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Development of a Dropwise Injection Liquid Chromatography Mass Spectrometry System

by

Nick Erfurth

A thesis

submitted in partial fulfillment

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To the Graduate Faculty:

The members of the committee appointed to examine the thesis of Nick Erfurth find it satisfactory and recommend that it be accepted.

Dr. Josh Pak,
Major Advisor

Dr. Rene Rodriguez,
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List of Abbreviations

Ce	cerium
cps	counts per second
DV1	diversion valve 1
DV2	diversion valve 2
EXC	extraction chromatography
FWHM	full width half maximum
GPEC	gas pressurized extraction chromatography
GSV1	gas supply valve 1
GUM	Guide to Uncertainty Measurements
H_2O	water
HCl	hydrochloric acid
HNO_3	nitric acid
ICP	inductively coupled plasma
ICP-TOF	inductively coupled plasma – time-of-flight
ICP-TOFMS	inductively coupled – time-of-flight mass spectrometry
IDMS	isotope dilution mass spectrometry
INL	Idaho National Laboratory
IV1	injection valve 1
k’	free column volumes to peak maximum
KE	kinetic energy
La	lanthanum
LA-MS	laser ablation – mass spectrometry
LC-MS	liquid chromatography – mass spectrometry
LOD	limit of detection
LOQ	limit of quantification
LRS	linear regression slope
M	molar
m/z	mass-to-charge
MCP	multichannel plate
MS	mass spectrometer/mass spectrometry
Nd	neodymium
PAI	peak area integration
PbP	point-by-point
Pr	praseodymium
Q-MS	quadrupole – mass spectrometer
Sm	samarium
SRM	standard reference material
TOF	time-of-flight
U	uranium
Wt %	Weight percent

Development of a Dropwise Injection Liquid Chromatography Mass Spectrometry System

Thesis Abstract--Idaho State University (2022)

A sample introduction technique has been developed to allow for on-line, dropwise injections of effluent into a mass spectrometer. The incorporation of a flowing rinse into the system makes dropwise resolution possible for any liquids capable of forming drops under ambient conditions. Additionally, this technique provides independent flow control of the liquid chromatography and mass spectrometry portions of liquid chromatography-mass spectrometry (LC-MS) systems. This allows for coupling of chromatography techniques that require slower flow rates than what are optimal for mass spectrometry instruments, as well as chromatographic systems that are not driven by pumps. The technique has been demonstrated utilizing Gas Pressurized Extraction Chromatography (GPEC) and Inductively Coupled Plasma-Time-of-Flight Mass Spectrometry (ICP-TOFMS) to illustrate its qualitative applications for rapid separation development and procedure evaluation. The method's quantitative applications were evaluated using single and double isotope dilution mass spectrometry (IDMS) with an external mass bias correction to measure analytes in volumes as small as single drops. The findings reported herein show that the developed sample introduction technique can be applied to generating chromatograms and k' plots for the separation conditions being tested. Linear regression slope (LRS) quantification through single and double IDMS of full samples returned elemental results that fell within the uncertainty of a surrogate fuel sample. The same measurements performed on drops that reached >10k cps Nd-144 gave results that were very similar to the full sample analyses. More dilute drops that were analyzed showed lower accuracy and precision.

Key Words: LC-MS, Extraction Chromatography, Dropwise, GPEC, ICP-TOFMS

1 Introduction

The coupling of liquid chromatography with mass spectrometry is well-studied, with new combinations being developed as new instrumentation on either end is introduced. The vast majority of LC-MS is performed using flow injection or sequential injection systems that rely on a continuous stream from eluent injection into the chromatographic column all the way through the sample introduction of the mass spectrometer. These types of systems ultimately rely on a peristaltic or syringe pump to provide a steady and continuous flow to both the column and the mass spectrometer. While there are many benefits to such a simplified system, there are also advantages that can be gained by independent flow control of the separation and the ensuing measurements.

1.1. Optimization of Separation and Measurement

The ability to control the separation and measurement streams individually can allow for optimal flow rates of each, while a continuous flow through both can necessitate a compromise to fit the needs of one or the other. For instance, for analytes in low concentrations the ability to increase flow to the mass spectrometer without altering the flow of the separation can result in more accurate and precise measurements by increasing the signal to noise ratio without having any negative effects on the separation.

1.2. Extending LC-MS to Other Separation Methods

Continuous flow systems are limited to chromatographic techniques driven by pumps. Traditional drip column separations are driven by gravity. The very nature of this technique disqualifies it for use in traditional LC-MS systems. The flows in gas pressurized systems, such as gas pressurized extraction chromatography[1–4] (GPEC) and the pressure injection systems described by Guerin et al.[5] and Miyamoto et al.[6], are regulated by the balance between the

pressure provided by the gas supply and the backpressure of the column, as well as the physical properties of the eluent being used. The addition of a nebulizer after the column would further complicate this relationship due to the backpressure it would introduce. One of the main advantages of the GPEC is the quantitative recovery of the liquid from the column[2]. This requires gas to be blown through the column after each injection to ensure as much liquid as possible is recovered. This hinders direct coupling as the gas would be blowing directly into the plasma between injections. Moreover, the gas needs to be shut off between injections to load the sample loop. In this scenario, a flowing rinse could not be used as nothing would be preventing it from flowing backwards through the column whenever the gas was turned off. While these factors would not disqualify hooking the GPEC directly to the nebulizer, they would make this a less than ideal instrumental set-up. It is evident that gas-pressurized and gravity assisted techniques cannot be reliably coupled to a mass spectrometer without a break in the flow between separation and measurement. The effluents must be collected and introduced into a mass spectrometer by some other means to negate the changes in flow rates throughout the separations, to release gases used to drive eluents, and to keep the downstream pump from pulling the eluents out of the columns in an undesired manner.

