Analysis of Extractable Compounds from a Pressurized Metered-Dose Inhaler (pMDI) Using GC/MSD Systems

Application Note

Pharmaceuticals

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Abstract

A pressurized metered-dose inhaler (pMDI) is an inhalation device developed for the direct delivery of active pharmaceutical ingredient (API) to the respiratory tract for the treatment of respiratory conditions. Rubber and plastic components in the pMDI are potential sources of extractables by the API/propellant. Therefore, volatile and semivolatile extractable compounds were investigated in these components using two 5977 GC/MSD systems. This application note focuses on identifying extractables in the pMDI using the complementation of headspace GC/MS and MMI GC/MS.

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Introduction

A regulatory expectation for drug manufacturers is to perform a safety risk assessment for the presence of potential leachable and extractable compounds in medical devices that may occur during the manufacturing process. Extractables are chemical compounds that can be extracted from a pharmaceutical packaging component using high temperatures to obtain a leachable profile at the worst case scenario or solvent extraction to mimic similar properties of the drug product. Leachables are chemical compounds from the packaging material that have leached into the drug product. Leachables are often a subset of extractables and new compounds may form due to the packaging-drug interaction. Compound migration involves correlating extractables to leachables. Extractables determine potential compound migration, while leachables determine actual compound migration. If leachables are identified, it is necessary to consult with the United States Food and Drug Administration (FDA) and toxicological safety guidelines for the acceptable amount. Sources of leachable/extractable compounds include plastic and elastomeric components, inks and adhesives from labeling, residual impurities from manufacturing, and degradation products from processing, storage, and sterilization [1,2].

Industry guidelines and working groups provide the basis for the analysis of extractables/leachables testing in drug delivery and medical devices. The Product Quality Research Institute (PQRI) is a leading working group established to develop regulatory guidance for extractables/leachables analysis. PQRI is recognized by the FDA and has released a recommendation document that includes safety thresholds for orally inhaled and nasal drug products (OINDP). Several other guidelines and assessments on extractable and leachable testing exist, including chapters from USP<661>, USP<1663>, USP<1664>, USP<1665>, and regulations from international organizations EP 3.2.2.1 and EP 3.2.8. The intent of this application note is not to provide safety impact or toxicological information. Recent articles by Dennis Jenke [3], PQRI working group [4,5], and the Extractable Leachable Safety Information Exchange (ELSIE) group address these issues [6].

A pressurized metered-dose inhaler (pMDI) is a pharmaceutical construct in the high risk category (Table 1). Inhalation aerosols/solutions have the highest degree of concern based on the route of administration [7]. The pMDI administers a precise amount of medication directly to the lungs in the form of a short burst of aerosolized drug suspension self-administered through inhalation for treating asthma and respiratory diseases [8].

Table 1. Risk Associated with Various Pack Types

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.

Elastomeric, plastic, and metal components of the pMDI are capable of leaching compounds into the API formulation due to the close contact. Components that have the highest likelihood of interaction with the API/propellant include: canister (metal), retaining cup (plastic), two gaskets (rubber), metering valve (plastic), o-ring (rubber), valve stem (plastic), spring (metal), and actuator nozzle (plastic) (Figure 1A). The API formulation is stored in the canister where the retaining cup fills with the precise dosage under gravity. When the canister is pressed, the metering valve delivers an accurate dose of medication through the stem to the actuator nozzle. The rubber components (gaskets and o-ring) are placed snugly around the stem to prevent leakage of API formulation when the valve is in the closed position. The mouthpiece directs the API formulation (Figure 1B).

Elastomeric components in the pMDI are considered the major source of extractables. Rubber seals can swell because of solubility with the propellant. Heptafluoroalkane (HFA) propellants have been identified as suitable alternatives to the traditional chlorofluorocarbon (CFC) propellants that have been implicated in stratospheric ozone depletion. HPA propellant is not soluble with surfactants that are necessary to create an API formulation. Thus, surfactant and ethanol (cosolvent) are commonly used in conjunction to increase solubility. However, ethanol causes swelling of elastomers, increases extractives of gasket material, and affects the amount of lubrication between the stem and gaskets. Efforts are in progress to reformulate HFA propellant and to create valves that exhibit low levels of extractables/leachables.

This application note focuses on identifying volatile and semivolatile extractable compounds in an expired pMDI device using two GC/MS systems. Two types of analysis were used: headspace sampling and large volume liquid injection. Plastic and rubber components were investigated using aggressive extraction conditions, which were intended for quantitative determination of chemical additives rather than simulation of a drug product leachable profile. Compounds in pMDI components were extracted using different solvents and using high-temperatures.

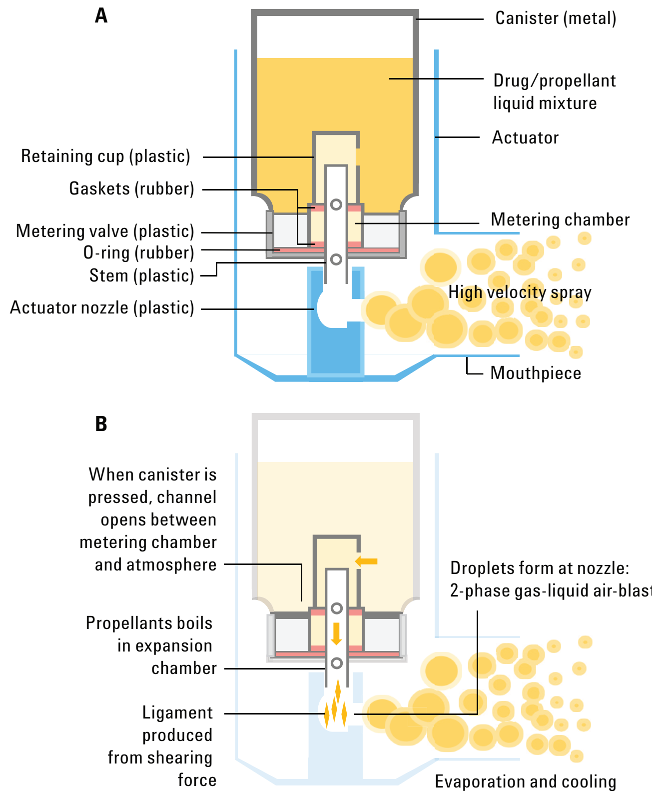


Figure 1. Design of a pressurized metered dosed inhaler (A) and operation of the metering valve (B).

Experimental Methods

Materials and instrumentation

The pMDI used in the investigation was expired for six months and was manufactured by a leading pharmaceutical company. The canister contained fluticasone propionate in HFA-134a propellant. Extractables analysis of pMDI components were investigated at high temperatures using the Agilent 7697A Headspace Sampler and an Agilent 7890 Series GC coupled with an Agilent 5977A MSD (Headspace GC/MS). Dichloromethane (DCM) (650463), hexane (34859), and ethanol (459844) were solvents used for extraction and were purchased from Sigma-Aldrich. Solvent extracts were analyzed using the Agilent 7693A Automatic Liquid Sampler (ALS) and a 7890 Series GC coupled with a 5977A MSD. The ALS was equipped with a multimode inlet (MMI) operated in solvent vent mode for large volume liquid injection (MMI GC/MS).

