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Gas Chromatograph Mass Spectrometer GCMS-TQ™8050 NX, HS-20 NX Trap

Application News

Extractable Study of Container Closure Pack Used to Store Oral Drug Product Using Dynamic Headspace Technique

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User Benefits

- ASSP™ and simultaneous Scan/MRM analysis facilitating accurate qualitative identification and quantitation at the same time.
- Dynamic headspace enables concentrating the analytes in cold trap with multi-injection count and helps to achieve higher sensitivity over static headspace, especially for trace level quantitation.

■ Introduction

Overview:
Extractable and leachable (E & L) studies are becoming increasingly important in the pharmaceutical industry as it is a mandatory requirement from FDA during filing of the drug product. The purpose of E & L studies is to identify and evaluate possible toxicological risks. In this study, the regulatory references aim to identify traces of potential chemical substances. These substances may be harmful to patients due to their toxicity or may impact the activity of the drug product. Hence, to ensure the safety and efficacy of the drug throughout its shelf-life, E & L studies play an important role.

What Are Extractables and Leachables ?
Extractables are organic and inorganic chemical entities that are released from a pharmaceutical packaging/delivery system, packaging component, or packaging material of construction into an extraction solvent under laboratory conditions[1].
Leachables are foreign organic and inorganic chemical entities that are present in a packaged drug product because they have leached into the packaged drug product from a packaging/delivery system, packaging component, or packaging material of construction under normal conditions of storage and use or during accelerated drug product stability studies [1].

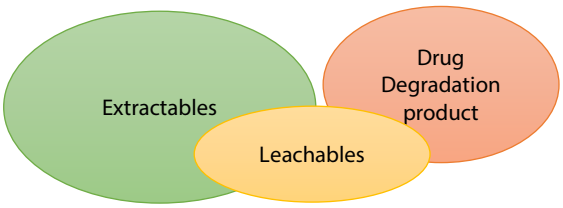

Figure 1: Extractables, Leachables and Drug degradation product

Figure 1 depicts hypothetical relation between Extractables, Leachables and Drug Degradation products.

Sources of Extractables:
Extractables are derived from a variety of sources and exhibit extensive chemical diversity. Few of the primary sources are listed below.

i. Chemical additives in individual polymeric packaging material
ii. Chemical entities that are present in the packaging components
iii. Monomers and higher molecular mass oligomers derived from incomplete polymerization
iv. Migrants from secondary and tertiary packaging materials such as inks, label adhesives etc.
v. Surface residues on metal canisters and containers
vi. Chemical substances on the surface of components fabrication machinery such as anti-static agents.

Safety Thresholds:
Product Quality Research Institute (PQRI) has specified the control thresholds like Safety Concern Threshold (SCT) and Analytical Evaluation Threshold (AET) to guide the direction for initial assessment.
SCT is the threshold below which a leachable has a dose so low that it presents negligible carcinogenic and non-carcinogenic toxic effects. In PQRI, it is specified as 1.5 µg/day for Parenteral and Ophthalmic Drug Products (PODP). AET is the threshold at or above which a leachable should be characterized and reported for toxicological assessment.
The AET can be mathematically derived from the SCT based on the factor that includes the dosing parameters of the drug product. For calculating the AET, formulae reported in the PQRI recommendation document were followed [2].

Before designing the extractable or leachable study, calculation of AET is a must. To calculate the AET, information of drug product such as maximum daily dose (MDD), Pack size, number of dose per container closure pack (CCP), root of administration and respective SCT etc is required. Penicillin V was available in lab and the same was considered for AET calculation. Some of the parameters which were considered for this calculation are mentioned in Table 1.

Table 1: Product information for AET calculation

Parameter	Value
Name of the product	Penicillin V
Route of administration	Oral
Pack size (mL)	100 mL
MDD (mL/day)	20 mL considering 4 doses of 5 mL
Material of construction (MOC) of CCP	Plastic, Glass
SCT for OINDP	1.5 µg/day
Posology or strength	125 mg / 5 mL and 250 mg / mL

Calculation of AET:

$$\text{AET (µg/Container)} = \frac{\text{SCT (µg/Day)}}{\text{MDD (mL/Day)}} \times \text{No. of doses per CCP}$$

$$= \frac{1.5\ (\mu g/Day)}{4\ (Doses/Day)} \times 20\ \text{doses /pack}$$

$$= 7.5\ (\mu g/Pack)$$

After applying uncertainty of 0.5 : **3.75 (µg/pack)**

For liquid dosage form = 3.75 (µg/pack) / Pack size (mL)

=3.75 µg / 100 mL = **0.0375 ppm**

As per above calculation, if the CCP under study is supposed to be used for the storage of the Penicillin V with above dosage form, then it should not leach any chemical above 0.0375 ppm. And if any chemical entity observed above this threshold, then identification and toxicological assessment of that entity is required. Figure 2 depicts typical image of CCP under study.

Note: Uncertainty factor is generally applied to overcome the risk associated due to extraction error and to evaluate the toxic entities below its accepted level.

Figure 2: Typical images of CCP

■ Experimental Design

There are many ways by which extractable study can be designed like generating extract by maceration (solvent soaking), by reflux/Soxhlet/sealed vessel/sonication or solvent extraction (manually and automated) etc [1]. However, one can perform this study by directly heating the CCP using the headspace injection technique.

Physical and chemical properties of the drug product such as pH, polarity and chemical composition plays an important role and need to be considered while designing the extraction experiments.

Extractable study is performed at accelerated temperature conditions considering worst case scenario for storage of the drug product. Since measured pH for the final drug product inside was slightly acidic, we conducted extractable study at similar pH by refluxing the CCP with solvents of different polarities. This scenario will be more effective in focusing on extractables that can migrate into the drug product, thereby increasing the probability of detecting them as potential leachables. As a result, it allows for a more realistic assessment of potential risks associated with the packaging or material components under actual use conditions.

