Direct, Multielement Determinations from Cotton Swipes via Plate Express Microextraction Coupled to an Inductively Coupled Plasma Mass Spectrometer (μEx-ICP-MS)

Journal:	*Journal of Analytical Atomic Spectrometry*
Manuscript ID	JA-TEC-07-2023-000248.R1
Article Type:	Technical Note
Date Submitted by the Author:	31-Aug-2023
Complete List of Authors:	Stouffer, Cameron; Clemson University, Chemistry Marcus, R.; Clemson University, Chemistry

Direct, Multielement Determinations from Cotton Swipes via Plate Express Microextraction Coupled to an Inductively Coupled Plasma Mass Spectrometer (μEx-ICP-MS)

Cameron J. Stouffer and R. Kenneth Marcus*

Department of Chemistry, Biosystems Research Complex, Clemson University,
Clemson, SC 29634-0973, USA

*Corresponding Author: Prof. R. Kenneth Marcus, Department of Chemistry,
Biosystems Research Complex, Clemson University, Clemson, SC 29634, USA;
marcusr@clemson.edu

Keywords: Inductively Coupled Plasma-Mass Spectrometry (ICP-MS), Microextraction (μEx), Cotton Swipes, Trace Metals

Submitted as a Technical Note to the Journal of Analytical Atomic Spectrometry

ABSTRACT

Cloth swipes are a fairly common sampling modality, having relevance across a wide variety of applications including environmental analysis, forensics, and bioassays. One of the biggest attractions of swipes (and related paper substrates) is the ease of sample collection and transportation, where just the swipe of a surface is required to collect particulates or solution-phase species, with the substrate then readily transported to laboratory facilities. Additionally, the possibility to sample low-volume analytes, such as blood, gunshot residue, etc., provides additional benefits. The modes for the analytical sampling of the immobilized material vary greatly based on the means of analysis. These vary from direct solid analysis by a variety of optical probing methods, to solvent rinsing/extraction, and complete ashing/digestion of the cloth to liberate adsorbed species. Of the methods applied for elemental (metals) analysis of swipe materials, inductively coupled plasma-mass spectrometry (ICP-MS) is the most versatile in terms of coverage and sensitivity. Recently, a direct microextraction approach has been described for uranium isotope ratio determinations. Here, we describe the initial methodology development towards the use of the Advion Plate Express microextraction device, coupled to an Advion Solation ICP-MS, for simultaneous, multielement analysis. Practical means of identifying test sites and evaluating elution quality are described. Methods of multielement quantification are identified with preliminary figures of merit presented. Finally, use of the method to quantify metals spiked into a synthetic urine matrix is demonstrated. While areas of improvement are clearly suggested, this rapid (<2 min) method of direct microextraction into the ICP (μEx-ICP-MS) shows great promise for use across diverse applications.

INTRODUCTION

Cloth swipe sampling is a mainstay in many environmental, forensic, and clinical applications, presenting perhaps the most convenient means of obtaining a “field sample” for subsequent analysis in a fixed-location laboratory.[1-5] Cloth swipes (usually woven but potentially non-woven) are extremely attractive as only a simple swipe of a surface is required to collect particulate specimens or a simple deposition/submersion for the immobilization of solution-phase species.[6-8] Beyond that point, the storage and transportation processes often only require placing the collected sample into a sealed bag for transport.[8] With typical sampling procedures requiring the shipment of liter-sized containers of liquids, the cloth swipe sampling modality allows for the immobilization of analytes, placement into a protected (non-contaminating) environment, and compact, low-weight shipment and storage.

Depending upon the means of analysis, collected species can be probed directly on the substrate surface, eluted/volatilized off, or may require the complete destruction of the substrate via ashing, digestion, etc. Examples include the adsorbed species being probed in-situ using optical methods such as in Fourier-Transform infrared (FT-IR) absorbance or fluorescence spectroscopy,[9] or the use of thermal desorption from the surface as the initial step in the common ion mobility spectrometry (IMS) analysis of swipes obtained in airport security screening.[10-12] More commonly used in the nuclear forensics community, where elemental/isotopic analyses are required, complete swipe ashing/digestion is required to ensure that all potential analyte particles are sampled.[13-15] This sampling process runs counter to those applications where individual particulates must be evaluated. In these instances, microprobe methods such as secondary ion MS (SIMS) or laser probing techniques such as laser-induced breakdown spectroscopy (LIBS), [16-21] laser ablation (LA)-ICP-MS,[22-26] and matrix-assisted laser desorption ionization (MALDI)-MS come into play. While extremely sensitive, these techniques are limited by problems in finding the analyte particles of interest on the substrate in an identifiable, representative quantity reflective of the bulk sample.[27]

Swipe sampling and analysis is a very common approach in the world of nuclear forensics/non-proliferation. An emphasis on the technique came years after the introduction of the Nuclear Non-Proliferation Treaty (NPT), which outlines environmental sampling in reference to nuclear activities.[2, 4, 28] Many methods have been developed for determining the isotopic compositions of environmental samples.[2, 28, 29] Remaining in the realm of composite sample characterization for nuclear forensics applications, whole swipes are typically ashed, with the remnant elemental species digested/resuspended and subjected to isotopic analysis by a multi-collector (MC)-ICP-MS.[3, 6, 23, 24, 30] In many instances, chemical separations are necessary prior to MS analysis[12, 30, 31] due to the potential introduction of isobaric interferents posed from the complex and concentrated substrate matrix contents after the cloth is ashed. With these requirements, these methods are often time intensive, require extensive sample manipulation, risk of analyte losses, and increase risk of sample contamination.[12, 30, 31] While the above methods have showed steady evolution and improvement, it would clearly be preferable if methods of direct particulate/residue elution from substrates could be implemented, presenting opportunities for more rapid analyses, the potential for automation, and alternative quantification schemes.