Sample preparation

Extractables analysis using MMI GC/MS

Rubber and plastic pMDI components (1-cm^2 pieces) were placed in separate vials for analysis. Components were rinsed with water to minimize any residue from the API formulation. Ethanol, DCM, and hexane were solvents used to extract elastomeric components. DCM and hexane were solvents used to extract plastic components. Elastomeric seals (80–90 mg) were extracted with 3.0 mL of solvent. The stem (100–120 mg) was extracted with 2 mL of solvent. The retaining cup (230–270 mg) was extracted with 3 mL of solvent. The metering valve (270–280 mg) was extracted with 5 mL of solvent. The actuator nozzle (140–170 mg) was extracted with 5 mL of solvent. Components were extracted with solvent in a 12-mL amber glass vial, sonicated for 5 hours, and allowed to sit at room temperature for 1–2 days. The organic layer was transferred to a glass insert placed inside an amber autosampler vial for GC/MS analysis. Ten microliters of extract were injected using the MMI operated in solvent vent mode. The solvent elimination wizard was used to develop parameters specific to the analysis of DCM, hexane, and ethanol extracts. Similar GC and MSD parameters were used for all extract analyses (Table 2).

Extractables analysis using headspace GC/MS

Components (1-cm^2 pieces) of pMDI were analyzed in separate 10-mL headspace vials. The components consisted of seals (90 mg), retaining cup (440 mg), valve stem (230 mg), metering valve (410 mg), and actuator nozzle (320 mg). Headspace vials were purged with nitrogen, sealed with a high-performance PTFE crimp cap, and investigated at headspace equilibration temperature of 250 °C. Table 3 lists the system parameters.

Table 2. GC and MSD Instrument Parameters for Analysis of DCM Extract Using MMI GC/MS

Gas chromatograph	**Agilent 7890 Series GC**
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, dimpled, ultra inert (p/n 5190-2297)
Inlet vent	100 mL/min (5 psi) until 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 350 °C (5 minutes) at 6 °C/min
Columns	Agilent J&W-5msUI, 30 m × 250 µm, 0.25 µm (p/n 19091S-433UI)
MSD	**Agilent 5977A MSD**
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 differs depending on solvent extract.

Table 3. Instrument Parameters Using Headspace GC/MS

Headspace	**Agilent 7697A Headspace Sampler**
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	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 minutes
Gas chromatograph	**Agilent 7890 Series GC**
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	30:1
Carrier gas	Helium
Oven program	35 °C (2 minutes) to 320 °C (3 minutes) at 8 °C/min
Columns	Agilent J&W-5ms UI, 30 m × 0.25 mm, 0.5 µm (p/n 19091S-133UI)
MSD	**Agilent 5977A MSD**
Transfer line	280 °C
MS Source	280 °C
MS Quad	180 °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

Compound identification

Chemical compounds were characterized using MSD Chemstation Data Analysis F.01.01, AMDIS 2.72, and Agilent MassHunter Unknowns Analysis B.07.00. Mass spectra of all compounds were matched with the NIST14 Library 2.2. Compounds with a match score ≥80 were considered and the top match was selected for investigation.

Results and Discussion

Elastomeric (rubber) seals

Volatiles and semivolatiles investigation of rubber seals using headspace GC/MS showed peaks attributed to (Figure 2A):

- Softening agent (1,3-dioxolane)
- Antioxidant in lubricant (1-naphthalenol)
- Releasing agents (palmitic acid)
- Rubber composition (octadecanamide, octadecanenitrile)
- Molding material (cyclohexasiloxane, dodecamethyl-)

Semivolatiles testing of solvent extracts of rubber seals using MMI GC/MS showed an extractable profile consisting of (Figure 2B):

Ethanol extract

- Curing agents in silicone rubber system (Dynasil A)
- Residual solvents (acetophenone)
- Surface active agents (myristic acid)
- Ingredients in rubber products (oleic acid)
- Lubricants (stearic acid)
- Slip agents (oleimide)
- Sealants (13-docosenamide)
- Stabilizers (*tris*(2,4-di-*tert*-butylphenyl)phosphate)

DCM extract

- Thermodegradation products (nonanal)
- Antioxidants (2,4-di-*tert*-butylphenol)
- Monomers (dodecyl acrylate)

Hexane extract

- Wax from the vulcanization of rubber (docosane)
- Antioxidant (Irganox 1076)