1.3. Dropwise Analysis

Traditional LC-MS systems evaluate a continuous stream of effluent. Breaking this stream up into several individual fractions can have several benefits. Post-column diffusion of analytes within continuous streams results in peak broadening. Dead volume in the transfer line between separation and measurement instruments contributes to post-column diffusion which increases peak broadening and tailing[7]. This type of diffusion can be limited by using as short of a transfer line as possible or breaking the effluent up into smaller injections. Instrument geometry

and facility limitations can limit how short of a transfer line is feasible. The diffusion effects influenced by the length of the line can be negated by introducing a break in the system via a drop collector. The continually running downstream pump introduces air gaps into the line as drops are forming in the collector. These air pockets essentially eliminate traditional continuous flow diffusion issues by limiting diffusion to within each droplet, regardless of how long of a transfer line is required to couple the instruments. Additionally, rinsing out the spray chamber between each drop with a flowing rinse eliminates carryover of highly concentrated or troublesome analytes which build up in the sample introduction system of the mass spectrometer and skew the data.

2 Background

2.1. Extraction Chromatography

Extraction chromatography (EXC) was developed at Argonne National Laboratory by Philip Horwitz. He and his team developed methods for absorbing commonly used liquid extractants onto inert supports. The term “extraction chromatography” is not well defined because of the large grey area between it and many other types of chromatography that it encompasses. The extractants used in EXC resins can operate through ion exchange mechanisms, chelation, or absorption. Nevertheless, the term is commonly used and accepted in nuclear, environmental, and geochemical analysis laboratories, and it can be found in thousands of publications. The generally accepted description of extraction chromatography is that it is reverse-phased, solid-phase extraction technique that is physically performed like resin chromatography but chemically functions like liquid-liquid extractions[8].

The hydrophobic extractants, aqueous mobile phases, and elemental selectivity of EXC resins make them an ideal choice for the separation of radiological samples prior to elemental or

isotopic measurements. Nuclear samples are typically dissolved in inorganic acids. Inorganic acids are the ideal sample loading matrix and mobile phase for EXC resins, and they are also the matrix that most liquid elemental standards are sold in. Ultimately, the samples and collected fractions are easily adjusted for separation and subsequent measurements by concentrating or diluting the matrices to the necessary levels because they are already in the same class of solutions at the start and end of an EXC separation. Additionally, analysis of nuclear samples is almost always a determination of elemental and isotopic composition, and organic molecules are rarely present or of interest. EXC resins are developed for elemental chromatography, and they are among the most effective and simple options for separation and/or concentration of actinides and lanthanides which are frequently the analytes of most interest in radiological samples. These characteristics of EXC resins make the separation process quicker, easier, and less wasteful than other options for many radiological sample analyses.

New extraction chromatography resins are the focus of entire research and development groups in industry (Eichrom and Triskem), academia (Washington State University), and government funded laboratories (Idaho National Laboratory and Oak Ridge National Laboratory). New extractants and resins are frequently found in modern literature and for sale from EXC resin vendors. With the advent of new resins comes the question of where they can be applied in a practical way. Accelerated separation scheme development is one of the benefits of liquid chromatography-mass spectrometry (LC-MS) systems.

2.2. Gas Pressurized Extraction Chromatography (GPEC)

Gas Pressurized Extraction Chromatography is a chemical separation technique that was developed at Idaho National Laboratory (INL). This technique was created with the intention of minimizing radiation exposure by decreasing the amount of radioactive sample required for

extraction chromatography processes, while also retaining the necessary accuracy and precision in subsequent measurements. The GPEC is also small, cheap, and easily maintained or replaced. These are all qualities that lend themselves well to work in a radiological facility where equipment is harder to work on and breaks down quicker through radiolysis. A GPEC is pictured in Figure 2-1.

