3-Propanetriol, 1-acetate
11.63	Benzenemethanamine, N,N-dimethyl-
11.81	Nonanal
13.21	Benzoic acid
13.43	Octanoic acid
13.94	1-Dodecene
14.47	2-Dodecene, (Z)-
15.67	Nonanoic acid
18.87	2,4,7,9-Tetramethyl-5-decyn-4,7-diol
19.08	1-Dodecanol
20.09	1,2-Benzenediol, O-(2-furoyl)-O'-(pentafluoropropionyl)-
20.23, 24.27	Dodecane, 1-chloro-
20.88	1-Undecanamine, N,N-dimethyl-
21.30	1-Dodecanamine, N,N-dimethyl-
24.95	1-Tetradecanamine, N,N-dimethyl-
29.18	*n*-Palmitic acid
31.07	Benzamphetamine
31.64	1,2-Ethanediamine, N,N'-dimethyl-N,N'-*bis*(phenylmethyl)-
31.93	3-Chloropropionic acid, tetradecyl ester
32.32	Stearic acid
34.67	N-Methyl-N-benzyltetradecanamine
35.57	Di(2-ethylhexyl) adipate
37.43	Di(2-propylpentyl) phthalate
38.89	Estradiol
39.60	Hexadecane
51.46	2-(4-Aminophenyl)-4,6-diphenylpyrimidine

SIM analysis confirmed the identification of DEHA and DPPP (Figure 4). DPPP exhibit similar MS fragmentation patterns as DEHP. However, the intensities of ions 113 and 279 acquired with the SIM analysis closely matched the reference MS of DPPP. High-resolution mass spectrometry analysis is necessary to further distinguish the presence of DPPP or DEHP.