Experiment-A (Incubation with acidic media):

To mimic the condition, acidic media was selected for evaluation. Two bottle caps were incubated at 85 ˚C for 72 hours with 50 mL Formic acid media having pH of 2. After incubation, 25 mL of incubated solution inside the packaging material was extracted using 25 mL of Ethyl acetate (EA) and the layer was transferred to a test tube prefilled with Sodium sulfate.

Experiment-B-1 (Reflux with Polar solvent):

Product under study contains water as a major constituent, which is highly polar. To mimic the same, polar solvent was considered for reflux experiment.

One cap of the CCP was cut in the small pieces and refluxed with 50 mL Ethanol at 80 ˚C for 2 hrs. Then this refluxed solution was cooled at room temperature, transferred 10 mL of solution from reflux flask in a test tube and evaporated till dryness using nitrogen evaporator. Contents left in the tube were re-constituted with 1 mL of Methanol, sonicated, filtered through 0.2 µ syringe filter and used for analysis.

Experiment-B-2 (Reflux with Non-polar solvent):

This experiment was performed in the same way as stated in the B-1. Only Hexane was used as reflux medium instead of Ethanol. Non-polar solvent was selected for reflux considering worst case scenario.

Entire experimental design flowchart is depicted in Figure 3 below.

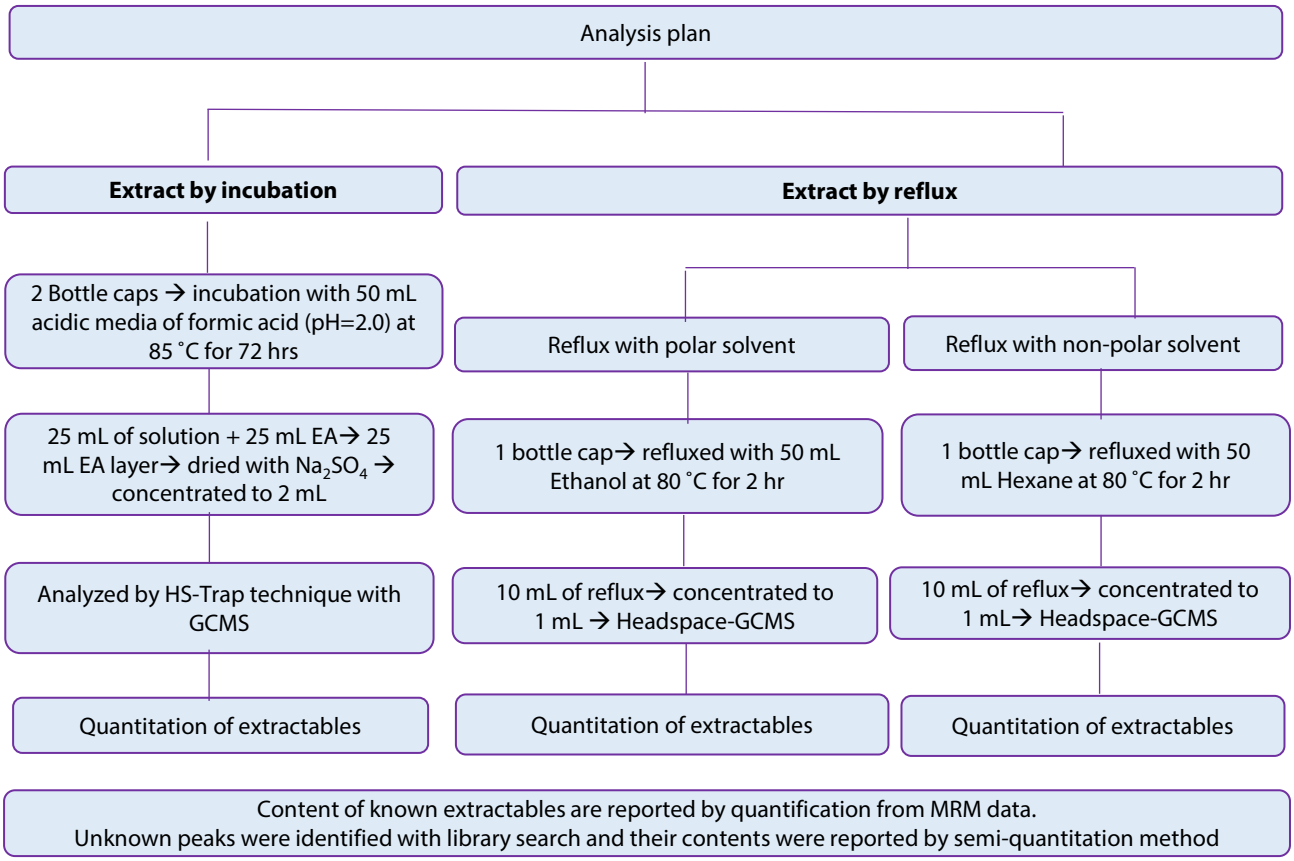

Figure 3 : Detailed layout of the experiments designed for sample preparation

■ Methods of Analysis

In this method, fifteen standards were analyzed by GCMS-TQ8050 NX with HS-20 NX (Trap) autosampler. For the method suitability, several important parameters like system suitability, linearity and precision were performed.
Instrument parameters and MRM transitions are shown in Tables 2 and 3, respectively.

