EXTRACTABLES & LEACHABLES USA

Originally set to take place April 20 - April 22, the ***Extractables & Leachables USA*** conference in Bethesda, MD, has been rescheduled for October 26-29. Boston Analytical is looking forward to meeting all conference attendees in person at this later date.

In a better effort to get to know the team that will be on site October 26-29, we invite you to attend our virtual conference series. Whether you were planning to attend the conference or are simply looking for a testing facility, our goal is to provide you with the ability to make an educated and informed decision as to why Boston Analytical is the best testing facility for your project.

At Boston Analytical we continuously pride ourselves in our ability to help you find the right service for your business. The following pages provide a snapshot of the services we offer, including links to our website that contains further information for your individual or business needs. This also includes ways to get in touch with our team of business development representative - please reach Christine to start your partnership with us today.

We'll see you in October!

meet & reach out to Christine!

an informational E&L poster provided by our director!

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Continue to next page for Informational poster >>

RESPONSE FACTOR VARIATION STUDY OF INTERNAL STANDARD FOR SEMI-QUANTITATION OF EXTRACTABLES AND LEACHABLES USING LC-MS

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ABSTRACT

Substances leached from pharmaceutical manufacturing components, package systems, and medical devices under laboratory conditions and clinical therapy have been increasingly emphasized by regulatory bodies such as the US Food and Drug Administration (FDA) and The European Medicines Agency (EMA). The qualification and quality control of all these components contacting with the drug formulation is an integral part of any FDA application process. The safety impact of the leached substances on patients depends on the discovery, identity and the amount. Currently, the concentration of the leached substances above the Analytical Evaluation Threshold (AET) is frequently quantitated using chromatographically techniques based on an internal standard assuming equivalent response factors. Such a semi-quantitation is accurate to the extent that the responses of the internal standard and the leached compound are similar. However, the extractables profile always demonstrates a wide variety of the compounds involved in the packaging components such as anti-oxidants, slip agents, plasticizers, surfactants, cross linking agents, residual monomers and oligomers.

Different compounds at the same concentration could present different detector responses due to the variety of the molecular structures. This can result in errors in quantitation due to the response factor variation. Therefore, not all the internal standards are suited for concentration estimation. Herein, to establish accuracy of the internal standard approach, a comprehensive response factor variation study for semi-quantitation of extractables and leachables was reported for the non-volatile internal standard candidates. In this study, LC-QTOF-MS was employed for scouting the LC-MS response factors. Internal standards presenting various polymer additive categories were used to estimate the nature of the response behavior. A comparison of internal standard response factors in different extraction solvents was also performed to determine if the extraction solvent affect the LC-MS response factors. The comparison results and recommendations will be given for selecting the suitable non-volatile internal standards to semi-quantitate the extractables and leachables to its greatest possible value.

EXPERIMENTAL

Common extractables compounds were chosen for this study, and analyzed by LC-MS using Boston Analytical's common extractables screening method. The responses for these compounds were gathered, and plotted versus the current internal standard compounds utilized in the common screening method to generate a relative response factor. These data were used to understand the relative response factors for the various selected compounds, and how the variation of this response factor can impact extractables semi-quantitation data. These data will be used by Boston Analytical to refine and improve our common extractables screening method and generate more accurate results.

COMPOUND SELECTION

The compound selection is based on the following key performance factors:

- Compound is representative of common polymer additives and preservatives.
- Compound contains components which can be ionized in positive or negative ion-modes.
- Compound covers a wide mass range (152 Da to 1176 Da).
- Compound has various functional groups.

