SHIMADZU
Excellence in Science

Application News

No. AD-0215

Pharmaceuticals / TD-30 & GCMS-QP2020 NX

Thermal Desorption – GC/MS Method for Screening Analysis of Extractables in Drug Packaging Materials

Cynthia Lahey[1], Elgin Ting[1], Dheeraj Handique[2], Yuvanesh Kumar[3], Yukihiko Kudo[4]
[1]Shimadzu (Asia Pacific) Pte Ltd, Singapore, [2]Shimadzu Analytical (India) Pvt Ltd, India,
[4]Shimadzu Corporation, Japan

❑ Introduction

Both extractables and leachables (E&L) from pharmaceutical packaging materials and products are of utmost concerns by authorities, since they may affect the efficacy, quality and safety [1]. Many regulatory guidance documents have been established regarding E&L approach and assessment. However, details on how to perform E&L evaluation in various packaging materials and products is still under discussion and development. Extractables are defined as the compounds that can be extracted from a drug packaging under certain conditions, e.g. in solvent and/or with heating. Meanwhile, leachables are compounds that migrate from the drug packaging into the drug under normal storage condition. Theoretically, leachables emerge from extractables, although not all leachables are extractables in practice (Figure 1) [2]. Analysis methods are needed for the detection and quantitation of extractables and leachables in pharmaceutical packaging and products. Here, we describe a screening analysis method for extractables in the packaging of ophthalmic solution by thermal desorption(TD)–GC-MS. The result is compared with leachables result of ophthalmic solution measured by GC-MS with liquid injection.

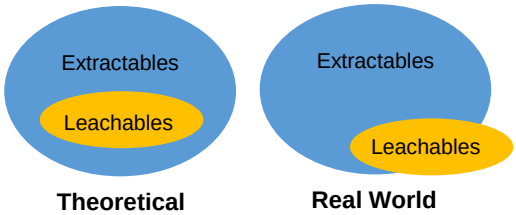

Figure 1: Relationship of Extractables and Leachables [2]

❑ Experimental

Analytical conditions

The extractables analysis was carried out using Shimadzu GCMS-QP™2020 NX coupled with thermal desorption system (TD-30). Leachables analysis was performed using the same GCMS with liquid autosampler (AOC™-20i Plus/ 20s Plus). The details of analytical conditions are shown in Table 1 and Table 2

[3]*Student from Nanyang Technological University (Singapore) for internship training program*

Table 1. Extractables Analytical Condition

Configuration	
Instrument	GCMS-QP2020 NX
Autosampler	TD-30
Analytical Condition	
GCMS Parameters	
Flow control mode	Linear velocity
Linear velocity	44.4 cm/s
Injection mode	Splitless
Carrier gas	Helium
Column	SH-Rxi™-5Sil MS (30 m length, 0.25 mm ID, df =0.25 µm)
Column temp program	50°C (hold time: 2 min) → rate: 10°C/min → 320°C (hold time: 6 min)
Ion source temp	200°C
Interface temp	250°C
Acquisition mode	Scan
Event time	0.3 s
m/z range	35-700 amu
TD-30 Parameters	
Tube desorb temp	150°C (15 min)
Tube desorb flow	120 ml/min
Second trap	Tenax® TA
Second trap cooling temp	-20°C
Second trap desorb temp	250°C (2 min)
Joint temp	250°C
Valve temp	250°C
Transfer line temp	250°C

Table 2. Leachables Analytical Condition

Configuration	
Instrument	GCMS-QP2020 NX
Autosampler	AOC-20i Plus/20s Plus
Analytical Condition	
GCMS Parameters	
Flow control mode	Linear velocity
Linear velocity	44.4 cm/s
Injection mode	Splitless
Carrier gas	Helium
Column	SH-Rxi™-5Sil MS (30 m length, 0.25 mm ID, df =0.25 µm)
Column temp program	50°C (hold time: 2 min) → rate: 10°C/min → 310°C (hold time: 7 min)
Ion source temp	200°C
Interface temp	250°C
Acquisition mode	Scan
Event time	0.3 s
m/z range	35-700 amu

Sample Preparation and Analysis of Extractables

In this study, we analyzed the extractables in the polymer packaging of ophthalmic solution, consisting of a bottle and a nozzle (both made of LDPE) as well as a cap (made of HDPE). These three samples were tested separately. 50 mg of each sample (cut into small pieces) was put inside an empty TD tube. Glass wool was placed on the sides of the sample to prevent it from being expelled out of the TD tube during analysis (Figure 2).