Table 2: Instrument parameters

Instrument used	:	**GCMS-TQ8050 NX with HS-20 NX (Trap)**
Column	:	SH-I-5Sil MS 0.25 mm I.D. X 30 m d.f=0.25 µm (P/N: 221-75954-30)
Injection Mode	:	Split (P/N : 227-35007-01)
Split ratio	:	10
Flow control mode	:	Linear velocity
Linear velocity	:	36 cm/sec
Carrier gas	:	Helium
Temp. Program	:	40 ˚C (1 min), 7 ˚C/min to 110 ˚C (3 min), 10 ˚C/min to 280 ˚C (4 min)
Ionization Mode	:	Electron Impact
Ion source Temp.	:	220 ˚C
Interface Temp.	:	280 ˚C
Acq. Mode	:	SCAN/MRM
Scan Range	:	45–500 *m/z*
Detector Voltage	:	Optimized by adjusting the intensity of *m/z* 314 = 500000 in autotuning

Parameters for Dynamic Headspace:

Mode	:	Trap
Oven Temp.	:	120 ˚C
Sample Line Temp.	:	170 ˚C
Transfer Line Temp.	:	200 ˚C
Trap cooling Temp.	:	-20 ˚C
Trap Desorb. Temp.	:	280 ˚C
Trap Equilibrium Temp.	:	-20 ˚C
Shaking Level	:	5
Multi Injection Count	:	3
Pressurization Gas Pressure	:	130 kPa
Dry Purge Gas Pressure	:	40 kPa
Equilibrating Time	:	10 min
Dry Purge Time	:	0 min
Injection Time	:	25 min
Needle Flush Time	:	25 min
GC Cycle Time	:	45 min

Table 3: MRM transitions

MRM Transitions				
Compound name	**Target MRM**	**CE-1**	**Reference MRM**	**CE-2**
Toluene D8	100.00>98.10	19	98.00>70.10	19
Cyclotrisiloxane, hexamethyl-	207.00>191.00	17	207.00>119.10	27
Alpha methyl benzene	117.00>115.10	13	117.00>91.10	19
2-Octanone	58.00>43.00	9	59.00>43.10	27
Isobutyl benzene	91.00>65.10	19	134.00>91.10	19
Cyclopentasiloxane, decamethyl-	73.00>45.00	13	267.00>250.90	19
Tridecane	71.00>43.10	9	85.00>43.10	9
1,1'-Biphenyl, 2-fluoro-	172.00>170.10	25	172.00>151.10	25
Tetradecane	71.00>43.10	9	85.00>43.10	9
Butyrated Hydroxy Toluene	205.00>57.10	19	220.00>205.20	13
2,6-Di-tert-butyl-4-ethylphenol	219.00>57.10	19	234.00>219.20	13
Benzophenone	105.00>77.10	13	105.00>95.10	19
3,5-di-tert-Butyl-4-hydroxybenzaldehyde	219.00>191.20	9	219.00>175.10	17
Eicosane	71.00>43.10	9	85.00>43.10	9
Docosane	71.00>43.10	9	85.00>43.10	9

■ Standard Preparation

Standard chemicals which are listed above, were procured and appropriately diluted with Methanol and Water to achieve the desired concentration as mentioned in Table 4. Preparation steps were followed as shown in Figure 4.
Linearity of the all above listed compounds was performed in the SCAN/MRM mode and used for semi-quantitation of unknown extractables.

- Prepared 10 ppm mix standard stock of all targeted impurities in Methanol
- From this stock, prepared linear level standards such as 0.1 ppm, 0.3 ppm, 0.5 ppm, 1 ppm and 2 ppm in methanol
- Transferred 1 mL MS grade water in a 20 mL HS vial, added 100 mg sodium sulfate and 25 µL of linearity level standard
- Crimped carefully and submitted for GCMS analysis

Figure 4 : Standard preparation procedure

■ Results and Discussion

Figure 5 to 10 depicts data for some of the representative analytes. Each figure shows data for one representative analyte and divided into 4 sections as follows, (a) calibration curve and (b) chromatogram at LOQ level for MRM mode. Similarly, (c) and (d) shows data for TIC response in SCAN mode .