A collaboration between this laboratory and the Oak Ridge National Laboratory (ORNL) introduced a simple method of extracting solution residues and particulates from standard cotton swipes for the determination of uranium and plutonium isotope ratios.[32] The approach was based on the use of the Advion (Ithaca, NY) Plate Express as a means of solution-microextraction from a cloth substrate and transporting the eluate first to a liquid sampling-atmospheric pressure glow discharge (LS-APGD) microplasma ionization source,[32] and more recently to ICP sources,[33-36] for MS detection. The device was originally designed as a means of extracting organic species from thin layer chromatography (TLC) plates,[37, 38] for their transport to electrospray ionization (ESI) sources for qualitative analysis. In this approach, cotton swipes are placed underneath a capillary sampling head, wherein the elution solvent (2% HNO_3) passes across the surface of the substrate, dissolving/desorbing (the exact process is not clear at this point) immobilized analyte and carrying those species to the respective ionization source.[32] The substrate sampling area is defined by the dimensions of a knife edge, a ca. 2 x 4 mm oval, which forms a seal as it is pressed against the substrate. The released species travel in a well-defined plug flow, producing a transient signal for those isotopes in the spectral response. Following the initial demonstration with the LS-APGD/Orbitrap coupling, more extensive reports from Manard and co-workers have described the performance of the swipe sampling methodology towards U and Pu isotopic analysis on a variety of ICP-MS instrument platforms.[33-36] The microextraction with plasma MS detection has proven to be simple and quantitative, requiring virtually zero sample preparation, with LODs, precision, and sensitivity that is quite sufficient for most U/Pu nuclear forensics applications.

Here we describe the first coupling of a Plate Express to the quadrupole-based Advion Solation ICP-MS, providing a method for rapid, multielement detection of solutions deposited onto cotton swipe substrates with high sensitivity. A number of new attributes to the sampling methodology are demonstrated here which are of broad interest to the field of elemental analysis via ICP-MS. First, we describe a novel, yet simple means of identifying the positions on the substrate where sample has been deposited. Second, we demonstrate the ability to perform multielement determinations, moving beyond U and Pu isotopics. In this regard, challenges in the microextraction apparatus are revealed towards determinations of common metals. Third, the use of simple response functions (both using raw intensities and an internal standard) are demonstrated to yield promising quantification characteristics. Finally, the potential use of the method for multielement bioassays is demonstrated through analysis of a mock urine matrix with trace elements at physiologically-relevant concentrations. The use of aqueous standards is projected to allow a common quantification approach for microextraction of solution residues and swipe particulate matter, with applications in environmental, nuclear, and clinical analyses. Extension of the methods to the traditional use of the Plate Express to TLC plates and common dried blood samples (DBS) on paper substrates is easily envisioned.

EXPERIMENTAL

Chemicals and sample preparation

Solutions of Co, Cu, Fe, Gd, Mn, Nd, Y, Yb, and Zn (High Purity Standards (HPC), North Charleston, SC) were purchased in stocks of 1000 mg L^{-1}. Ag (High Purity Standards (HPC), North Charleston, SC) was purchased in a stock of 10 mg L^{-1}.

Analytical solutions of these metals were made in a concentration ranging from 10 ng L^{-1} to 5 mg L^{-1} and dissolved in 2% HNO_3 made from ultra-pure (UP) HNO_3 (VWR Chemicals, Radnor, PA) and Aristar ultra-pure water (VWR Chemicals, Radnor, PA). Synthetic urine samples were made using a previously employed recipe (9.7 g urea (VWR Chemicals, Radnor, PA), 0.3 g $CaCl_2$ (Mallinckrodt, Paris, KY), 0.5 g $MgSO_4$ (VWR Chemicals, Radnor, PA), and 4.0 g NaCl (Sigma Aldrich, St. Louis, MO), diluted in 50 mL of ultra-pure water),[39] and then spiked with varying levels of the test metals. To be able to visualize the deposited solutions on the cloth, one crystal of cresol red (Ward's Science, Mississauga, ON) was added to each sample to dye the sample red. All samples were then placed on an Analog Vortex Mixer (VWR International, Radnor, PA) and vortexed for 30 seconds to ensure the analytes were completely dissolved. Samples were deposited at a volume of 5 µL onto the cotton cloth sample.

Instrumentation

Microextraction system coupling to ICP-MS Microextraction was performed with an Advion Plate Express (Ithaca, NY, USA). The microextraction probe is ca. 2 × 4 mm and is lowered onto the swipe, with 250 N of force applied, sealing the surface. Once sealed, an extraction solvent (2% HNO_3) flows through the probe head at a rate of 200 µL min^{-1}, releasing the solution residues from the cloth and transporting the eluate to the ICP-MS for detection. The microextraction probe was integrated to the ICP-MS via a 200 µL min^{-1} optimized glass nebulizer (Twister Spray Chamber with Helix CT, Glass Expansion, West Melbourne, Australia) housed within a glass cyclonic spray chamber. The Solation ICP-MS (Advion Corp., Ithaca, NY, USA) contains an octupole He-based collision cell operating in a kinetic energy discrimination (KED) mode to address interferences from polyatomic ions, especially those effecting the transition metal elements. Sampled ions passing through the skimmer cone are turned 90˚ and is focused into the entrance of the octapole using a quadrupole deflector. In this way, photons and neutral particles continue through the quadrupole deflector and not along the ion path. The ICP-MS operating parameters are presented in Table 1. In order to accurately capture the eluting signal transients, a dwell time of 50 ms was set for sequential measurement of the target isotopes: ^{55}Mn, ^{57}Fe, ^{59}Co, ^{63}Cu, ^{66}Zn, ^{89}Y, ^{107}Ag, ^{146}Nd, ^{160}Gd, and ^{172}Yb. The transient signal was integrated in the newly updated Advion Data Express for ICP-MS software using the “Process List for Quantitation” peak integration function. The analyte signals were integrated for a total time of 60 seconds, with the elution time set to the center of the signal transient of each elution sequence.

Imaging – As described above, simple addition of a crystal of cresol red allows ready identification of sample spots for placement under the sampling head. Optical images of the cloth fibers before and after extraction were taken using a MiScope MP4k digital microscope (Zarbeco, Succasunna, NJ). The MiScope is a handheld digital microscope that connects to a computer using a USB port, having magnification abilities ranging from 10X-360X with an ultimate resolution of 1 micron. Images can be taken using white, ultraviolet (UV), or infrared (IR) light. Here images were taken using white light. Using the MiScope-MP4k software length measurement feature, the extraction area of the sampling head was confirmed.

