Analysis of Extractable/Leachable Compounds from Transdermal Patches Using GC/MSD Systems

Application Note

Pharmaceutical

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Abstract

A lidocaine adhesive patch and film release liner were used to investigate extractable and leachable compounds in transdermal drug delivery systems using two Agilent 5977A Series GC/MSD Systems. Plastic and adhesive additives were identified in acetone, dichloromethane, and hexane extracts using the large volume liquid injection technique. Pharmaceutical ingredients were also identified using high temperature headspace and liquid sampling techniques.

Introduction

Particular interest has been given to extraction techniques in container closure systems (CCS) used in the pharmaceutical industry. Regulators have become increasingly aware of the need to understand whether chemical species can be extracted from the primary packaging material (package with direct contact to the drug product), as well as whether the extracted species (from the package) will appear as leachable species in the drug product. Extractables analysis involves extracting compound from the packaging material using elevated temperatures and solvents related to the packaging composition. Leachables analysis involves identifying compounds in the drug formulation that may have leached from the primary packaging material.

The major source of extractables and leachables are additives that provide physical and protective properties to packaging material, such as flexibility, rigidity, stability, and barrier. Extractables include plastic and elastomeric components, inks and adhesives from coating, and degradation products during processing, storage, and sterilization. Leachables are usually a subset of extractables, however new compounds can form from the interaction between drugs and packaging material.

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Guidance for extractables and leachables testing has become progressively more comprehensive. General guidance and recommended testing has been provided by the Product Quality Research Institute (PQRI), International Organization for Standardization (ISO), United States Pharmacopeia (USP), European Pharmacopeia (EP), Japanese Pharmacopeia (JP), and the International Conference on Harmonization (ICH). Assessments for extractables and leachables in pharmaceutical packaging systems are described in the following chapters: USP<87>, USP <88>, USP <661>, EP 3.1, EP 3.2, ISO 10993, and ICH Q6A. These guidelines do not contain mandatory requirements, only optional testing for the evaluation of medical devices.

The U.S. Food and Drug Administration (FDA) Guidance for Industry has categorized transdermal patches as a pack type with a high concern associated with the route of administration, and a high likelihood of interaction between the packaging-component and the dosage form [1]. The transdermal drug delivery system (patches) is a technology used to incorporate the active ingredient of the drug into the circulatory system through the skin [2,3]. Transdermal patches are desirable because drug dosage can be controlled through the skin over a period of time. Drug dosing can also be terminated by the removal of the adhesive patch.

In this application note, a typical lidocaine adhesive patch was used as a model for extractables and leachables study of transdermal patches. The patch was comprised of an adhesive material containing 5 % lidocaine, which was applied to a nonwoven polyester felt backing and covered with a polyethylene terephthalate (PET) film release liner (Figure 1) [4,5]. The film release liner was removed prior to the application of the patch to the skin. Extractable and leachable compounds in the patch and the film were analyzed using headspace sampling and large volume liquid injection techniques. Volatile and semivolatile organic compounds were identified using gas chromatography-mass spectrometry (GC/MS).

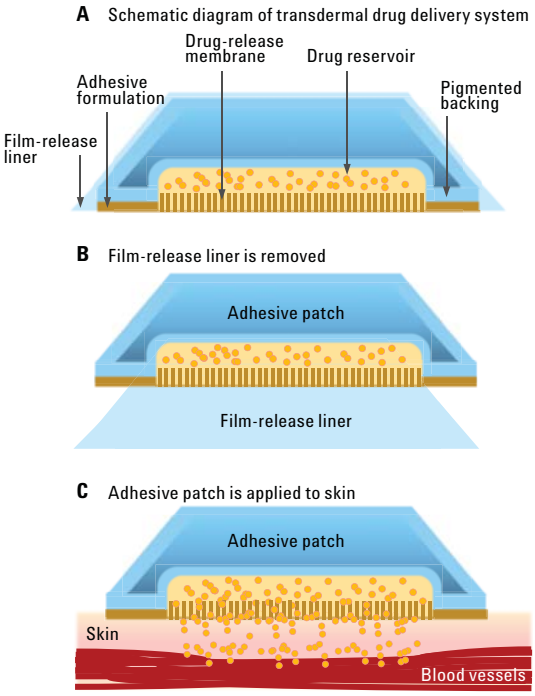


Figure 1. Schematic diagram of transdermal drug delivery system (A) consisting of an adhesive patch and a film release liner (B) with the mode of application to skin (C).

Experimental

Materials and instrumentation

The 5% lidocaine patch was manufactured by a leading pharmaceutical company. Extractable/leachable compounds in the lidocaine patch was analyzed at high temperatures using the 7697A Headspace Sampler and a 7890A GC coupled with a 5977A MSD (headspace GC/MS). Solvent extracts were analyzed using the 7693A Automatic Liquid Sampler and a 7890A GC coupled with a 5977 MSD (ALS GC/MS). The ALS GC/MS is equipped with a Multimode inlet (MMI) and operated in solvent vent mode for large volume liquid injection. The patch used in this work was expired for 1 year. Acetone (650501), dichloromethane (DCM) (650463), and hexane (34859) were purchased from Sigma-Aldrich.