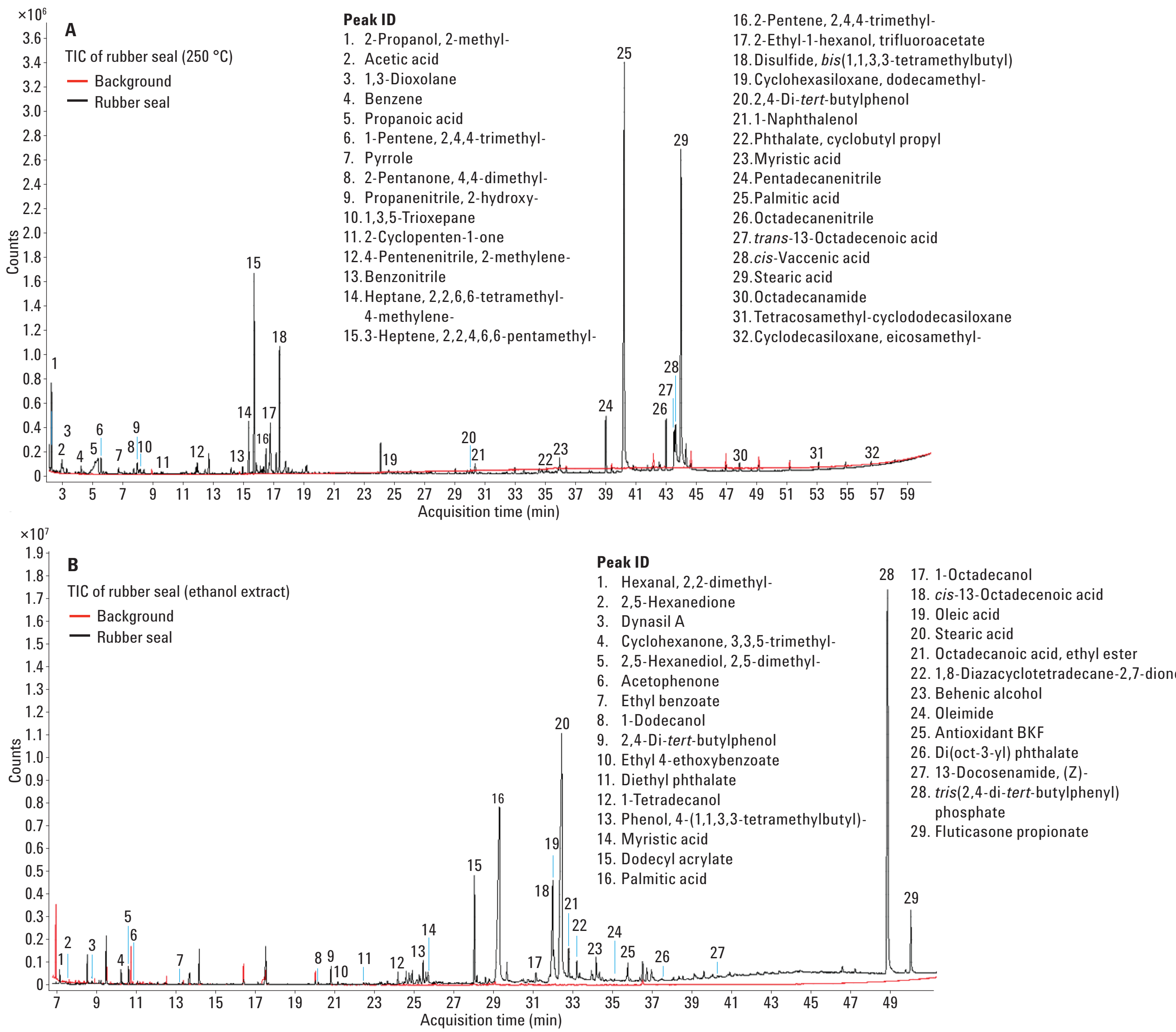


Figure 2. Extractables analysis of a rubber seal using headspace equilibrium temperature of 250 °C (A) and ethanol extraction by MMI GC/MS (B).

Retaining cup

Volatiles and semivolatiles investigation of retaining cup using headspace GC/MS showed peaks attributed to (Figure 3A):

- Flavor/fragrance (2,3-butanedione)
- Softening agent (1,3-dioxolane)
- Thermoplastic composition (eicosamethyl cyclodecasiloxane)

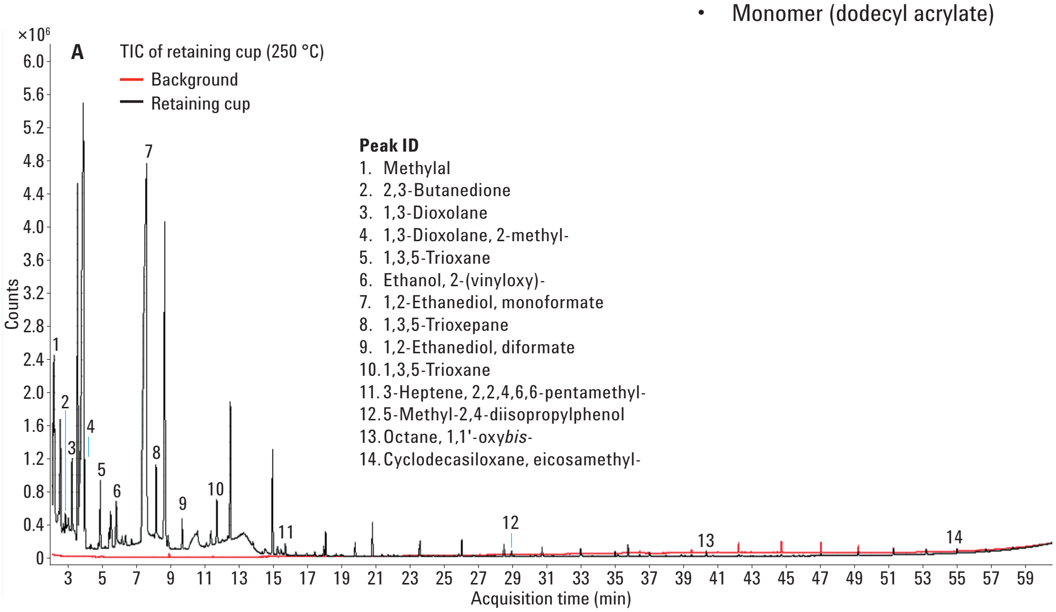
Semivolatiles testing of solvent extracts of retaining cup using MMI GC/MS showed an extractable profile consisting of (Figure 3B):

DCM extract

- Antioxidant (2,4-di-*tert*-butylphenol)
- Plasticizers (Kodaflex TXIB)
- Lubricants (1-hexadecanol)
- Stabilizer (Metilox)

Hexane extract

- Catalyst (ethyl 4-ethoxybenzoate)
- Phthalate plasticizers (diethyl phthalate)
- Monomer (dodecyl acrylate)



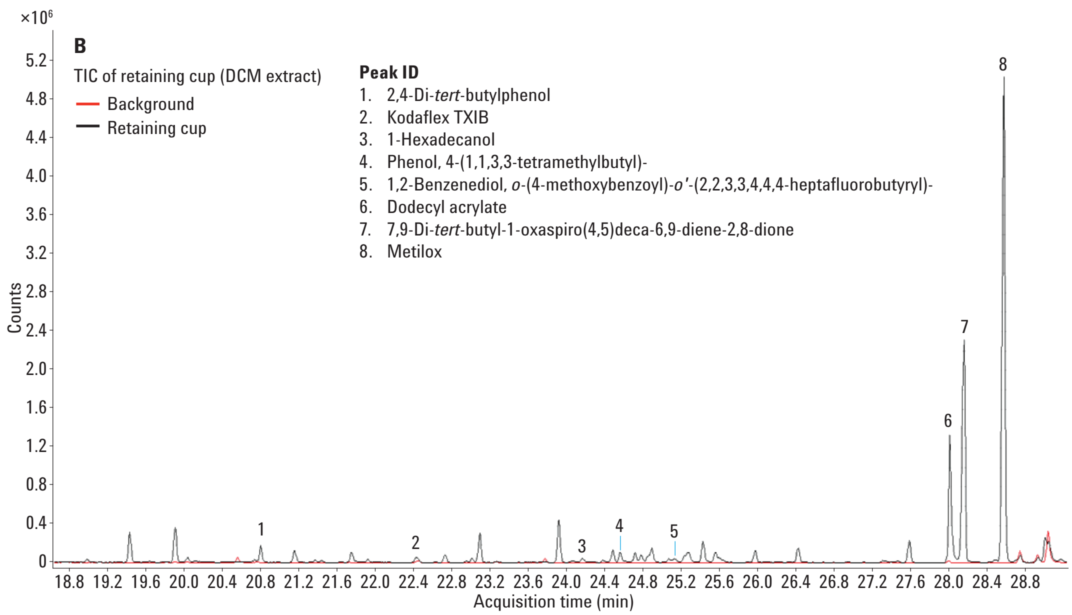


Figure 3. Extractables analysis of a retaining cup using headspace equilibrium temperature of 250 °C (A) and DCM extraction by MMI GC/MS (B).

Metering valve

Volatiles and semivolatiles investigation of plastic metering valve using headspace GC/MS showed peaks attributed to the compounds listed below (Figure 4A). Octadecanitrile was also observed in headspace GC/MS analysis of elastomeric seal at a similar retention time (Figure 2A), indicating potential compound migration.