RESULTS AND DISCUSSION

Initial μEx-ICP-MS Sampling Considerations for Multielement Analysis – Each of the previous reports involving the use of the Plate Express to sample solutions residues and particulates into plasma sources (LS-APGD and ICP) dealt solely with the determination of either uranium or plutonium in what would be termed ‘neat’ matrices. By the same token, neither of these elements is likely to exist as solvent contaminants or as constituents in hardware making up the experimental apparatus. As such, the observed blank levels and memory effects were extremely low.[32, 34] Extension of the methodology to multielement scenarios involves a completely different sort of considerations, including the efficient use of sample material, the potential for blank interferences towards the additional elements, and establishing methods of quantification. While both the microextraction and ICP-MS components of the system are produced by the same manufacturer (Advion Corp.), this report is the first to describe the interfacing and initial performance attributes. Minimal changes have been made to either instrument for this method development, with data analysis systems being updated for chromatographic calculation, similar to the Advion Compact MS (CMS) Data Express, to suit the collection of data by the ICP-MS.

Previous methods for uranium isotope measurements deposited standard samples onto the cloth by folding the cloth and depositing the material in the crosshairs.[32, 33] To ensure proper identification and sampling of the sample deposition, as well as provide a visual means of extraction confirmation, a single crystal of cresol red dye was added to the standard and test solutions. When the samples were deposited, a bright pink spot was visible, which was used to guide the correct sampling head position. This allows for far greater substrate utilization, with a maximum of 6 x 8 spots (48 spots in total) onto a singular cloth in contrast with previous 9 spots at the fold cross hairs. Figure 1 presents photographs of as-deposited 5 μL solution applications taken at magnifications of 40 and 120X (Figs. 1a and 1b, respectively). The initial spot is nominally circular, with a diameter of ca. 10 mm. The magnified photograph clearly reveals the woven structure of the cotton swipe. Engaging the microextraction sampling head, with initiation of a 2% HNO_3 solution flowing at a rate of 200 μL min^{-1}, for a period of 1 min, is seen to remove the central portion of the spot (Fig. 1c), outlining the ca. 2 x 4 mm sampling area. The magnified photograph (Fig. 1d) provides greater detail, with the oval impression of the sampling head into the cloth clearly seen. In this instance (for a 5 μL drop applied to the cloth), approximately 20% of the actual application area is sampled. The relative sample utilization (i.e., the amount extracted versus what is deposited) is a factor in performing quantitative analysis, and will be addressed in subsequent sections.

As the sample material is extracted from the cloth, it (ideally) travels as a plug to the ICP nebulizer and generates a temporally well-behaved signal transient for each of the elements/isotopes. Figure 2 presents example signal transients obtained for the elution of a 5 μL spot of a multielement solution composed of 10 μg L^{-1} of each of the test elements. Figure 2a displays the total ion current (TIC) chromatogram of a 500 s extraction (head engaged for 500 s), representing what might be called an exhaustive extraction as the trailing signal effectively reaches a steady level after ca. 250 s following engagement of the microextraction head. A few key aspects of the extraction/detection process are revealed in the TIC response. First, the original signal of ca. 6000 counts shows an increase after about 60 s, representing the onset of the flow from the head. Subsequently, a sharp peak in intensity is observed when the front of the elution plug reaches the ICP-MS and slowly decreases over time as the bulk of the sample elutes over the course of ca. 100 s. Finally, a steady state is reached, but here the value centers around 12,000 counts, not returning to the original, pre-injection level. Clearly, there are multiple effects occurring versus what would ideally be expected in terms of some sort of immediate onset and signals reflecting an exhaustive extraction.

When the extracted ion current (XIC) chromatograms (Fig. 2b and 2c) are plotted, the sources of the non-idealities become evident. Most specifically, as seen in Fig. 2b, five metals (^{55}Mn, ^{57}Fe, ^{59}Co, ^{63}Cu, and ^{66}Zn) display the same transient traits as the TIC, while the four others (^{107}Ag, ^{146}Nd, ^{160}Gd, or ^{172}Yb) exhibit what would be projected as the expected response. It is not a coincidence that the former elements naturally occur in plant-based materials (e.g., cotton swipes)[13] as well as being prominent in scientific hardware (e.g., fluidic components).[40, 41] In either case, those signals would exist as background signal contributions, limiting analytical limits of detection and linear dynamic ranges for those elements. On the other hand, the elements present in the traces of Fig. 2c show very little that reflects any sources other than the analytical swipe sampling.

As earlier works in U/Pu determinations using the Plate Express clearly exhibited signal transients that illustrated what would be called exhaustive extractions based on repetitive samplings from the same position on the swipe,[32, 33] the same sort of experiment was applied for a multielement (each of the elements listed above) solution deposition. It would be expected that if the elements originated from the cloth, the successive elution steps would lead to a depletion in the responses, while a constant response would be reflective of a separate, non-depleting source. Five consecutive, 100 second microextractions were performed on the same spot, with the isotope-specific XIC traces shown in Fig. 3. Here, each of the metals are observed to elute in the first microextraction with the transient widths of ca. 60 s. When the 2nd, 3rd, 4th, and 5th microextractions are executed, there are no peak observed for ^{107}Ag, ^{146}Nd, ^{160}Gd, or ^{172}Yb, however ^{55}Mn, ^{57}Fe, ^{59}Co, ^{63}Cu, and ^{66}Zn are observed to “elute” with each engagement of the sampling head, with equal peak areas for each. As the peak areas did not decrease over the multiple extractions, it was concluded that these background species were not coming from the cloth itself, but instead coming from the extraction process/hardware. Direct sampling of a ‘blank’ swipe as well as a ‘chemically-resistant’ PTFE polymer sheet yielded signals for those elements at levels correlated to the latter samplings in Fig. 3. As such, it is not unreasonable to predominately attribute these species as coming from the stainless-steel extraction head and the associated capillary fluidics as the 2% HNO_3 eluate passes through the assembly. These effects would not have been observed in the prior U/Pu studies, and certainly not in the case of using organic solvents to elute TLC plates prior to ESI-MS analysis. It is acknowledged that these background species inhibit the trace level detection capabilities of this method and represent a design challenge as the methodology evolves. That said, at this point the quantitative analysis results for the non-contaminated elements are excellent, and those for the problematic elements still suggest high levels of applicability.