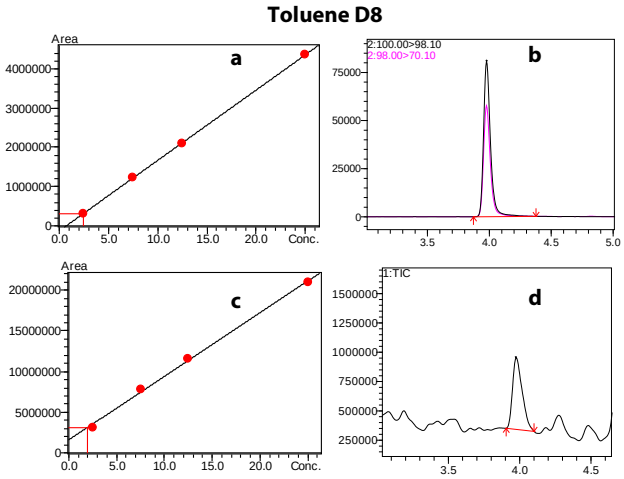

Figure 5: Data for Toluene D8

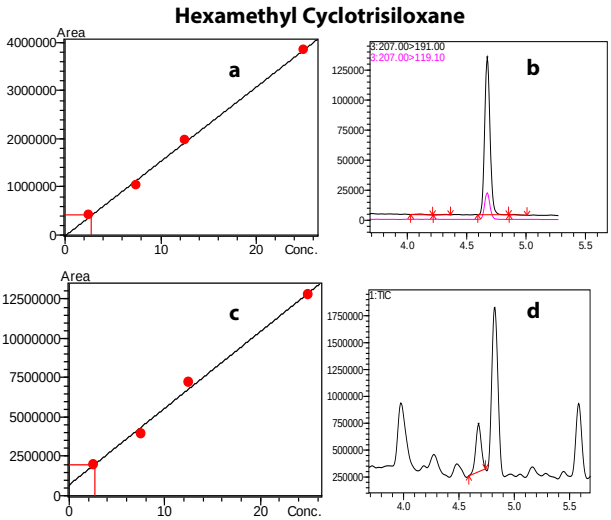

Figure 6: Data for Hexamethyl Cyclotrisiloxane

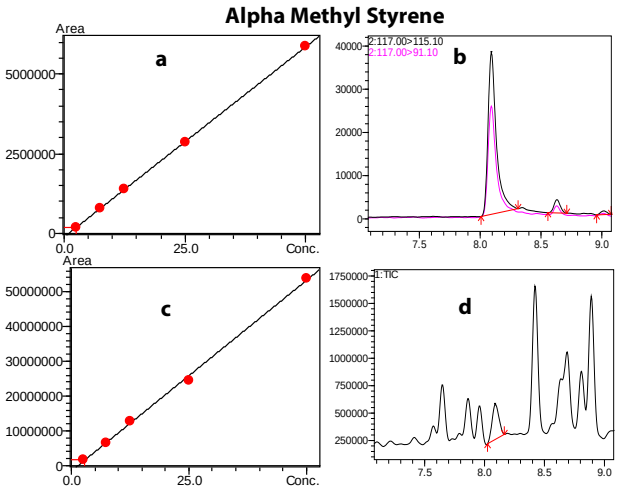

Figure 7: Data for Alpha Methyl Styrene

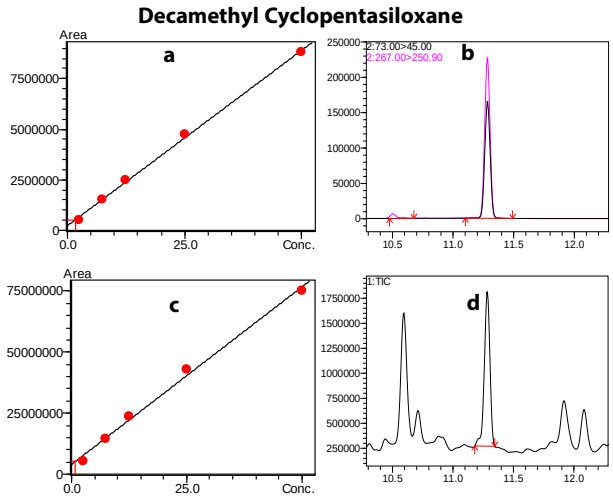

Figure 8: Decamethyl Cyclopentasiloxane

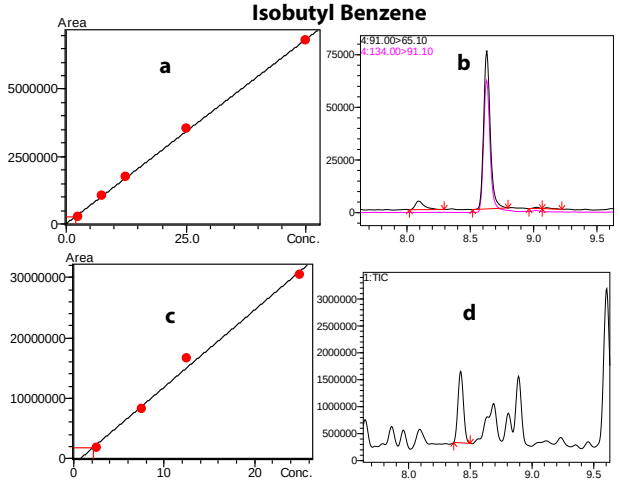

Figure 9: Isobutyl Benzene

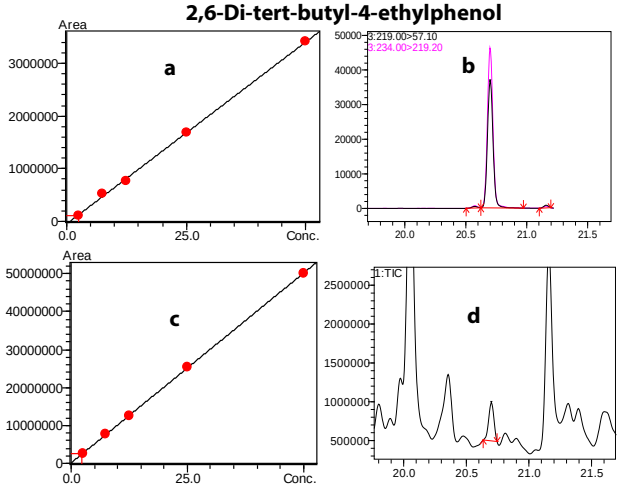

Figure 10: 2,6-Di-tert-butyl-4-ethylphenol

The noise levels in SCAN mode are generally high. This can be further confirmed by the LOQ chromatograms displayed in section (d) of each figure. However, this data were used for semi-quantitation of unknown extractable impurities only. Average of slope and intercept values from the calibration plot of targeted compounds were used for the quantifying unknown impurities.

Fifteen compound were selected for analysis which generally observed in extractable study and they have potential to leach into the drug product.

Results obtained from the standard data acquisition are reported as shown in the below Table 4. All the compounds are complying with the acceptance criteria for correlation coefficient (not less than 0.99) and S/N ratio (not less than 10).

Table 4 : Results of standard acquisition

Sr. No.	Compound Name	RT (min)	Linearity range (ppb)	LOQ (ppb)	Correlation coefficient (r^2)		S/N* ratio at LOQ
					MRM	SCAN	
1	Toluene D8	4.0	2.5 to 25	2.5	1.000	0.998	1530
2	Cyclotrisiloxane, hexamethyl-	4.7	2.5 to 25	2.5	0.997	0.994	93
3	Alpha methyl benzene	8.1	2.5 to 50	2.5	1.000	0.999	70
4	2-Octanone	8.2	2.5 to 50	2.5	0.995	0.992	32
5	Isobutyl benzene	8.6	2.5 to 25	2.5	0.999	0.993	71
6	Cyclopentasiloxane, decamethyl-	11.3	2.5 to 50	2.5	0.998	0.994	66
7	Tridecane	16.1	2.5 to 50	2.5	0.997	0.994	543
8	1,1'-Biphenyl, 2-fluoro-	17.6	2.5 to 50	2.5	0.997	0.991	11
9	Tetradecane	18.2	2.5 to 50	2.5	0.991	0.991	47
10	Butyrated Hydroxy Toluene	20.0	2.5 to 50	2.5	0.997	0.991	11
11	2,6-Di-tert-butyl-4-ethylphenol	20.7	2.5 to 50	2.5	0.999	1.000	31
12	Benzophenone	21.9	2.5 to 50	2.5	0.997	0.991	1589
13	3,5-di-tert-Butyl-4-hydroxybenzaldehyde	23.4	2.5 to 50	2.5	0.995	0.994	11
14	Eicosane	25.8	2.5 to 50	2.5	0.991	0.991	2676
15	Docosane	27.7	2.5 to 50	2.5	0.998	0.996	11