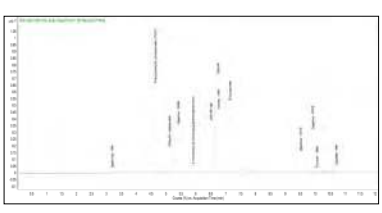
CANDIDATE INTERNAL STANDARDS

Compound	Chemical Formula	CAS #	Mass	ESI (+)	ESI (-)
Methylparaben	$C_8H_8O_3$	99-76-3	152.0473		+
Irganox 154	$C_{15}H_{24}O_2$	947-19-3	204.1150	+	
TINUVIN P	$C_{13}H_{11}NO$	2440-22-4	225.0902	+	
Bisphenol A	$C_{15}H_{16}O_2$	80-05-7	228.1150		+
Stearic acid	$C_{18}H_{36}O_2$	57-11-4	284.2715		+
Dibutyl sebacate	$C_{18}H_{34}O_4$	109-43-3	314.2457	+	
Stearic acid-d35	$C_{18}HD_{35}O_2$	17660-51-4	319.4912		+
2-Hydroxy-4-(octyloxy)benzophenone	$C_{21}H_{26}O_3$	1843-05-6	326.1882	+	+
Erucamide	$C_{22}H_{43}NO$	112-84-5	337.3345	+	+
Tris(p-cresyl) phosphate	$C_{21}H_{21}O_4P$	78-32-0	368.1177	+	+
DEHP	$C_{24}H_{38}O_4$	117-81-7	390.2770	+	
DEHP-d4	$C_{24}H_{34}H_{4}O_4$	93951-87-2	394.3021	+	
Uvinul OH	$C_{34}H_{50}N_2O_3S$	7128-64-5	430.1715	+	
Irganox 1076	$C_{35}H_{62}O_3$	2082-79-3	530.4699	+	+
Irganox 1098	$C_{40}H_{64}N_2O_4$	23128-74-7	636.4866	+	+
Irgafos 168	$C_{42}H_{63}O_3P$	31570-04-4	646.4515	+	+
Tinuvin 900	$C_{34}H_{53}N_5O_2$	103597-45-1	658.3993	+	+
Irganox 1010	$C_{73}H_{108}O_{12}$	6683-19-8	1176.7841	+	+

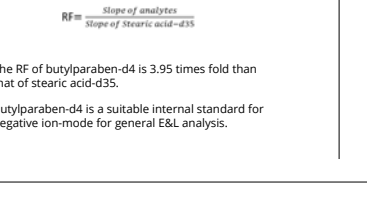
INSTRUMENTAL CONDITIONS

Parameter	Value
System	Agilent 6550 iFunnel Q-TOF LC/MS system
Mobile phase	A: 100 mg/L ammonium acetate in water B: 100 mg/L ammonium acetate in methanol
Gradient	Time (min) %A %B 0.0 70 30 2.5 20 80 9.5 0 100 12.0 0 100 12.1 70 30 (3-min post-time)
Flow rate	0.4 mL/min
Injection volume	1.0 µL
Analytical Column	Agilent ZorBax RRHD Eclipse Plus C8, 1.8 µm, 2.1 × 50 mm
Column temperature	45 °C
Ionization mode	Dual AJS-ESI
Polarity	Positive and Negative
Drying gas	Nitrogen, 13 L/min at 150 °C
Nebulizer pressure	35 psi
Sheath gas	Nitrogen, 11 L/min at 250 °C
Capillary voltage	3500 V
Nozzle voltage	0 V
Fragmentor	175 V
Scan range	50–1700 m/z
Scan rate	3 spectra/s
Reference ions	Positive: 121.0509 and 922.0098 Negative: 119.0363 and 980.0164

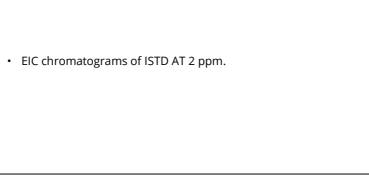
PEAK AREA VS. CONCENTRATION (0.01 MG/ML TO 10 MG/ML) IN POSITIVE ION-MODE



EIC CHROMATOGRAMS IN NEGATIVE ION-MODE (0.5 MG/ML)



