FP 252

Simple and Accurate Analysis of Extractables from Pharmaceutical Packaging Materials using Headspace GC-MS and Special Mass Spectral Library for Additives

Kazuhiro Kawamura[1], Yukihiko Kudo[1], Noriyuki Ojima[1], Koki Tanaka[1]
1 Shimadzu Corporation, Kyoto, Japan

1 Introduction

- The concern about risk of extractables and leachables (E&L) from pharmaceutical packaging materials has been increasing.

Degree of Concern Associated with the Route of Administration	Likelihood of Packaging Component-Dosage Form Instruction		
	High	Medium	Low
Highest	Inhalation Aerosols and Solutions; Injections and Injectable Suspensions	Sterile Powders and Powders for Injection; 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 and Oral (Hard and Soft Gelatin) Capsules

*Guidance for Industry Container Closure Systems for Packaging Human Drugs and Biologics (FDA)

	Extractables	Leachables
Overview	Chemical compound that can be extracted out of packaging material	Chemical compound from packaging material that leach into the drug product
Extraction Conditions	- Solvent extraction - High-temperatures	- Normal usage conditions

- We performed GC-MS analysis of extractables from pharmaceutical packaging materials by solvent extraction and high temperature extraction.
- High temperature extraction produces a complicated chromatogram due to the decomposition of the extracted compounds and qualitative analysis becomes difficult. In this study we proposed a simple and accurate extractables analysis using headspace(HS)-GC-MS in combination with a special mass spectral library, which contains mass spectrum and retention indices of polymer additives and these decomposition products.

2. Methods and Materials

2-1. Sample Preparation

A plastic bag for liquid formulation was used as a sample. Polyvinyl chloride (PVC) was used as the base material for the bag.

- **Solvent extraction (Liquid Injection (LI)-GC-MS)**

Ethanol, dichloromethane (DCM) and hexane were used as the extraction solvents. The sample was cut into 1 cm squares, approx. 400 mg was put in a vial containing 5 mL of each solvent. The vial was sonicated for 5 hours and then left at room temperature for 3 days.

- **High temperature extraction (HS-GC-MS)**

The sample was cut into 1 cm squares, then approx. 400 mg was put and sealed in a headspace vial whose inside was replaced with nitrogen gas. A highly heat-resistant septum (Shimadzu) that can minimize bleeding in the high-temperature range was used as the septum for the vial.

2-2. Analytical Conditions

LI sampler: AOC-20i (Solvent extraction) (Shimadzu)
HS sampler: HS-20 (High temperature extraction) (Shimadzu)
GC-MS: GCMS-QP2020 NX (Shimadzu)
Column: SH-I-5ms (L=30m, 0.25 mm I.D., df=0.25 um) (Shimadzu)

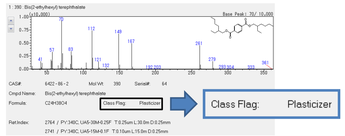
[AOC-20i]
Injection Volume: 1 µL

[HS-20]
Mode: Loop
Oven Temp.: 250 ˚C
Vial Pressure: 150 kPa
Vial Heat Time: 10 min

[GC-MS]
Injection Mode: Splitless (AOC) / Split (1:10) (HS)
Gas Control: Constant Liner Velocity (36.1 cm/s)
Oven Program: 40 ˚C (3 min) - 10 ˚C /min - 330 ˚C (15 min)
Interface Temp.: 300 ˚C
Ion Source Temp.: 230 ˚C
MS Mode: Scan（*m/z* 29～800）

2-3. Compound Identification using Polymer Additives Library

For compound identification of detected peaks, we used the Polymer Additives Library (Shimadzu) in addition to the NIST library. The Polymer Additives Library contains mass spectrum of a wide range of additives used in polymeric materials and the decomposition products of these additives. Retention index information is also registered for each compound, which enables highly accurate identification by narrowing down the retention index. The classification information of polymer additives is registered, so it is possible to find out the additive information of the identified peaks easily.



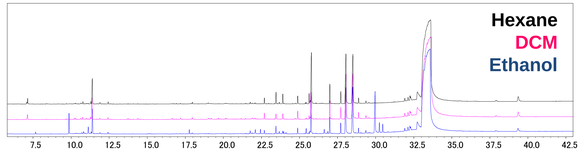
・Number of compounds 4,869
- Additives in polymer materials
- Decomposition compounds of additives

・Registered information
- Mass spectra
- Retention Indices
- Classification of additives

etc.

