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Pharma

Multi-detector platform for comprehensive identification and quantitation of extractables and leachables

Authors

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Keywords

Extractables, leachables, E&L methods pharma, Orbitrap Exploris 120 mass spectrometer, high-resolution accurate mass (HRAM), Vanquish Inverse Gradient LC system, Hypersil GOLD column, HRMS, charged aerosol detection (CAD), multi-detector, compound identification

Application benefits

- Simultaneous acquisition of orthogonal UV, CAD, and MS data enables comprehensive untargeted extractables and leachables (E&L) screening.
- Mass proportional response of charged aerosol detection reduces the need for analytical uncertain factors (UF).
- Thermo Scientific™ Vanquish™ Inverse Gradient LC system allows higher confidence in semi-quantitation by providing uniform signal response for CAD.
- The workflow provides increased confidence and completeness of E&L analysis by extracting more data from a single injection and enabling coverage of nearly all semi-volatile to non-volatile compounds.

Goal

To develop a comprehensive multi-detection workflow utilizing LC, UV, CAD, and HRAM MS for confident extractables screening and HRAM MS-based compound identification. By utilizing universal mass proportional response detectors such as CAD, elimination of analytical uncertainty factors will be explored.

Introduction

The goal of an extractables study is the unbiased detection of all compounds contained in the different extracts obtained from the drug packaging, medical device, or component thereof, to allow the determination of an extractable profile that will guide the design of the subsequent leachables study (in the case of drug packaging) and toxicological risk assessment. To cover the wide range of organic and inorganic potential extractable compounds, multiple separation and detection techniques are used, most commonly utilizing LC/MS, GC/MS, and ICP/MS for non-volatile, volatile and semi-volatile, and inorganic species, respectively. LC/MS, often hyphenated with UV detection, is commonly used to detect and annotate the non-volatile fraction of extractable compounds. Due to the untargeted nature of the experiment and the need to determine confident elemental composition in the identification process, high-resolution accurate-mass (HRAM) mass spectrometry is routinely employed.

While it is not generally possible or feasible to determine the identity of all extractables in a study, relevant industry guidance and regulatory requirements indicate an analytical evaluation threshold (AET), above which the identification of the compounds in question is necessary for toxicological risk assessment. The AET is a sample- and analysis-specific threshold that can be derived, e.g., for drug packaging materials, from the safety concern threshold and the dose form and frequency, among others.[1] The use of AET requires quantitation of compounds during the identification process, which, due to the unavailability of reference standards, is commonly carried out with surrogate standards. Multiple such standards are used to provide estimated quantitation of unknown MS peaks. However, MS signal intensity, while typically linear across large concentration ranges for a given analyte, can vary significantly between different compounds. UV detection is often employed as an alternative technique; however, it requires that the analyte contains a chromophore. Due to the uncertainty of the analyte response for unknown/unspecified compounds, the AET is adjusted using an uncertainty factor.

To overcome these limitations and lower the uncertainty of the concentration estimate of unknowns, charged aerosol detection (CAD) has been proposed as an orthogonal detector of non-volatile compounds. One benefit of CAD is that with constant mobile phase composition, the signal response is more uniform, enabling surrogate quantitation of unknown compounds based on an internal standard in a more confident way than using MS or UV response.[2,3] To facilitate the use of CAD for semi-quantitation of unknown non-volatile compounds in the analysis of E&L samples, an inverse gradient setup can be used to compensate for the change in mobile phase composition during gradient separations of complex extractable mixtures. This is made possible in a compact and straightforward way using the Vanquish Inverse Gradient LC system.[3] Briefly, the Vanquish Inverse Gradient LC system setup utilizes two UHPLC pumps incorporated into one module in the Thermo Scientific™ Vanquish™ Dual Pump F, with one pump generating the gradient flowing through autosampler and the analytical column and the other pump generating the inverse of the gradient in terms of the mobile phase composition (i.e., if the gradient pump provides a 1:9 ratio of mobile phases A:B, the inverse pump is set to 9:1). The two flow paths are merged behind the diode array detector (DAD) to result in a constant mobile phase composition at the CAD detector.

Here, we demonstrate the combination of the three detection techniques in one system to allow the concurrent measurement of UV absorption, CAD signal, and high-resolution accurate mass (HRAM) mass spectra from one injection. The performance of this system for extractables analysis is demonstrated in the analysis of an E&L standard mixture. Additionally, the application to the analysis of a sample extract and the workflow for identification of compounds prioritized based on CAD response is highlighted.

Experimental

Reagents and consumables	Part number
Water, UHPLC grade, Thermo Scientific™	W81
Acetonitrile, UHPLC grade, Thermo Scientific™	A9561
Formic acid, 99.0+%, Optima™ LC/MS grade, Fisher Chemical™	A117-50
Thermo Scientific™ SureSTART™ screw glass vial, 2 mL, Level 3	6PSV9-1PSS
Thermo Scientific™ SureSTART™ 9 mm screw caps, Level 3	6PSC9TST
TraceCERT™ Extractables and Leachables Screening Standard for LC, MilliporeSigma™ Supelco™	95636-1ML

Inverse gradient instrument setup

The setup discussed hereafter utilized a Thermo Scientific™ Vanquish™ Inverse Gradient LC system, consisting of:

- Thermo Scientific™ Vanquish™ System Base (P/N VF-S01-A-02)
- Thermo Scientific™ Vanquish™ Dual Pump F **(P/N VF-P32-A-01)**
- Thermo Scientific™ Vanquish™ Split Sampler FT **(P/N VF-A10-A-02)**
- Thermo Scientific™ Vanquish™ Column Compartment H **(P/N VH-C10-A-03)**
- Thermo Scientific™ Vanquish™ Diode Array Detector HL **(P/N VH-D10-A)** with Vanquish™ LightPipe™ flow cell, 60 mm **(P/N 6083.0200B)**
- Thermo Scientific™ Vanquish™ Charged Aerosol Detector H **(P/N VH-D20-A)**

The UHPLC system was connected to a Thermo Scientific™ Orbitrap Exploris™ 120 mass spectrometer **(P/N BRE725531)**. The flow path and the utilized components to enable the inverse gradient and simultaneous acquisition of CAD and MS data are detailed in Figure 1 and Table 1.