**Note: Reported S/N values are from MRM acquisition and calculated as per ASTM method. Reported concentration are as such concentrations.*

The commonly available technique across all the instrument provider is static headspace injection technique, wherein only limited volume of the analyte gas will be used for the analysis. Generally, it is 1 mL and not sufficient to achieve the sensitivity at trace level.

Shimadzu's dynamic headspace technique enables multiple headspace extractions (up to 10 times) from the same vial and allows to concentrate the analytes on the cold trap. This enhances the sensitivity and allows trace level detection which static headspace fails to achieve under similar conditions.

Furthermore, users can perform maximum headspace extractions from same vial up to 10 times and enhance the method capability to detect the analytes at trace level where static headspace technique fails to achieve under similar condition. Figure 11 depicts Shimadzu GCMS-TQ8050 NX instrument with HS-20 NX (Trap) autosampler.

Figure 11: Shimadzu GCMS-TQ8050 NX with HS-20 NX (Trap)

To compare the sensitivities between these two-injection techniques especially for extractable and leachable study, we performed the screening of this CCP. The steps are shown in Figure 12.

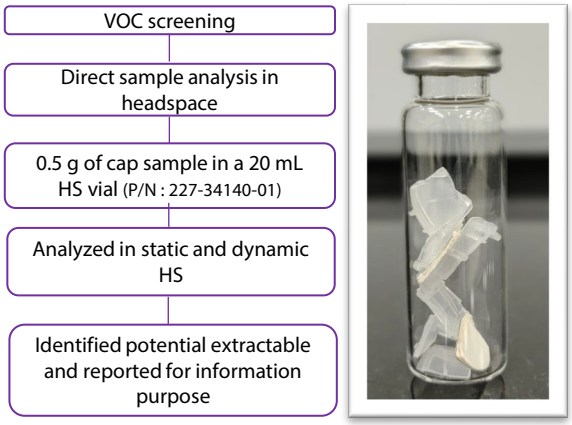

Figure 12: Sample preparation procedure and image of the HS vial with sample

In the sample analyzed by static headspace (with 1 mL loop), only few peaks were detected. When the same sample was injected in dynamic headspace keeping other method parameters same, the number of compounds detected increased drastically. The chromatograms of CCP sample obtained in both the techniques and air blank are compared in Figure 13.

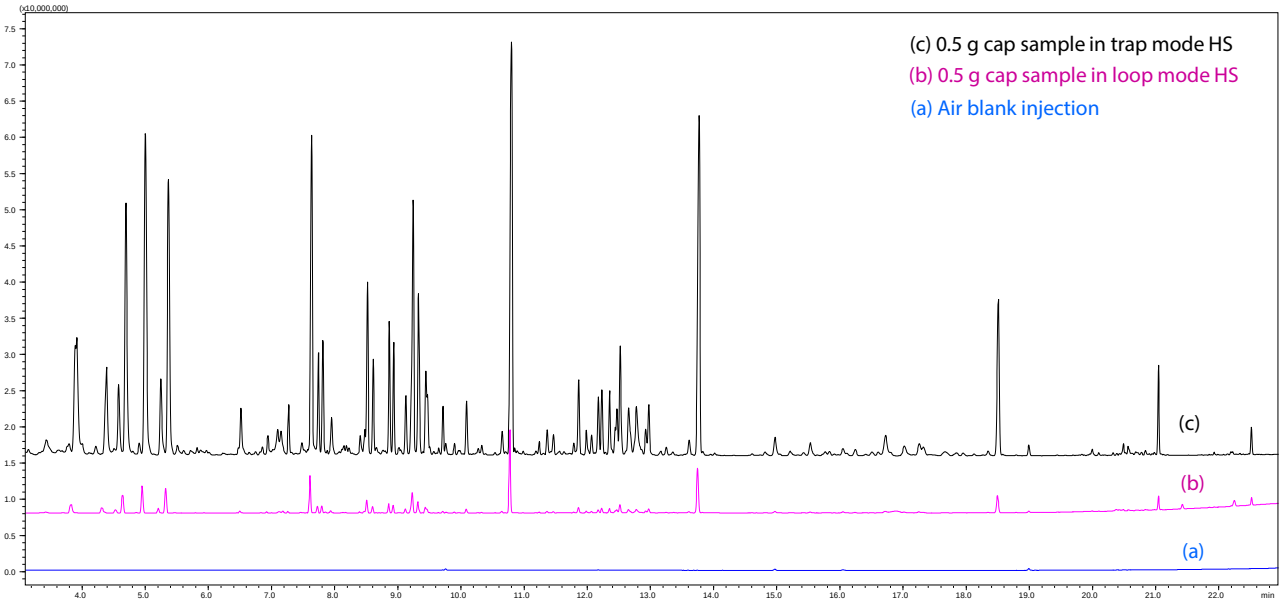

Figure 13: Overlayed chromatograms of sample analyzed by static mode and dynamic mode with blank injection

Extracts were prepared by two techniques as stated under experimental design. From which, Figure 14 depicts the chromatogram of the sample extract which was prepared by incubation of the sample in acidic media for 72 hours and at 85 °C.