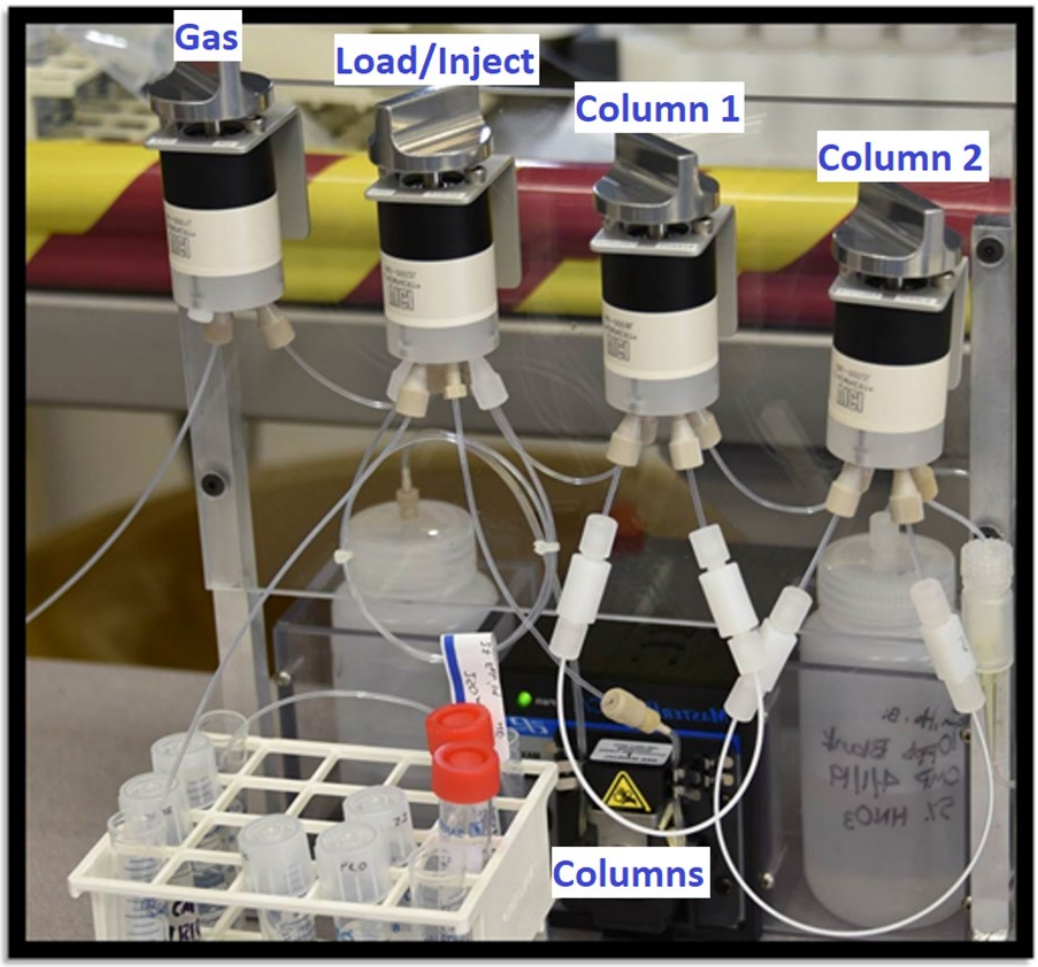

Figure 2-1: GPEC with two column capabilities. Tubing at left is connected to the regulator of an inert gas bottle. Drop collector can be seen at far right.

Having been developed in 2009 by Sommers et al.[1], GPEC is a relatively new and understudied technique. The few research publications that have reported using the technique all pertain to the separation of cesium from barium utilizing Eichrom Technologies' Sr Resin for

mass spectrometric quantification of each elements' isotopes[1–4]. However, the author and other researchers at the Idaho National Laboratory (INL) frequently use GPEC for several other extraction processes but none of this work has been published.

The GPEC is set up much like every other liquid chromatography system but with one minor difference. Instead of relying on gravity or pumps to drive samples and eluents through chromatographic columns, the GPEC relies on pressurized argon or nitrogen to drive the mobile phase. Once the sample loop has been completely filled by a peristaltic pump, the injection valve is turned to expose one end of the loaded liquid to the pressurized gas and the other end of the liquid to the extraction column, and the pressure of the gas will drive the liquid through the column. Many systems work in this manner, but syringe pumps or peristaltic pumps are much more frequently used to drive the mobile phase. This subtle difference gives the GPEC some advantages for extraction chromatography. A diagram of this system is shown in Figure 2-2.

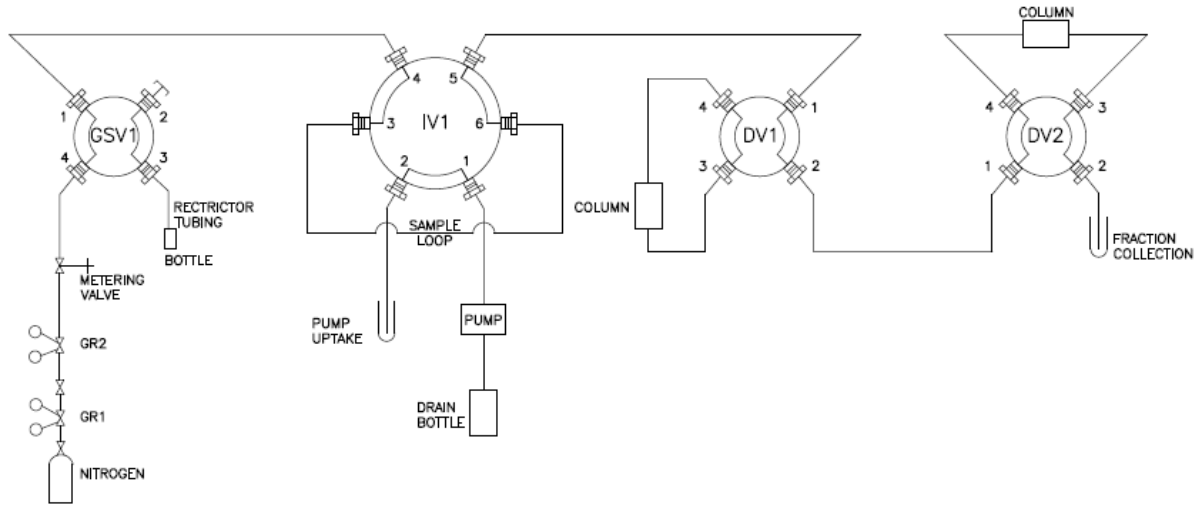

Figure 2-2: Component and flow diagram for a GPEC with the system set to "inject" at IV1, "bypass" at DV1, and "column" at DV2. Turning IV1 to "load" connects the pump to the sample loop, allowing it to be filled. Image reproduced from INL internal procedure.

There are two main characteristics of GPEC that set it apart from other extraction chromatography techniques. One of these unique characteristics is the physical dimensions of the microcolumns. The inner diameter of the tubing that is used to produce GPEC columns is 0.75-1 mm, while the column length can range from 5-30 cm. This gives a length to diameter ratio of up to 400 for separations with high column resolution requirements. Other liquid chromatography systems that employ extraction resins, such as the Hidex Q-ARE 100 and the ESI PrepFast, often incorporate much shorter, wider columns similar to the commercially available 2 mL columns that Eichrom offers. GPEC columns are made in-house to fit the requirements of the analysis, and they contain a bed volume of no more than 250 µL. This makes them less wasteful in terms of resin and eluent required to perform the necessary separation, and the amount of sample required is typically 250 to 500 µL. The ability to separate small samples without losing data quality is especially important in the nuclear field because it limits the amount of radiation an analyst is exposed to during the process.