In the thermal desorption system (TD-30), the sample in the TD tube was heated to desorb its extractables. In this experiment, heating was done at 150^{0}C desorb tube temperature. The desorbed compounds were then transferred to a second trap (containing adsorbents) for concentration and focusing. Subsequently, the extractables were released from the second trap and transferred to GCMS for analysis. These steps are illustrated in Figure 2.

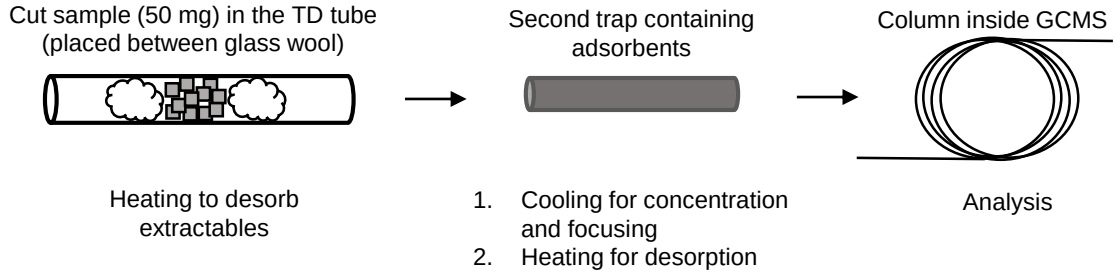

Figure 2: Schematic Diagram of Extractables Analysis on TD-GCMS

❑ Results and Discussion

Extractables Result

The chromatograms of the samples are displayed in Figure 3-5. Most of the peaks detected are hydrocarbons, which possibly came from the breakdown of lubricant wax. The bottle and nozzle samples (both LDPE) exhibit similar chromatogram profiles, while the cap sample (HDPE) has higher amount of hydrocarbons extracted.

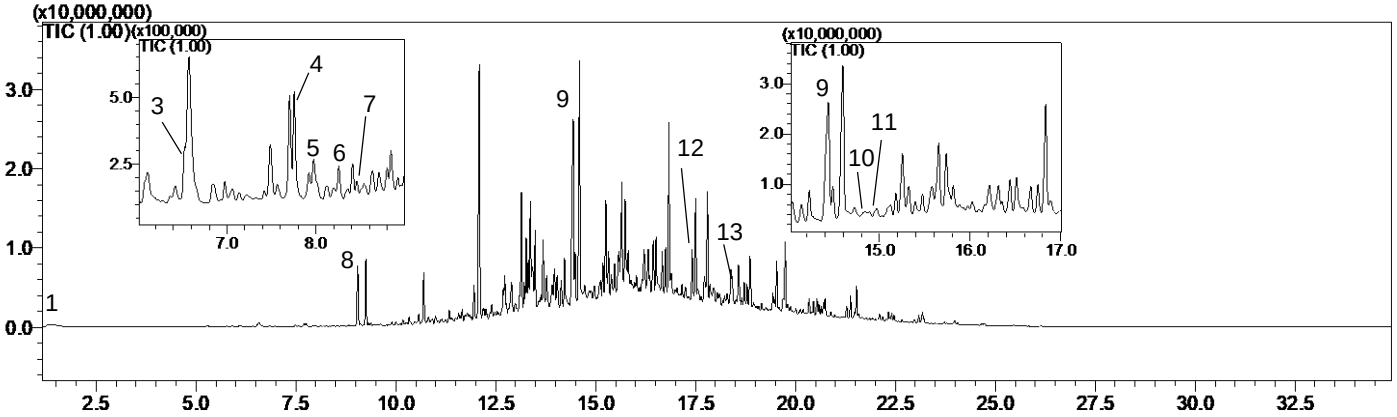

Figure 3: Total Ion Chromatogram (TIC) of Extractables in the Bottle of Ophthalmic Solution Packaging by TD-GCMS