Extractables and leachable analysis using ALS GC/MS

Sample preparation

A 5-cm × 7-cm sheet of film (1-cm^2 pieces) and 400 mg of a patch (1-cm^2 pieces) were placed in separate vials for extraction. The film was quickly rinsed with ethanol and water to minimize any residue from the patch. The patch and film were submerged in 5.0 mL of solvent (acetone, DCM, or hexane) in a separate 12-mL amber vial. The vials were sonicated for 5–16 hours, and allowed to sit at room temperature for 24 hours. The organic layer was transferred to a glass insert placed inside an amber autosampler vial for GC/MS analysis. Ten microliters of extract was injected using the MMI in solvent vent mode. The solvent elimination wizard was used to develop parameters specific for the analysis of acetone, DCM, and hexane extracts. Acetone, DCM, and hexane extracts were investigated at solvent vent times ranging 0.65 to 2.0 minutes, 0.6 to 2.0 minutes, and 0.15 to 0.30 minutes,

respectively. The initial hold times in the MMI was altered to match the solvent vent times used in the analysis. Similar GC and MSD parameter were used for all solvent analysis (Table 1).

Table 1. GC and MSD Instrument Parameters for Analysis of DCM Extract Using ALS GC/MS

GC	**Agilent 7890A**
Injection port	Multimode Inlet (MMI)
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 J&W HP-5ms UI, 30 m × 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/second
Threshold	150
Gain factor	1.0
Software	Agilent MassHunter B.07.00

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

Extractables and leachables analysis using Headspace GC/MS

An adhesive patch and film liner were analyzed in separate headspace vials. The film liner was quickly rinsed with ethanol and water to remove any residue from the adhesive patch. Three 1-cm^2 pieces (300 mg) of the patch and a 5-cm × 7-cm sheet of film (1-cm^2 pieces) were used for headspace GC/MS analysis. The film and patch were transferred to separate 10-mL headspace vials, purged with nitrogen, and sealed with a high-performance PTFE crimp cap. The patch and film were investigated at a headspace equilibration temperature of 250 °C with system parameters listed in Table 2.

Table 2. Instrument Parameters for Analysis Using Headspace GC/MS

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	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	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 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 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 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.

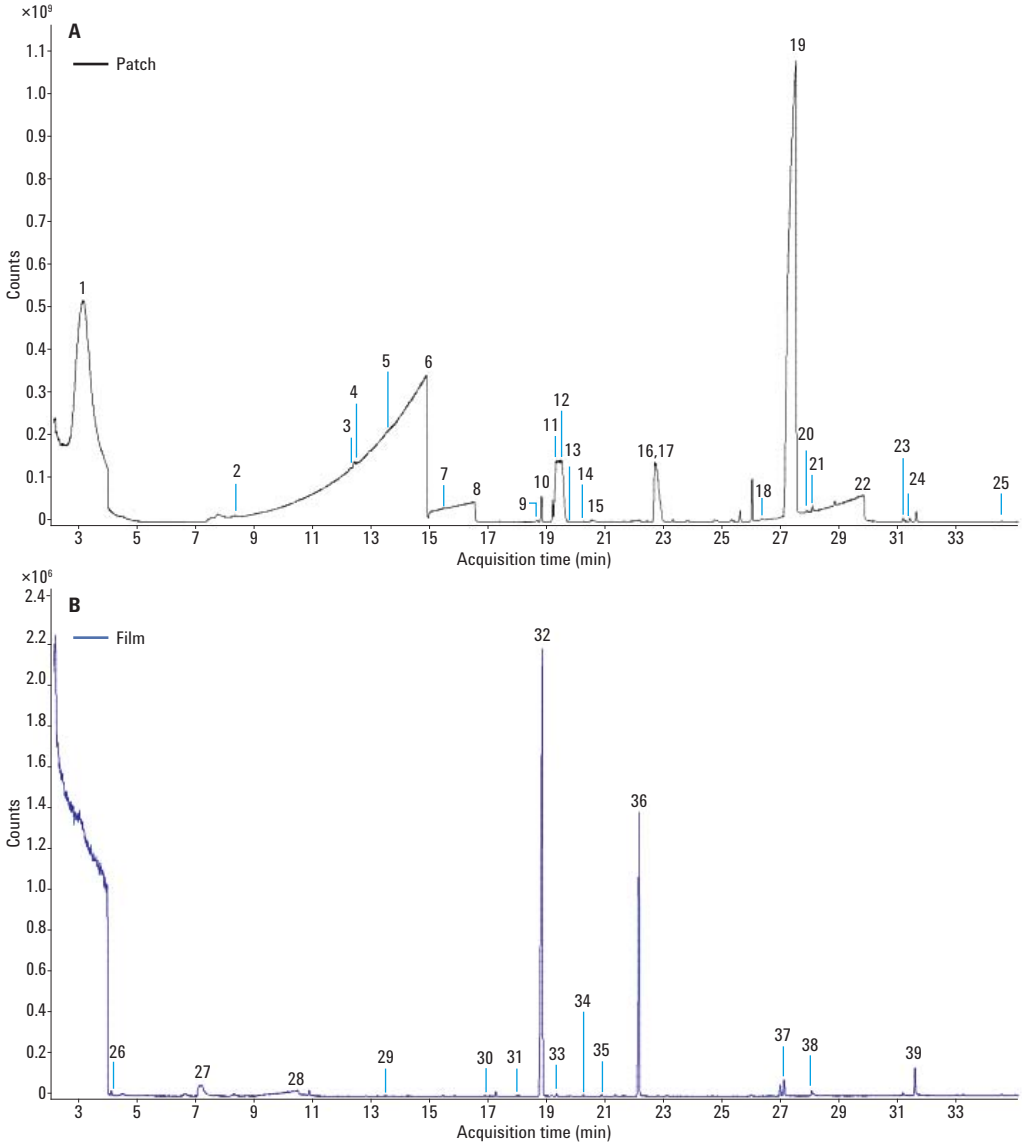
Results and Discussion

Active and inactive ingredients in the patch were identified using headspace GC/MS and ALS GC/MS. The adhesive patch contained 700 mg of the active ingredient, lidocaine (50 mg lidocaine/g of adhesive). The inactive ingredients identified were propylparaben, methylparaben, urea, propylene glycol, glycerin, and sorbitol [6].