- Solvents (pyridine)
- Processing aids (butyrolactone)
- Catalysts (propylbenzene)
- Monomers (succinimide)
- Odor agents (2-pentylcyclopentanone)
- Antioxidant for lubricants (1-naphthalenol)
- Releasing agents (palmitic acid)
- Lubricants (stearic acid)
- Plasticizers (diisooctyl phthalate)
- Rubber component (octadecanenitrile)

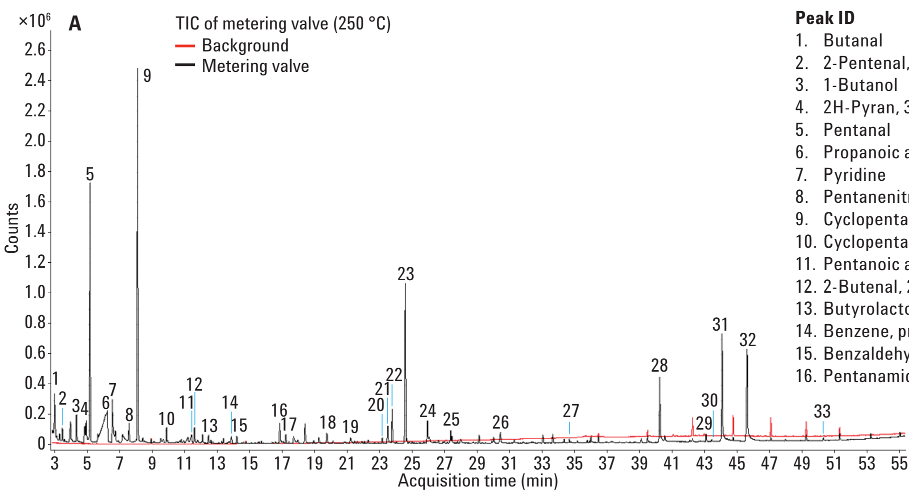
Semivolatiles testing of solvent extracts of the plastic metering valve using MMI GC/MS showed an extractable profile consisting of (Figure 4B):

Hexane extract

- Plasticizer (Kodaflex TXIB)
- Thermoplastic decomposition (eicosamethyl cyclodecasiloxane)
- Antioxidants (Antioxidant BKF)
- Stabilizers (*tris*(2,4-di-*tert*-butylphenyl)phosphate)

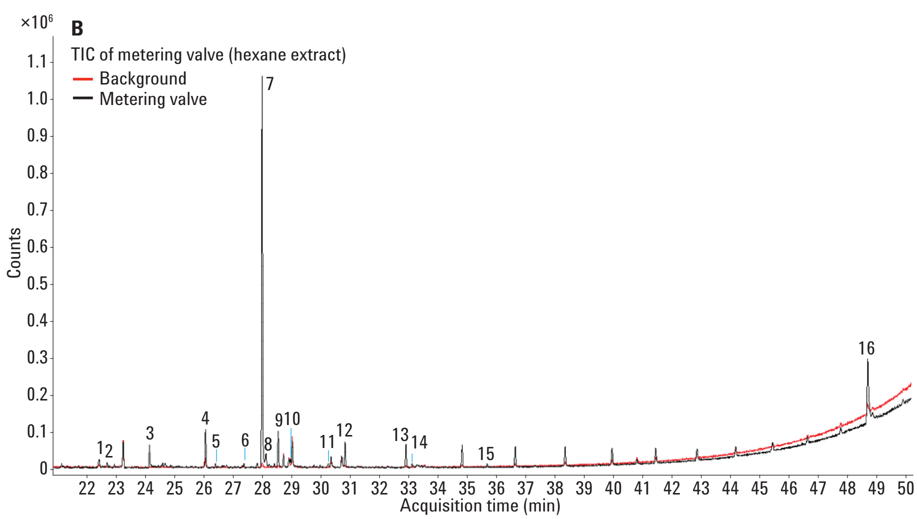
DCM extract

- Plasticizers (Kodaflex TXIB)
- Catalyst (ethyl 4-ethoxybenzoate)
- Polymer byproducts (styrene-acrylonitrile trimer)
- Lubricant (13-docosenamide)



Peak ID

1. Butanal
2. 2-Pentenal, (E)-
3. 1-Butanol
4. 2H-Pyran, 3,4-dihydro-
5. Pentanal
6. Propanoic acid
7. Pyridine
8. Pentanenitrile
9. Cyclopentanone
10. Cyclopentanone, 2-methyl-
11. Pentanoic acid
12. 2-Butenal, 2-ethenyl-
13. Butyrolactone
14. Benzene, propyl-
15. Benzaldehyde
16. Pentanamide
17. 2H-Pyran-2-one, tetrahydro-
18. Succinimide
19. 2-Piperidinone
20. 2-Pentylcyclopentanone
21. Caprolactam
22. Benzenebutanal
23. [1,1'-Bicyclopentyl]-2-one
24. Benzenebutanol
25. Cyclopropylphenylmethane
26. 1-Naphthalenol
27. 3-Octadecene, (E)-
28. Palmitic acid
29. Octadecanenitrile
30. Methyl stearate
31. Stearic acid
32. 1,8-Diazacyclotetradecane-2,7-dione
33. Diisooctyl phthalate



Peak ID

1. Kodaflex TXIB
2. Hexadecane
3. 1-Tetradecanol
4. Cyclononasiloxane, octadecamethyl-
5. Octadecane
6. Isobutyl 4-octyl phthalate
7. Dodecyl acrylate
8. Phenanthrene, 1-methyl-
9. Cyclodecasiloxane, eicosamethyl-
10. Butyl 4-methylpent-2-yl phthalate
11. Phenanthrene, 2,5-dimethyl-
12. Cyclodecasiloxane, eicosamethyl-
13. Tetracosamethyl-cyclododecasiloxane
14. *bis*(2-ethylhexyl) fumarate
15. Antioxidant BKF
16. *tris*(2,4-di-*tert*-butylphenyl) phosphate

Figure 4. Extractables analysis of a metering valve using headspace equilibrium temperature of 250 °C (A) and hexane extraction by MMI GC/MS (B).