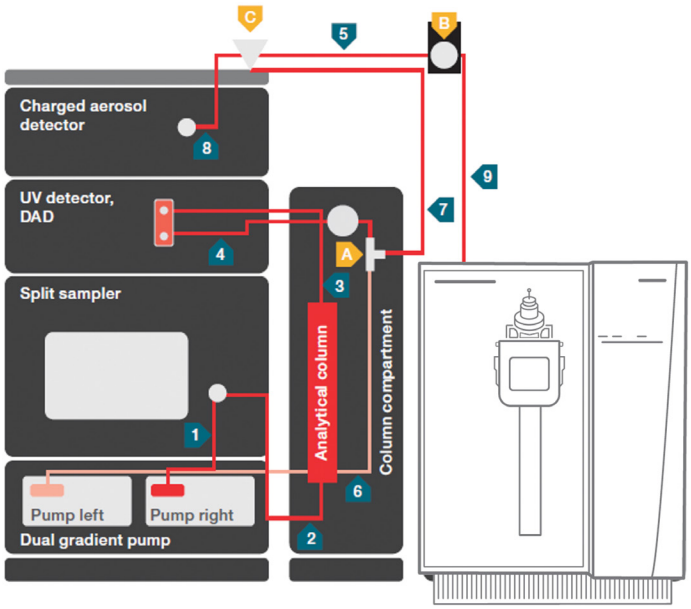

Figure 1. Inverse gradient setup schematic, with labeled flow path components described in Table 1

Table 1. Flow path components used in the inverse gradient setup, as depicted in Figure 1

No.	Description	Part number
1.	Thermo Scientific™ Viper™ capillary, ID x L, 0.1 × 350 mm, MP35N	**6042.2340**
2.	Active preheater, 0.1 × 380 mm, MP35N	**6732.0110**
3.	Viper capillary, 0.1 × 250 mm, MP35N	**6042.2330**
	Overpressure relief valve 60 bar VH-D1	6083.9260
	Viper capillary, 0.1 × 65 mm, MP35N	**6042.2306**
4.	Viper capillary, 0.1 × 65 mm, MP35N	**6042.2306**
5.	Viper capillary, 0.1 × 750 mm, MP35N	**6042.2390**
6.	Viper capillary, 0.1 × 950 mm, MP35N and	**6042.2395**
	Thermo Scientific™ nanoViper™ capillary, 75 µm × 650 mm (to provide additional backpressure)	**6041.5775**
	connected by Viper union	**6040.2304**
7.	Viper capillary, 0.1 × 150 mm, MP35N	**6042.2320**
8.	Viper capillary, 0.1 × 350 mm, MP35N	**6042.2340**
9.	Viper capillary, 0.1 × 300 mm, MP35N	6042.7950
A.	T-piece 500 µm ID	6263.0035
B.	Divert valve for Orbitrap Exploris series, 2 position – 6 port, Thermo Scientific™ Rheodyne™ MXT715-004	00109-99-00046
C.	Adjustable analytical flow splitter, 1:1 to 20:1, ASI	70-6337A

Sample preparation

The TraceCERT Extractables and Leachables Screening Standard compound mixture (50 µg/mL solution in methanol (MEOH)) was diluted in 50% MeOH to working solutions ranging from 10 µg/mL to 1 ng/mL and placed in the autosampler. A representative extract was prepared from commercially available rubber stoppers for pharmaceutical applications by extraction using isopropanol at 50 ˚C for 72 h, alongside a blank extraction.

Liquid chromatography – mass spectrometry

The LC/UV/CAD/MS^2 analysis was carried out using the following conditions:

Table 2. UHPLC experiment conditions

Parameter	Value
Column	Thermo Scientific™ Hypersil GOLD™ Vanquish C18, 1.9 µm, 2.1 × 100 mm **(P/N 25002-102130-V)**
Mobile phase	A: 0.1% formic acid in water B: 0.1% formic acid in acetonitrile
Flow rate	0.4 mL/min
Column temperature	45 ˚C (still air mode)
Autosampler temperature	6 ˚C
Injection volume	2 µL
Needle wash solvent	25% acetonitrile
Mixer volume	300 µL (250 µL static + 50 µL capillary mixer)
Flow split ratio	1:10 (MS:CAD)
Divert valve timing	Flow to waste from 0–0.9 min and 25.1–30 min
DAD settings	Wavelength 200–680 nm, 10 Hz acquisition speed
CAD settings	2 Hz acquisition speed, 35 ˚C Evaporator temperature, 1.00 Power function

Table 3. UHPLC gradient conditions

Time (min)	Analytical gradient pump mobile phase B (%)	Inverse gradient pump mobile phase B (%) – delay time offset of 0.755 min*
0.0	5	99
1.0	5	99
18.0	99	5
25.0	99	5
25.1	5	99
30.0	5	99

*Time offset for the Inverse Gradient was calculated based on the difference in flow paths with the help of the Chromeleon Inverse Gradient Wizard, as described in more detail in the Results section.

