



INTRODUCTION

Foil laminate film, a major packaging component of blister packs, is widely used in medical devices and the healthcare industry. Foil laminate films are multilayered and manufactured with materials such as aluminum foil, polyester/PP/PE, adhesives, inks, etc. There is increasing concern of the possibility of leachables to migrate from the foil laminate 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 foil laminate film 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.

METHODOLOGY

GC/MS System: Agilent, 6890N GC with MS 5975 inert XL Mass Selective Detector (Figure 1). EI Mode.

Column: J & W Scientific, DB-5ms, 2.0 m × 0.18 mm ID, 0.18 mm film thickness.

Oven Temperature Program: Initial Temperature 40°C hold 6 min, 40°C to 300°C at 15°C/min hold 5 min. Total run time: 28.33 min. Injection Temperature: 250°C. MS Detector Temperature: 230°C. Flow Rate: 1.0 mL/min.

Autosampler: CTC, Combi PAL with incubator. Incubator Temperature: 170°C.

Headspace Vial: A 3.0 cm × 2.5 cm of foil laminate film placed into a 23 × 46 mm 12-mL headspace vial. Foil laminate film was cut into 3.0 cm × 2.0 cm pieces, after washed with water, weighed and dried, it was put into 12-mL Headspace Vial, capped using a 20 mm magnetic crimp cap with a PTFE/Silicon septum.

Soxhlet Extraction use extraction media as solvent and reflux for 24 hours (Figure 2). Extraction media are: Isopropanol (for polar organic compounds) and Water (for aqueous soluble compounds).

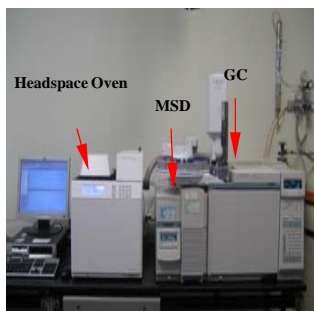


Figure 1: Agilent GC/MS Headspace System



Figure 2: Soxhlet Solvent Extraction Apparatus

RESULTS

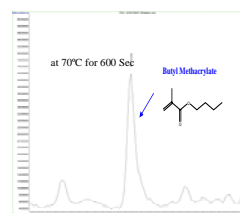


Figure 3: GC/MS TIC of Headspace Volatile – Butyl Methacrylate

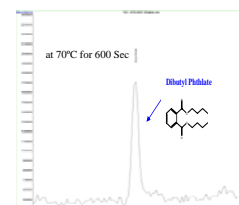


Figure 4: GC/MS TIC of Headspace Volatile – Dibutyl Phthalate

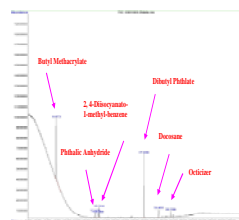


Figure 5: GC/MS TIC of Soxhlet Isopropanol Extractables

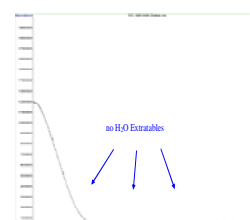


Figure 6: GC/MS TIC of Soxhlet H₂O Extractables

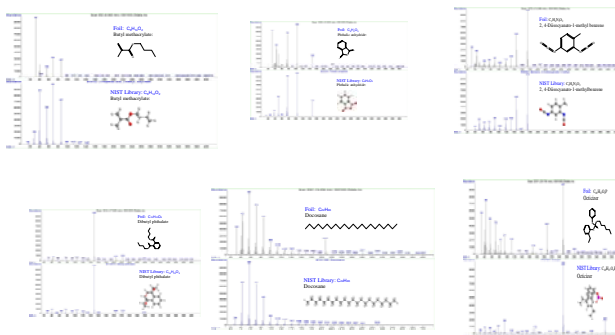


Figure 7: Mass Spectra of Stress Solvent Extractables From Foil Laminate Using Soxhlet Isopropanol Extraction

DISCUSSION

In the heat-induced headspace study, all experiments were performed in duplicate using GC/MS analysis to evaluate the headspace gases evolved at different incubation times in the absence of solvent. In general, foil laminate strips were preincubated at the certain temperature value which was chosen near the actual temperature used in the manufacturing process. Six incubation time points were chosen - 10, 30, 60, 180, 300, and 600 seconds. The results of the headspace analysis for the foil laminate films demonstrated that two heat-induced volatile extractables were detected - Butyl Methacrylate (Figure 3, retention time of 8.81 minutes) and Dibutyl Phthalate (Figure 4, retention time of 17.95 minutes).

Foil laminate from the Soxhlet IPA extraction was found to release six chemicals using GC/MS (Figure 5). No extractables were found in the foil laminate extracts from the Soxhlet H₂O extraction (Figure 6). Interpretation of the MS spectra from Figure 7 shows a total of six compounds were found from the GC/MS studies: Butyl Methacrylate, Phthalic Anhydride, 2,4-Diisocyanato-1-methylbenzene, Dibutyl Phthalate, Docosane and Octicizer. The information of all six solvent-stressed extractables are listed in Table 1. Table 1 also lists the industrial application for all six extractables and demonstrates that all of the compounds are related to foil laminate composition and/or its manufacturing process.

Table 1: Solvent-stressed Extractables List Tested by GC/MS

No.	Chemical Name	Synonyms	Formula	CAS #	Molecular Wt	Application
1	Butyl Methacrylate	2-Methyl-2-propenoic Acid Butyl Ester	C ₉ H ₁₀ O ₂	97-88-1	140.20	Resins, Solvent, Adhesives
2	Phthalic Anhydride	1,3-Dioxaphthalan	C ₈ H ₆ O ₃	85-44-9	148.10	Plasticizer
3	2,4-Diisocyanato-1-methylbenzene	Toluene Diisocyanate	C ₉ H ₈ N ₂ O ₂	584-84-9	174.16	Polyurethane
4	Dibutyl Phthalate	DBP	C ₁₆ H ₂₂ O ₄	84-74-2	278.35	Plasticizer
5	Docosane	Alkane (C ₂₂)	C ₂₂ H ₄₆	629-97-0	310.60	Additive
6	Octicizer	2-Ethylhexyl Diphenyl Phosphate	C ₂₀ H ₂₂ O ₄ P	1241-94-7	362.40	Flame Retarding Plasticizer

CONCLUSION

This study provided information on the composition of extractables obtained from a foil laminate packaging material. Headspace and direct-injection GC/MS methodologies are useful tools to identify, characterize and quantitate the volatile and semi-volatile extractables that have been obtained from heat or solvent induction, respectively. A case study for a specific foil laminate film showed two heat-induced extractables and six solvent-induced extractables were identified, characterized and quantitated.

REFERENCES

- Physicochemical Tests for Plastic Containers/Closure systems, USP method <661>
- Elastomeric Closures for Injections, USP Method <381>
- Extractables and Leachables Testing: Points to Consider, ITFG/IPAC-RS, March 2001.