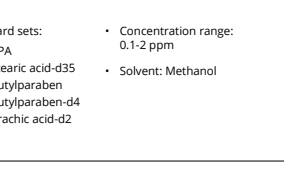
PEAK AREA VS. CONCENTRATION (0.01 MG/ML TO 10 MG/ML) IN POSITIVE ION-MODE



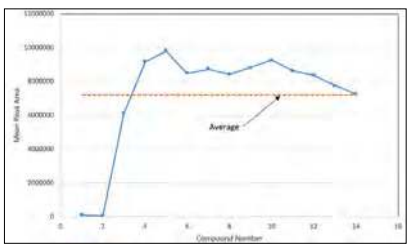
RELATIVE RESPONSE FACTOR (RRF) AT 0.5 MG/ML IN POSITIVE ION-MODE

Internal Standard: DEHP-d4

$$RRF = \frac{Peak\ area\ of\ analytes}{Peak\ area\ of\ DEHP\text{-}d4}$$

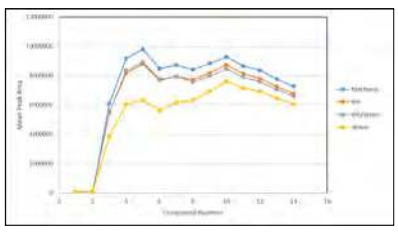


MEAN PEAK AREA VS. COMPOUND NUMBER AT 0.5 MG/ML IN POSITIVE ION-MODE



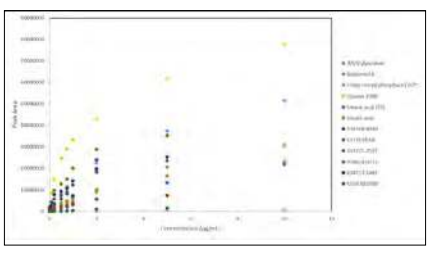
- The peak area of an ideal internal standard should be close to the mean peak area of candidate internal standards.
- The MS response of DEHP-d4 is higher than the mean MS response of candidate internal standards.
- DEHP-d4 should be divided by a RF of 1.4 when used as an internal standard in extractables & leachables studies.

SOLVENT EFFECTS ON RESPONSE FACTOR AT 0.5 MG/ML IN POSITIVE ION-MODE

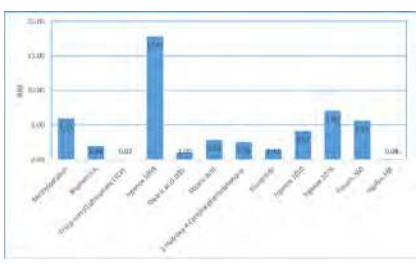


- The MS response factor of candidate internal standards in different solvents is different.
- Standards in methanol have highest MS response, while standards in water have lowest MS response.

PEAK AREA VS. CONCENTRATION (0.01 MG/ML TO 10 MG/ML) IN NEGATIVE ION-MODE



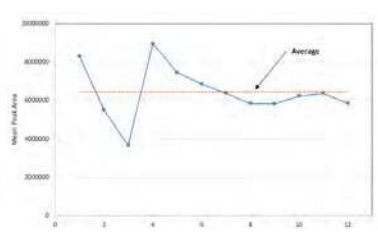
RELATIVE RESPONSE FACTOR (RRF) AT 0.5 MG/ML IN NEGATIVE ION-MODE



Internal Standard: DEHP-d4

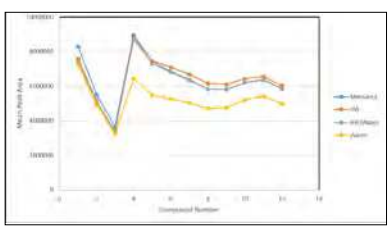
$$RRF = \frac{Peak\ area\ of\ analytes}{Peak\ area\ of\ Stearic\ acid\text{-}d35}$$

MEAN PEAK AREA VS. COMPOUND NUMBER AT 0.5 MG/ML IN NEGATIVE ION-MODE



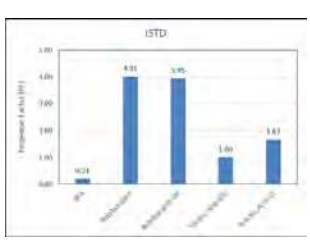
- The peak area of an ideal internal standard should be close to the mean peak area of candidate internal standards.
- The MS response of stearic acid-d35 is much lower than the mean MS response of candidate internal standards.
- An RF of 4.6 should be multiplied when Stearic acid-d35 is used as an internal standard to quantitate the extractables/leachables.