In the incubated extract, only few compounds were detected which were semi-quantified using standard data. Content for all these peaks were found to be below AET level. Table 5 elaborates the results of incubation experiment.

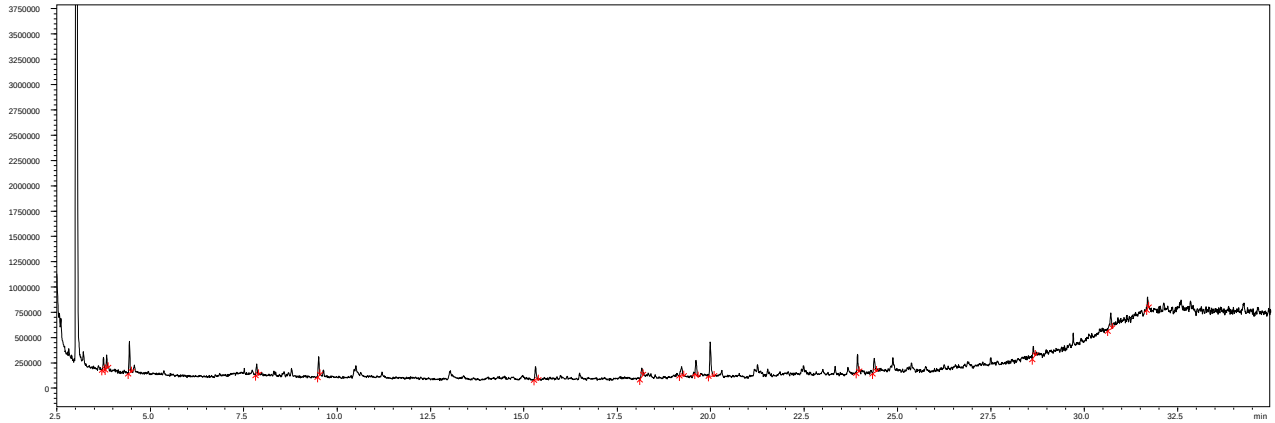

Figure 14: Chromatogram of sample incubated with acidic media for 72 hours at 85 °C

Table 5: Results of incubation experiment

RT (min)	Identified name of the unknown imp.	SI	Content (PPM)
3.75	1,3,5-Cycloheptatriene	87	0.00
3.83	Acetic acid, butyl ester	85	0.00
4.44	Cyclotrisiloxane, hexamethyl-	74	0.01
7.85	Cyclotetrasiloxane, octamethyl-	67	0.00
9.51	Octane, 3-ethyl-2,7-dimethyl-	87	0.00
15.31	Decane, 2,3,5,8-tetramethyl-	84	0.00
18.16	Octane, 3,4,5,6-tetramethyl-	78	0.00
19.22	Decyl isopropyl ether	50	0.00
19.61	Heptacosane	87	0.00
19.99	2,4-Di-tert-butylphenol	89	0.01
23.93	Isopropyl myristate	79	0.00
24.38	Phthalic acid, isobutyl nonyl ester	83	0.00
28.64	Cyclodecasiloxane, eicosamethyl-	56	0.00
30.71	Cyclononasiloxane, octadecamethyl-	67	0.01
31.70	Cyclooctasiloxane, hexadecamethyl-	55	0.00

Also, same CCP was analyzed by preparing extract by reflux experiment which is performed considering its importance in leachable assessment and investigating the source of any unknown impurity detected in the future sample. Here, two solvents were taken for reflux i.e Ethanol to extract polar organic impurities and Hexane to extract non-polar organic impurities. Samples were refluxed as stated in the Figure 15 and analyzed by GCMS technique. Figure 16 depicts the chromatogram of sample refluxed with Ethanol and Figure 17 depicts the chromatogram of sample refluxed with Hexane.

There were more number of peaks in the Hexane reflux sample in comparison with Ethanol reflux sample. All the peaks were integrated and their probable names were reported as per NIST-23 library. Also, their semi-quantitated content is reported below in Table 6. Only content from Hexane reflux sample is reported considering the worst-case scenario.

