Identification and Quantitation of Plastic Additives in Medicine Containers by HR LC-MS, GC-MS and ICP-MS

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Overview

Purpose: Identification and Quantitation of Plastics Additives in Medicine Containers by high-resolution (HR)-LC-MS, GC-MS and ICP-MS.

Methods: HR-LC-MS, GC-MS and ICP-MS and data processing software.

Results: Comprehensive analysis of extractables for medicine container by multiple techniques and data analysis software. Confident component detection, unknown structure identification, and quantification were achieved.

Introduction

Plastics additives are widely used in food and pharmaceutical containers and medical devices for a variety of essential polymer performance functions. Some of the additives, if leached out, could pose health risks when they come in contact with food, medicine, and the human body. It is required by government agencies that materials used for these purposes comply with regulations to ensure consumer safety and the integrity of medicine/medical devices.

In this study, medicine containers were analyzed by a Thermo Scientific™ Q Exactive™ bench-top Orbitrap™ mass spectrometer and a Thermo Scientific™ ISQ™ Single Quadrupole GC-MS system to identify and quantify plastic additives. Elemental analysis was carried out on a Thermo Scientific™ iCAP Q ICP-MS. The data were processed by software Thermo Scientific™ SIEVE™ 2.1 and Thermo Scientific Mass Frontier™ 7.0 software.

Methods

Sample Preparation

•Commercial Polypropylene (PP) pill bottles were used for this analysis.

•The bottles were filled with isopropanol (IPA) and maintained in an oven at 50 ^{0}C for five days.

•The extracts were directly injected for analyses.

Liquid Chromatography

Thermo Scientific™ Dionex™ Ultimate™ 3000 RS UHPLC system consisting of:

Pump:	DGP-3000RS
Autosampler:	WPS-3000RS
UV detector:	DAD-3000RS
Column:	Thermo Scientific™ Acclaim™ RSLC 120 C18 150 x 2.1 mm 2.6µm
Injection volume:	10 µL
Flow rate:	0.5 ml/min.

LC Gradient:

Eluent A:	H_2O/0.1% formic acid
Eluent B:	CH_3CN/0.1% formic acid

Time (min)	0.0	8.0	21.0	35.0	35.1	40.0
B%	15	65	95	95	15	15

Mass Spectrometry

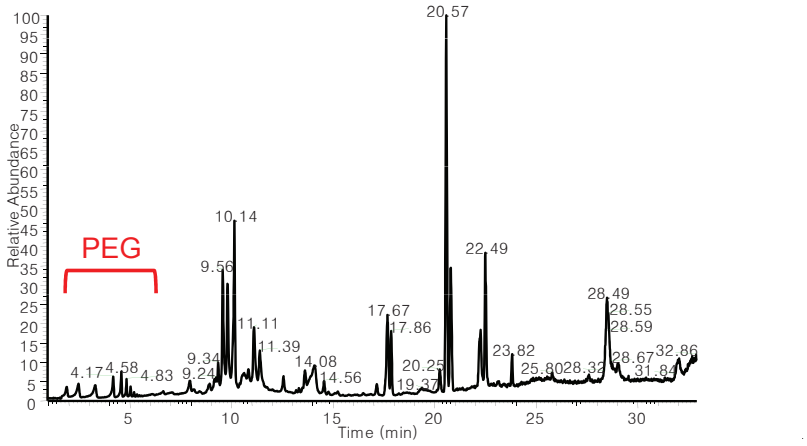
•The MS analyses were carried out on Thermo Scientific Q Exactive mass spectrometer using electrospray ionization in positive mode.
•High resolution full-scan MS and top3 MS/MS data were collected in a data-dependent fashion at resolving power of 70,000 and 35,000 at FWHM m/z 200 respectively.
•HCD normalized collision energy: 30% with 25% ramping.

Analysis and Results

LCMS Analysis

Full scan at resolution 70,000 and top3 data-dependent MS/MS provided high quality high-resolution, accurate-mass (HRAM) data for molecular weight determination and structure elucidation. Figure 1 shows the MS base peak chromatograms. The data was processed with SIEVE 2.1 software for component extraction and the structures of extracted components were identified via ChemSpider database search (Figure 2). To further confirm the proposed structures of components, MS/MS data were used in conjunction with Mass Frontier 7.0 software as illustrated in Figure 3. The HighChem Fragmentation Library in Mass Frontier software has substantial published literature references. For each proposed structure, Mass Frontier software generates "fragment and mechanism" through a HighChem library search. In addition, Mass Frontier automatically annotates fragment ions based on corresponding "fragment and mechanism" (Figure 3).

