Analytical Workflow for Elemental Extractables and Leachables in reference to USP and ICH Guidelines: Intravenous Bag Case Study

Solomon, P. E.*, Nelson, J.*, Jordi, M.**
*Agilent Technologies (Santa Clara, CA)
**Jordi Labs (Mansfield, MA)

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Introduction

As a component of safety testing for pharmaceutical products, government and consortia require analysis of packaging and container/closure materials for potential extractable and leachable (E&L) contaminations.

Designing and optimizing a thorough, robust analysis requires multivariate consideration of many factors, which are depicted in the decision-tree/dependency diagram below:

Contaminant			
Type of impurity			**Level of contamination**
Small molecule contaminations can result from the production process (additives and cross-linking agents) or can migrate from the packaging material into the drug formulation based on the polymer composition and its interactions with the drug matrix.	**Semi-volatile, volatile** →	**GC-MS**	**Background research** on production process and polymer materials can inform expected levels of contamination. **Daily exposure limits** for contaminants will vary based on the route of administration. → **Extraction solvent stoichiometry** can be optimized for accurate quantitation. **Analytical technique** and **calibration standard range** should achieve the adequate **LOQ**.
	Non-volatile →	**LC-MS**	
Elemental impurities are also introduced to the plastic container during polymer production, generally as metal-ion salts added for thermal stabilization. →		**ICP-MS, ICP-OES**	

Container	
Sampling	
Assess only the parts that are in **contact** with the matrix. →	Including extraneous packaging components can dilute the contamination levels detected, resulting in **false negatives**.
Drug formulation/Extraction solvent	
Drug formulation or representative extraction solvent of **similar acidity** and **polarity** →	Minimum representative set of contaminants
Additional solvents of **varied polarity** and **acidity** →	Exaggerated set of extractables, accounting for **potential decomposition** of the drug formulation that can alter the matrix properties and extractability
Extraction conditions	
Extraction conditions should predict/simulate realistic as well as worst-case transportation and storage stressors - high temperature, shaking, extended storage →	Minimum representative set of contaminants
Additionally can test **extremely aggressive conditions** →	Exaggerated and exhaustive scope of extractables
Quality Control (QC)	
CCV/CCB requirements →	Second source QC tested every 10 samples to validate accuracy and reproducibility throughout entire analysis
Sample spikes →	Second dimension of data validation

Agilent 7800 ICP-MS

In this study, we analyzed the elemental E&L profile for intravenous (IV) bags made of a polymer material in reference to US Pharmacopeia (USP) and International Council for Harmonization (ICH) guidelines. Instrument choice can significantly facilitate the time and effort spent on method development, sample preparation, and analysis. For the elemental contamination profiles of IV bags, the **Agilent ICP-MS** was chosen for its robust performance and compatability with these sample analytes, concentrations, and matrices:

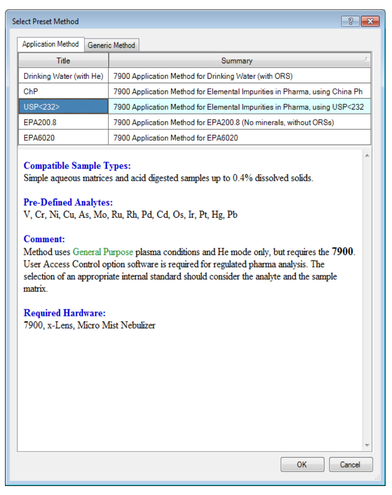
- Ultra High Matrix Introduction System can handle a matrix of up to **25% total dissolved solids (TDS),** such as the high Sodium content saline matrix tested
- **10 orders of magnitude dynamic range** afforded the reliable detection of 70 elements, in two different matrices, in a single analysis. Trace impurities as well as major constituents such as Sodium could be studied simultaneously, reducing sample preparation and analysis time
- The **limit of quantitation** exceeds the sensitivity needed for USP-ICH legal daily exposure limits
- The **Octopole Reaction System Helium Mode** effectively **removes common polyatomic interferences** in the samples for accurate results
- **Agilent ICP-MS MassHunter** software includes a **preset USP-ICH Method** for easy set-up

Experimental

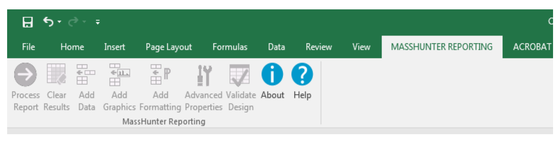
Extraction method:
The filter, tube, and bag components of the IV bag were determined to be in direct contact with the drug, and were separately treated with both water and saline extraction solvents at 50°C with shaking at 50 rpm for 72 hours.

Standard, quality control, and sample preparation:

1. Standard stocks for 70 elements were prepared wt/wt and by serial dilution of the standard stocks into 5% nitric acid in DI water. Calibration standard concentrations were 0.1-10 ppb with additional 100-1000 ppb levels for anticipated major component elements such as Na in saline.
2. Separately-sourced QC standards were prepared at 0.5 and 5 ng/g. Sample spikes were prepared at 0.1 and 1 ug/kg with QC standard for further validation of results.
3. Extracted samples were diluted 10-fold with 5% nitric acid in DI water and tested in triplicate.



Data acquisition:
MassHunter software provided automated analytical workflow platform for USP-ICH applications, including instrument set-up and viability checks, autotune capabilities, USP-ICH applications pre-set method, add-in/interface to Excel for data analysis and reporting, and automated USP reports.