Mass spectrometry analysis was carried out on an Orbitrap Exploris 120 mass spectrometer equipped with a Thermo Scientific™ OptaMax™ NG HESI ion source. Initial method development experiments and dilution series experiments using the Supelco TraceCERT Extractables and Leachables Screening Standard mixture were carried out using Full Scan experiments employing polarity switching at a resolution setting of 60,000 (at *m/z* 200).

Untargeted screening experiments on the representative extract were carried out using single polarity data-dependent MS^2 (ddMS^2) experiments and the optional Thermo Scientific™ AcquireX™ intelligent data acquisition workflow (iterative precursor exclusion workflow).[4] The MS source conditions for both methods and important MS experiment parameters are detailed in Tables 4 and 5.

Table 4. MS source conditions

Parameter	Value
Spray voltage	+3,250 V / –3,000 V
Sprayer position	1.2, M/H, center
Vaporizer temperature	75 ˚C
Ion transfer tube temperature	325 ˚C
Sheath gas	25 arbitrary units
Aux gas	5 arbitrary units
Sweep gas	0 arbitrary units

Table 5. MS experiment parameters

Parameter	Value
Polarity switching MS^1 method	
MS1 mass range	*m/z* 120–1,200
RF level (%)	70
Easy-IC	Scan-to-Scan
Single polarity ddMS^2 method (Top 4)	
MS^1 mass range	*m/z* 120–1,200
MS^2 isolation window (*m/z*)	1.5
HCD collision energies (Normalized, %)	20, 50, 80
MS^2 resolution	15,000 @ *m/z* 200
Maximum injection time (ms)	100
Easy-IC	Scan-to-Scan
Intensity threshold	2.0e4
Dynamic exclusion	5 s, Exclude Isotopes
Targeted mass exclusion	*m/z* and RT determined by AcquireX software

Data processing software

The Thermo Scientific™ Xcalibur™ 4.5 software was used for data acquisition and Thermo Scientific™ Freestyle™ 1.8 SP2 software for initial data review. For qualitative data processing, data were imported into Thermo Scientific™ Compound Discoverer™ 3.3 SP1 software for spectral deconvolution and compound identification using the workflow template "E and L Unknown ID with Online and Local Database Searches" with modifications to create additional analog traces and addition of the 'Fill Gaps' node.

Results and discussion

In this study, data acquisition was carried out using the Vanquish Inverse Gradient LC system with DAD and CAD detection, coupled to the Orbitrap Exploris 120 MS for HRAM full scan and ddMS^2 acquisition. This system effectively uses two UHPLC pumps within one module, with one pump providing the analytical gradient to separate the analytes using the analytical column, which is merged with the inverse gradient flow from the second pump. As detailed in Figure 1, the flow path of the analytical and inverse gradient pump was merged after the UV detector to avoid diluting the analyte concentration. The difference in the flow paths can be calculated with the help of the Chromeleon Inverse Gradient Wizard.[5] Taking into account the differences between the capillary configuration used here and the Vanquish Inverse Gradient Capillary kit, a time offset of 0.755 min was determined. Alternatively the difference in the flow paths can be determined by sending an acetonitrile plug through the two. During the method file creation, the gradient delay parameter was entered in the Inverse Gradient options, facilitating the automatic calculation of the inverse gradient based on the parameters of the analytical gradient conditions (Table 3). After the two flow paths merge, they are split using a variable flow splitter to provide a 1:10 split ratio with the lower flow passing to the HESI source of the Orbitrap Exploris 120 MS and higher flow passing to the CAD emitter. This split ratio was employed to optimize the mass-dependent CAD signal without reducing the concentration-dependent ESI signal, as shown in Figure 2.

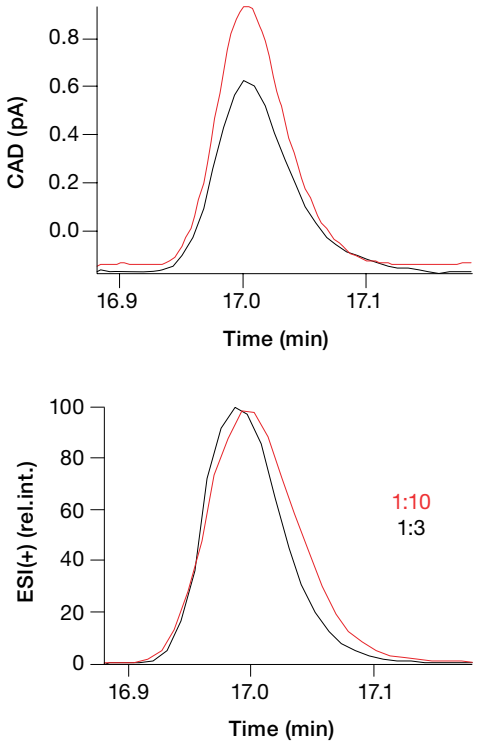

Figure 2. Comparison of CAD (top) and ESI(+) (bottom) signals for oleamide ([M+H]$^+$ *m/z* 282.2791, 17.0 min) at split ratios of 1:10 (red) and 1:3 (black). Higher slit ratio results in stronger signal at the CAD detector without impacting the MS signal.

Standard analysis

The TraceCERT Extractables and Leachables Screening Standard for LC (MilliporeSigma) was used to demonstrate the performance of the system. This mixture of 21 compounds relevant to E&L analyses contains compounds of different physical and chemical properties, covering a range of compound classes. Some of the compounds in the mixture, such as 2,4-di-*tert*-butylphenol, were not expected to give a CAD response due to their volatile nature.[3] However, these compounds would be captured in the separate analysis of volatile compounds by GC/MS, as described in a previous application note.[6] Figure 3 gives an overview of the elution profile obtained from the injection of 2 µL of the standard mixture at 1 µg/mL (1 ppm).