Valve stem

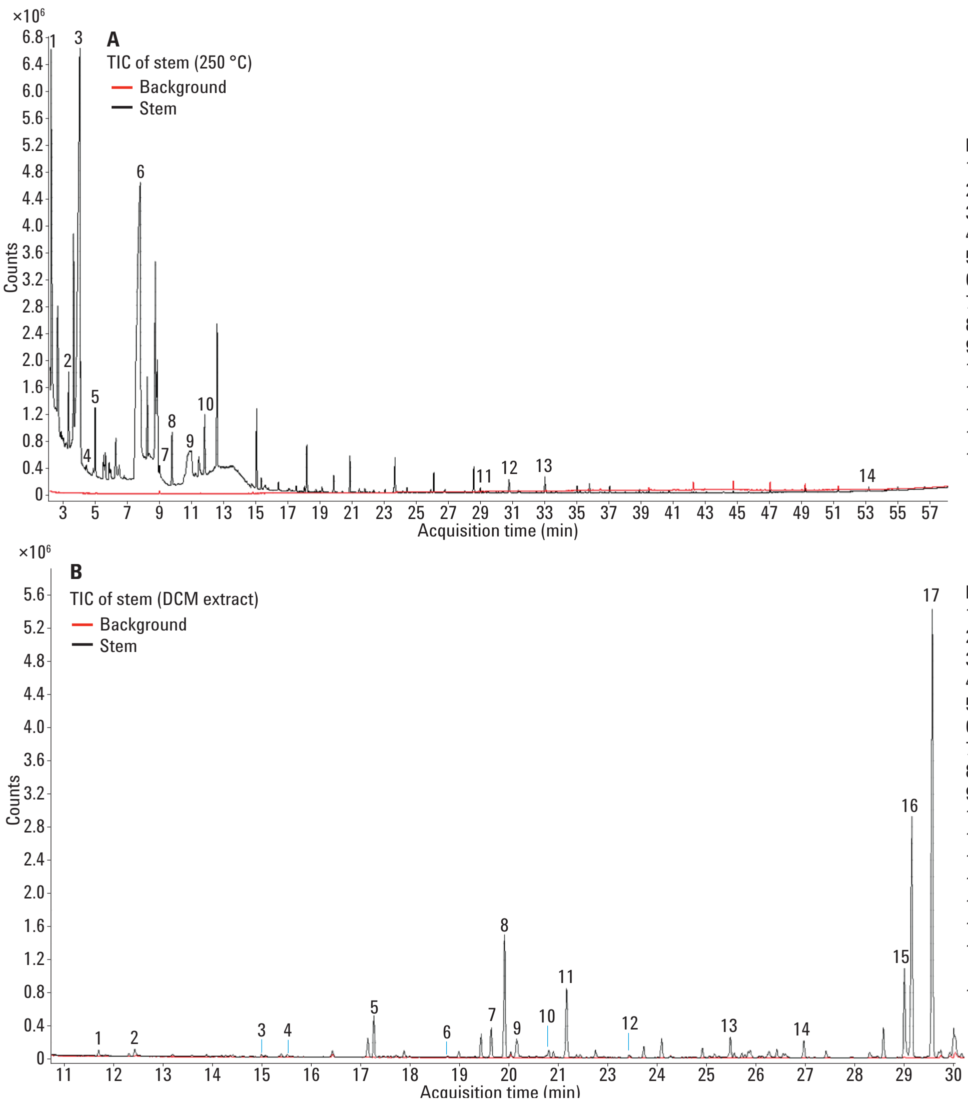
Volatiles and semivolatiles testing of valve stem using headspace GC/MS showed an extractable profile consisting of (Figure 5A):

- Preservatives (formic acid)
- Softening polymer (1,3-dioxolane)
- The manufacture of polyols (hydroxyacetone)
- Catalysts (ethyl 4-ethoxybenzoate)
- Thermoplastic compositions (eicosamethyl cyclodecasiloxane)
- Resins (hexadecamethyl cyclooctasiloxane)

Semivolatiles investigation of solvent extracts in valve stem using MMI GC/MS showed peaks attributed to (Figure 5B):

DCM extract
- Odor agents (nonanal)
- Resins (dimethyl adipate)
- Adhesives (2,4,7,9-Tetramethyl-5-decyn-4,7-diol)
- Lubricants (1-dodecanol)
- Antioxidants (2,4-di-*tert*-butylphenol)
- Plasticizers (Kodaflex TXIB)
- Photoinitiators (Irgacure 184)
- Comonomer/intermediate (dodecyl acrylate)
- Antioxidant in polypropylene (7,9-di-*tert*-butyl-1oxaspiro(4,5)deca-6,9-diene-2,8-dione)
- Plasticizer (Irganox 1076)

Hexane extract
- Odor agents (nonanal)
- Molding material (dodecamethyl cyclohexasiloxane)
- Phthalate plasticizer (hept-4-yl isobutyl phthalate)



Peak ID
1. Formic acid
2. 1,3-Dioxolane
3. 1,3-Dioxolane, 2-methyl-
4. Hydroxyacetone
5. 1,3,5-Trioxane
6. 1,2-Ethanediol, monoformate
7. 1,3,5-Trioxepane
8. 1,2-Ethanediol, diformate
9. 1,3-Propanediol
10. 1,3,5-Trioxane
11. 5-Methyl-2,4-diisopropylphenol
12. Ethyl 4-ethoxybenzoate
13. Cyclooctasiloxane, hexadecamethyl-
14. Cyclodecasiloxane, eicosamethyl-

Peak ID
1. Nonanal
2. Dimethyl glutarate
3. Dimethyl adipate
4. Nonanoic acid
5. Glycerol 1,2-diacetate
6. 2,4,7,9-Tetramethyl-5-decyn-4,7-diol
7. *p*-Diacetylbenzene
8. 2,6-Di-*tert*-butyl-*p*-benzoquinone
9. 1-Dodecanol
10. 2,4-Di-*tert*-butylphenol
11. Ethyl 4-ethoxybenzoate
12. Kodaflex TXIB
13. Irgacure 184
14. 3,5-di-*tert*-Butyl-4-hydroxybenzaldehyde
15. Dodecyl acrylate
16. 7,9-Di-*tert*-butyl-1-oxaspiro(4,5)deca-6,9-di-ene-2,8-dione
17. Irganox 1076

Figure 5. Extractables analysis of the valve stem using headspace equilibrium temperature of 250 °C (A) and DCM extraction by MMI GC/MS (B).

Actuator nozzle

Volatiles and semivolatiles analysis of plastic nozzle using headspace GC/MS showed peaks attributed to the compounds listed below (Figure 6A). Dye additive could be attributed to the colorant in the actuator.

- Monomers (acetic acid)
- Manufacture of dyes (hydroxyacetone)
- Paint/coating (2-pentanone)
- Solvents for polymers (methyl isobutyl ketone)
- Fragrances (4-methyl-4-penten-2-one)
- UV stabilizer (2,4-di-*tert*-butylphenol)
- Catalysts (ethyl 4-ethoxybenzoate)
- Releasing agents (palmitic acid)
- Lubricants (stearic acid)
- Antioxidants (Irgafos 168)
- Stabilizers (*tris*(2,4-di-*tert*-butylphenyl) phosphate)

Semivolatiles testing of solvent extract in plastic nozzle using MMI GC/MS showed peaks attributed to (Figure 6B):

DCM extract

- Odor agents (2,7-dimethyl-1-octanol)
- Antioxidants (butylated hydroxytoluene, Irgafos 168, 4,4'-ethylene*bis*(2,6-di-*tert*-butylphenol))
- Catalysts (ethyl 4-ethoxybenzoate)
- Releasing agents (palmitic acid)
- Stabilizers (*tris*(2,4-di-*tert*-butylphenyl) phosphate)

Hexane extract

- Lubricants (phytane)
- Antioxidants (butylated hydroxytoluene)
- Catalysts (ethyl 4-ethoxybenzoate)
- Monomers (dodecyl acrylate)
- Thermal conversion of plastics (heneicosane)
- Wax (hentriacontane)
- Antioxidants (Irgafos 168)
- Stabilizers (*tris*(2,4-di-*tert*-butylphenyl) phosphate)