Different plasticizers were identified by extraction with different solvents. Several terephthalate plasticizers, a component of the film release liner, were identified using acetone extraction (Table 3, Figure 2). While DEHP and benzophenone, were observed using DCM extraction (Table 4, Figure 3) [7,8], DEHA and other phthalate plasticizers were characterized using hexane extraction (Table 5, Figure 4). Fatty acid plasticizers, such as butyl ester palmitic acid and 2-methylpropyl ester stearic acid, were identified using high temperature headspace analysis (Table 6, Figure 5). Phthalate plasticizers were not identified using headspace GC/MS, which could be attributed to the high concentration of lidocaine or the strong retention and poor chromatographic performance of glycerin and propylene glycol.

Table 3. Extractable Compounds Identified in Lidocaine Patch and Film Using Acetone Extraction and ALS GC/MS

RT (min)	Patch	RT (min)	Film
3.11	Propylene glycol	4.12	2-Pentanone, 4-hydroxy-4-methyl-
8.33	1,1-Ethanediol, diacetate	7.12	Glycerin
12.29	2,6-Xylidine	10.48	Urea
12.40	2,6-Dimethylphenyl isocyanate	13.48	Phenol, 2-methoxy-
13.50	Mequinol	16.87	2-Acetyl-2-methyltetrahydrofuran
14.88	Glycerin	17.97	1,2-Ethanediol, monobenzoate
15.45	4-Methylformanilide	18.84	Methylparaben
16.53	Urea	19.32	Benzoic acid, 4-(acetyloxy)-, methyl ester
18.61	Formamide, N-(2,4-dimethylphenyl)-	20.23	Benzoic acid, 4-ethoxy-, ethyl ester
18.81	Methylparaben	20.86	Ethylparaben
19.18	1-Dodecanol	22.13	Propylparaben
19.49	Methylparaben	27.08	Lidocaine
19.72	Dimethyl terephthalate	28.09	Butyl 2-chloropropyl phthalate
20.25	Benzoic acid, 4-ethoxy-, ethyl ester	31.55	*Bis*(2-hydroxyethyl) terephthalate
20.52	*d*-Mannitol, 1,4-anhydro-		
22.68	Propylparaben		
22.75	Isobutyl 4-hydroxybenzoate		
26.32	2-Hydroxyethyl methyl terephthalate		
27.49	Lidocaine		
28.06	*n*-Palmitic acid		
28.14	Butyl cyclobutyl phthalate		
29.81	Sorbitol		
31.15	Stearic acid		
31.38	*Bis*(2-hydroxyethyl) terephthalate		
34.53	*Bis*(2-ethylhexyl) adipate		