The other characteristic that differentiates the GPEC from other extraction chromatography systems is its ability to quantitatively recover the same volume of liquid that was injected. Once the injected liquid clears the column, inert gas continues to flow through the resin bed at 10 mL/min to remove any liquid that remains. The narrow columns are no wider than the rest of the tubing in the system, so gas moves over the entire column to efficiently push out any liquid retained in the resin bed in a manner of seconds or a couple minutes, depending on the dimensions of the column used. This means that the amount of sample loops used to create each fraction can be used as a dilution factor in situations where volumetric dilutions are acceptable.

2.3. Inductively Coupled Plasma – Time-of-Flight Mass Spectrometry (ICP-TOFMS)

Time-of-Flight mass spectrometry (TOF-MS) was first proposed by W.E. Stephens in 1946[9]. The Bendix Corporation created the first commercially available TOF-MS in 1957 based on the further developments and demonstrations by both Wolff et al.[10] and Wiley and McLaren[11]. Whereas other types of mass analyzers employ electrostatic and magnetic forces to selectively control ion beams, the time-of-flight (TOF) mass analyzer differentiates between the mass-to-charge (m/z) of ions by measuring how long they take to get from point A to point B in a field-free drift tube. Point A can be the ionization source in linear TOF mass spectrometers or a pulsed plate in orthogonal TOF mass spectrometers, while point B is the detector in either type of TOF. The ions are given the same amount of kinetic energy at point A, and are then allowed to drift towards point B. Kinetic energy (KE) is defined in eq. 1 as

$$KE = \frac{1}{2}mv^2 \qquad \text{eq. (1)}$$

so equal amounts of kinetic energy for all ions equates to ions with smaller masses having greater velocities. This relationship is the basis for mass resolution in TOF analyzers because lighter ions will reach the detector quicker than heavier ions. In other words, lower m/z ions will have a shorter "time-of-flight".

TOF-MS has been primarily used for identifying molecules because of its ability to measure high m/z ions and cover a large m/z range in one analysis with no temporal spectral skew from one m/z to the rest. This is due to the mass analyzer having essentially no limits on how large of an m/z signal it can measure if all other requirements are met. In recent years, TOF instruments have experienced a revival in inorganic analysis laboratories. Laser ablation technology and advancements in the field of laser ablation-mass spectrometry (LA-MS) have increased the impact of utilizing TOF-MS over more common types, such as quadrupole mass

spectrometry (Q-MS)[12,13]. This technique makes use of the speed of the TOF to measure transient, short-lived signals over a wide range of m/z. The speed of the TOF and the simultaneous acquisition of signals in the tuned range allow for better quantification of very short-lived signals than a slower, scanning mass analyzer could achieve.

Inductively Coupled Plasma (ICP) torches are the ionization source most widely used for atomic mass spectrometry due to their high ionization potential, the atomization of particles, and the vaporization of solutions in the plasma. However, this type of ionization source was not commonly found in combination with TOF mass analyzers because TOF was mainly reserved for molecular mass spectrometry analyses, and ICP torches result in excessive molecular fragmentation due their high temperatures and great potential for ionization. For these reasons, the somewhat obscure inductively coupled plasma time-of-flight (ICP-TOF) combination was only available on one instrument for many years. Two more ICP-TOF instruments have been developed and released in the last decade due to increased demand for the instruments.

2.3.1 TOFWERK icpTOF R

One of the relatively new ICP-TOFMS instruments that is available commercially is the TOFWERK icpTOF R[14]. The scientists at TOFWERK opted to start with already established technology for the front end of the instrument and add on their own TOF components at the back end. The body, sample introduction system, collision cell, and ion optics are all retained from Thermo-Fisher's iCAP RQ quadrupole mass spectrometer. The original quadrupole and detector were removed, and a notch filter was installed in their place inside the original Thermo body by the scientists at TOFWERK. A pulsed extraction plate, orthogonal flight tube, reflectron, and multichannel plate (MCP) detector were added to the top of the Thermo instrument's body in a TOFWERK casing, making up the TOF mass analyzer. The pulsed extraction plate directs the

ion beam orthogonally into the flight tube. At the end of the tube the ions are reflected via a reflectron, effectively doubling the flight distance and resolution of the instrument. Finally, the ions reach the MCP detector at the other end of the flight tube, as shown in Figure 2-3.