3. Result of Solvent Extraction (LI-GC-MS)

Plasticizers such as tris (2-ethylhexyl) trimellitate (TOTM), bis (2-ethylhexyl) phthalate (DEHP), bis (2-ethylhexyl) adipate (DEHA) and lubricants such as palmitic acid and ethyl palmilate were detected. The detected compounds differed in part depending on the extraction solvent. The difference in the detected components is considered to be due to the difference in the polarity of the extraction solvent.

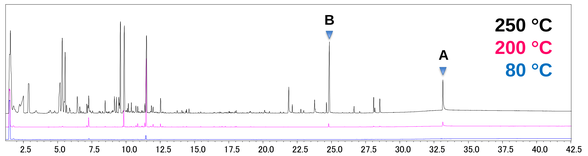


Compound Name	Hexane R.T. (min)	DCM R.T. (min)	Ethanol R.T. (min)
Isophorone	11.37	11.40	11.40
Palmitic acid	-	21.77	21.77
Ethyl palmitate	-	-	22.10
2-Ethylhexyl methyl isophthalate	23.46	23.46	23.46
Stearic acid	-	23.67	23.67
Butyl palmitate	-	23.91	23.90
Butyl stearate	-	25.63	-
Bis(2-ethylhexyl) adipate	25.75	25.78	25.78
Ethyl stearate, 9,12-diepoxy	-	-	26.63
Bis(2-ethylhexyl) phthalate	27.00	26.99	26.99
Bis(2-ethylhexyl) isophthalate	28.03	28.05	28.04
Bis(2-ethylhexyl) terephthalate	28.48	28.51	28.50
Epoxidized 2-ethylhexyl oleate	29.37	-	29.36
Tris(2-ethylhexyl) trimellitate	33.67	33.65	33.59

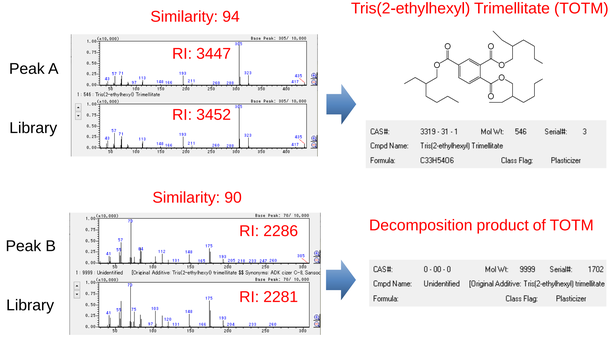
R.T.: Retention Time

4. Result of High Temperature Extraction (HS-GC-MS)

To optimize the heating temperature of the sample, we performed the analysis under the conditions of 80, 100, 150, 200, and 250 °C vial heating temperatures, and found that the maximum extraction efficiency was achieved at 250 °C.



The peak “A” was identified as TOTM from library searching. TOTM is a plasticizer often used in pharmaceutical packaging materials with PVC as the base material. Although the peak “B” was not able to be identified by the NIST library, it was found that this peak was a decomposition product of TOTM by library searching and retention index information of the Polymer Additives Library. In addition to these compounds, plasticizers such as DEHP and DEHA, and lubricants such as palmitic acid and stearic acid were identified,



Compound Name	R.T. (min)	Comment
Benzene	2.87	Solvent
2-Ethyl-1-hexene	5.52	Decomposition product of TOTM
2-Chloro-octane	9.27	Decomposition product of PVC
3-(Chloromethyl)heptane	9.57	Decomposition product of PVC
2-Ethylhexanol	9.85	Decomposition product of TOTM
Isophorone	11.47	Solvent
Palmitic acid	21.85	Lubricant
Stearic acid	23.73	Lubricant
Butyl palmitate	23.95	Lubricant
Unidentified	24.80	Decomposition product of TOTM
Bis(2-ethylhexyl) adipate	25.79	Plasticizer (DEHA)
Bis(2-ethylhexyl) phthalate	27.03	Plasticizer (DEHP)
Bis(2-ethylhexyl) isophthalate	28.05	Plasticizer
2-Ethylhexyl stearate	28.14	
Bis(2-ethylhexyl) terephthalate	28.50	Plasticizer
Tris(2-ethylhexyl) trimellitate	33.10	Plasticizer (TOTM)

5. Conclusions

- Extractables from pharmaceutical packaging material were identified by both solvent and high temperature extraction methods.
- The solvent extraction method can cover a wide range of compounds by using various solvents.
- The high temperature extraction method using HS-GC-MS can be performed more easily and in a shorter time than the solvent extraction method. The Polymer Additive Library can be used to identify the extract accurately and easily.