Quantitative evaluation - As suggested by the transients of Fig. 2 and Fig. 3, there is reasonable proof that this method of extraction has the potential to be a quantitative means of extraction, as complete extraction of the sample was observed for the high-mass (non-background contributing) species. A question exists as to the minimum volume of sample needed to be deposited to affect the greatest signal recovery. Two competing processes take place as the liquid sample is applied to the swipe; adsorption of the solutes at the point of deposition, and the spreading of the droplet to larger areas that may not be sampled by the microextraction head. A study was performed wherein increasing volumes of the 10 μg L^{-1} test solution was applied, from 1-to-10 μL. Based on photographs of the cresol red-doped solutions, the dried spot area (as determined photographically) increases linearly with the volume of the aliquot as plotted in Fig. 4. Presented for each spot size is the percentage of the spot sampled by the extraction head. Obviously, lesser fractional areas are sampled as the spot size increases. Also plotted is the sum of the high-mass analyte (^{107}Ag, ^{146}Nd, ^{160}Gd, or ^{172}Yb) responses for each of the deposits. Perhaps not surprisingly, the analyte signal recoveries increase to some extent up to a volume of approximately 5 μL, beyond this point it is clear that the added sample volume is wasted. One might question if there is a difference in recovery if said volume is applied in one spotting, or perhaps sequential applications of smaller volumes (1 μL), which are allowed to dry. In fact, there is no statistical difference across these instances, and so single 5 μL aliquots are applied in all subsequent measurements.

Elemental response curves were constructed for the entire suite of elements, covering a range of concentrations ranging from 10 ng L^{-1} to 5 mg L^{-1}; covering more than 6 orders of magnitude. Additionally, each test solution was spiked with Y at a concentration of 100 μg L^{-1} as an internal standard to perhaps compensate for plasma fluctuations/drift. Each concentration solution was analyzed as triplicate, 5 μL spots and the quantitative data extracted as the integrated peak areas of the respective isotopic transients. In practice, while the ^{89}Y responses varied by less than 3 %RSD across the entirety of the samplings, ratioing of the elemental responses to the internal standard yielded no appreciable improvement in overall precision, thus raw peak areas were used for all future discussions. That said, it would surely be recommended to consider the use of such an internal standard approach as future analyses across different matrices are undertaken.

Table 2 presents the respective elemental response curve characteristics, derived from log-log plots of the raw signals (covering >5 orders of magnitude concentration), for the suite of test elements applied as triplicate, multielement solutions. Based on the background signals present in Fig. 2 and Fig. 3, there is a clear difference in the quality of the response curves (both slope and R^2) for the first five elements when compared to the higher-mass test elements. Indeed, in each case the background/blank effected elements exhibit flat responses up to applied masses in the mid-picogram range, where proportional responses are then observed with increasing concentrations. Simply put, the background (blank) equivalent concentrations (BECs) are of the order of 10's of parts-per-billion. Not surprisingly, Fe is the worst-behaved of those elements as it is the predominant component element in stainless steel. To the alternative, the behavior of the higher-mass elements (Ag, Nd, Gd, and Yb), which are not components in the fluidic tubing, show outstanding responsivity across the six orders of magnitude of concentration/mass applied to the swipes. For those elements, the LOD (defined as $3\sigma_{blank}$/slope) are on the single-femtogram level (i.e., single ng L^{-1} for 5 μL applications). The sensitivity of these elements suggests great promise for the overall method following sampling head re-engineering which will incorporate a metal-free extraction head and transfer fluidics.

As ICP-MS is, by definition, a multielement/isotope measurement method, it is instructive to evaluate potential perturbations of isotope ratio performance of the μEx-ICP-MS approach as perturbations could result from either the extraction process itself, or the fact that the isotopic signals are transient in nature. The isotope ratio performance of two test elements, Cu and Ag, were evaluated. Triplicate 5 μL spotting of the complete elemental suite were applied at concentrations of 10 μg L^{-1} (50 pg deposited) each, with three separate swipe samples analyzed (n=9). The corresponding theoretic isotopic fractions, the average of the determined values, the percent error and relative standard deviations are presented in Table 3. To be clear, no form of mass bias correction or internal standardization were applied, and so the results present a worst-case scenario. The percent error for each of the ratios was calculated to be 5.8%, which is lower than previous microextraction extraction methods that evaluated uranium isotopes.[32] The isotope ratio values are naturally expected to be less than the theoretical values because the ICP-MS favorably transmits heavier isotopes through the interface and ion lenses.[42] The %RSD for the ratios across the nine samples were calculated to be 4.3% and 4.4% for the two elements, demonstrating the reproducibility of the extraction method. Given this, our method has proven to produce relatively accurate isotope ratios intrasample, with far better performance expected through standard mass-bias corrections. Likewise, without use any form of internal standard, the standard deviations of the determined values and the percentage relative standard deviation precision statistics are very encouraging as the method moves forward.

As a final preliminary assessment of the quantification potential of the μEx-ICP-MS approach, the recoveries of the suite of test metals doped into a mock urine matrix were evaluated. The matrix was chosen as a representative biofluid, having a modest level of organic (3.2 M urea) and salt (ca.1.5 M) content as presented in detail in the Experimental section.[40] As such, there may be complications regarding the elution of the metals, as well as potential ICP-based matrix effects. Two test solutions were synthesized, one with "low" metal levels and one with "high" metal levels spiked into the urine as presented in Table 4. The concentration of the metal spikes were determined by using reported reference levels,[43-49] with the lanthanide concentrations (as they are not typically found in any measurable amount) made to test the recoveries of those elements of diverse chemistries at concentrations within 2 orders-of-magnitude of their LODs. It is important to keep in mind that the deposited sample volumes were 5 μL, emphasizing the mass-sensitivity of the method.