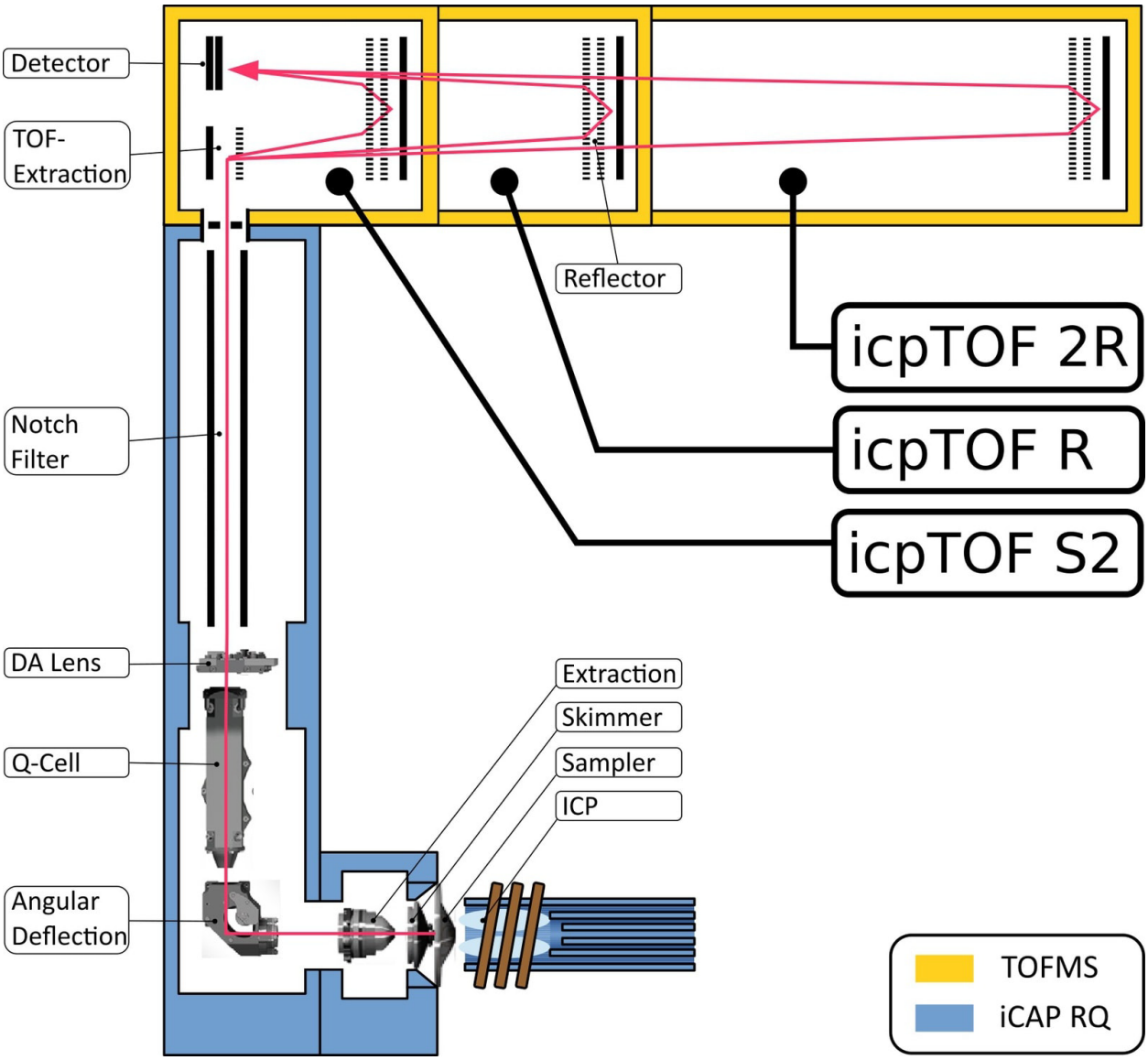

Figure 2-3: Diagram of TOFWERK icpTOF R and it's variants[15].

TOFWERK's icpTOF R offers the latest technology in atomic ICP-TOF-MS. A range of 6-280 m/z and an acquisition rate of 33,000 spectra/second make this instrument ideal for obtaining

data from transient introduction techniques, such as LA-MS, LC-MS, and single particle analyses. A summary of specifications can be found in Table 2-1.

Table 2-1: Select icpTOF R specifications[16].

Parameter	unit	value icpTOF R
Extractions per s	#	33000
Mass Res Power ^{238}U *	Th/Th	> 3000
Abund Sens (high mass side)	#	^{238}U +1Th 3.0E-04
Abund Sens (low mass side)	#	^{238}U -1Th 4.0E-04
Mass Range	Th	6-280
Linear Dynamic Signal Range	cps	1 - > 1.0E+06
Integration time minimum	ms	0.030
Sensitivity in liquid ^{59}Co *	cps/ppb	10000
Sensitivity in liquid ^{115}In *	cps/ppb	20000
Sensitivity in liquid ^{238}U *	cps/ppb	50000
Oxides from liq sample $^{140}Ce^{16}O/^{140}Ce$ *	%	< 2.5
Double charged $^{137}Ba^{++}/^{137}Ba^{+}$ *	%	< 5
Short term stability 10 min ^{238}U *	%	2
Long term stability 6h ^{238}U	%	5
Bkg at 220Th	cps	< 10
Mass accuracy ^{238}U *	mTh	< 5

2.4. Linear Regression Slope Quantification Method

Quantification of transient signals requires suitable methods. External calibration curves are not reliable because they ultimately rely on the relation of the intensity of stable signals to their known concentrations. LC-MS does not provide stable signals, regardless of whether the LC-MS is a traditional continuous flow system or an intermittent injection system like the one that is the focus of this work, because the elution of the analytes of interest is not equivalent throughout the separation. Users of continuous flow LC-MS systems often overcome this by

performing full width half maximum (FWHM) calibrations using standards of known analytes in known concentrations. However, any technique that introduces samples in pulses or intermittent injections requires a separate technique because neither of the aforementioned techniques would be reliable.

There have been several methods reported that are suitable for quantification of even the most transient of signals. Notable examples are the point-by-point (PbP), peak area integration (PAI), and linear regression slope (LRS) quantification techniqies[13,17–19]. PAI was shown to be the most precise of this group in the determination of isotopic ratios in a continuous flow LC-MS system when 50% of the chromatographic peak was taken into account[18]. This method requires integration of all peaks of interest and evaluating the integration limits of each peak[19]. This type of quantification is best suited for data sets that do not contain a large number of peaks due to the large amount of work that it would entail. The PbP and LRS methods are more suitable for large data sets that contain numerous peaks of interest because they can be applied much more easily. Of the two, LRS was shown to be superior in LC-MS[18,19]. Additionally, Epov et al.[19] reported that LRS is the most accurate and precise of the three techniques when the concentrations of the standards and samples are not equivalent.