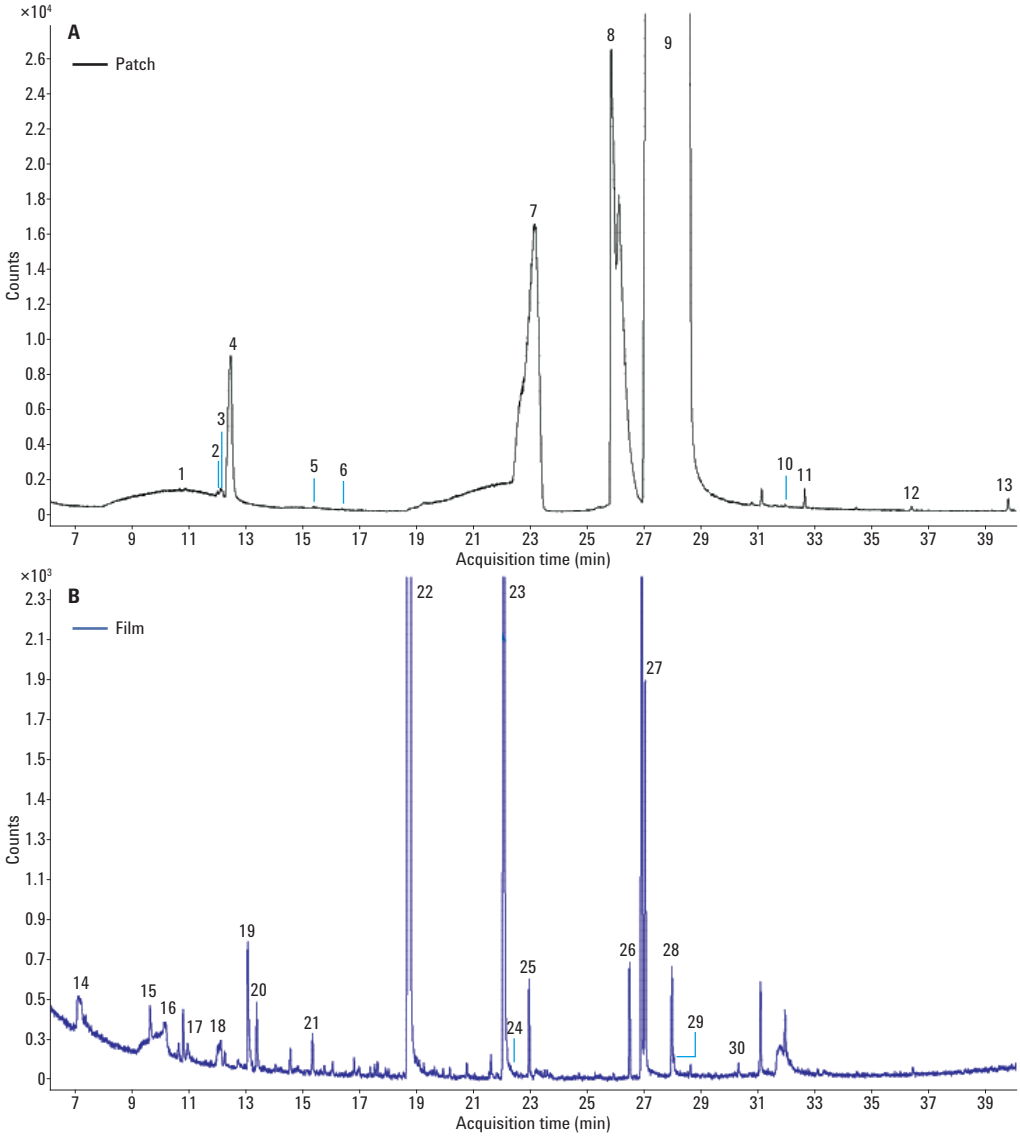


1. Propylene glycol
2. 1,1-Ethanediol, diacetate
3. 2,6-Xylidine
4. 2,6-Dimethylphenyl isocyanate
5. Mequinol
6,27. Glycerin
7. 4-Methylformanilide
8,28. Urea
9. Formamide, N-(2,4-dimethylphenyl)-
10,32. Methylparaben
11. 1-Dodecanol
12. Methylparaben
13. Dimethyl terephthalate
14,34. Benzoic acid, 4-ethoxy-, ethyl ester
15. *d*-Mannitol, 1,4-anhydro-
16,36. Propylparaben
17. Isobutyl 4-hydroxybenzoate
18. 2-Hydroxyethyl methyl terephthalate
19,37. Lidocaine
20. *n*-Palmitic acid
21,38. Butyl cyclobutyl phthalate
22. Sorbitol
23. Stearic acid
24,39. *Bis*(2-hydroxyethyl) terephthalate
25. *Bis*(2-ethylhexyl) adipate
26. 2-Pentanone, 4-hydroxy-4-methyl-
29. Phenol, 2-methoxy-
30. 2-Acetyl-2-methyltetrahydrofuran
31. 1,2-Ethanediol, monobenzoate
33. Benzoic acid, 4-(acetyloxyl)-, methyl ester
35. Ethylparaben

Figure 2. Extractables analysis of lidocaine patch (A) and film (B) using acetone extraction and ALS GC/MS.

Table 4. Extractable Compounds Identified in Lidocaine Patch and Film Using DCM Extraction and ALS GC/MS

RT (min)	Patch	RT (min)	Film
10.91	Glycerin	7.19	Glycerin
12.12	Benzene, 2-isocyano-1,3-dimethyl-	9.72	Acetophenone
12.22	Benzenamine, 2,4-dimethyl-	10.28	Urea
12.48	2,6-Dimethylphenyl isocyanate	11.04	2-Ethyl-hexoic acid
15.43	4-Methylformanilide	12.21	Benzenamine, 2,4-dimethyl-
16.42	N-(2-Phenylethenyl)acetamide	13.14	Thiophene, tetrahydro-, 1,1-dioxide
23.21	Methylparaben	13.46	Mequinol
25.91	Propylparaben	15.41	4-Methylformanilide
28.68	Lidocaine	18.84	Methylparaben
32.04	1,3-Butadiyne, 1,4-difluoro-	22.14	Propylparaben
32.72	Tributyl acetylcitrate	22.23	Benzophenone
36.48	*Bis*(2-ethylhexyl) phthalate	23.01	1,3,5-Triazine-2,4,6(1H,3H,5H)-trione, 1,3,5-tri-2-propenyl-
39.87	Squalene	26.53	*Bis*(2-methylpropyl) phthalate
		27.08	Lidocaine
		28.01	Tridecanoic acid
		28.08	Cyclobutyl tridecyl phthalate
		30.36	Pyrene