Table 4 presents the expected and determined concentrations for the suite of test elements. As can be seen, the recoveries for these samples is quite good, with an average value of 95.8% for the low concentration set and 101.3% for the higher concentration sample. It is too early in the course of the method development to prescribe any significance in the differences between the two spike levels. It is instructive to stress here the fact that the quantification here was based on the aqueous (2 % HNO_3) response curves described with regards to Table 2. While one might be concerned with not having matrix-matched standards for urine samples, the results obtained in the use of aqueous standards here points to minimal matrix effects. That said, use of matrix-matched standards would likely be a normal plan of action. To a first approximation, the preliminary results presented here suggest a great deal of promise regarding quantification in the μEx-ICP-MS method.

CONCLUSIONS

The collection of solid and liquid samples from environmental surfaces using cloth swipes is a ubiquitous technique. Such techniques are attractive due to their ease of collection and readily transportable nature. Complications are introduced when the analytes need to be removed from the cloth for analysis. Typically, whole swipes are ashed and the elemental species are resuspended for analysis by a variety of atomic spectroscopic methods. In many instances, chemical separations are necessary prior to the ICP-MS analysis increasing the difficulty, timeline, and price of analysis. In effort to develop a sensitive, quantitative, and rapid method of detection, the Advion Plate Express was coupled to the Advion Solation ICP-MS for microextraction sampling and detection of trace-level metals. As the extraction system was designed for the sampling of organic species from TLC plates using organic extraction solvents, complications were found in terms of the presence of appreciable background signal levels for those elements making up the sampling head and transfer fluidics as 2% HNO_3 was employed. For those elements not common to those components (Ag, Nd, Gd, and Yb), quantitative extractions were observed after only 60 s. Response curves obtained for deposited masses of 10 fg- 25 ng showed very good linearity with LODs on the single-fg level. For the metals making up the system components (Mn, Fe, Co, Cu, and Zn), high

BECs were observed, limiting the LODs to the tens of fg. An analysis of ^{63}Cu /^{65}Cu and ^{107}Ag /^{109}Ag isotope replicates produced accuracies of ca. 5.8% below the theoretical values, and precisions of ca. 4.4 %RSD for n=9 replicates; without the use of any mass bias correction or internal standards. Finally, 5 μL solutions of metals spiked into a mock urine matrix were quantified based on aqueous standard solutions, yielding recoveries varying between ca. 84 – 112 %, with an average of 98.5% across all of the elements.

The results presented here suggest a good deal of promise for the overall approach, but clearly point to needed hardware improvements and experimental optimization in relation to specific elements. First, in much the same way as early couplings of high performance liquid chromatography with ICP-MS, the components of the sampling head and fluids must be converted to polymeric materials. Second, there will be a need to independently optimize the swipe sampling parameters including solvent flow rates and composition. In fact, those studies will certainly be dictated in some respect by the sample matrix as well as the substrate material. For example, the removal of ligated metals from services of various hydrophobicities would likely involve the use of organic solvents. Ultimately, this μEx-ICP-MS method and apparatus could be implemented across the breadth of ICP-MS/OES instrumentation to address a wide variety of environmental, medical, and forensic challenges.

Acknowledgements

Financial and system development support from Advion Corporation (Ithaca, NY), are gratefully acknowledged, as are insightful discussions with Dr. Benjamin

Manard of the Oak Ridge National Laboratory.

References

1. W. Chouyyok, J. T. Bays, A. A. Gerasimenko, A. D. Cinson, R. G. Ewing, D. A. Atkinson and R. S. Addleman, *RSC Adv.*, 2016, **6**, 94476-94485.
2. D. L. Donohue, *J. Alloys Compd.*, 1998, **271**, 11.
3. S. C. Metzger, K. T. Rogers, D. A. Bostick, E. H. McBay, B. W. Ticknor, B. T. Manard and C. R. Hexel, *Talanta*, 2019, **198**, 257.
4. R. S. Addleman, B. E. Naes, B. K. McNamara, K. B. Olsen, W. Chouyyok, D. G. Willingham and A. C. Spigner, *Materials and Methods for Streamlined Laboratory Analysis of Environmental Samples, FY 2016 Report*, United States, 2016.
5. J. P. Gorce and M. Roff, *J. Occup. Environ. Hyg.*, 2015, **12**, 699.
6. S. C. Metzger, B. W. Ticknor, K. T. Rogers, D. A. Bostick, E. H. McBay and C. R. Hexel, *Anal. Chem.*, 2018, **90**, 9441.
7. S. K. Y. Yuen, M. C. Taylor, G. Owens and D. A. Elliot, *J Forensic Sci*, 2017, **62**, 1037-1042.
8. C. Koester, C. Thompson, T. Doerr and R. Scripsick, *Appendix C. Collection of Samples for Chemical Agent Analysis*, United States, 2005.
9. F. Esaka, K. Watanabe, H. Fukuyama, T. Onodera, K. T. Esaka, M. Magara, S. Sakurai and S. Usuda, *Journal of Nuclear Science and Technology*, 2004, **41**, 1027-1032.
10. Y. Shen, Y. Zhao, S.-L. Guo, J. Cui, Y. Liu, J. Li, J. Xu and H. Zhang, *Radiat. Meas.*, 2008, **43**, S299-S302.
11. X. Z. "Zhang, F. "Esaka, H. "Fukuyama, K. T. "Esaka, S. "Ichimura, M. "Magara, S. "Sakurai, K. "Watanabe and S. "Usuda, *Application of ICP-MS to measurement of uranium isotope ratio for sub micrometer particles*, ; The organizing committee of APSORC05, Beijing (China), China, 2005.
12. D. Fisher, R. Zach, Y. Matana, P. Elia, S. Shustack, Y. Sharon and Y. Zeiri, *Talanta*, 2017, **174**, 92-99.
13. I. Rujido-Santos, P. Herbello-Hermelo, M. C. Barciela-Alonso, P. Bermejo-Barrera and A. Moreda-Piñeiro, *Int. J. Environ. Res. Public Health*, 2022, **19**, 944.
14. T. Yang, X. Liu, Z. Liu, L. Tang and K. Long, *Nucl. Techn*, 2007, **30**, 208-212.

15. É. Széles, Z. Varga and Z. Stefánka, *J. Anal. At. Spectrom.*, 2010, **25**, 1014-1018.

