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Thermal Desorption – GCMS Method for Screening Analysis of Extractables in Drug Packaging Materials

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1. Overview

- Extractables are compounds extracted from drug packaging materials under certain conditions. Leachables are compounds that migrate from the packaging to the drug product under normal storage condition.
- Analysis of extractables was developed using thermal desorption (TD) – GCMS with minimal sample preparation.
- Volatiles and semi-volatiles extractables were able to be identified from the packaging of ophthalmic solution.
- The results of the extractables was compared with leachables result of the ophthalmic solution by GCMS with liquid injection.

2. 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. Analysis methods are needed for the detection and quantitation of extractables and leachables in pharmaceutical packaging and products. Solvent extraction steps for extractables are usually time-consuming, including heating, liquid-liquid extraction, concentration and so forth. Here, we describe a simpler screening analysis method for volatile and semivolatile extractables in the packaging of ophthalmic solution by thermal desorption (TD) – GCMS. The results were compared with leachables result of ophthalmic solution measured by GCMS with liquid injection.

Figure 1: GCMS-QP2020 NX with TD-30

3. Method

The analysis of extractables was performed using Shimadzu GCMS-QP2020 NX coupled with thermal desorption system (TD-30) (Figure 1). The details of analytical conditions are shown in Table 1.

Table 1. Analysis Conditions of Extractables Analysis

Configuration	
Instruments	GCMS-QP2020 NX and TD-30
GCMS Parameters	
Flow control mode	Linear velocity
Linear velocity	44.4 cm/s
Injection mode	Splitless
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

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.

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°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.

4. Results

The chromatograms of the samples are displayed in Figures 2-4. Most of the peaks detected were hydrocarbons, which possibly came from the breakdown of lubricant wax. The bottle and nozzle samples (both LDPE) exhibited similar chromatogram profiles, while the cap sample (HDPE) had higher amounts of hydrocarbons extracted.

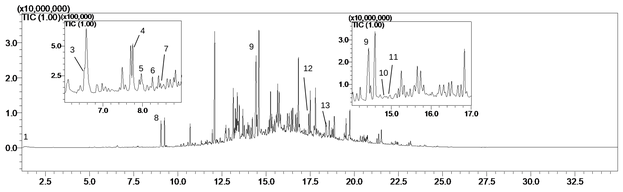

Figure 2: Profile of extractables in the bottle of ophthalmic solution packaging

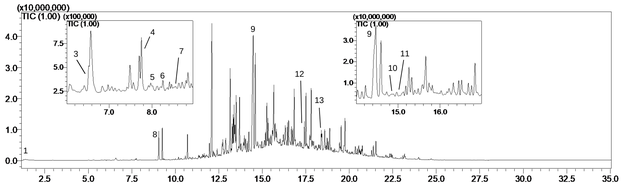

Figure 3: Profile of extractables in the nozzle of ophthalmic solution packaging

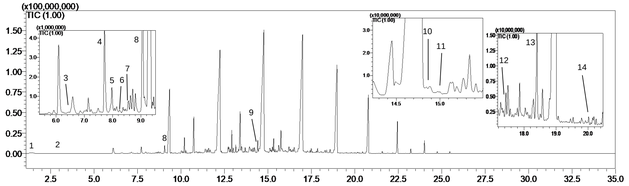

Figure 4: Profile of extractables in the cap of ophthalmic solution packaging

Table 2. 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 2. Identification was carried out using NIST 14 Library and Shimadzu Polymer Additives Library. Three types of plasticizers (peaks 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 2. Acetone, a residual solvent, was also identified in all samples.

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 5.

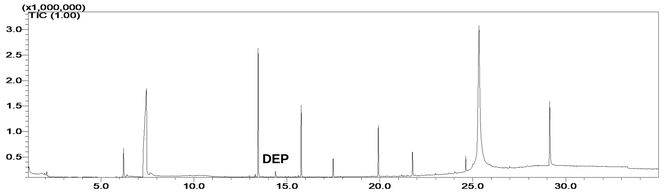

Figure 5: GCMS result of Leachables in the Ophthalmic Solution by Liquid Injection

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 2) by TD-GCMS.

5. Conclusions

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 ophthalmic solution. Three types of plasticizers, a number of breakdowns of polymer additives, as well as other volatiles and semi-volatiles were detected and identified using NIST 14 Library and Shimadzu Polymer Additives Library. As a comparison, analysis of leachables in 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.

6. Acknowledgement

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7. References

1. Yu, X., Wood, D., Analytical Testing – Extractables and Leachables Testing for Pharmaceutical Products, Pharmaceutical Outsourcing, Nov/Dec 2017.