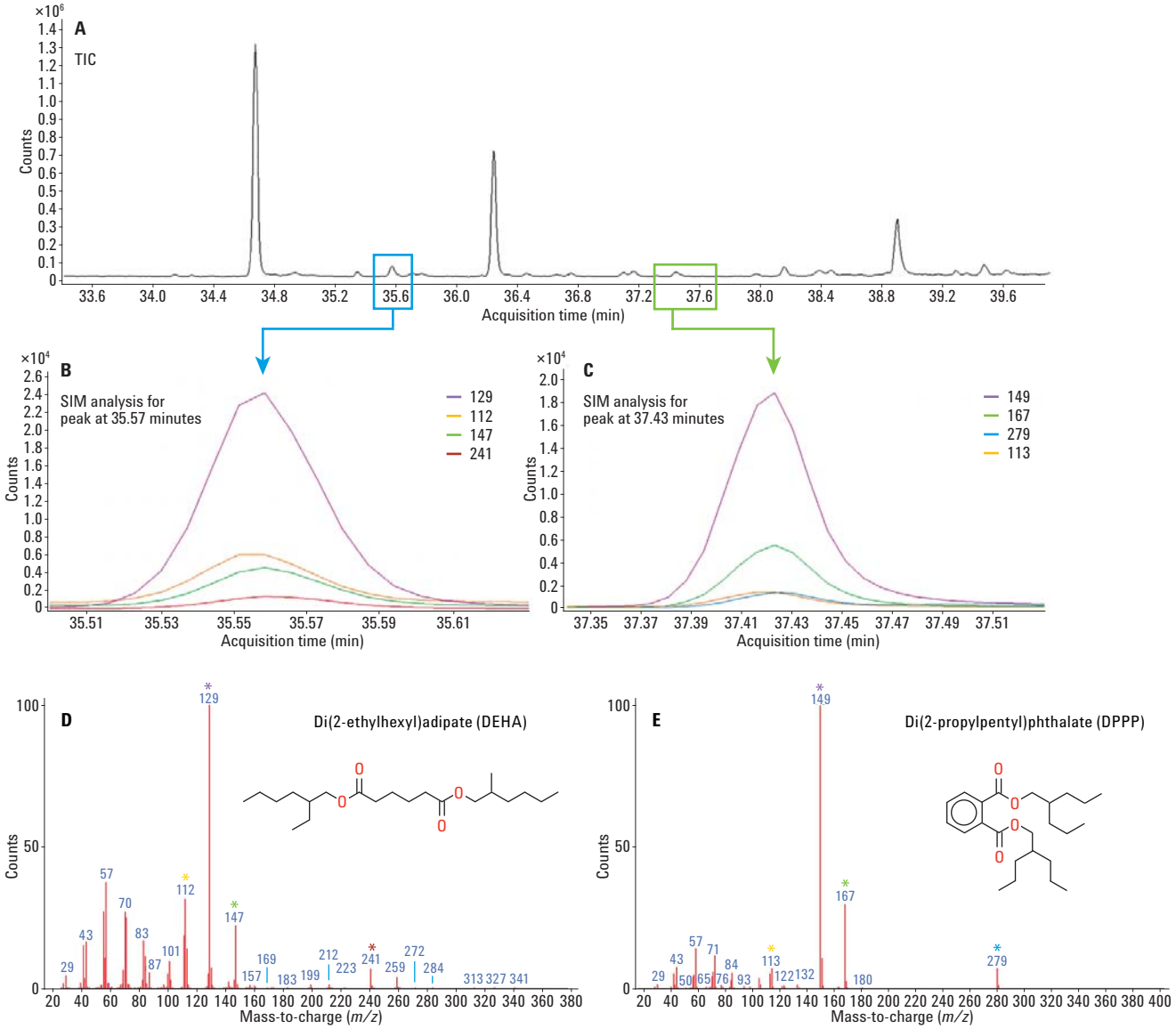


Figure 4. SIM of plasticizers identified using ALS GC/MS in drug suspension (A). SIM data were collected for DEHA at 35.57 minutes (B) and DPPP at 37.43 minutes (C). Reference MS of DEHA (D) and DPPP (E) were obtained from the NIST MS Search 2.2. (*) ions used for SIM anlaysis and color coded to match EIC.

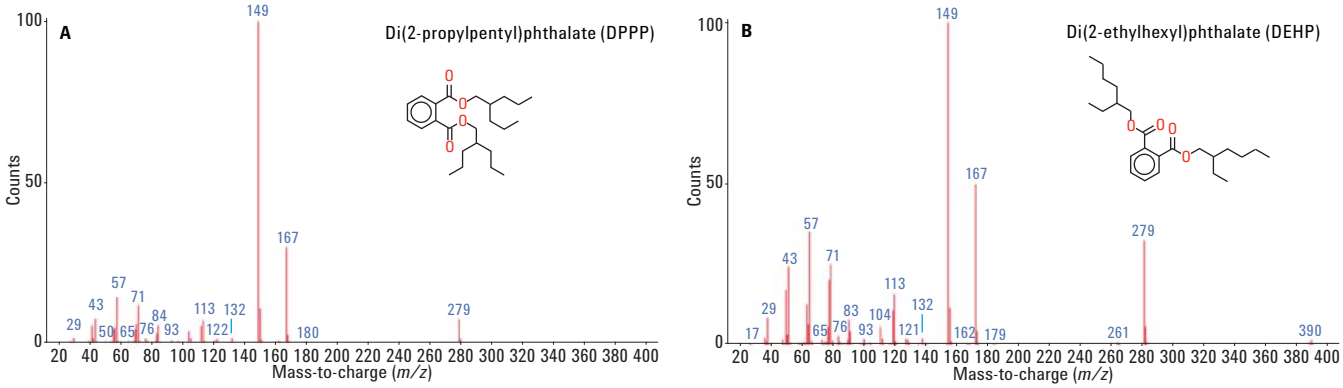


Figure 5. Reference MS of DPPP and DEHP for intensity comparison of SIM ions.

Conclusion

The complementation of headspace sampling and large volume liquid injection techniques allows for the broad identification of leachable plasticizers in pharmaceutical formulations. Fatty acid plasticizers were identified using headspace GC/MS. Phthalate plasticizers were characterized using solvent extraction with ALS GC/MS analysis. A two pronged approach using high temperature headspace and liquid sampling techniques can be used to obtain a significant amount of information regarding leachables and extractables. These analytical methods are applicable to analyzing liquid drug products in all risk categories

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