16. D. W. Hahn and N. Omenetto, *Appl. Spectrosc.*, 2010, **64**, 335a.

17. A. Williams and S. Phongikaroon, *Appl. Spectrosc.*, 2018, **72**, 1029.

18. R. E. Russo and A. W. Miziolek, *Laser-Induced Breakdown Spectroscopy (LIBS) Fundamentals and Applications Preface*, 2006.

19. B. T. Manard, M. F. Schappert, E. M. Wylie and G. E. McMath, *Anal. Methods*, 2019, **11**, 752.

20. J. E. Barefield, E. J. Judge, K. R. Campbell, J. P. Colgan, D. P. Kilcrease, H. M. Johns, R. C. Wiens, R. E. McInroy, R. K. Martinez and S. M. Clegg, *Spectrochim. Acta, Part B*, 2016, **120**, 1.

21. R. Chinni, D. A. Cremers and R. Multari, *Appl. Opt.*, 2010, **49**, C143.

22. E. G. Gamaly, A. V. Rode, B. Luther-Davies and V. T. Tikhonchuk, *Phys Plasmas*, 2002, **9**, 949-957.

23. L. Dorta, R. Kovacs, J. Koch, K. Nishiguchi, K. Utani and D. Gunther, *J. Anal. At. Spectrom.*, 2013, **28**, 1513.

24. S. Kappel, S. F. Boulyga, L. Dorta, D. Gunther, B. Hattendorf, D. Koffler, G. Laaha, F. Leisch and T. Prohaska, *Anal. Bioanal. Chem.*, 2013, **405**, 2943.

25. A. L. Ronzani, F. Pointurier, M. Rittner, O. Borovinskaya, M. Tanner, A. Hubert, A. C. Humbert, J. Aupiais and N. Dacheux, *J. Anal. At. Spectrom.*, 2018, **33**, 1892.

26. B. T. Manard, C. D. Quarles, E. M. Wylie and N. Xu, *J. Anal. At. Spectrom.*, 2017, **32**, 1680.

27. R. C. Machado, D. F. Andrade, D. V. Babos, J. P. Castro, V. C. Costa, M. A. Sperança, J. A. Garcia, R. R. Gamela and E. R. Pereira-Filho, *J. Anal. At. Spectrom.*, 2020, **35**, 54-77.

28. D. L. Donohue, *Anal. Chem.*, 2002, **74**, 28A.

29. D. L. Donohue, *Anal. Chem.*, 2002, **74**, 28 A-35 A.

30. J. Karasinski, E. Bulska, M. Wojciechowski, A. A. Krata and L. Halicz, *J. Anal. At. Spectrom.*, 2016, **31**, 1459-1463.

31. E. Goudsmits, G. P. Sharples and J. W. Birkett, *Trends Analyt Chem*, 2015, **74**, 46-57.

32. H. W. Paing, B. T. Manard, B. W. Ticknor, J. R. Bills, K. A. Hall, D. A. Bostick, P. Cable-Dunlap and R. K. Marcus, *Anal. Chem.*, 2020, **92**, 8591-8598.

33. V. C. Bradley, T. L. Spano, S. C. Metzger, B. W. Ticknor, D. R. Dunlap, N. A. Zirakparvar, B. D. Roach, C. R. Hexel and B. T. Manard, *Anal. Chim. Acta*, 2022, **1209**, 339836.

34. B. T. Manard, K. T. Rogers, B. W. Ticknor, S. C. Metzger, N. A. Zirakparvar, B. D. Roach, D. A. Bostick and C. R. Hexel, *Analytical Chemistry*, 2021, **93**, 11133-11139.

35. B. T. Manard, S. C. Metzger, K. T. Rogers, B. W. Ticknor, N. A. Zirakparvar, B. D. Roach, D. A. Bostick and C. R. Hexel, *Journal of Analytical Atomic Spectrometry*, 2021, **36**, 2202-2209.

36. V. C. Bradley, T. L. Spano, C. V. Thompson, B. W. Ticknor, D. R. Dunlap, S. C. Metzger, C. R. Hexel and B. T. Manard, *Analytical Methods*, 2022, **14**, 4466-4473.

37. R. S. Ibrahim and A. A. El-Banna, *RSC Adv.*, 2021, **11**, 18717-18728.

38. M. Aranda, J. Carrasco and K. Henríquez, in *Mass Spectrometry for Food Analysis*, ed. H. Koolen, Springer US, New York, NY, 2022, DOI: 10.1007/978-1-0716-2107-3_16, pp. 213-218.

39. L. Wang, M. A. Pierson and R. K. Marcus, *Anal. Methods*, 2016, **8**, 8410-8419.

40. X. Wang, J. Hedberg, H.-Y. Nie, M. C. Biesinger, I. Odnevall and Y. S. Hedberg, *Materials & Design*, 2022, **215**, 110524.

41. K. Qiu, D. Yang, X. Zhu, H. Sui and G. Wu, *Food Additives & Contaminants: Part A*, 2021, **38**, 2091-2101.

42. P. A. Penanes, A. R. Galán, G. Huelga-Suarez, J. Á. Rodríguez-Castrillón, M. Moldovan and J. I. Garcia Alonso, *J. Anal. At. Spectrom.*, 2022, **37**, 701-726.

43. Y. Li, H. Yu, S. Zheng, Y. Miao, S. Yin, P. Li and Y. Bian, *Int. J. Environ. Res Public Health*, 2016, **13**.

44. D. C. Paschal, B. G. Ting, J. C. Morrow, J. L. Pirkle, R. J. Jackson, E. J. Sampson, D. T. Miller and K. L. Caldwell, *Environ. Res.*, 1998, **76**, 53-59.