SOLVENT EFFECTS ON RESPONSE FACTOR AT 0.5 MG/ML IN NEGATIVE ION-MODE



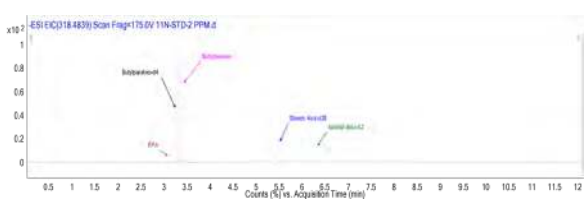
- The MS response factor of candidate internal standards in different solvents is different.
- Standards in water have lowest MS response, while standards in methanol, IPA, and IPA/water (50/50) have similar MS response.

INVESTIGATION OF BUTYLPARABEN-D4 AND ARACHIC ACID-D2

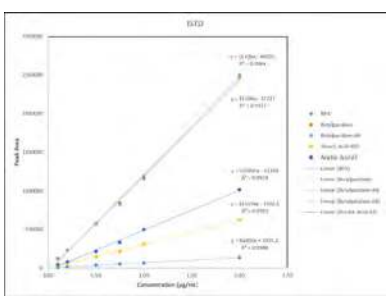


$$RF = \frac{Slope\ of\ analytes}{Slope\ of\ Stearic\ acid\text{-}d35}$$

- The RF of butylparaben-d4 is 3.95 times fold than that of stearic acid-d35.
- Butylparaben-d4 is a suitable internal standard for negative ion-mode for general E&L analysis.



- EIC chromatograms of ISTD AT 2 ppm.



- Standard sets:
  - BPA
  - Stearic acid-d35
  - Butylparaben
  - Butylparaben-d4
  - Arachic acid-d2
- Concentration range: 0.1-2 ppm
- Solvent: Methanol

CONCLUSIONS

- Candidate Internal standards presenting various polymer additive categories were used to estimate the nature of the response behavior.
- The MS response of an ideal internal standard should be close to the mean MS response of candidate internal standard database.
- DEHP-d4 can be used as an internal standard to quantitate non-volatile extractables/leachables in positive ion-mode for E&L studies.
- Butylparaben-d4 can be used as an internal standard to quantitate non-volatile extractables/leachables in negative ion-mode for E&L studies.
- The MS response of candidate internal standards varies for different solvents. Standards in alcohol solutions give similar responses, while standards in water gave lower MS responses.

SNAPSHOT **OF OUR E&L SERVICES**

CLICK ANY SERVICE FOR FURTHER INFORMATION

E&L SERVICES

We offer full Extractables & Leachables testing for the Pharmaceutical, Bio-Pharmaceutical, Medical Device, and Consumer Products industries. Extractables & Leachables in drug products have become an area of concern to patient safety and to the FDA. We have staff with vast experience working directly with the FDA to address concerns and demonstrate drug product safety. Our processes adhere to ISO 10993, USP <661.1>, <661.2>, <1663>, <1664>, <1664.1>, as well as industry best practices from the Product Quality Research Institute (PQRI) and BioPhorum Operations Group (BPOG). ***Learn More.***

SNAPSHOT OF OUR E&L SERVICES

CLICK ANY SERVICE FOR FURTHER INFORMATION

EXTRACTABLE STUDIES

Boston Analytical has extensive experience with extractables testing of all forms of drug product packaging, processing components, and medical devices. Our knowledgeable staff can guide you through the regulatory process and industry best practices to put the best plan in place for producing safe products. ***Learn More.***