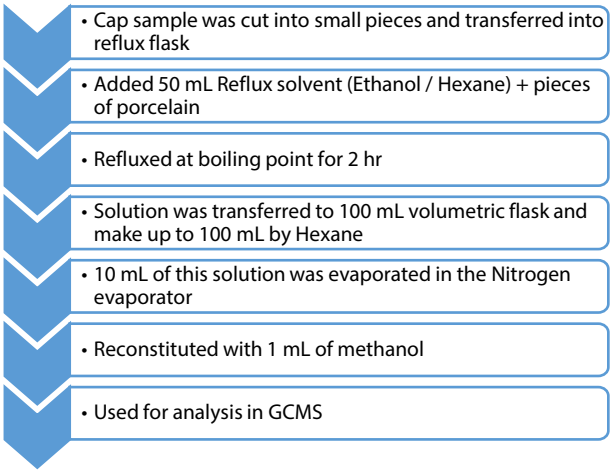

Figure 15: Procedure for obtaining sample extract by reflux method

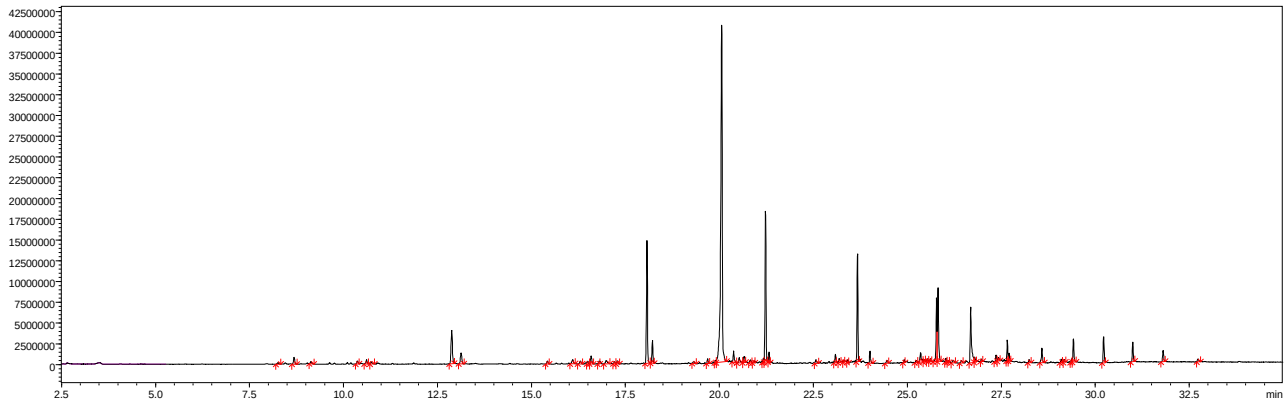

Figure 16: Chromatogram of sample refluxed with Ethanol for 2 hours at 80 °C

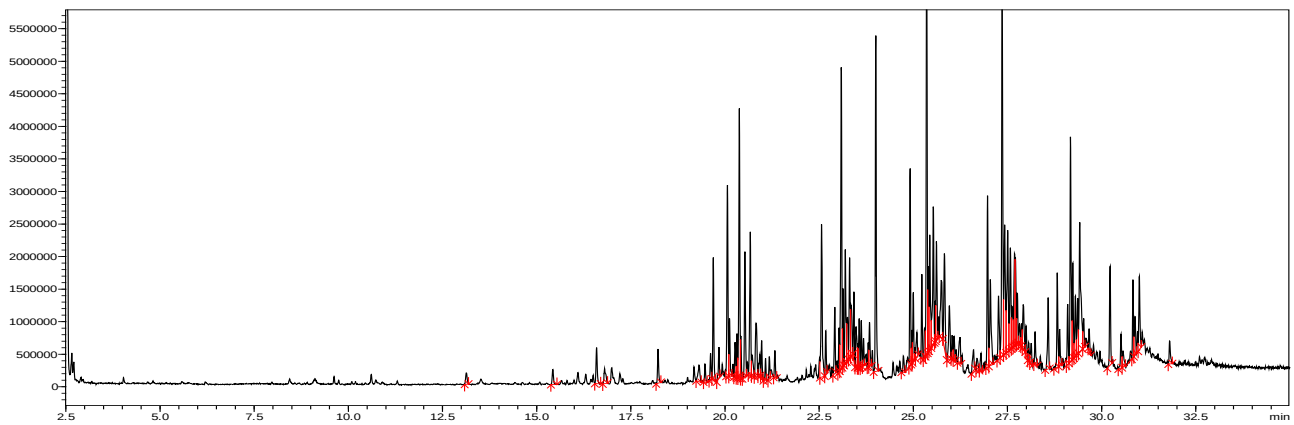

Figure 17: Chromatogram of sample refluxed with Hexane for 2 hours at 70 °C

Table 6 : Results of Unknown compounds

Sr. No.	Name of Unknown extractable	RT (min)	SI	Content (ppm)
1	Dodecane, 2,6,11-trimethyl-	13.13	92	0.44
2	Decane, 2,3,5,8-tetramethyl-	15.43	93	0.51
3	Decane, 3,7-dimethyl-	16.59	94	1.18
4	Dodecane, 4,6-dimethyl-	16.81	92	0.65
5	Hexadecane	18.23	95	1.09
6	Tridecane, 4-methyl-	19.31	87	0.95
7	Decane, 2,3,5,8-tetramethyl-	19.47	90	0.5
8	Heptadecane, 2,6,10,15-tetramethyl-	19.62	91	0.82
9	Heptadecane, 2,6,10,15-tetramethyl-	19.69	93	3.48
10	Dodecane, 2,6,11-trimethyl-	19.84	92	1.01
11	2,4-Di-tert-butylphenol	20.07	93	5.95
12	11-Methyldodecanol	20.12	90	1.87
13	11-Methyldodecanol	20.27	88	1.06
14	Dodecane, 1-iodo-	20.32	91	1.19
15	Dodecane, 2,6,11-trimethyl-	20.38	93	7.54
16	Nonane, 3-methyl-5-propyl-	20.42	88	0.88
17	Carbonic acid, eicosyl vinyl ester	20.53	92	3.77
18	Nonadecane	20.67	93	4.11
19	Heptacosane	20.72	85	1.05
20	Heptadecane, 2,6,10,15-tetramethyl-	20.83	94	2.6
21	Heptadecane, 2,6,10,15-tetramethyl-	20.93	94	0.95
22	Heptadecane, 2,6,10,15-tetramethyl-	20.98	93	1.04
23	Dodecane, 4,6-dimethyl-	21.08	92	0.53
24	Pentanoic acid, 2,2,4-trimethyl-3-carboxyisopropyl, isobutyl ester	21.18	88	0.64
25	Hexadecane	21.33	94	0.92
26	Heneicosane	22.57	93	4.86
27	Hexadecane	22.68	93	1.29
28	11-Methyldodecanol	22.92	89	2.01
29	11-Methyldodecanol	23.03	88	1.28
30	Heneicosane	23.09	93	9.35
31	Carbonic acid, eicosyl vinyl ester	23.13	88	2.2
32	Heneicosane	23.2	93	3.96
33	Cyclohexane, 1-ethyl-2-propyl-	23.25	82	2.1
34	3-Ethyl-2,6,10-trimethylundecane	23.31	90	3.63
35	1,7-Dimethyl-4-(1-methylethyl)cyclodecane	23.35	85	2.52
36	Hexadecane	23.42	93	2.35
37	Carbonic acid, eicosyl vinyl ester	23.48	90	1.82
38	Decane, 3,7-dimethyl-	23.53	84	0.57
39	Hexadecane	23.57	92	1.5
40	1-Dodecanol, 2-hexyl-	23.62	88	1.4
41	Carbonic acid, eicosyl vinyl ester	23.68	92	0.97
42	Dodecane, 1-iodo-	23.8	87	0.69
43	Carbonic acid, hexadecyl prop-1-en-2-yl ester	23.84	90	1.63
44	Isopropyl myristate	24.01	87	8.88
45	Dodecane, 4,6-dimethyl-	24.74	89	0.63
46	Heneicosane	24.92	93	5.08
47	3-Ethyl-3-methylheptane	24.96	79	1.01
48	Tridecanol, 2-ethyl-2-methyl-	25	79	2.14
49	Hexadecanoic acid, methyl ester	25.1	86	1.94
50	1-Decanol, 2-hexyl-	25.23	91	2.78
51	Tetracontane	25.3	86	1.86
52	Eicosane	25.36	93	13.19
53	Octacosane, 1-iodo-	25.4	85	2.85
54	Heptadecane	25.44	92	4.81
55	Heneicosane	25.53	92	7.01
56	Hexatriacontyl trifluoroacetate	25.59	77	1.61
57	Heneicosane	25.62	91	4.09
58	Eicosane	25.74	90	5.08
59	Eicosane	25.83	85	4.91
60	Carbonic acid, octadecyl vinyl ester	25.96	89	2.74
61	1-Naphthalenepropanol, .alpha.-ethenyldecahydro-2-hydroxy-.alpha.,2,5,5,8a-pentamethyl-, [1R-[1.alpha.(R*),2.beta.,4a.beta.,8a	26.03	71	0.65
62	1-Decanol, 2-hexyl-	26.08	84	0.72
63	11-Methyltricosane	26.24	81	1.13
64	Cyclohexene, 3-(1-methylethyl)-	26.6	77	1.06
65	Heptafluorobutyric acid, pentadecyl ester	26.69	81	0.67
66	Dodecane, 2,6,11-trimethyl-	26.8	90	0.56
67	Eicosane	26.97	91	5.08
68	Tridecanoic acid, 4,8,12-trimethyl-, methyl ester	27.05	80	4.13
69	1-Decanol, 2-hexyl-	27.26	89	2.98
70	Eicosane	27.36	92	12.63