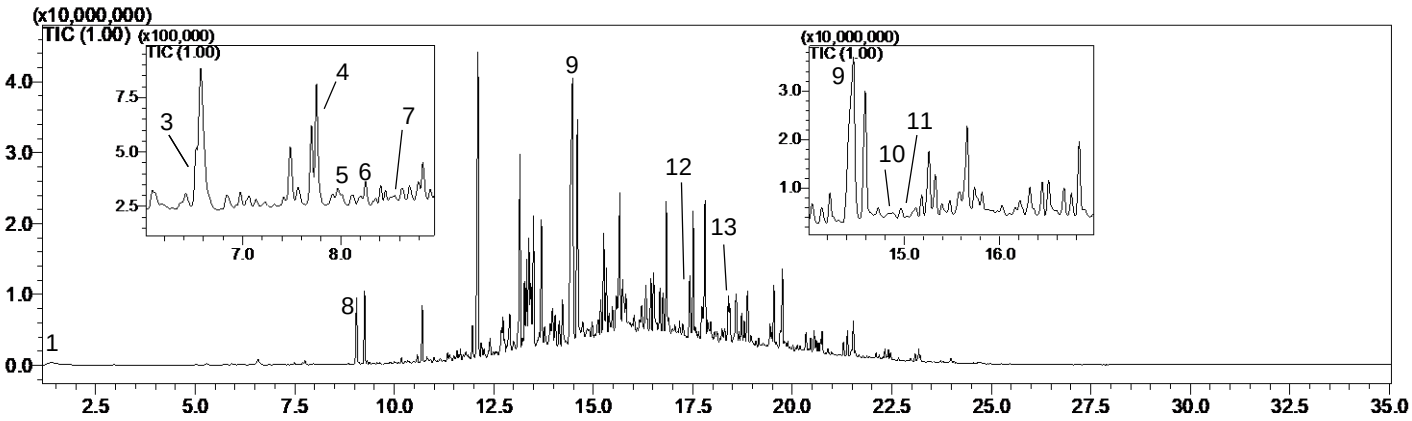

Figure 4: Total Ion Chromatogram (TIC) of Extractables in the Nozzle of Ophthalmic Solution Packaging by TD-GCMS

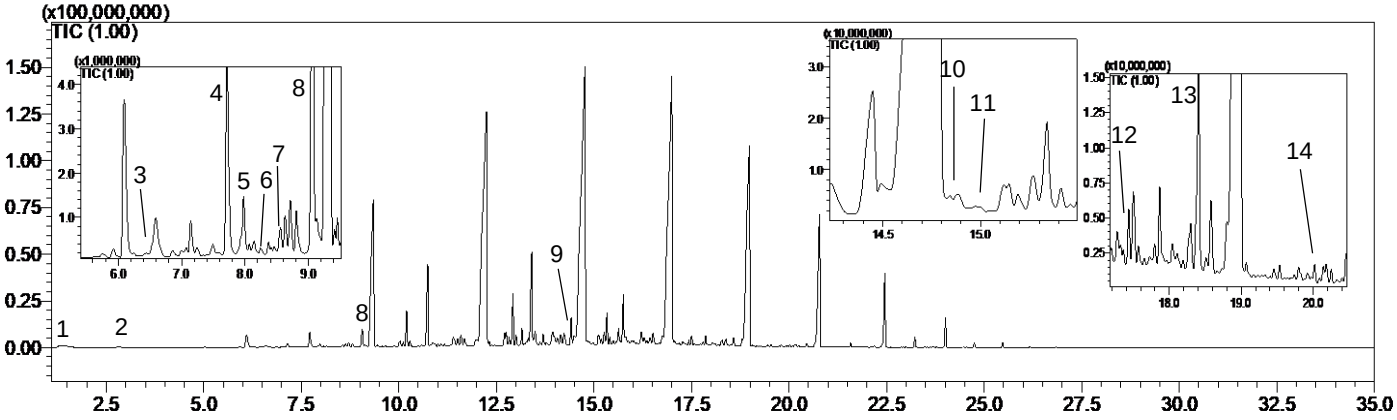

Figure 5: Total Ion Chromatogram (TIC) of Extractables in the Cap of Ophthalmic Solution Packaging by TD-GCMS

Table 3. Detection Results of Extractables in Packaging Materials by TD-GCMS (✓ Detected, × Not detected)

Peak No.	Compound	Possible source	Bottle	Nozzle	Cap
1	Acetone	Residual solvent	✓	✓	✓
2	1,3-dichloropropane		×	×	✓
3	2-Ethyl-1-hexanol	Breakdown of plasticizer or antioxidant	✓	✓	✓
4	Nonanal	Breakdown of lubricant or stabilizer	✓	✓	×
5	2-chlorobenzaldehyde		✓	✓	✓
6	Decamethylcyclopentasiloxane (D5)	Breakdown of resin modifier or lubricant	✓	✓	✓
7	Benzoic acid		✓	✓	✓
8	Naphthalene	Breakdown of fire retardant	✓	✓	✓
9	Diethyl Phthalate (DEP)	Plasticizer	✓	✓	✓
10	2,6-Bis(tert-butyl)-4-ethenylphenol	Breakdown of antioxidant	✓	✓	✓
11	Benzophenone	Breakdown of stabilizer	✓	✓	✓
12	Diisobutyl phthalate (DIBP)	Plasticizer	✓	✓	✓
13	Dibutyl phthalate (DBP)	Plasticizer	✓	✓	✓
14	Methyl stearate	Breakdown of plasticizer	×	×	✓

The results of identified extractables are presented in Table 3. Identification was carried out using NIST 14 Library and Shimadzu Polymer Additives Library. Three types of plasticizers (peak 9, 12 and 13), common additives in polymers, were detected. Various breakdown species of polymer additives (e.g. antioxidant, lubricant, fire retardant) were detected, as remarked in Table 3. Acetone, a residual solvent, was also identified in all samples.