LRS is applied through measuring two isotopes simultaneously (or as close as possible) and determining their concentration ratio through a linear regression analysis. The raw data from this type of analysis would look something like what is portrayed in Figure 2-4.

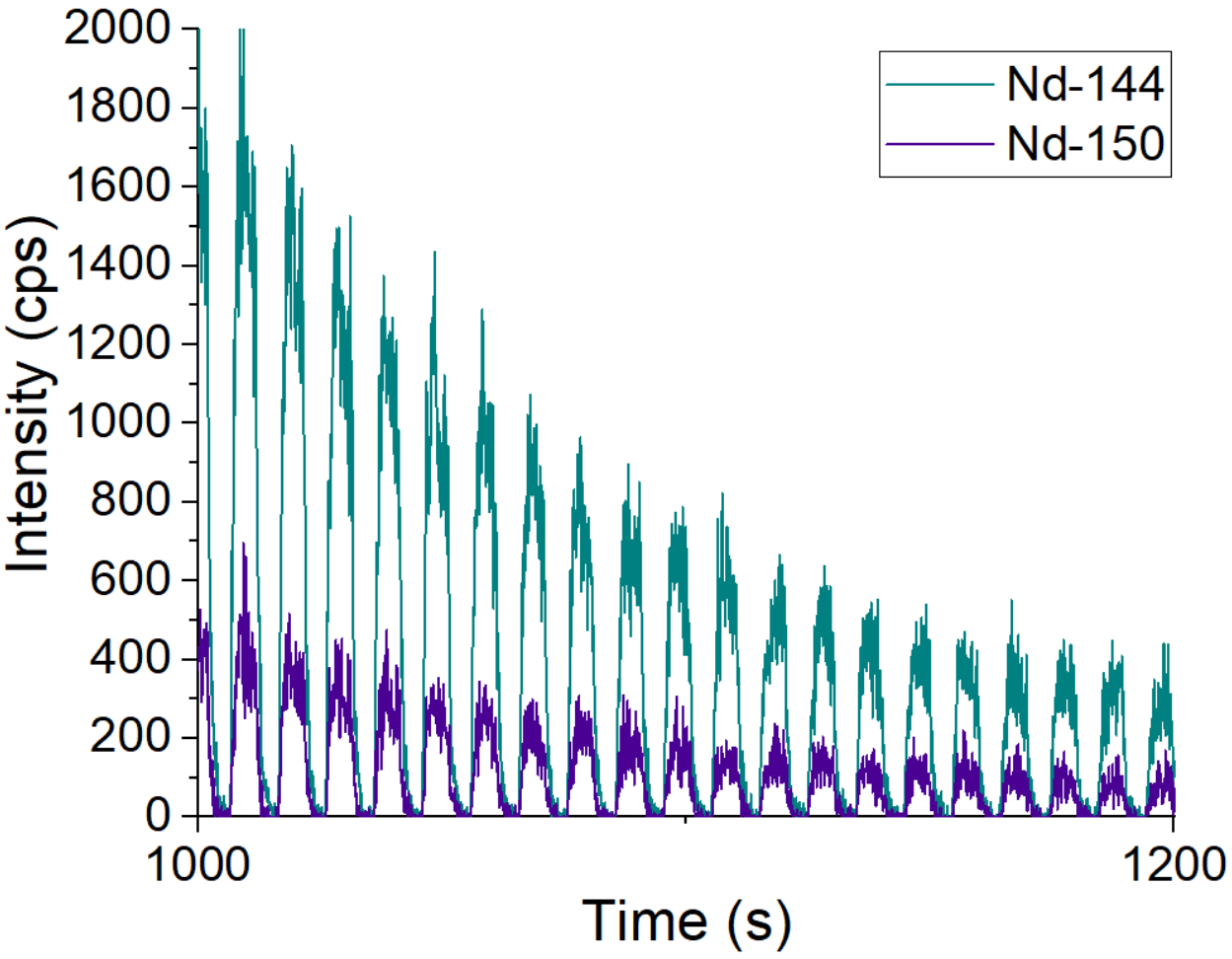

Figure 2-4: Plot showing raw LC-MS data of two isotopes of interest

Clearly, a linear regression analysis would be of no use in data presented in this form. However, one can eliminate time as an axis and replace it with a second intensity axis. Using the example above, at any given point on the x-axis there are there are two points for intensity. One is for Nd-144 and the other is for Nd-155. Making the intensity value of one of these isotopes your x-coordinate and the other one your y-coordinate would result in a new type of plot where each point is a relation of one isotope to the other. Performing this action for the entire data set would give the plot shown in Figure 2-5. Performing a linear regression analysis on the generated plot would result in a line with a slope and its associated uncertainty. The slope of this

line is the isotopic ratio of the two isotopes in question, and the uncertainty of that slope is the uncertainty in that ratio.

