

Heat-Induced and Soxhlet Solvent Extraction Profile Study in Medical Rubber Component used for Container Closure System Using GC/MS Methodology

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Abstract

Rubber products such as Stoppers and O-rings, as a packaging component of container closure system, are widely used in medical devices and the healthcare industry. Rubber stoppers are widely used by medical injectable bottles and Rubber o-ring are widely used by medical syringe etc. There is increasing concern of the possibility of leachables to migrate from the rubber products container closure system onto the drug product. Headspace GC/MS methodology is utilized to perform a controlled extraction study and quickly determine the heat-induced volatile extractables from the rubber products at specific incubation times and temperatures. Direct-injection GC/MS methodology is also utilized to determine the semi-volatile solvent-induced extractables obtained from Soxhlet extraction.

Methods

GC/MS System: Agilent, 6890N GC/MS 5973 inert XL MS Detector with Agilent G1888 Headspace Sampler. EI Mode. **Column:** Agilent, DB-5ms, 20 m x 0.18 mm ID, 0.18 mm film thickness. **GC Oven Temperature Program:** Initial Temperature: 80°C hold 6 min, 80°C to 320°C at 15°C/min hold 8 min. Total run time: 30 min. Injection Temperature: 180°C. MS detector Temperature: 280°C. Flow rate: 1.0 mL/min. Injection volume: 1 mL for Headspace method, 1 µL for directly injection method. **Headspace extraction:** four Rubber stoppers placed into a 23 x 46 mm, 12- mL vial at 105°C for 40 min. **Soxhlet extraction:** use Isopropyl Alcohol with Rubber o-rings in heating manifold to reflux for 24 hours.

Data

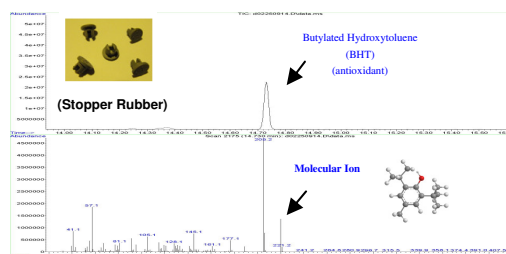


Figure 1: GC/MS Headspace Extractable Profile of Rubber Stopper at 105°C for 40 min Incubation Time

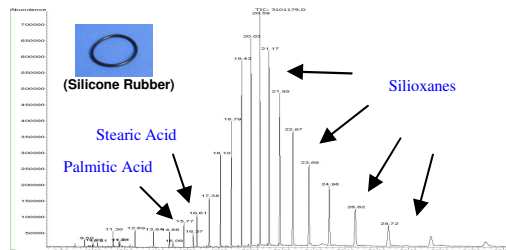


Figure 2: GC/MS Solvent-stressed Soxhlet Extractables from Rubber O-Ring after 24 Hours Reflex

Table 1: List of Solvent-induced Extractables from O-ring by GC/MS

No.	RT (min)	Chemical Name	Formula	CAS Number	MW (g/mol)
1	9.50	Dodecane(1,1,1-trichloro)ethane	C ₁₂ H ₂₁ O ₂ Si ₂	540-97-6	444.11
2	11.29	Tetradecane(1,1,1-trichloro)ethane	C ₁₄ H ₂₇ O ₂ Si ₂	107-50-6	518.43
3	12.69	Hexadecane(1,1,1-trichloro)ethane	C ₁₆ H ₃₃ O ₂ Si ₂	N/A	593.23
4	13.84	Octadecane(1,1,1-trichloro)ethane	C ₁₈ H ₃₉ O ₂ Si ₂	556-71-8	666.17
5	14.28	Eicosane(1,1,1-trichloro)ethane	C ₂₀ H ₄₁ O ₂ Si ₂	18772-96-6	741.54
6	15.10	Palmitic Acid	C ₁₆ H ₃₂ O ₂	57-10-3	256.54
7	16.38	Stearic Acid	C ₁₈ H ₃₆ O ₂	57-11-4	284.27
8	16.60	Dodecane(1,1,1-trichloro)ethane	C ₁₂ H ₂₁ O ₂ Si ₂	141-66-8	310.13
9	16.60	Dodecane(1,1,1-trichloro)ethane	C ₁₂ H ₂₁ O ₂ Si ₂	141-69-9	384.15
10	17.37	Tetradecane(1,1,1-trichloro)ethane	C ₁₄ H ₂₇ O ₂ Si ₂	N/A	461.99
11	18.10	Hexadecane(1,1,1-trichloro)ethane	C ₁₆ H ₃₃ O ₂ Si ₂	N/A	533.46

Results

For the stopper rubber, one heat-induced extractable-Butylhydroxytoluene (BHT) - was detected by Headspace GC/MS analysis at 105°C for 40 minutes incubation time, as shown in **Figure 1**. BHT is fat-soluble organic compound used as an antioxidant additive in pharmaceutical drugs and rubber etc.

For the O-Ring sample, a number of compounds were identified by Direct Injection GC/MS analysis after solvent IPA Soxhlet extraction. Except for palmitic acid and stearic acid, all of the compounds corresponded to siloxane derivatives. As an example as to the types of siloxanes, **Table 1** lists a total of nine different siloxanes. No extractables were detected from the Soxhlet H₂O extraction for the O-Ring samples. **Figure 2** illustrates a representative GC/MS total ion chromatogram demonstrating the chromatographic profile obtained from Soxhlet extraction of the O-Ring sample. Information including structural information, CAS number and molecular weight is listed in **Table 1**.

Conclusion

Headspace and direct-injection GC/MS methodologies are useful tools to identify, characterize, and quantitate the organic extractables that have been obtained from heat or solvent induction, respectively.

Two case studies were summarized for rubber products. For a specific rubber stoppers, one heat-induced extractable-Butylhydroxytoluene (BHT) was detected by Headspace GC/MS. For a specific rubber o-ring, two acids and a series of siloxanes as solvent-induced extractables were detected by directly injection GC/MS. All extractables also were identified, characterized, or quantitated.