71	Heptadecane	27.43	89	5.98
72	Eicosane	27.51	90	5.83
73	Eicosane	27.58	92	4.33
74	Carbonic acid, decyl nonyl ester	27.62	79	2.45
75	Dotriacontane, 1-iodo-	27.69	82	3.86
76	Tetratriacontyl heptafluorobutyrate	27.71	83	3.06
77	Eicosane	27.76	88	2.52
78	1-Decanol, 2-hexyl-	27.82	85	1.9
79	Tetrapentacontane	27.88	77	1.3
80	11-Methyldodecanol	27.92	85	2.56
81	11-Methyltricosane	27.99	88	1.37
82	Eicosane	28.06	87	0.72
83	Nonahexacontanoic acid	28.13	85	0.65
84	1-Decanol, 2-hexyl-	28.24	79	0.98
85	Hexacosane	28.58	95	2.17
86	Eicosane	28.82	91	2.89
87	Tetrapentacontane	28.89	88	1.28
88	Pentatriacontane	29.1	83	1.83
89	Eicosane	29.17	92	7.36
90	Eicosane	29.24	92	2.85
91	Eicosane	29.31	89	2.46
92	Tetrapentacontane	29.37	87	2.25
93	Heneicosane	29.42	93	7.03
94	Eicosane	29.52	84	1.74
95	Tetrapentacontane, 1,54-dibromo-	29.67	85	1.38
96	Octacosane, 2-methyl-	30.23	94	2.84
97	Tetrapentacontane	30.52	89	1.07
98	Tetrapentacontane	30.57	80	0.7
99	Tetrapentacontane	30.83	89	2.4
100	Triacontane, 1-iodo-	30.89	86	2
101	Tetratetracontane	31	94	3.3
102	Tetratetracontane	31.8	91	0.75

Continued…..

Here, most of the extractables show their presence above AET level in the CCP under study. It means that those chemical compounds were present in the CCP and leached out when exposed to the Hexane under hot condition. Hexane reflux condition is not a reasonable with respect to the nature and storage condition of the drug product inside.

On the other hand, this CCP will be used to store the Penicillin V product which is supposed to be consumed with water and pH of the final solution is slightly acidic. Hence, incubation with acidic- aqueous medium will be more relatable for this CCP considering real-time scenario.

However, this data can be considered for leachable assessment, wherein user must identify the source of the particular leachable.

■ Conclusion

- The chromatographic profile of solvent reflux experiment shows higher number of extractables than aqueous incubation. Furthermore, in aqueous incubation, the content of extractables is well below the AET level. Since, placebo of the ophthalmic drug product is completely aqueous, CCP used in the analysis is totally safe and can be used for the storage of Penicillin V.

- Shimadzu's GCMS-TQ provides high scan speed of 20000 amu/sec with ASSP technology enabling simultaneous SCAN/MRM analysis which is crucial in E&L study.

- Generally, if the drug product falls under parenteral and oral drug product (PODP), evaluation threshold will be at higher side due to having wider SCT. However, AET for Penicillin V was at too low to evaluate with liquid injection and static headspace technique. This has been proved with the trap headspace technology.

- To analyze the complete extractable profile with the sample screening is only possible with dynamic headspace as most of the extractables were not detected in the injection acquired with static headspace.

■ References

[1] USP <1663> Assessment of Extractables Associated with Pharmaceutical Packaging/Delivery Systems

[2] Product Quality Research Institute "Safety Thresholds and Best Demonstrated Practices for Extractables and Leachables in Parenteral Drug Products (Intravenous, Subcutaneous, and Intramuscular) "
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06-SIP-GC-044-EN First Edition: Jun. 2026

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