LEACHABLES STUDIES

Boston Analytical regularly performs leachables studies with all drug forms; including parenterals, inhalation products, topicals, opthalmics, combination products, biopharmaceuticals, and medical devices. Our team of experts can help you identify and address potential risks to ensure effective closure systems, process equipment and packaging. ***Learn More.***

BPOG PROTOCOL TESTING

Boston Analytical is well versed in the BPOG protocol, “Standardized Extractables Testing Protocol for Single-Use Systems in Biomanufacturing.” We can help you navigate the protocol and develop strategies to meet compliance requirements. ***Learn More.***

OTHER SERVICES WE PROVIDE

CLICK ANY SERVICE FOR FURTHER INFORMATION

ANALYTICAL DEVELOPMENT & VALIDATION

FEASIBILITY / OPTIMIZATION / DEVELOPMENT
VALIDATION / TROUBLESHOOTING

ANALYTICAL TESTING

ELEMENTAL IMPURITIES / DISSOLUTION TESTING
IN-PROCESS & LOT RELEASE TESTING / RAW MATERIAL TESTING
PRODUCT CHARACTERIZATION

MICROBIOLOGY TESTING

MICROBIOME / MICROBIAL IDENTIFICATION
PHARMACEUTICAL TESTING / MEDICAL DEVICES TESTING
CLEANROOM / UTILITIES TESTING / CONTAMINATION RESPONSE INVESTIGATION

BIOLOGICS

PROTEIN ANALYSIS / PROTEIN CHEMISTRY CHARACTERIZATION

STABILITY & STORAGE

STABILITY STORAGE / THERMAL CYCLING STABILITY TESTING PHOTOSTABILITY TESTING & PHOTODEGRADATION STUDIES
CLINICAL REGISTRATION & ANNUAL STABILITY STUDIES
BLIND COMPARATOR STABILITY STUDIES

OUR FAQ'S

HERE ARE SOME OF THE MOST FREQUENTLY ASKED QUESTIONS FROM LAST YEAR'S E&L CONFERENCE

Q: Full E&L studies tend to be expensive, what is BA's recommendation to start? (ie Risk Assessments)
A: We recommend starting with a Materails Risk Assessment. This will evalute and document the leachables risk for the study, and recommend an appropriate study to mitigate this risk to ensure patient safety & compliance. This approach also assures unnecessary tests are not performed.

Q: What is BA's experience and lab capacity regarding E&L testing?
A: The E&L team at BA has an average of 8+ years of experience. The director of the group has 21 years of experience in polymer material characterization and E&L testing. We recognize the growing need for E&L testing, and are maintaining resource levels (both personnel and instrumentation) to allow us to start studies withing 1-2 weeks of the approval of a quotation.

Q: How does BA approach an E&L Study?
A: BA takes a materials based approach to all E&L studies. We follow PQRI and USP guidance for container closure systems and manufacturing componets. For medical devices, we follow ISO 10993.

Q: Are E&L studies similar for different product types, medical device, sterile syringe etc?
A: No, the risks and requirements for these different types of products are quite different. We tailor all E&L studies to the product type, the risk, and regulatory expectations.

Q: Do you have experience with all of these product types?
A: Yes, we have experience conducting E&L studies on drug products, combination products, transdermal patch products, medical devices, implantables, and manufacturing equipment.

Q: Does BA do Container Closure testing?
A: Yes, we offer full Extractables & Leachables testing on all forms of container closure systems. This includes USP <661.1>, <661.2>, <1663>, and <1664> methods.

Q: I don't want to commit to a full BPOG, what are the different options that BA offers?
A: We can test per USP <665>, as well as design a custom program that meets the needs of you manufacturing process and drug product/substance.

Q: Most labs I talk to have a long start time, what is BA's? Do you have the capacity to take on new projects?
A: We have the capacity to take on new projects, and typically can start within 1-2 weeks of receiving a PO. We are adding capacity all the time to maintain the ability to start new projects immediately.

Q: Can BA help support biocompatibility?
A: Yes, we do help support this.