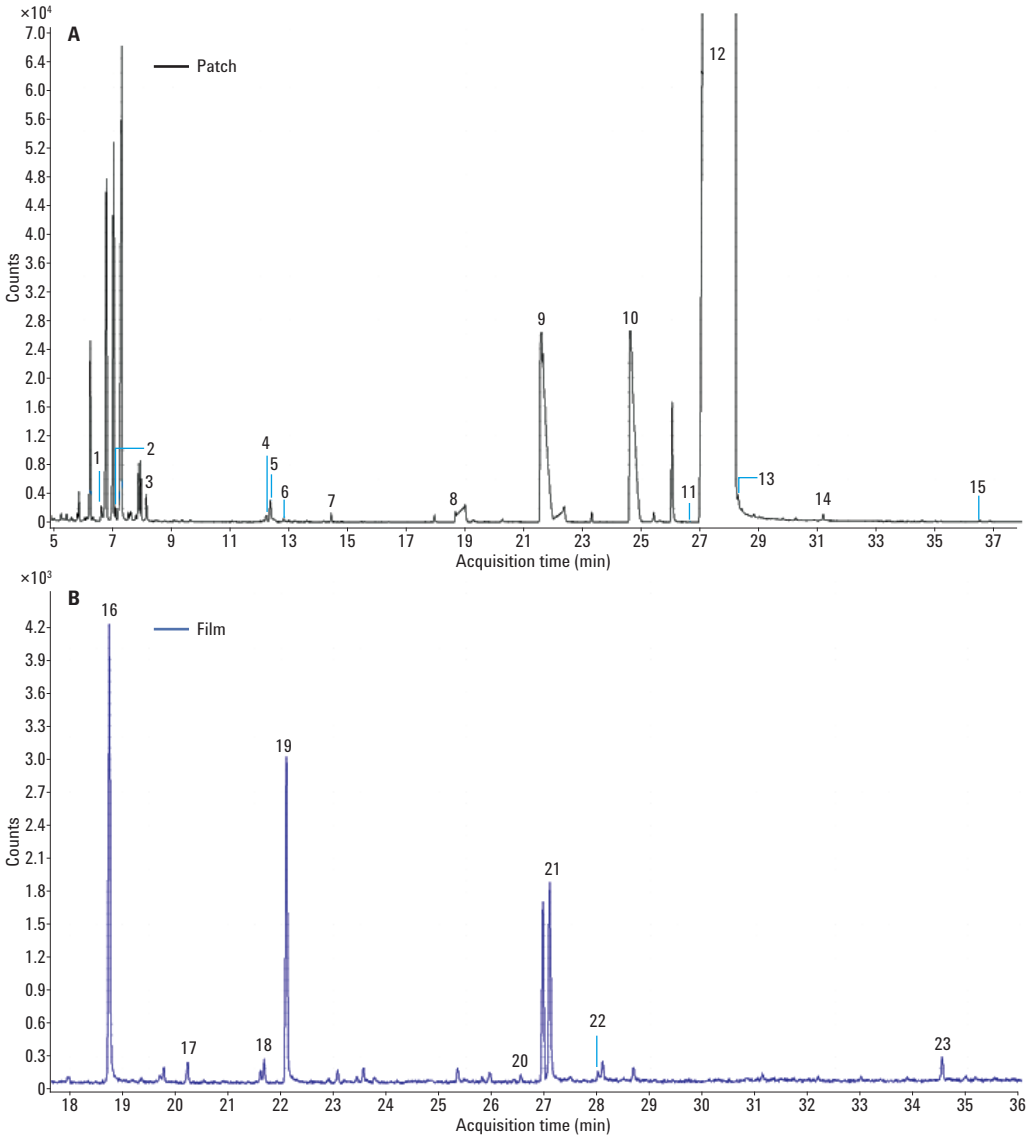


1,14. Glycerin
2. Benzene, 2-isocyano-1,3-dimethyl-
3,18. Benzeneamine, 2,4-dimethyl-
4. 2,6-Dimethylphenyl isocyanate
5. 4-Methylformanilide
6. N-(2-phenylethenyl)acetamide
7,22. Methylparaben
8,23. Propylparaben
9,27. Lidocaine
10. 1,3-Butadiyne, 1,4-difluoro-
11. Tributyl acetylcitrate
12. *Bis*(2-ethylhexyl) phthalate
13. Squalene
15. Acetophenone
16. Urea
17. 2-Ethyl-hexoic acid
19. Thiophene, tetrahydro-,1,1-dioxide
20. Mequinol
21. 4-Methylformanilide
24. Benzophenone
25. 1,3,5-Triazine-2,4,6(1H,3H,5H)-trione, 1,3,5-tri-2-propenyl-
26. *Bis*(2-methylpropyl) phthalate
28. Tridecanoic acid
29. Cyclobutyl tridecyl phthalate
30. Pyrene

Figure 3. Extractables analysis of lidocaine patch (A) and film (B) using DCM extraction and ALS GC/MS.

Table 5. Extractable Compounds Identified in Lidocaine Patch and Film Using Hexane Extraction and ALS GC/MS

RT (min)	Patch	RT (min)	Film
6.58	Formamide, N,N-diethyl-	18.75	Methylparaben
7.28	Cyclopropane, 2-bromo-1,1,3-trimethyl-	20.23	Benzoic acid, 4-ethoxy-, ethyl ester
8.20	Benzene, 2-isocyano-1,3-dimethyl-	21.61	Diethyl phthalate
12.20	2,6-Xylidine	22.10	Propylparaben
12.33	2,6-Dimethylphenyl isocyanate	26.54	Cyclobutyl heptyl phthalate
12.77	Ethanol, 1-(2-butoxyethoxy)-	27.09	Lidocaine
14.40	Tetramethyl succinimide	28.09	Dibutyl phthalate
18.63	2',6'-Formoxylidide	34.52	*Bis*(2-ethylhexyl) adipate
21.54	Methylparaben		
24.58	Propylparaben		
26.60	Cyclobutyl isobutyl phthalate		
27.01	Lidocaine		
28.40	6-Ethyl-3-octyl butyl phthalate		
31.16	Stearic acid		
36.48	*Bis*(2-pentyl) phthalate		



1. Formamide, N,N-diethyl-
2. Cyclopropane, 2-bromo-1,1,3-trimethyl-
3. Benzene, 2-isocyano-1,3-dimethyl-
4. 2,6-Xylidine
5. 2,6-Dimethylphenyl isocyanate
6. Ethanol, 1-(2-butoxyethoxy)-
7. Tetramethyl succinimide
8. 2′,6′-Formoxylidide