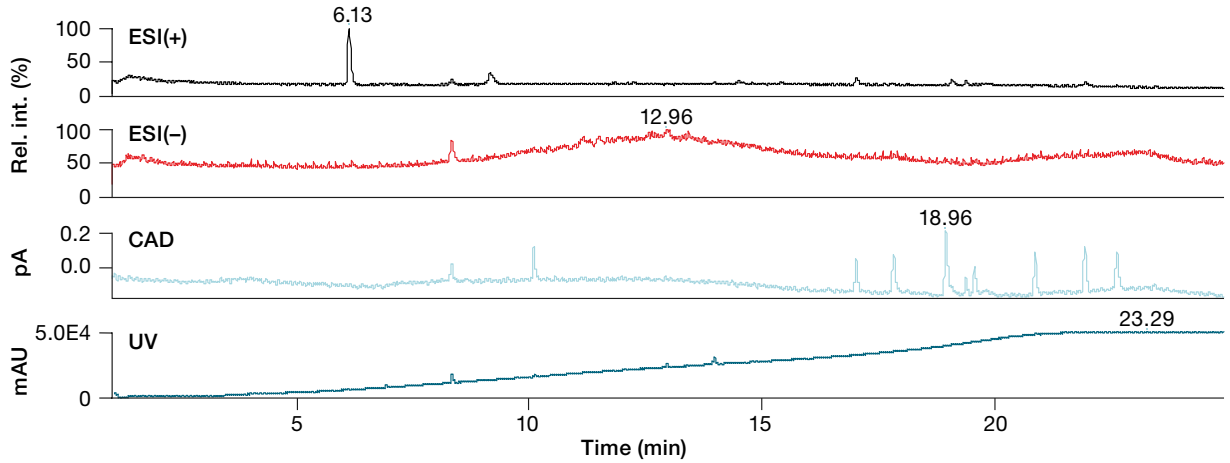

Figure 3. Overview of ESI(+) total ion chromatogram, ESI(–) total ion chromatogram, CAD and UV traces for E&L standard mixture injected at 1 ppm

Some compounds, such as dibenzylamine (peak at 6.13 min in the ESI(+) trace), which showed high ionization efficiencies, were readily detected in the total ion chromatograms. Due to the high data quality of the fast polarity switching HRAM MS data from the Orbitrap Exploris 120 MS, 16 of the 21 compounds could be detected with electrospray ionization (ESI) in either positive or negative mode at 1 µg/mL (with three additional compounds detected at higher concentration). Two compounds, namely 1,3-di-*tert*-butylbenzene and 2,6-di-*tert*-butyl-4-methylphenol, were not detected in this analysis, however both are expected to show better response using GC/MS. As indicated in Table 6, those compounds carrying chromophores, such as aromatic or conjugated double bonds, were detectable by UV, while 11 compounds were detectable by CAD. Those compounds not detectable at 1 µg/mL with CAD had lower molecular weights, indicating higher volatility. Notably, of the 19 compounds detected in this analysis, 15 were detectable by at least two detectors.

To assess the sensitivity of the different detectors, the standard mixture was injected at different concentrations ranging down to 1 ng/mL. As illustrated for 2-mercaptobenzothiazole in Figure 4, MS sensitivity was generally higher than UV or CAD, with the latter having detection limits in the range of 0.1–1 µg/mL.

Table 6. Summary of results for analysis of E&L standard mixture at 1 µg/mL

Compound	MW	RT	Detected by ESI(+)	Detected by ESI(–)	Detected by CAD	Detected by UV (200–680 nm)
Caprolactam	113.16	3.7	X			
Dibenzylamine	197.28	6.1	X			X*
Benzoic acid	122.12	7.0		X		X
2-Mercaptobenzothiazole	167.25	8.3	X	X	X	X
Bisphenol A	228.29	10.1		X*	X	X
2-Ethylhexanoic acid	144.21	10.4		X*		
3,5-Di-*tert*-butyl-4-hydroxybenzyl alcohol	236.35	12.3	X	X*		X
Bis(4-chlorophenyl) sulfone	287.16	13.0	X	X		X
2-(2-Hydroxy-5-methylphenyl)benzotriazole	225.25	14.0	X			X
2,4-Di-*tert*-butylphenol	206.32	15.9	X			X
Oleamide	281.48	17.0	X		X	
Palmitic acid	256.42	17.8	X*	X	X	
Stearic acid	284.48	19.0	X*	X	X	
Bis(2-ethylhexyl) phthalate	390.56	19.1	X		X	X*
Erucamide	337.58	19.4	X		X	
Irganox™ 3114	784.08	19.6	X		X	X
Irganox™ 1010	1177.63	20.9	X	X	X	X
Tris(2,4-di-*tert*-butylphenyl)phosphate	662.92	22.0	X	X	X	X*
Irganox™ 1076	530.86	22.7	X	X*	X	X*
1,3-Di-*tert*-butylbenzene	190.32	n.d.				
2,6-Di-*tert*-butyl-4-methylphenol	220.35	n.d.				