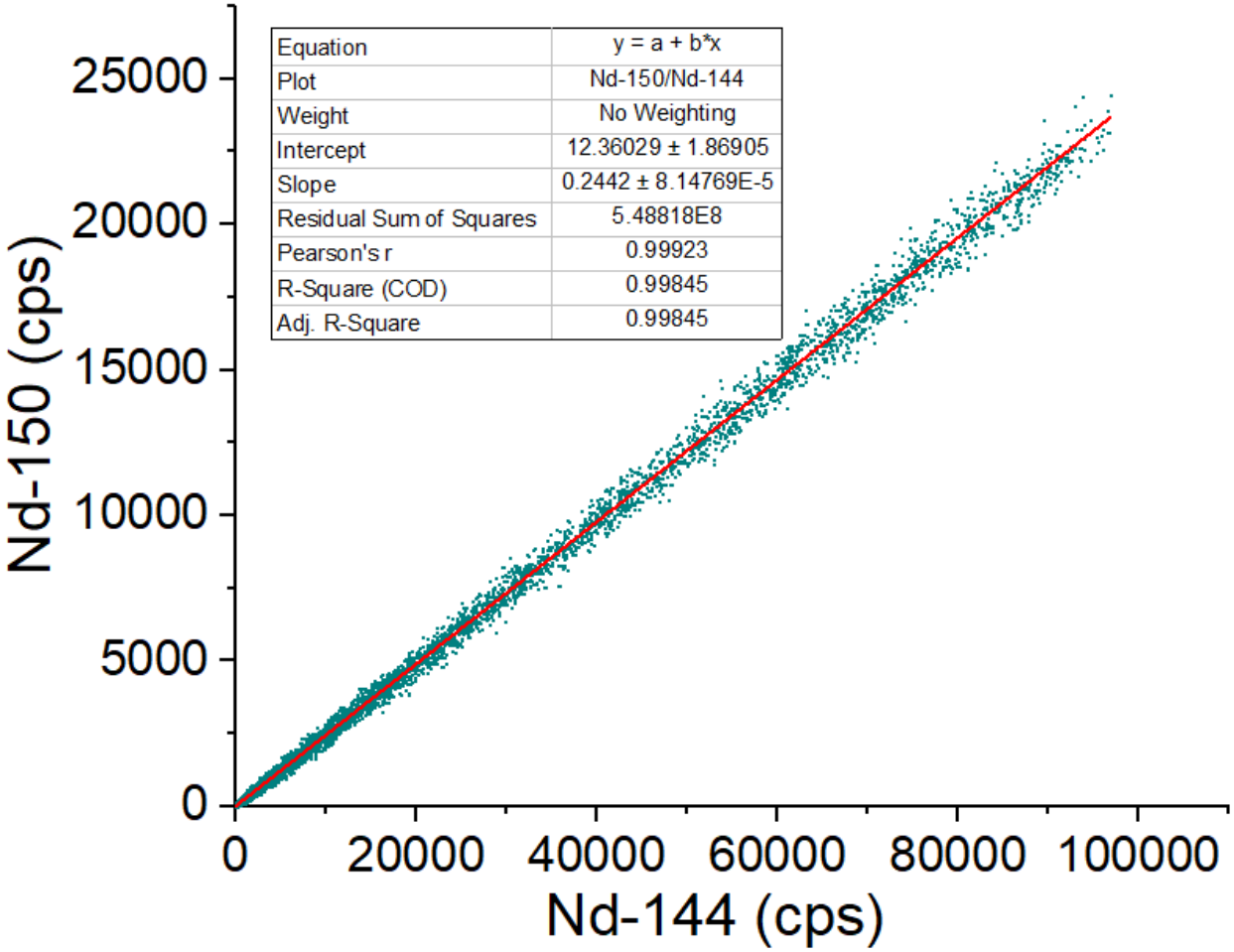

Figure 2-5: LRS plot example using LC-MS data from Figure 2-4.

Intermittent injections are not common in LC-MS. Perhaps the most similar data sets to such a system would be those from laser ablation-mass spectrometry, where LRS is commonly used[13]. LRS has been shown to produce results with large uncertainties when only a portion of the peak was integrated. This was attributed to no background or near background points being included in the calculation because it was performed on a continuous flow technique where background can only be found at the beginning and end of the elution[19]. In an intermittent

injection or pulsed system like LA-MS, this problem is overcome because each pulse or injection will have background points on both sides of it that can be included in the calculation. While LRS can provide isotopic ratios without any type of calibration, it cannot provide elemental totals without the supplementation of an internal calibration method.

2.5. Isotope Dilution Mass Spectrometry (IDMS)

The most widely used internal calibration method for elemental analysis is isotope dilution mass spectrometry (IDMS). This technique comes with a plethora of advantages. Most notably, proper utilization of IDMS with a well-characterized spike gives more accurate and precise results than external calibration methods[20,21]. Over the years, several versions of IDMS have been developed. The two most common types are described below.

2.5.1 Single IDMS

The oldest and simplest version of IDMS is known as single IDMS[20–23]. A visual representation of single IDMS is shown in Figure 2-6.