FIGURE 1. Base Peak Chromatograms of IPA Extract of Polypropylene Pill Bottle.



mzCloud Spectral Database

The newly developed high resolution spectral database, mzCloud, allows direct substructure search and improves unknown structure elucidation by using a new spectral correlation algorithm (Figure 4).

FIGURE 2. Components Identified for PP Bottle (partial list).

	Measured Mass $(M+H)^+$	Calculated Mass $(M+H)^+$	Elemental Composition $(M+H)^+$	Error (ppm)	Proposed Structure
*	288.2900	288.2897	$C_{17}H_{38}O_2N$	0.3	
	415.2116	415.2113	$C_{24}H_{31}O_6$	-0.2	
*	316.3212	316.3210	$C_{19}H_{42}O_2N$	0.2	
	277.1799	277.1798	$C_{17}H_{25}O_3$	-0.2	
	235.1120	235.1117	$C_{17}H_{15}O$	0	
	548.4675	548.4673	$C_{34}H_{62}O_4N_1$	0.4	
	327.1958	327.1955	$C_{21}H_{26}O_3$	0.9	
	316.1204	316.1211	$C_{17}H_{19}O_1N_3Cl$	-2.2	
	939.5950	939.5957	$C_{56}H_{84}O_{10}Na$	-0.7	
	1199.7727	1199.7733	$C_{72}H_{108}O_{12}Na$	-0.5	

* **Multiple Isomers Present**

FIGURE 3. MS/MS Data for Structure Confirmation / Mass Frontier Auto Annotation

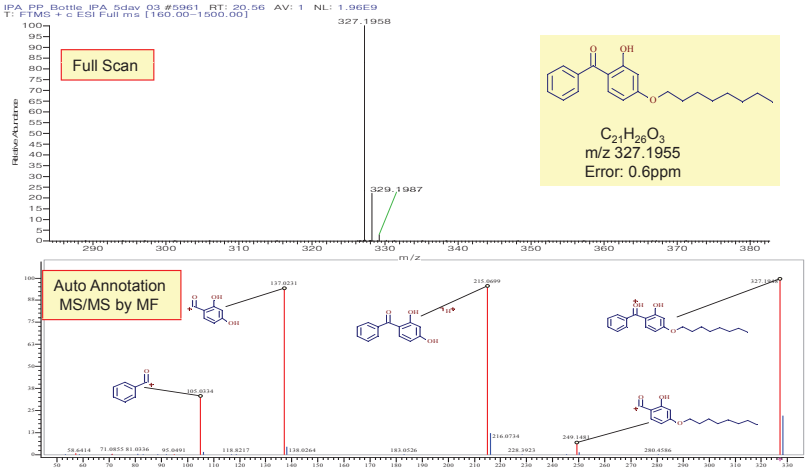
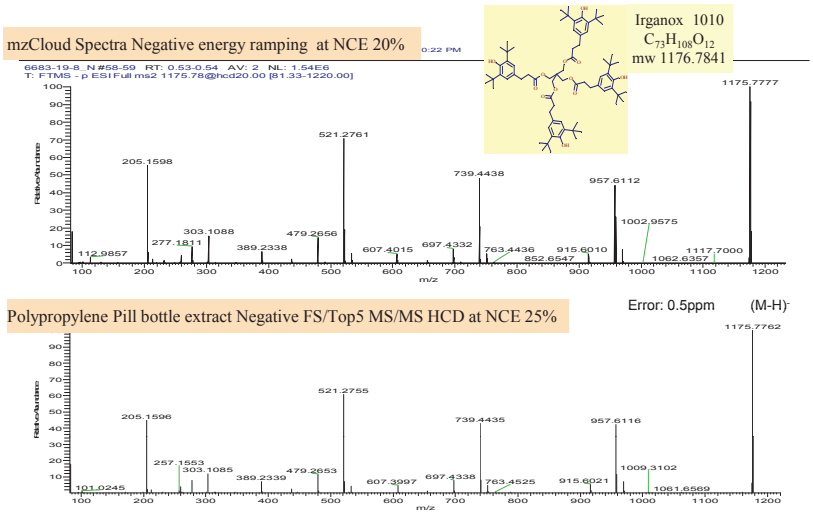