*Detected only in higher concentration sample

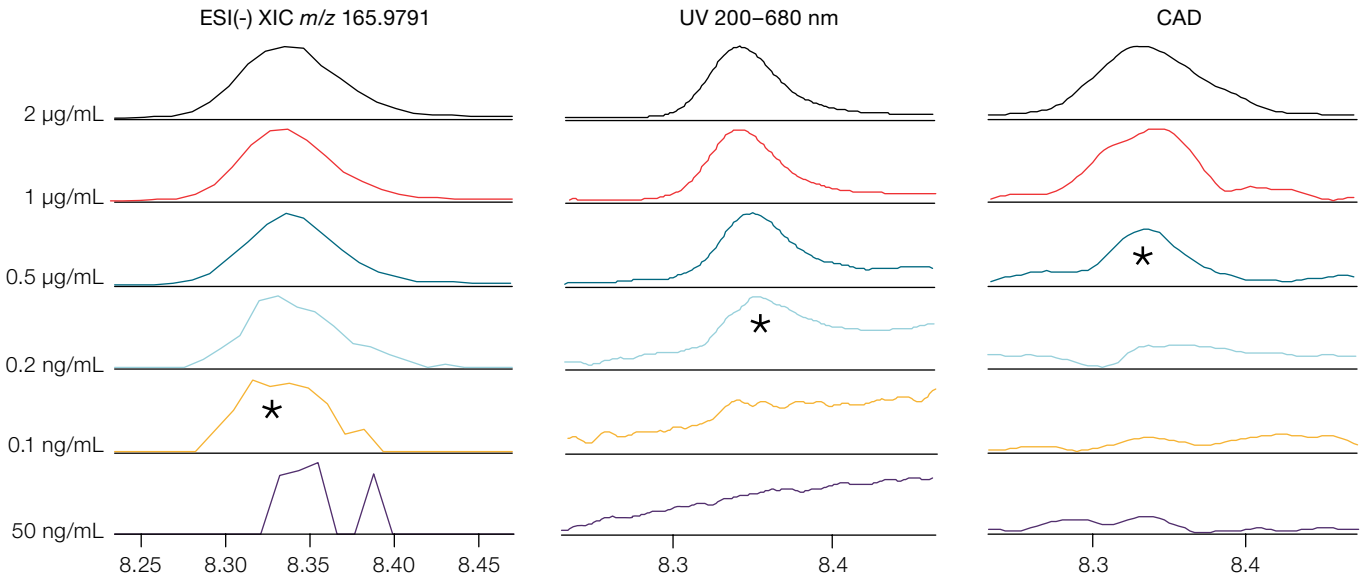

Figure 4. Comparison of signal response from the different detectors at varying concentrations for 2-mercaptobenzathiazole, with ESI(–) showing the highest sensitivity and approximate detection limit denoted with an asterisk.

For all detected compounds in the standard mixture, their response factor was calculated relative to Irganox 1010, and the respective values are given in Table 7 and plotted in Figure 5. Notably, the MS response (black) shows the largest variance in response across the different compounds, with dibenzylamine giving over 300-fold response, while the response from CAD was much more uniform with smaller variance, as demonstrated previously.[3]

Table 7. Summary of relative response factors calculated for the E&L standard mixture at 1 µg/mL relative to Irganox 1010, with ESI relative response calculated for most abundant ion in positive polarity, unless noted otherwise

Compound	MS base ion	Relative response factor		
		ESI	UV	CAD
Caprolactam	$[M+Na]^+$	0.54		
Dibenzylamine	$[M+H]^+$	375.13		
Benzoic acid	$[M-H]^-$	0.25 (–)	9.62	
2-Mercaptobenzothiazole	$[M-H]^-$	23.35 (–)	39.46	0.52
Bisphenol A	$[M-H]^-$	-	6.69	0.75
3,5-Di-*tert*-butyl-4-hydroxybenzyl alcohol	$[M-H_2O+H]^+$	13.71	1.99	
Bis(4-chlorophenyl) sulfone	$[M+H]^+$	0.03	18.63	
2-(2-Hydroxy-5-methylphenyl)benzotriazole	$[M+H]^+$	10.38	35.24	
2,4-Di-*tert*-butylphenol	$[M+H]^+$	0.08	1.23	
Oleamide	$[M+H]^+$	34.91		0.81
Palmitic acid	$[M-H]^-$	0.38 (–)		1.03
Stearic acid	$[M-H]^-$	0.03 (–)		1.91
Bis(2-ethylhexyl) phthalate	$[M+H]^+$	18.10		0.20
Erucamide	$[M+H]^+$	12.47		0.45
Irganox 3114	$[M+NH_4]^+$	2.18	1.46	0.65
Irganox 1010	$[M+NH_4]^+$ / $[M-H]^-$	1.00 (+/–)	1.00	1.00
Tris(2,4-di-*tert*-butylphenyl)phosphate	$[M+H]^+$	11.90		1.31
Irganox 1076	$[M+NH_4]^+$	4.14		1.01
Standard deviation		**89.21**	**14.39**	**0.46**