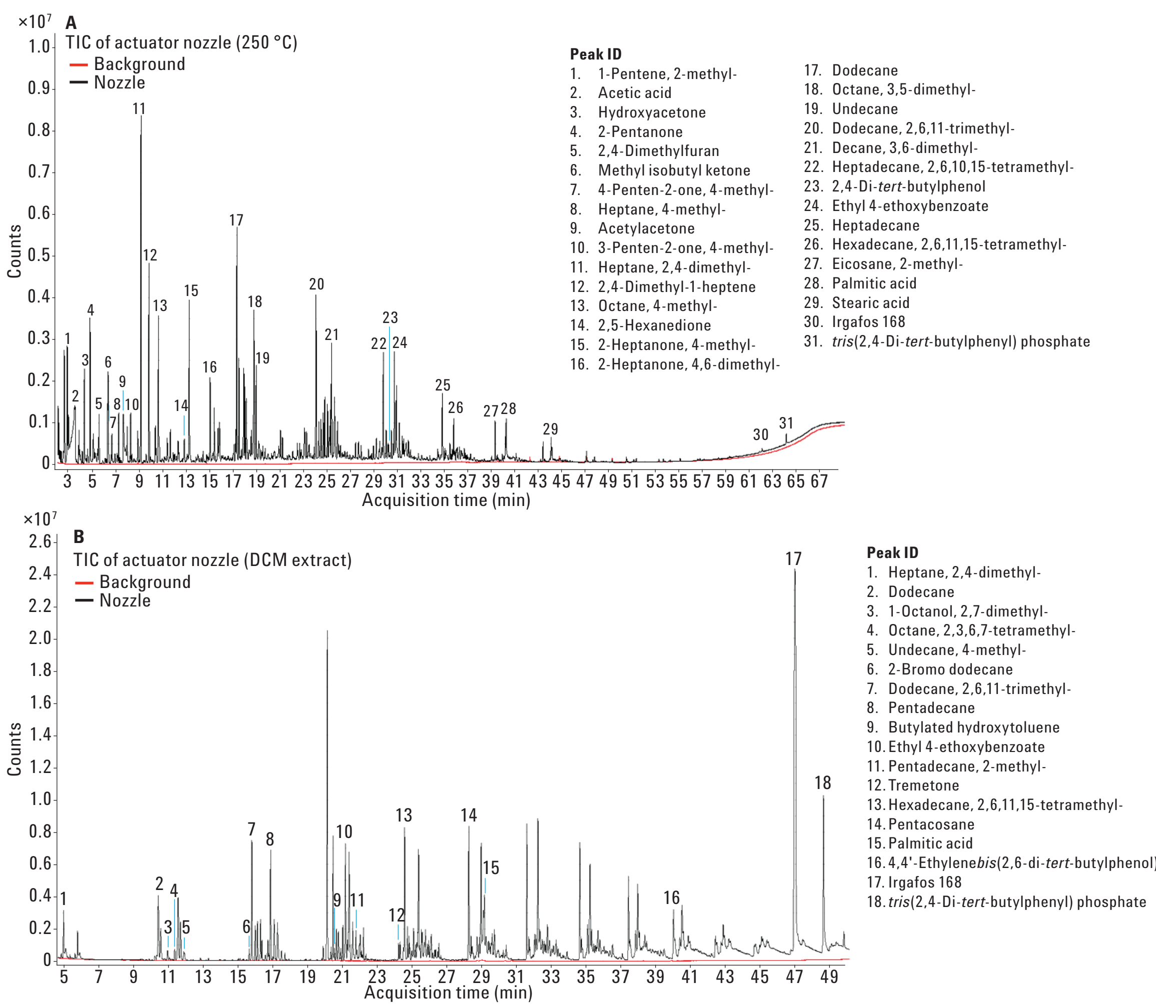


Figure 6. Extractables analysis of an actuator nozzle using headspace equilibrium temperature of 250 °C (A) and DCM extraction by MMI GC/MS (B).

Volatile and semivolatile extractable compounds identified in pMDI components included monomers, polymers, adhesives, lubricants, surfactants, odor agents, paint additives, coating additives, plasticizers, resins, intermediates, antioxidants, UV-stabilizers, stabilizers, flavor and fragrance byproducts, colorants, regulators, processing aids, thermoplastic compositions, adhesives, wax from vulcanization of rubber, preservatives, photoinitiators, rubber ingredients, curing agents, finishing agents, dyes, and residual solvents. Table 4 contains a list of all extractables identified in pMDI.

Most extractables were identified only by solvent extraction or only by high-temperature headspace sampling. For instance, oleimide is a slip agent/lubricant that was identified by ethanol extraction. Irganox 1076 is an antioxidant that was characterized using hexane extraction. 3-chlorophenyloctyl terephthalate is used in the production of polyester that was identified by DCM extraction. 2-pentanone is a painting/coating additive that was characterized using high-temperature headspace sampling. Table 3 lists the extraction technique and pMDI component used to identify the particular extractable.

Table 4. Extractables identified in pMDI device

Compound[a]	**Extraction (component)**[b]	**Origin**[c]
[1,1'-Bicyclopentyl]-2-one	HS(V)	
1,2-Benzenediol, *o*-(4-methoxybenzoyl)-*o'*-(2,2,3,3,4,4,4-heptafluorobutyryl)-	D(C)	
1,2-Ethanediol, diformate	HS(C);HS(S)	
1,2-Ethanediol, monoformate	HS(C);HS(S)	
1,3,5-Trioxane	HS(C);HS(S)	
1,3,5-Trioxepane	HS(R);HS(C);HS(S)	
1,3-Dioxolane	HS(R);HS(C);HS(S)	Softening polymer (PA and PVC)
1,3-Dioxolane, 2-methyl-	HS(C);HS(S)	
1,3-Propanediol	HS(S)	Polyester polymer
1,8-Diazacyclotetradecane-2,7-dione	E(R); D,HS(V)	Ingredient in polymer
13-Docosenamide, (Z)-	E(R),D(V)	Adhesives, sealant, lubricants
1-Butanol	HS(V)	Manufacture of polymers, pyroxylin, plastics
1-Dodecanol	D(S), E(R)	Surfactants, lubrication, polymers
1-Hexadecanol	D(C), H(R)	Lubrication, odor agent, paint and coating additive, plasticizer
1-Naphthalenol	HS(R,V)	Intermediate for antioxidants in lubricants
1-*n*-Hexyladamantane	H(R)	
1-Octadecanol	E(R)	Lubricants, resins
1-Octanol, 2,7-dimethyl-	D(N)	Odor agent
1-Pentene, 2,4,4-trimethyl-	HS(R)	
1-Pentene, 2-methyl-	HS(N)	
1-Phenoxypropan-2-ol	H(S)	
1-Tetradecanol	E(R),H(C);H(V);H(S)	
2,2,4-Trimethyl-1,3-pentanediol diisobutyrate	D(C);D,H(V);D(S)	Plasticizer
2,3-Butanedione	HS(C)	Flavor
2,4,7,9-Tetramethyl-5-decyn-4,7-diol	D(S)	Adhesives, surfactants
2,4-Dimethyl-1-heptene	HS(N)	
2,4-Dimethylfuran	HS(N)	
2,4-Di-*tert*-butylphenol	D(C,S); HS(N); E,H,D,HS(R)	UV stabilizer, potential migrant
2,5-Cyclohexadiene-1,4-dione, 2,6-*bis*(1,1-dimethylethyl)-; 2,6-di-*tert*-butyl-p-benzoquinone	D(S)	