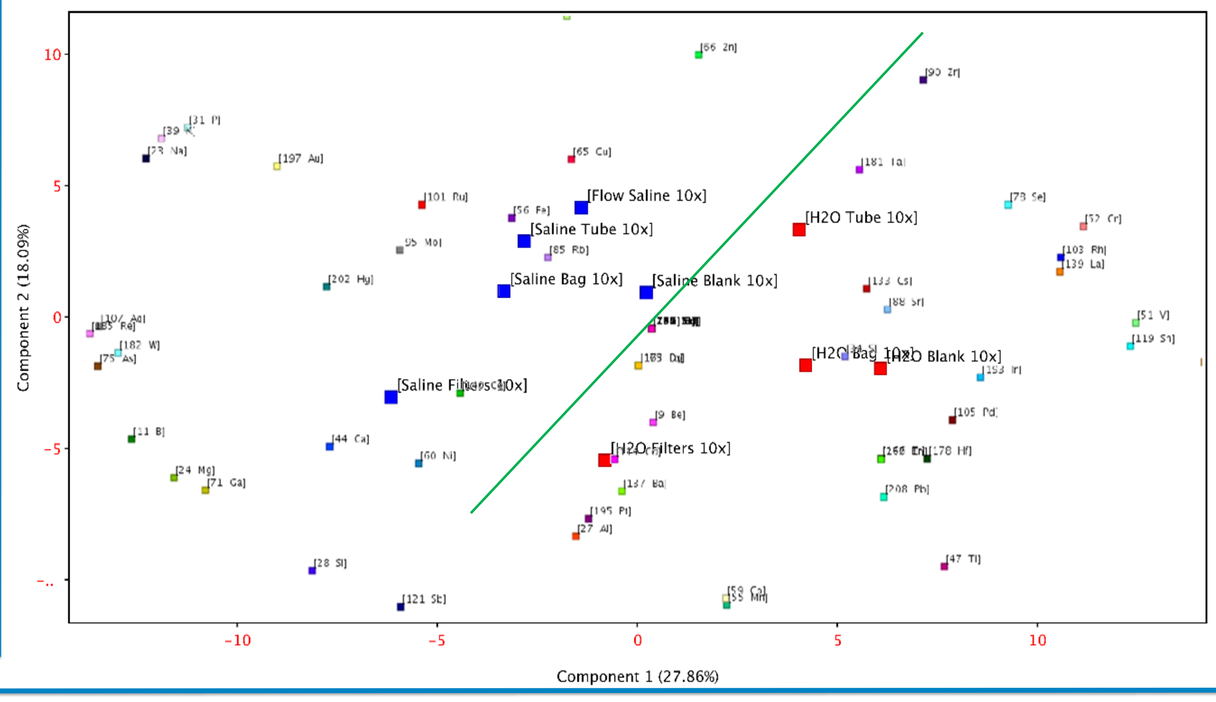


Results

ALL (ppb)	As	Cd	Hg	Pb	Co	Ni	Cr	Mo	Sb	Ba
Class (ICH Guidelines)	1	1	1	1	2A	2A	3	3	3	3
Saline Filters	0.063	<DL	0.024	0.010	<DL	<DL	0.076	0.243	104.918	0.307
Saline Tube	0.033	0.010	0.017	0.022	0.190	<DL	0.049	0.184	0.042	0.311
Saline Bag	0.035	0.005	0.012	0.024	<DL	<DL	0.043	0.173	1.029	0.588
Flow Saline	0.048	0.003	0.023	0.085	0.082	<DL	<DL	0.227	0.270	0.016
H2O Filters	0.074	<DL	0.012	<DL	<DL	<DL	0.029	0.009	20.033	0.199
H2O Bag	0.004	0.010	0.012	0.027	<DL	<DL	<DL	<DL	<DL	0.102
H2O Tube	0.004	0.017	0.012	0.013	0.323	0.169	<DL	0.011	<DL	0.057
H2O Blank	0.003	<DL	0.007	<DL	<DL	<DL	<DL	0.007	<DL	<DL
Saline Blank	0.033	0.001	0.004	0.015	<DL	<DL	0.039	0.201	0.012	0.302

Example of 10 toxic metals detected at trace/low levels: As, Cd, Hg, Pb, Co, Ni, Cr, Mo, Sb, Ba.

Data Interpretation & Statistical Analysis



Results were imported into Agilent Mass Profiler Professional (MPP) software for statistical analysis and data visualization.

Principal component analysis generated with MPP determined the major elemental concentration differences between extraction solvents. For example Zn was detected at high level in a saline matrix but is a lesser concern in a water matrix.

Conclusions

- ✓ E&L analysis must consider analytes of interest, drug matrix properties, packaging material properties, and real-world production, transportation, and storage conditions.
- ✓ Instrument choice is integral to meet necessary sensitivity requirements. Instrument and software can also simplify time spent on method development, sample preparation, analysis, and validation.
- ✓ The Agilent ICP-MS was used to completely profile IV bags for 70 elements in a single analysis. We demonstrated easy and rapid sample preparation, method set-up, and analysis with this advanced technology and related software.
- ✓ All 70 elements tested were confirmed to comply with USP-ICH daily exposure limits. However, more than 10 toxic metals were determined to have migrated from the polymer bag into the saline and water extraction solvents. These can be deleterious at trace concentrations in the body.
- ✓ MPP statistical analysis allowed easy visualization of the effect of extraction solvent on E&L profiling. Saline and water each produced a unique set of elemental levels, suggesting different pharmaceutical matrices have different contamination risks in this polymer material.
- ✓ These results support the utility of E&L testing for consumer safety.

Acknowledgements

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Khera, S., Jordi, M., Arnaud, C., *Chemical & Engineering News*, 2016, "Analysis of Extractables and Leachables: Methodologies, Regulations, Best Practices Series"