45. S. S. Kim, J. D. Meeker, R. Carroll, S. Zhao, M. J. Mourgas, M. J. Richards, M. Aung, D. E. Cantonwine, T. F. McElrath and K. K. Ferguson, *Environ. Int.*, 2018, **121**, 582-590.
46. H. M. Perry, Jr. and E. F. Perry, *J Clin Invest*, 1959, **38**, 1452-1463.
47. G. H. O. Rocha, C. Steinbach, J. R. Munhoz, M. A. O. Madia, J. K. Faria, D. Hoeltgebaum, F. Barbosa, B. L. Batista, V. C. O. Souza, S. B. Nerilo, E. Bando, S. A. G. Mossini and P. Nishiyama, *J. Trace Elem. Med. Bio.*, 2016, **35**, 61-65.
48. A. Błażewicz, M. Klatka, A. Astel, M. Partyka and R. Kocjan, *Biol Trace Elem Res*, 2013, **155**, 190-200.
49. J.-P. Goullé, L. Mahieu, J. Castermant, N. Neveu, L. Bonneau, G. Lainé, D. Bouige and C. Lacroix, *Forensic Sci Int*, 2005, **153**, 39-44.

Figures and Tables:

Figure 1. Images of 5 µL deposition before extraction at (a) 40X and (b) 120X and after extraction at (c) 40X and (d) 120X.

Figure 2. Total ion current (TIC) chromatogram (a) of a 500-second extraction (engaged for 500s) on a 5 µL deposition. Extracted ion current (XIC) chromatogram (b) of a 500-second extraction on a 5 µL deposition and (c) of a 500-second extraction on a 5 µL deposition of ^{107}Ag, ^{146}Nd, ^{160}Gd, and ^{172}Yb.

Figure 3. Extracted ion current (XIC) chromatogram of 5 consecutive, 100-second extractions on the same spot of a 5 µL deposition.

Figure 4. Varying deposition volumes (1-10 µL) for a 10 ng L^{-1} sample. Presented for each spot size is the percentage of the spot area which is sampled by the extraction head (black) and the sum of the high-mass analyte responses for each of the deposits (green).

Table 1, ICP-MS operating conditions.

Parameter	Unit	Setting
Plasma gas flow rate	L min^{-1}	16.0
Auxiliary gas flow rate	L min^{-1}	0.8
Carrier gas flow rate	L min^{-1}	1.43
Peristaltic pump speed	rpm	30
RF power	W	1400
Sampling depth	mm	8
Einzel lens 1	V	-8
Einzel lens 2	V	-30
Octapole exit	V	-18
Octapole bias	V	-21
Collision gas flow rate	L min^{-1}	6.0

Table 2. Summary of metal response curve LODs, correlation coefficients (R^2), and slopes. Elemental concentration from 10 ng L^{-1}to 5 mg L^{-1} (50 fg- 25 ng mass deposited).

	^{55}Mn	^{57}Fe	^{59}Co	^{63}Cu	^{66}Zn	^{107}Ag	^{146}Nd	^{160}Gd	^{172}Yb
Slope	0.272	0.070	0.353	0.243	0.248	0.798	0.680	0.831	0.818
R^2	0.8791	0.1682	0.7288	0.8117	0.7754	0.9503	0.9606	0.9708	0.9449
LOD (fg)	46	153	22	41	33	7	5	7	3

Table 3. Theoretical and determined isotope fractions of the ^{63}Cu/^{65}Cu, ^{107}Ag/^{109}Ag pairs for triplicate extraction of three different swipes (n=9) of a multielement solution deposition. Amount deposited = 50 pg each, sample volume = 5 μL.

Analyte	**Theoretical Isotopic Fraction**	**Measured Isotopic Fraction**	**% Error**	**Standard Deviation**	**% RSD (n=9)**
^{63}Cu/^{65}Cu	0.69	0.65	5.8	0.028	4.4
^{107}Ag/^{109}Ag	0.52	0.49	5.8	0.021	4.3

Table 4. Recovery analysis of synthetic urine sample spikes.

	^{55}Mn	**^{57}Fe**	**^{59}Co**	**^{63}Cu**	**^{66}Zn**	**^{107}Ag**	**^{146}Nd**	**^{160}Gd**	**^{172}Yb**
Low value -									
Spike amount, ppb (fg)	10 (50)	350 (1750)	8.3 (41.5)	7 (35)	117 (585)	0.7 (3.5)	11 (55)	19 (95)	9 (45)
Determined, ppb (fg)	10.3 (51.3)	307.6 (1538)	8.6 (42.9)	6.1 (30.5)	97.8 (490)	0.66 (3.3)	11.1 (55.3)	20.3 (101.4)	8.7 (43.4)
Recovery, %	102.5	87.9	103.4	87.1	83.8	94.3	100.5	106.7	96.4
High value -									
Spike amount, ppb (fg)	19.5 (97.5)	620 (3100)	16 (80)	31 (155)	233 (1165)	4.5 (22.5)	19 (95)	28 (140)	16 (80)
Determined, ppb (fg)	22 (110.2)	578.2 (2891)	15.6 (77.9)	34.8 (174)	225 (1225)	4.4 (22.2)	18.6 (92.8)	26.7 (134)	16.6 (83.1)
Recovery, %	113.0	93.6	97.4	112.5	105.1	98.7	97.7	95.7	103.9

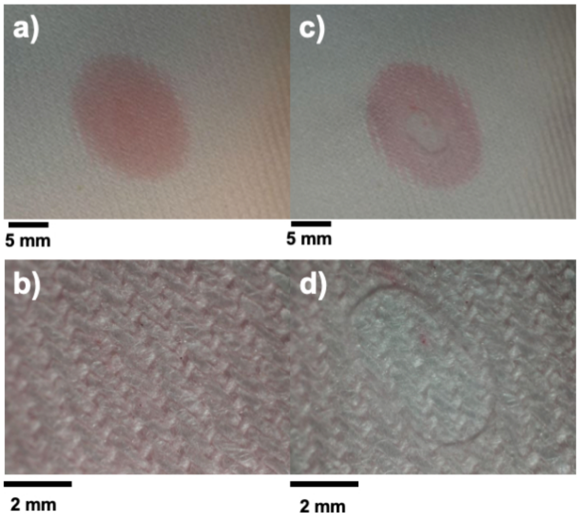

Fig. 1

Figure 1

278x214mm (96 x 96 DPI)