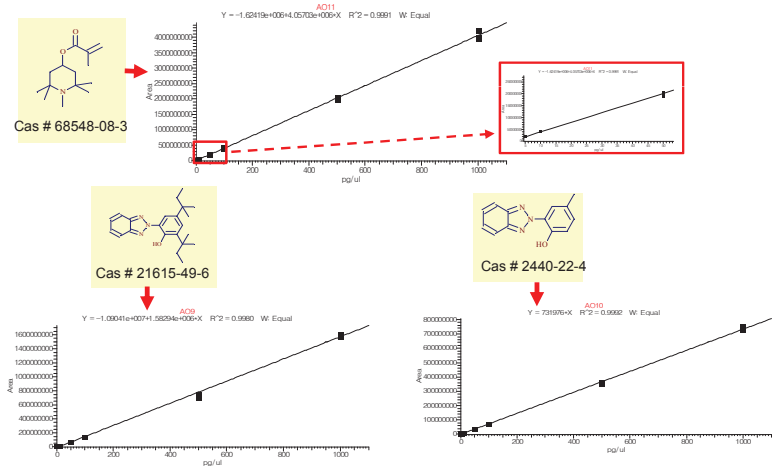
FIGURE 4. mzCloud Spectral Database Search Result



Quantitation

Quantitation is an important part of E&L analysis. The calibration curves of three antioxidants demonstrate the quantitation capability of Q Exactive for E&L analysis (Figure 5).

FIGURE 5. Calibration Curve of Neat Antioxidants over the range of 1- 1000 ppm, Linear regression and equal weighting.

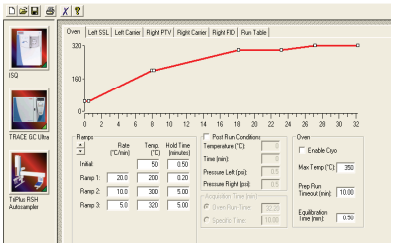


GCMS Analysis

Method and Instrument

The sample in a 2.0-mL GC vial was introduced by split injection mode into the Thermo Scientific™ Trace Ultra GC using a Thermo Scientific™ Triplus RSH autosampler. Compounds were detected and identified with the ISQ single quadrupole mass spectrometer.

GCMS Instrument Conditions



Components identified by GC-MS analysis are consistent with the LC-MS result (Figure 6). In addition, GC-MS has outstanding quantitation capability for volatile and semi-volatile compounds (Figure 7). The results demonstrate the capabilities of GC-MS to identify and quantify antioxidants and plasticizers present in the medicine container. The LC-MS and GC-MS results complement each other for comprehensive extractable & leachable analysis.

FIGURE 6. GC-MS Spectrum for Polypropylene Pill Bottle.

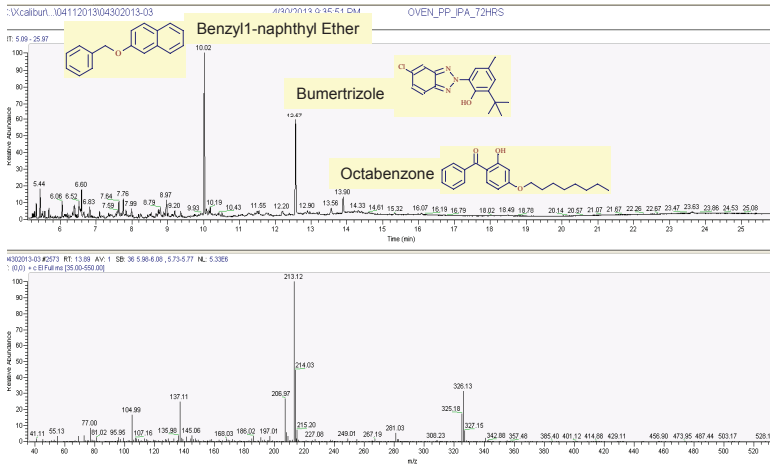
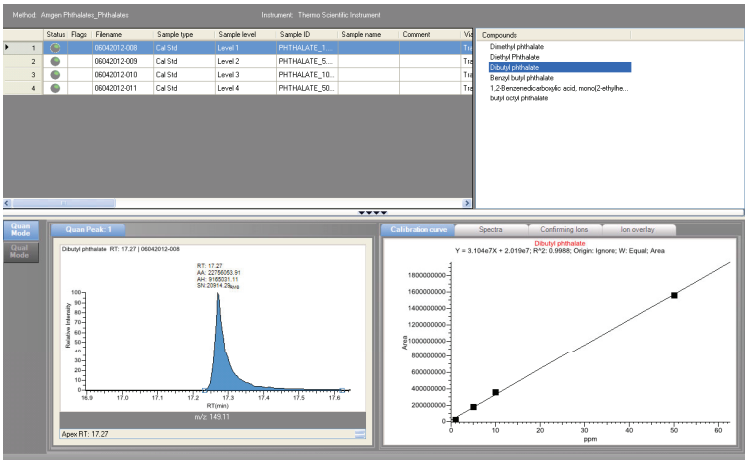