9,16. Methylparaben

10,19. Propylparaben

11,20. Cyclobutyl isobutyl phthalate

12,21. Lidocaine

13. 6-Ethyl-3-octyl butyl phthalate
14. Stearic acid
15. *Bis*(2-pentyl)phthalate
17. Benzoic acid, 4-ethoxy-, ethyl ester

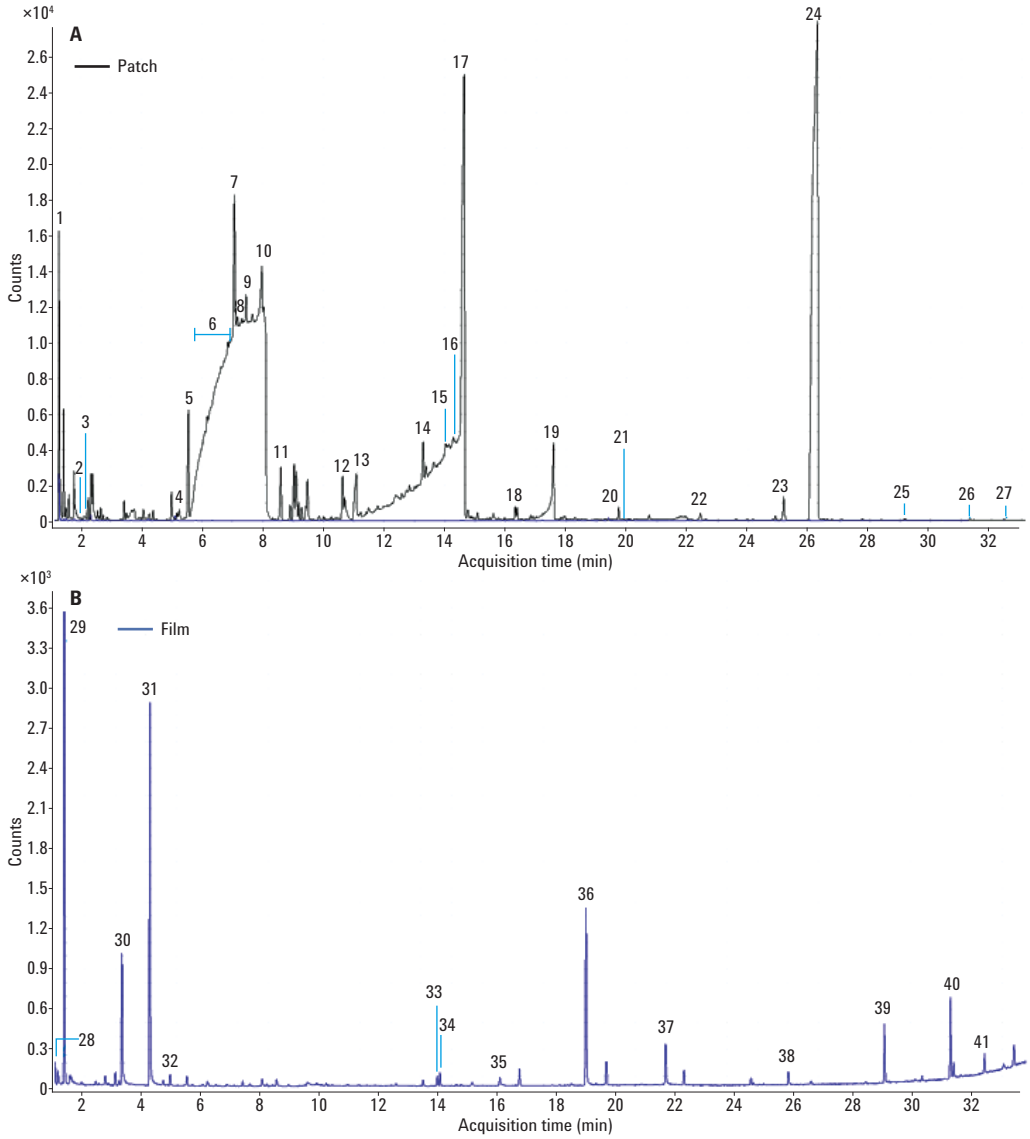
18,22. Diethyl phthalate

23. *Bis*(2-ethylhexyl) adipate

Figure 4. Extractables analysis of lidocaine patch (A) and film (B) using hexane extraction and ALS GC/MS

Table 6. Extractable Compounds Identified in Lidocaine Patch and Film using Headspace GC/MS