Compound[a]	Extraction (component)[b]	Origin[c]
2,5-Hexanediol, 2,5-dimethyl-	E,D(R)	Intermediate
2,5-Hexanedione	E(R);HS(N)	Deodorizing agent
2-[1-(4-Cyano-1,2,3,4-tetrahydronaphthyl)]propanenitrile; styrene-acrylonitrile trimer	D(V)	Byproduct in acrylonitrile styrene plastics
2-Bromo dodecane	D(N)	
2-Butenal, 2-ethenyl-	HS(V)	
2-Butenedioic acid (E)-, *bis*(2-ethylhexyl) ester; *bis*(2-ethylhexyl)fumarate	H(V)	
2-Cyclopenten-1-one	HS(R)	
2-Ethyl-1-hexanol, trifluoroacetate	HS(R)	
2-Heptanone, 4,6-dimethyl-	HS(N)	
2-Heptanone, 4-methyl-	HS(N)	
2H-Pyran, 3,4-dihydro-	HS(V)	
2H-Pyran-2-one, tetrahydro-; δ-valerolactone	HS(V)	Intermediate (copolymer) in polyester
2-Pentanone	HS(N)	Paint and coating additives
2-Pentanone, 4,4-dimethyl-	HS(R)	
2-Pentenal, (E)-	HS(V)	Flavor and fragrance agent
2-Pentene, 2,4,4-trimethyl-	HS(R)	
2-Pentylcyclopentanone	HS(V)	Odor agent
2-Piperidinone	HS(V)	Intermediate (copolymer)
2-Propanol, 2-methyl-	HS(R)	
2-Propanone, 1-hydroxy-; hydroxyacetone	HS(S);HS(N)	Manufacture of polyols, acrolein, dyes
3,5-di-*tert*-Butyl-4-hydroxybenzaldehyde	D(C,S)	
3-[1-(4-Cyano-1,2,3,4-tetrahydronaphthyl)]propanenitrile	D(V)	
3-Heptene, 2,2,4,6,6-pentamethyl-	HS(C); H,D,HS(R)	
3-Octadecene, (E)-	HS(V)	
3-Penten-2-one, 4-methyl-	HS(N)	Flavor and fragrance
4,4'-Ethylenebis(2,6-di-*tert*-butylphenol)	D(N)	Stabilizer and antioxidant for polyolefins
4-Penten-2-one, 4-methyl-	HS(N)	Flavor and fragrance
4-Pentenenitrile, 2-methylene-	HS(R)	
5-Methyl-2,4-diisopropylphenol	HS(C,S)	
7,9-Di-*tert*-butyl-1-oxaspiro(4,5)deca-6,9-diene-2,8-dione	D(C,S)	Antioxidant in polypropylene
9-Octadecenamide, (Z)-; oleimide	E(R)	Slip agent, lubricant, corrosion inhibitor; potential to leach
Acetic acid	HS(R,N)	Production of vinyl acetate monomer
Acetophenone	E(R)	Solvent for plastic and resins
Acetylacetone	HS(N)	
Behenic alcohol	E,H(R)	Lubricant
Benzaldehyde	HS(V)	Precursor to plastic additives
Benzene	HS(R)	
Benzene, propyl-	HS(V)	Catalyst for olefin polymerization
Benzenebutanal	HS(V)	
Benzenebutanol	HS(V)	
Benzenepropanoic acid, 3,5-*bis*(1,1-dimethylethyl)-4-hydroxy-, methyl ester; Irganox 1076	D(C);D(S); H(R)	Polymer stabilizer

Compound[a]	Extraction (component)[b]	Origin[c]
Benzoic acid, 4-ethoxy-, ethyl ester; ethyl 4-ethoxybenzoate	E(R);H(C);D(V);D,HS(S); D,H,HS(N)	Catalyst for olefin polymerization
Benzoic acid, ethyl ester; ethyl benzoate	E(R)	Fragrance
Benzonitrile	HS(R)	
Butanal	HS(V)	Intermediate
Butylated hydroxytoluene (BHT)	D,H(N)	Antioxidant
Butyrolactone	HS(V)	Colorant; intermediates, process regulators, processing aid, solvents
Caprolactam	HS(V)	Precursor to nylon 6, a widely used synthetic polymer
cis-13-Octadecenoic acid	E,H,D(R)	Lubrication in plastics and coatings
cis-Vaccenic acid	HS(R)	
Cyclodecasiloxane, eicosamethyl-	HS(R);HS(C);H(V);HS(S)	Thermoplastic
Cycloheptasiloxane, tetradecamethyl-	H(S)	Resin
Cyclohexanone, 3,3,5-trimethyl-	E(R)	Monomer for polycarbonate; polymerization initiator, coating, paint, gloss and surface finish
Cyclohexasiloxane, dodecamethyl-	HS(R);H(S)	Intermediate, solvent, molding material
Cyclononasiloxane, octadecamethyl-	H(C);H(V);H(S)	Polymer synthesis
Cyclooctane, 1,4-dimethyl-, *trans*-	H(N)	
Cyclooctasiloxane, hexadecamethyl-	H,HS(S)	Thermoplastic, resin
Cyclopentanone	HS(V)	Fragrance
Cyclopentanone, 2-cyclopentylidene-	D(V)	
Cyclopentanone, 2-methyl-	HS(V)	
Cyclopropylphenylmethane	HS(V)	
Decane, 3,6-dimethyl-	HS(N)	
Dibutyl phthalate	H(C)	Potentially toxic plasticizer
Diethyl phthalate	E,H(R);H(C)	Potentially toxic plasticizer
Diisooctyl phthalate	HS(V)	Potentially toxic plasticizer
Disulfide, *bis*(1,1,3,3-tetramethylbutyl)	HS(R)	
Docosane	H(R)	Wax in vulcanization of rubber
Dodecane	D,H,HS(N)	
Dodecane, 2,6,11-trimethyl-	D,H,HS(N)	
Dodecyl acrylate	E,D(R);D,H(C);H(V);D,H(S); H(N)	Intermediate, comonomer
Eicosane, 2-methyl-	HS(N)	
Ethanol, 2-(vinyloxy)-	HS(C)	
Ethanone, 1,1'-(1,4-phenylene)*bis*-; *p*-diacetylbenzene	D(S)	
Fluticasone propionate	E(R);D(V)	Corticosteroid used to treat asthma
Formic acid	HS(S)	Preservative and antibacterial agent
Glycerol 1,2-diacetate	D(S)	Thermal conversion of plastics
Heneicosane	H(N)	
Hentriacontane	H(N)	Wax
Heptadecane	HS(N)	
Heptadecane, 2,6,10,15-tetramethyl-	HS(N)	
Heptane, 2,2,6,6-tetramethyl-4-methylene-	HS(R)	
Heptane, 2,4-dimethyl-	D,H,HS(N)	