FIGURE 7. GC-MS Quantitation of Regulated Phthalate Compounds.



ICP-MS Analysis

The ICP-MS sample was prepared by filling the polypropylene bottle with 2% nitric acid and left at room temperature for 24 hours. The analysis was conducted on a Thermo Scientific iCAP Q ICP-MS with He KED (Kinetic Energy Discrimination) interference reduction mode setting to determine if trace and potentially toxic metals are leached from containers. The USP<232> requires toxic metals as well as catalytic metals to be determined. The USP<232> elements are included in the results.

Additional elements which are commonly analyzed by ICP-MS were also determined. The result for polypropylene pill bottle showed that the sample is clean in terms metals, all elements are below thresholds. Figure 8 shows the ICP-MS results for polypropylene pill bottle. The system's new Qtegra software is 21 CFR part11 compliant and has a full 21CFR part 11 tool set (Figure 9).

FIGURE 8. ICP-MS Results for Polypropylene Pill Bottle.

USP<232> Elements (ppb)			
Element	**PP ***	**Blank**	**LOD**
75As (KED)	0.003	0.003	0.009
111Cd (KED)	-0.001	0.000	0.000
208Pb (KED)	-0.002	0.014	0.005
202Hg (KED)	-0.001	-0.006	0.001
101Ru (KED)	0.001	0.000	0.002
103Rh (KED)	0.000	0.002	0.001
105Pd (KED)	0.000	0.000	0.003
189Os (KED)	0.002	0.000	0.002
193Ir (KED)	0.001	0.003	0.000
195Pt (KED)	0.000	0.000	0.001
52Cr (KED)	0.000	0.007	0.003
95Mo (KED)	-0.174	0.018	0.002
60Ni (KED)	0.043	0.160	0.018
51V (KED)	0.001	0.002	0.000
65Cu (KED)	0.044	0.083	0.016

Other Elements (ppb)			
Element	**PP ***	**Blank**	**LOD**
48Ti (KED)	0.620	0.046	0.013
55Mn (KED)	0.005	0.017	0.007
59Co (KED)	0.342	0.567	0.006
66Zn (KED)	0.055	0.541	0.076
88Sr (KED)	-0.003	0.019	0.002
107Ag (KED)	-0.006	-0.007	0.001
118Sn (KED)	-0.002	0.021	0.060
137Ba (KED)	-0.044	0.255	0.012
182W (KED)	0.000	0.006	0.007
205Tl (KED)	0000	0.004	0.004

*** Polypropylene Pill Bottle**

FIGURE 9. Compliance - Full 21CFR Part 11 tool set.

Supported 21 CFR 11 Sections	
1.10	Controls for closed systems
11.30	Controls for open systems
11.50	Signatures manifestations
11.70	Signature / record linking
11.100	General requirements for electronic signatures
11.200	Electronic signatures components and controls
11.300	Controls for identification codes / passwords

Conclusion

This study demonstrated comprehensive extractable and leachable analysis workflow, which includes multiple techniques: HR-LC-MS, GC-MS and ICP-MS, with SIEVE 2.1 and Mass Frontier 7.0 data processing software, and the mzCloud spectral database. From separation, detection, quantification, to structure identification, this workflow streamlines E&L analysis for pharmaceutical containers and packaging. It can also apply to extractable and leachable analysis for the food and beverage industries.

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