RT (min)	Patch	RT (min)	Film
1.29	(2-Aziridinylethyl)amine	2.03	Acetic acid, methyl ester
2.03	Acetic acid, methyl ester	2.52	Acetic acid
2.16	2-Propen-1-ol	4.22	1,2-Ethanediol
5.18	Glycidol	5.13	Propylene glycol
5.55	Pyrrole	5.79	Cyclobutene, 2-propenylidene-
7.03	Propylene glycol	14.53	Benzenamine, 2,5-dimethyl-
7.08	Pyrazine, methyl	14.62	2,6-Dimethylphenyl isocyanate
7.29	Furfural	16.57	Isosorbide
7.45	1H-Pyrole, 2-methyl	19.39	Methylparaben
7.41	1,2-Ethanediol	21.99	Propylparaben
8.60	1,2-propanediol, 1-acetate	26.01	Lidocaine
10.62	Phenol	29.15	Butyl ester palmitic acid
11.09	Pyrazine, 2-ethyl-5-methyl	31.30	2-Methylpropyl ester stearic acid
13.29	1,2,3-Propanetriol, 1-acetate	32.42	Nonadecane
14.04	5H-5-Methyl-6,7-dihydrocyclopentapyrazine		
14.53	Glycerin		
14.64	2,6-Xylidine		
16.38	1,2-ethanediamine, N,N-diethyl		
17.58	Isosorbide		
19.72	1-Dodecanol		
19.88	Methylparaben		
22.42	Propylparaben		
25.16	Acetamide, N-(2,6-dimethylphenyl)-2-(ethylamino)-		
26.08	Lidocaine		
29.15	Butyl ester palmitic acid		
31.30	2-Methylpropyl ester stearic acid		
32.42	Nonadecane		



1. (2-Aziridinylethyl)amine
2,28. Acetic acid, methyl ester
3. 2-Propen-1-ol
4. Glycidol
5. Pyrrole
6,31. Propylene glycol
7. Pyrazine, methyl
8. Furfural
9. 1H-Pyrole, 2-methyl
10,30. 1,2-Ethanediol
11. 1,2-Propanediol, 1-acetate
12. Phenol
13. Pyrazine, 2-ethyl-5-methyl
14. 1,2,3-Propanetriol, 1-acetate
15. 5H-5-Methyl-6,7-dihydrocyclopentapyrazine
16. Glycerin
17. 2,6-Xylidine
18. 1,2-Ethanediamine, N,N-diethyl
19,35. Isosorbide
20. 1-Dodecanol
21,36. Methylparaben
22,37. Propylparaben
23. Acetamide, N-(2,6-dimethylphenyl)-2-(ethylamino)-
24,38. Lidocaine
25,39. Butyl ester palmitic acid
26,40. 2-Methypropyl ester stearic acid
27,41 Nonadecane
29. Acetic acid
32. Cyclobutene, 2-propenylidene-
33. Benzeneamine, 2,5-dimethyl-
34. 2,6-Dimethylphenyl isocyanate

Figure 5. Extractables analysis of lidocaine patch (A) and film (B) using headspace GC/MS.

Plasticizers can originate from the composition of the adhesive patch or migration from the film release liner. The patch itself is composed of an adhesive material with a polyester felt backing, while the film release liner is made of PET. Extractables identified in the patch have the potential to migrate to the drug reservoir as leachables. Table 7 shows a combined list of extractable and potentially leachable compounds identified in the patch and the film using headspace GC/MS and ALS GC/MS. These compounds consisted of components in plastics, rubber, adhesives as well as pharmaceutical ingredients and precursors.

Table 7. Summary of Extractable Compounds Identified in Lidocaine Adhesive-Patch and Film-Release Liner

Compound	GC/MSD	Device	Uses
(2-Aziridinylethyl)amine	HS	Patch	
1,1-Ethanediol, diacetate	ALS (A)	Patch	
1,2-Ethanediamine, N,N-diethyl	HS	Patch	
1,2-Ethanediol	HS	Patch	
1,2-Ethanediol, monobenzoate	HS, ALS (A)	Film	Plasticizer
1,2-Propanediol, 1-acetate	HS	Patch	
1,2,3-Propanetriol, 1-acetate	HS	Patch	
1,3,5-Triazine-2,4,6(1H,3H,5H)-trione, 1,3,5-tri-2-propenyl-	ALS (D)	Film	
1,3-Butadiyne, 1,4-difluoro-	ALS (D)	Patch	
1-Dodecanol	HS and ALS (A)	Patch	Lubrication
1H-Pyrole, 2-methyl	HS	Patch	
2,6-Dimethylphenyl isocyanate	HS	Film	
2,6-Dimethylphenyl isocyanate	ALS (A, D, H)	Patch	
2',6'-Formoxylidide	ALS (H)	Patch	
2,6-Xylidine	HS and ALS (A, H)	Patch	Lidocaine precursor
2-Acetyl-2-methyltetrahydrofuran	ALS (A)	Film	
2-Ethyl-hexoic acid	ALS (D)	Film	
2-Pentanone, 4-hydroxy-4-methyl-	ALS (A)	Film	
2-Propen-1-ol	HS	Patch	
4-Methylformanilide	ALS (A, D)	Patch	
4-Methylformanilide	ALS (D)	Film	
5H-5-Methyl-6,7-dihydrocyclopentapyrazine	HS	Patch	Fragrance
Acetamide, N-(2,6-dimethylphenyl)-2-(ethylamino)-	HS	Patch	
Acetic acid	HS	Film	
Acetic acid, methyl ester	HS	Patch, film	Adhesives
Acetophenone	ALS (D)	Film	Adhesives
Benzenamine, 2,4-dimethyl-	ALS (D)	Patch, film	
Benzenamine, 2,5-dimethyl-	HS	Film	
Benzene, 2-isocyano-1,3-dimethyl-	ALS (D, H)	Patch	
Benzoic acid, 4-(acetyloxy)-, methyl ester	ALS (A)	Film	
Benzoic acid, 4-ethoxy-, ethyl ester	ALS (A)	Patch	
Benzoic acid, 4-ethoxy-, ethyl ester	ALS (A, H)	Film	
Benzophenone	ALS (D)	Film	Plasticizer
Cyclobutene, 2-propenylidene-	HS	Film	
Cyclopropane, 2-bromo-1,1,3-trimethyl-	ALS (H)	Patch	
d-Mannitol, 1,4-anhydro-	ALS (A)	Patch	

HS: headspace GC/MS, ALS: automatic liquid sampler GC/MS, A: acetone, D: dichloromethane, H: hexane

Table 7. Summary of Extractable Compounds Identified in Lidocaine Adhesive-Patch and Film-Release Liner (cont.)