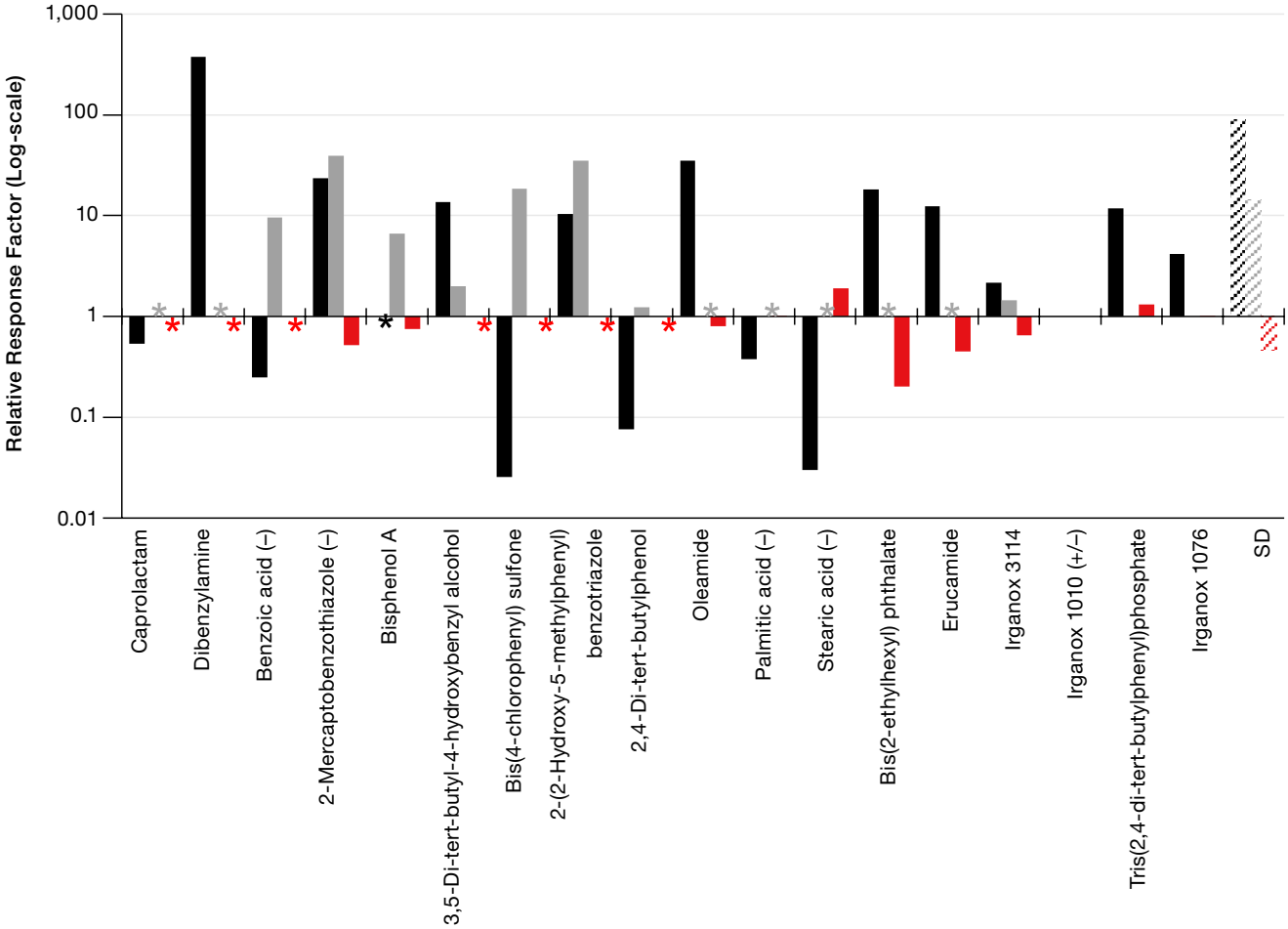

Figure 5. Plot of relative response factors (Log scale) for all compounds in the standard mixture from the MS, UV, and CAD detectors, determined at 1 µg/mL compared to the response of Irganox 1010, with the standard deviation (SD) plotted on the far right, illustrating the lower deviation in CAD response between the different analytes. (*denotes compounds without response from the respective detector.)

Sample analysis

To demonstrate the application of the multidetector system to the analysis of an extractables solution, it was used to analyze the isopropanol extract of pharmaceutical-grade rubber stoppers. While, as described above, any volatile extractables are expected not to show significant CAD response, the more universal nature of this detector can guide the identification process. Given an exemplary AET of 0.5 µg/mL, the CAD signal from the E&L standard mixture analyzed previously was used to estimate a threshold based on CAD response. Figure 6 shows the CAD response for the extract sample along with that for the 0.5 µg/mL level of the standard mixture. Comparing the response levels, compounds that showed detectable CAD peaks in the rubber stopper extract at or above the peak areas for the standard mixture components could be prioritized for annotation, such as the peaks highlighted at RT 19.38 min and 21.51 min.

Compound identification based on the collected HRAM-MS and MS/MS data was performed using Compound Discoverer 3.3 SP1 software using the workflow template “E and L Unknown ID with Online and Local Database Searches” with modifications to create Specialized Traces from the UV and CAD data. The databases used for compound annotation in this workflow included the Thermo Scientific™ mzCloud™ spectral library, the NIST HRMS ESI tandem mass spectral library, ChemSpider™, and an E&L compound mass list. A more detailed description of the data processing and tools available for E&L compound annotation in Compound Discoverer software can be found in a separate application note.[7]

In the Result View, the CAD traces could be manually investigated to integrate peaks, which could then be correlated with detected compounds from the mass spectral data. Figure 7 shows the example of a peak at RT 19.38 min, which correlated with two co-eluting compounds with monoisotopic MW 338.3344 Da (“compound A”) and 227.1885 Da (“compound B”), respectively. Based on the accurate mass and relative isotopic peak abundance of the adducts detected in ESI(+), the elemental compositions were determined as $C_{22}H_{43}NO$ and $C_{13}H_{25}NO_2$ for compounds A and B, respectively, and MS/MS fragmentation of the $M+H^+$ precursor for the former compound resulted in a spectral library match to eucamide with high confidence, as shown in Figure 8. Additionally, the observed retention time matched that of the reference standard in the standard mixture (Table 6).