Compound[a]	Extraction (component)[b]	Origin[c]
Heptane, 4-methyl-	HS(N)	
Hexadecane	H(V)	Pyrolysis of plastic
Hexadecane, 2,6,10,14-tetramethyl-; phytane	H(N)	Plasticizers, lubricant
Hexadecane, 2,6,11,15-tetramethyl-	D,HS(N)	
Hexadecanoic acid; palmitic acid	E,H,D,HS(R);HS(V); D,HS(N)	Releasing agent, plasticizer
Hexanal, 2,2-dimethyl-	E(R)	
Hexanedioic acid, dimethyl ester; dimethyl adipate	D(S)	
Hexestrol	D(R)	
Isophthalic acid, 3,5-difluorophenyl octyl ester; 3,5-difluorophenyl isophthalate	D(R)	
Isophthalic acid, ethyl tridec-2-ynyl ester; ethyl tridec-2-ynyl isophthalate	D(R)	
Methanone, (1-hydroxycyclohexyl)phenyl-; Irgacure 184	D(S)	Photoinitiator
Methyl isobutyl ketone	HS(N)	Solvent for lacquers, polymers and resin
Methyl stearate	HS(V)	Lubricant and surfactants
Methylal	HS(C)	Blowing agent in PU foam system
Nonanal	D(R);D,H(S)	Causes off-taste/odor due to thermo degradation of polyolefins containers, antioxidants are usually added to counter
Nonanoic acid	D(S)	Plasticizers; lubricants, paints and coating, plastic and rubber products
Octadecanamide	HS(R)	Additives in rubber
Octadecane	H(V)	Plasticizer in PVC
Octadecanenitrile	HS(R);HS(V)	Rubber composition
Octadecanoic acid, 2-propenyl ester; allyl stearate	H(R)	Lubricant
Octadecanoic acid, ethyl ester; ethyl stearate	E(R)	Fragrance, plasticizer, lubricant
Octadecanoic acid; stearic acid	E,H,D,HS(R);HS(V);HS(N)	Lubricant, softening, and release agents; soften PVC; potential to migrate
Octane, 1,1'-oxy*bis*-	HS(C)	
Octane, 2,3,6,7-tetramethyl-	D(N)	
Octane, 3,5-dimethyl-	HS(N)	
Octane, 4-methyl-	H,HS(N)	
Oleic acid	E(R)	Plasticizer; ingredient in rubber
Pentacosane	D,H(N)	Plasticizer
Pentadecane	D(N)	Aliphatic hydrocarbon plasticizer with potential to migrate
Pentadecane, 2-methyl-	D(N)	
Pentadecanenitrile	HS(R)	
Pentanal	HS(V)	Odor agent
Pentanamide	HS(V)	PA-6 additives (potential migration)
Pentanedioic acid, (2,4-di-t-butylphenyl) mono-ester	H(C)	
Pentanedioic acid, dimethyl ester; dimethyl glutarate	D(S)	Resin, viscosity
Pentanenitrile	HS(V)	
Pentanoic acid; valeric acid	HS(V)	Lubricant
Phenanthrene, 1-methyl-	H(V)	
Phenanthrene, 2,5-dimethyl-	H(V)	

Compound[a]	Extraction (component)[b]	Origin[c]
Phenol, 2,2'-methylenebis[6-(1,1-dimethylethyl)-4-methyl-; Antioxidant BKF	E,D(R);H(V)	Antioxidant in rubber and plastic
Phenol, 2,4-*bis*(1,1-dimethylethyl)-, phosphite (3:1); Irgafos 168	D,H,HS(N)	Antioxidant, potential migration
Phenol, 4-(1,1,3,3-tetramethylbutyl)-	E,H,D(R);D(C)	
Phthalic acid, butyl 4-methylpent-2-yl ester; butyl 4-methylpent-2-yl phthalate	H(V)	Phthalate plasticizer; potentially toxic
Phthalic acid, di(oct-3-yl) ester; di(oct-3-yl) phthalate	E(R)	Phthalate plasticizer; potentially toxic
Phthalic acid, hept-4-yl isobutyl ester; hept-4-yl isobutyl phthalate	H(S)	Phthalate plasticizer; potentially toxic
Phthalic acid, isobutyl 4-octyl ester; isobutyl 4-octyl phthalate	H(V)	Phthalate plasticizer; potentially toxic
Propanenitrile, 2-hydroxy-	HS(R)	
Propanoic acid	HS(R);HS(V)	Antimicrobial packaging material
Propanoic acid, 2-methyl-, 3-hydroxy-2,2,4-trimethylpentyl ester; 2,4,4-trimethyl-1,3-pentanediol monoisobutyrate (Kodaflex TXIB)	D(V)	Plasticizer
Pyridine	HS(V)	Solvent and reagent
Pyrrole	HS(R)	Monomer
Silane, diethylheptyloxyoctadecyloxy-	D(N)	
Succinimide	HS(V)	Monomer
Terephthalic acid, 3-chlorophenyl octyl ester; 3-chlorophenyl octyl terephthalate	D(R)	Monomer
Tetracosamethyl-cyclododecasiloxane	HS(R);H(C);H(V);H(S)	
Tetracosane	H(R)	Plastic decomposition; diffusion out of rubber
Tetradecanoic acid; myristic acid	E,D,HS(R)	Adhesives, sealant, finishing agent, lubrication, surface active agents
Tetraethyl silicate; Dynasil A	E(R)	Curing agent; crosslinker in silicone rubber system
trans-13-Octadecenoic acid	HS(R)	
Tremetone	D,H(N)	Toxic compound
tris(2,4-Di-*tert*-butylphenyl) phosphate	E,H(R);H(V);D,H,HS(N)	Stabilizer for polymers
Undecane	HS(N)	Lubricant
Undecane, 4-methyl-	D(N)	

[a] Compounds are alphabetized based on name listed in NIST14 library. Common names are indicated in blue.

[b] Solvent extraction: ethanol (E), dichloromethane (D), and hexane (H). High-temperature headspace sampling (HS). pMDI components: rubber seal (R), retaining cup (C), valve stem (S), metering valve (V), and actuator nozzle (N)

[c] Origin of compounds are based on literature reference [3].

Conclusion

The complementation of headspace GC/MS and MMI GC/MS provided a broad extractables profile of compounds that can be extracted from a pMDI. Most of the compounds identified were specific to high-temperature headspace sampling or solvent extraction techniques. The MMI in solvent vent mode allows for the detection of low-level leachable/extractable compounds by making large volume injection. Headspace sampling simplifies sample preparation as the pMDI component can be placed directly into the headspace vial for analysis. MMI GC/MS and headspace GC/MS provide a nontargeted approach to determine an extractables/leachables profile. GC/Q-TOF and GC/MSMS would be the next step for targeted compound analysis. This application note is not intended to do quantitation on the extractable and leachable components. Literature contains references on using GC/MS and GC/MSMS to quantify the presence of potential endrocrine disruptors, such as phthalates, extracting from pMDI devices [9,10].

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