Compound	GC/MSD	Device	Uses
Ethanol, 1-(2-butoxyethoxy)-	ALS (H)	Patch	
Ethylparaben	ALS (A)	Film	Preservative
Formamide, N-(2,4-dimethylphenyl)-	ALS (A)	Patch	
Formamide, N,N-diethyl-	ALS (H)	Patch	
Furfural	HS	Patch	Fragrance
Glycerin	HS and ALS (A, D)	Patch	Pharmaceutical
Glycerin	ALS (A, D)	Film	Pharmaceutical
Glycidol	HS	Patch	Plasticizer
Hexadecanoic acid	ALS (A);	Patch	Plasticizer
Hexadecanoic acid, butyl ester	HS	Patch, film	Plasticizer
Hexanedioic acid, *bis*(2-ethylhexyl) ester (DEHA)	ALS (H)	Film	Plasticizer
Hexanedioic acid, *bis*(2-ethylhexyl) ester (DEHA)	ALS (A)	Patch	Plasticizer
Isobutyl 4-hydroxybenzoate	ALS (A)	Patch	
Isosorbide	HS	Patch, film	Pharmaceutical
Lidocaine	HS	Patch, film	Anesthetic
Lidocaine	ALS (A, D, H)	Patch, film	Anesthetic
Mequinol	ALS (A)	Patch	
Mequinol	ALS (D)	Film	
Methylparaben	HS, ALS (A, D, H)	Patch, film	Preservative
N-(2-Phenylethenyl)acetamide	ALS (D)	Patch	
Nonadecane	HS	Patch, film	Plasticizer
Octadecanoic acid	ALS (A, H)	Patch	Plasticizer
Octadecanoic acid, 2-methylpropyl ester	HS	Patch, film	Plasticizer
Phenol	HS	Patch	Plastic precursor
Phenol, 2-methoxy-	ALS (A)	Film	
Phthalate, 6-ethyl-3-octyl butyl	ALS (H)	Patch	Plasticizer
Phthalate, bis(2-methylpropyl)	ALS (D)	Film	Plasticizer
Phthalate, bis(2-ethylhexyl)	ALS (D)	Patch	Plasticizer
Phthalate, *bis*(2-pentyl)	ALS (H)	Patch	Plasticizer
Phthalate, butyl 2-chloropropyl	ALS (A)	Film	Plasticizer
Phthalate, butyl cyclobutyl	ALS (A)	Patch	Plasticizer
Phthalate, cyclobutyl heptyl	ALS (H)	Film	Plasticizer
Phthalate, cyclobutyl isobutyl	ALS (H)	Patch	Plasticizer
Phthalate, cyclobutyl tridecyl	ALS (D)	Film	Plasticizer
Phthalate, dibutyl	ALS (H)	Film	Plasticizer
Phthalate, diethyl	ALS (H)	Film	Plasticizer
Propylene glycol	HS and ALS (A)	Patch	Pharmaceutical
Propylene glycol	HS	Film	Pharmaceutical
Propylparaben	HS and ALS (A, D, H)	Patch, film	Preservative
Pyrazine, 2-ethyl-5-methyl	HS	Patch	Fragrance
Pyrazine, methyl	HS	Patch	Fragrance
Pyrene	ALS (D)	Film	

HS: headspace GC/MS, ALS: automatic liquid sampler GC/MS, A: acetone, D: dichloromethane, H: hexane

Table 7. Summary of Extractable Compounds Identified in Lidocaine Adhesive-Patch and Film-Release Liner (cont.)

Compound	GC/MSD	Device	Uses
Pyrrole	HS	Patch	
Sorbitol	ALS (A)	Patch	Pharmaceutical
Squalene	ALS (D)	Patch	Pharmaceutical
Terephthalate, 2-hydroxyethyl methyl	ALS (A)	Patch	Plasticizer
Terephthalate, *bis*(2-hydroxyethyl)	ALS (A)	Patch, film	Plasticizer
Terephthalate, dimethyl	ALS (A)	Patch	Plasticizer
Tetramethyl succinimide	ALS (H)	Patch	Monomer
Thiophene, tetrahydro-, 1,1-dioxide	ALS (D)	Film	
Tributyl acetylcitrate	ALS (D)	Patch	Plasticizer
Tridecanoic acid	ALS (D)	Film	
Urea	ALS (A)	Patch	Pharmaceutical
Urea	ALS (A, D)	Film	Pharmaceutical

HS: headspace GC/MS, ALS: automatic liquid sampler GC/MS, A: acetone, D: dichloromethane, H: hexane

Conclusion

Headspace GC/MS simplifies the analysis of extractables in transdermal patches by minimizing sample preparation, while the ALS GC/MS provides capability for the analysis of extracts from various organic solvents. Large volume liquid injection improves detection of low level compounds. Phthalate plasticizers were only observed using large volume injection, suggesting that these additives could be present at low levels. Solvent extraction could be a more favorable method for detecting phthalates in transdermal patches containing high concentrations of drug ingredients. Fatty acid plasticizers were identified using headspace sampling.

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