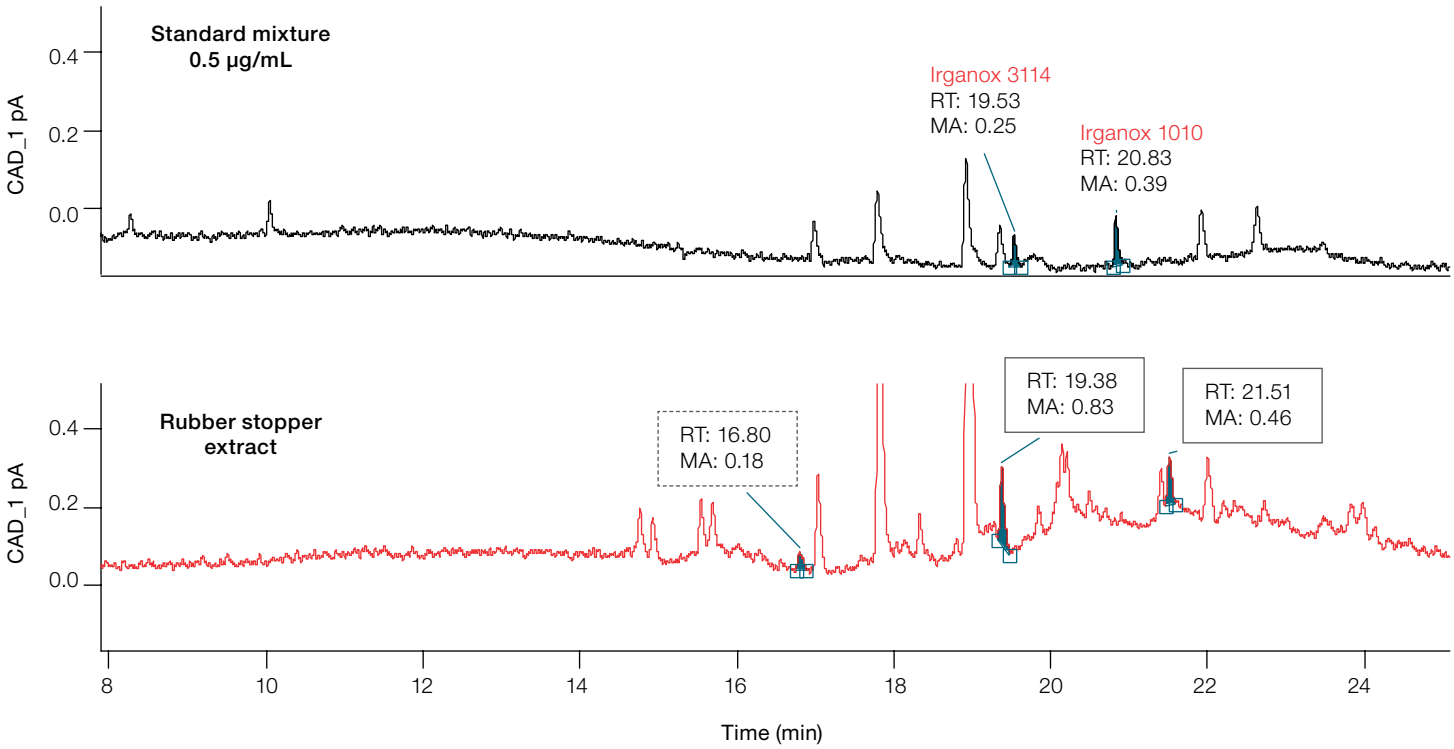

Figure 6. Comparison of CAD response from analysis of E&L standard mixture at a level corresponding to an exemplary AET (0.5 µg/mL) and the sample extract – zoomed to the retention time range from 8 to 25 min. Comparing to the labeled peak for Irganox 1010 with a peak area (denoted MA in figure) of 0.39, several compounds in the rubber extract, such as those denoted at 19.38 min and 21.51 min, have larger peak areas and can thus be prioritized for identification over those with smaller peak areas (e.g., the highlighted peak at RT 16.80).

Figure 7. Correlation of CAD peak at 19.38 min with MS compounds with monoisotopic molecular weight of 337.3344 Da ($C_{22}H_{43}NO$, erucamide, identified based on MS/MS spectral match) and 227.1885 Da ($C_{13}H_{25}NO_2$, 1-aminocyclododecanecarboxylic acid, putative annotation based on mzLogic ranking of mass list and ChemSpider matches) with their XICs and MS1 spectrum shown