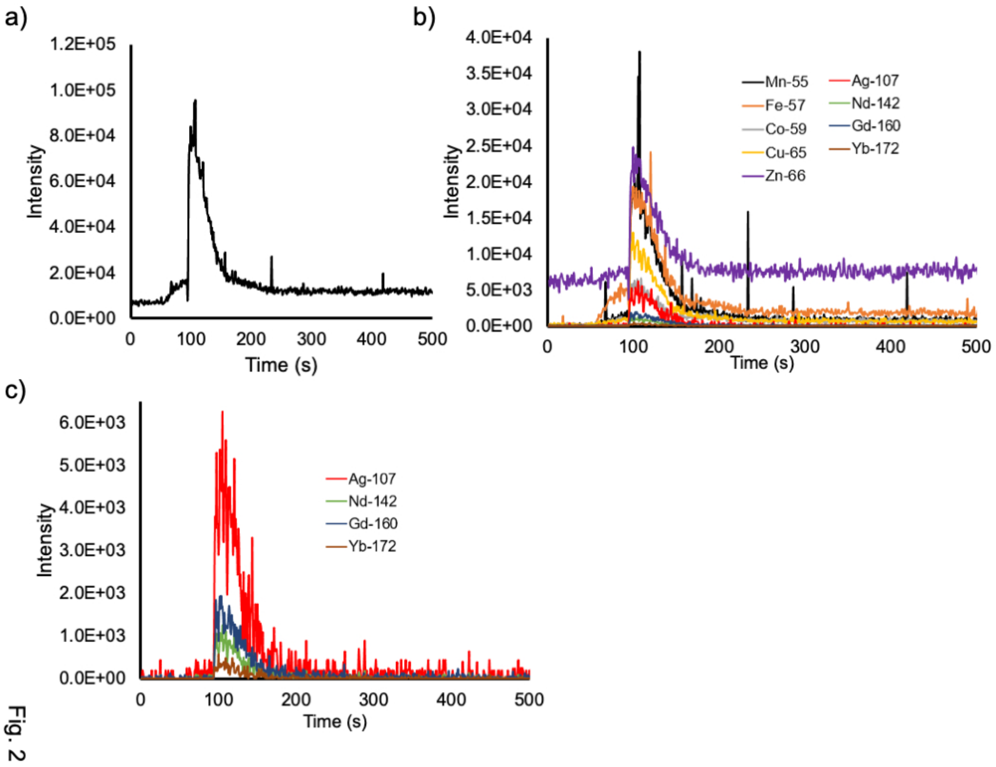

Figure 2

278x214mm (96 x 96 DPI)

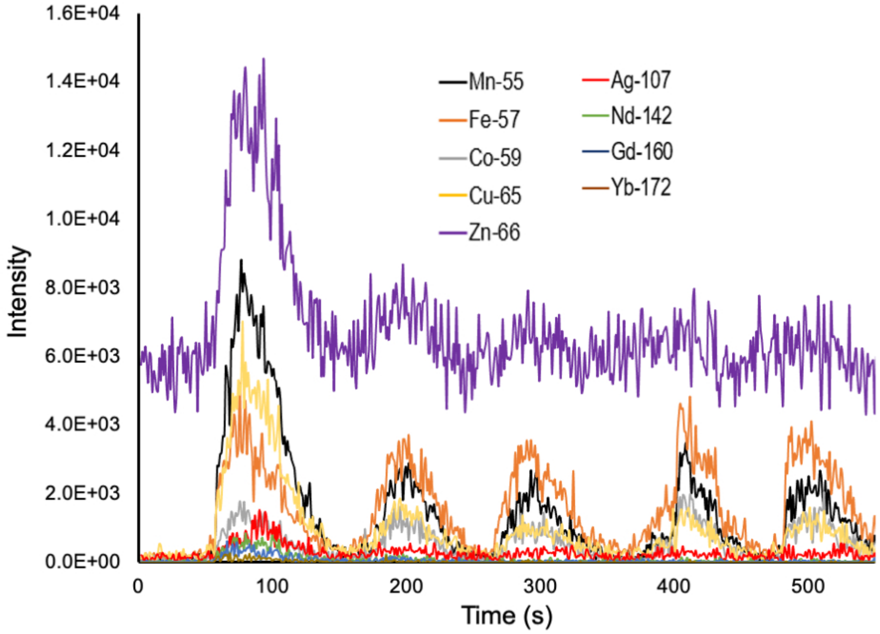

Fig. 3

Figure 3

278x214mm (96 x 96 DPI)

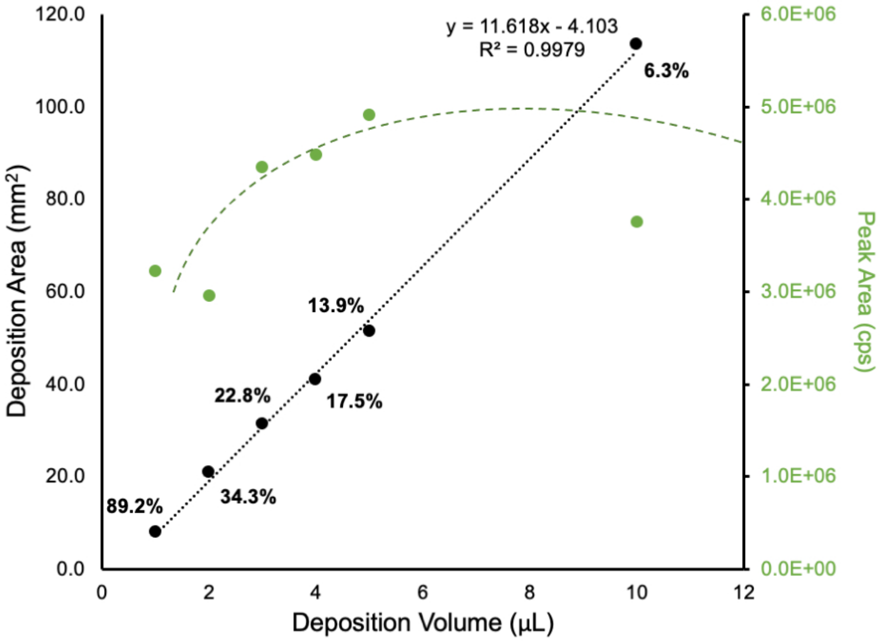

Fig. 4

Figure 4

278x214mm (96 x 96 DPI)