Comparison with Leachables Result

The results of extractables obtained above are compared with that of leachables of the ophthalmic solution. The solution was stored in the complete packaging (including the bottle, nozzle and cap) under normal storage condition. The leachables analysis was performed by liquid injection of the sample to GCMS. The chromatogram profile is shown in Figure 6.

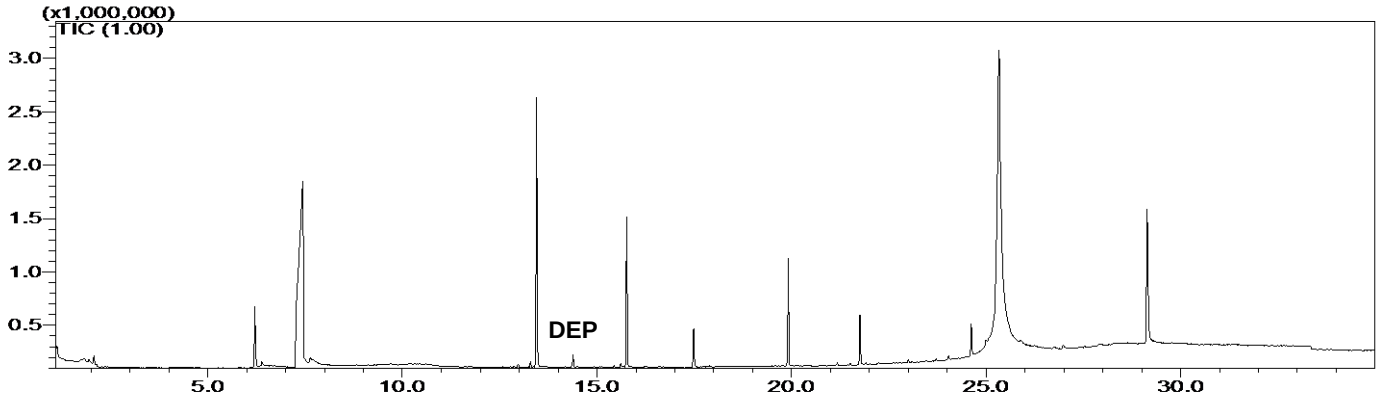

Figure 6: Total Ion Chromatogram (TIC) of Leachables in Ophthalmic Solution by Liquid Injection to GCMS

The peaks in the ophthalmic solution were mainly the content of the drug itself, except diethyl phthalate (DEP). This plasticizer was also detected in the preceding extractables analysis (peak 9, Table 3) by TD-GCMS.

❑ Conclusion

A fast and straightforward screening analysis for extractables in drug packaging was established on Thermal Desorption – GCMS system. This method is primarily suitable for qualitative screening of extractables in the drug packaging of the ophthalmic solution. Three types of plasticizers, a number of breakdowns of polymer additives, as well as other volatiles and semivolatiles were detected and identified using NIST 14 Library and Shimadzu Polymer Additives Library. As a comparison, leachables analysis of the ophthalmic solution contained in the packaging was also carried out by liquid injection of the solution to GCMS. Only one of the found extractables, i.e., DEP, was detected in the leachable analysis.

❑ References

1. Yu, X., Wood, D., Analytical Testing – Extractables and Leachables Testing for Pharmaceutical Products, Pharmaceutical Outsourcing, Nov/Dec 2017.
2. Wood A., Extractables and Leachables Analysis of Pharmaceutical Products, https://www.outsourcing-pharma.com/Headlines/Promotional-Features/Extractables-and-leachables-analysis-of-pharmaceutical-products

Shimadzu GCMS-QP™2020 NX and TD-30

SHIMADZU (Asia Pacific) Pte. Ltd
79 Science Park Drive, #02-01/08 Cintech IV, Singapore 118264,
www.shimadzu.com.sg; Tel: +65-6778 6280 Fax: +65-6778 2050