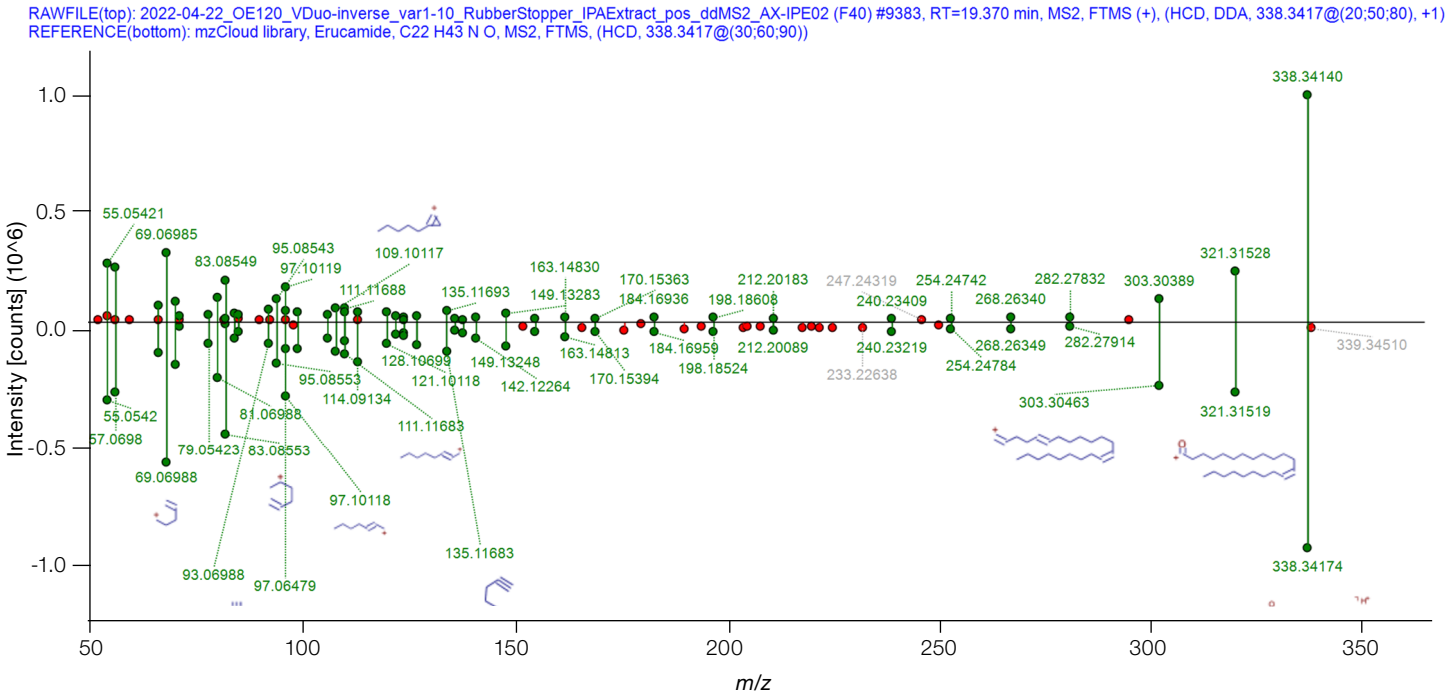

Figure 8. Mirror plot of experimental MS² spectrum for compound A with a molecular weight of 337.3344 Da @ 19.38 min and the library spectrum for erucamide, showing a confident match with a match score of 94.3 and confidence score of 82.0

Notably, erucamide (compound A) was not initially listed in the Compounds table, as its MS peak area in the sample did not exceed the Sample/Blank area ratio of 5 set in the Mark Background Compounds node, and it was automatically filtered from view. For the coeluting compound B, there was no library match based on the fragmentation spectrum, however the Compound Discoverer software determined multiple potential candidate structures from the included Extractables and Leachables HRAM Compound Database and ChemSpider database based on the determined elemental composition of $C_{13}H_{25}NO_2$. These compounds were ranked using the Thermo Scientific™ mzLogic™ algorithm, which rank-orders candidate structures based on their structural similarity to compounds in the mzCloud spectral library and gives similarity matches to the experimental fragmentation spectrum.[8] Based on this ranking, the compound was putatively identified as 1-aminocyclododecanecarboxylic acid.

Conclusion

- UV, CAD, and HRMS provide orthogonal detection based on different properties, which increases compound coverage and annotation confidence.
- The universal response of the CAD detector, when used with the Vanquish Inverse Gradient LC system, enables semi-quantitation of unknown compounds against surrogate standards, aiding in determining which compounds need to be identified in the context of extractables studies.
- The HRAM MS/MS data provided by the Orbitrap Exploris 120 MS together with Compound Discoverer software enable identification of unknown extractables based on elemental composition, fragmentation spectral library, and compound database matches.

References

1. Safety thresholds and best practices for extractables and leachables in orally inhaled and nasal drug products. PQRI Leachables and Extractables Working Group, 2016. https://pqri.org/wp-content/uploads/2015/08/pdf/LE_Recommendations_to_FDA_09-29-06.pdf
2. Menz, M.; Eggart, B.; Lovejoy, K.; Acworth, I.; Gamache, P.; Steiner, F. Charged aerosol detection – factors affecting uniform analyte response. Thermo Fisher Scientific Technical Note 72806, 2018.
3. Meding, S.; Lovejoy, K.; Swart, R.; Steiner, F.; Ruehl, M. A multi-detector platform comprising UV/Vis, charged aerosol, and single quadrupole mass spectrometric detection for comprehensive sample analysis. Thermo Fisher Scientific Application Note 72869, 2018.
4. Thermo Scientific AcquireX intelligent data acquisition workflow is a factory installed OPTON for the Orbitrap Exploris 120 MS (BRE0026990, AcquireX License for Orbitrap Exploris 120 - factory installed), and included by default with the Thermo Scientific Orbitrap Exploris 240 MS and Thermo Scientific Orbitrap IQ-X™ Tribrid™ MS. For additional information, visit thermofisher.com/AcquireX
5. Installation Guide: Thermo Scientific Vanquish Inverse Gradient LC Systems Rev. 1.0, March 2018. https://knowledge1.thermofisher.com/@api/deki/files/432/4820.3616_-_Rev_1.0_-_Installation_Guide_-_Vanquish_Duo_for_Inverse_Gradient.pdf?revision=1
6. Lu, D.; Hower, D.; Liu, C.; Comstock, K. Extractable analysis of rubber stoppers for pharmaceutical applications. Thermo Fisher Scientific Application Note 419, 2021.
7. Cooper, J.; Cojocariu, C.; Roberts, D. Non-targeted screening of extractables from vial septa using high-resolution Orbitrap GC-MS. Thermo Fisher Scientific Application Note 206, 2021.
8. Smart Note: Accelerating small-molecule unknown identification with mzLogic. Thermo Fisher Scientific, 2019. https://assets.thermofisher.com/TFS-Assets/CMD/brochures/sn-65387-ms-mzlogic-data-analysis-algorithm-sn65387-en.pdf

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