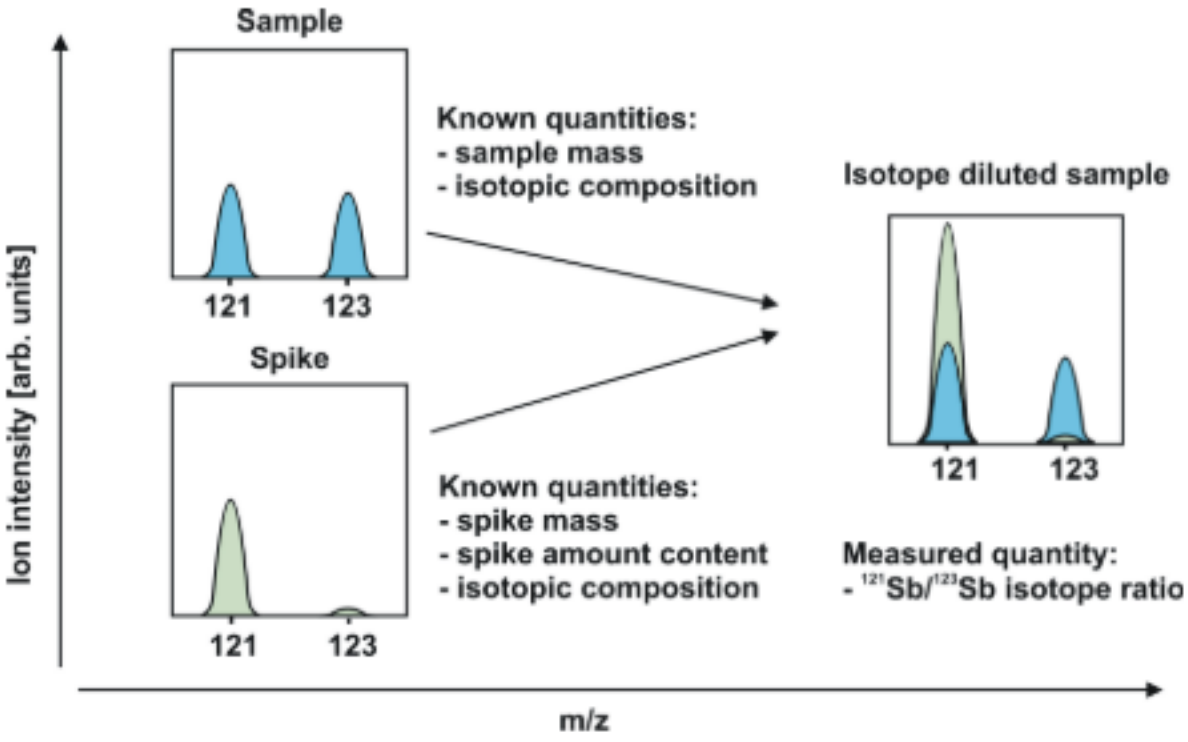

Figure 2-6: Schematic explaining single IDMS[20].

This technique requires an enriched spiking solution with its isotopic abundances and elemental totals being well-defined prior to use, standard reference material (SRM) for performing mass bias corrections (typically natural abundance, pure elemental standard), and a sample spiked with the enriched spiking solution. If the spiking solution and the sample contain any of the same isotopes, a separate unspiked sample will need to be run in order to obtain the isotopic abundances of the unaltered sample. The calculation ultimately relies on the mass bias corrected ratios measured in the spiked sample, the masses of the sample and spike, and the known abundances and concentration of the spike, as shown in eq. (2):

$$w_x = w_{y,b} * \frac{M_x * m_y}{M_b * m_x * a_{x,b}} * \left(\frac{R_y - R_{xy}}{R_{xy} - R_x}\right) \qquad \text{eq. (2)}$$

The definitions for these variables and the variables in eq. (3) can be found in Table 2-2.

Table 2-2: Abbreviations used to define variables in the IDMS equations[20].

Symbol	Unit	Explanation	Symbol	Unit	Explanation
N_a, N_b	-	Number of atoms of isotope a and b	$m'_{y,element}$	mg	Mass of spike element
N_x, N_y		Number of atoms in sample, in spike	$w_{y,b}$	mg kg^{-1}	Mass fraction of isotope b in the spike
$a_{x,a}$, $a_{y,a}$, $a_{z,a}$	-	Abundance of isotope a in sample, in spike and in back spike	w_x, w_y, w_z	mg kg^{-1}	Mass fraction of the element in the sample, in the spike, in the back spike
$a_{x,b}$, $a_{y,b}$, $a_{z,b}$	-	Abundance of isotope b in sample,	$w_{x\text{-}Blk}$	mg kg^{-1}	Blank corrected mass fraction of the element in the sample
R_{xy}, R_{yz}, R_{Blk}	-	Isotope ratio (a/b) in sample-spike, in spike and in spike-back spike & blank-spike blend			
kg		The twelfth part of the mass of an atom of the isotope ^{12}C			
R_x, R_y, R_z	-	Isotope ratio (a/b) in the sample, spike and back-spi	M_x, M_y, M_z	-	Standard atomic weight of the element in sample, spike, back-spike
$R_{opt,theor}$	-	Theoretical optimum blend ratio for smallest error magnification factors	M_b	-	Atomic weight of isotope b
R_{obs}, R_{x_obs}		Observed isotope ratio, eg. in the sample	c_x, c_y	mol kg^{-1}	Amount content of the element in the sample, in the spike
R_{true}		Best estimate for the "true value"of an isotope ratio, e.g. certified	MF_x, MF_y, MF_{Blank}	ng s^{-1}	Mass flow of the element in sample line, spike line, blank
K		Correction factor for mass discrimination/fractionation	ρ_{air}, ρ_{bal}, ρ_x	kg m^{-3}	Density of the air, the balance's weight and the sample
m_x, m_z	kg	Mass of sample, of back-spike solution	m_{x_obs}	kg	Observerd mass of the sample without correction of air buoyancy
m_y, m_y, $m_{y,Blk}$	kg	Mass of spike solution in sample-spike,spike-back spike & blank	I_t, I_0	counts s^{-1}	on count rate corrected for dead time effects, not corrected for dead time
$m_{x,element}$, $m_{y,element}$	kg	Mass of analyte element, spike element			
m'_x	g	Mass of sample			

Essentially, accurately measuring or knowing the isotopic composition of a sample and spiking that sample with a known amount of spike will allow one to determine the elemental total by monitoring how the spike changes the isotopics of the sample. Single IDMS can provide very accurate and precise results with great sample preparation techniques, proper mass bias

standards and corrections, and a well-characterized spiking solution with small associated uncertainties. However, some of these qualifications can be removed by performing double IDMS.

2.5.2 Double IDMS

Double IDMS functions in much the same way. However, in addition to the solutions required in single IDMS, a separate solution will need to be prepared and run. This solution is a known as a spiked back-spike, where the spike is the same enriched spike used in the sample and the back-spike is the same SRM used for mass bias corrections. The double IDMS equation is shown in eq. (3):

$$w_x = w_z * \frac{m_y * m_z}{m_x * m_{y'}} * \left(\frac{R_y - R_{xy}}{R_{xy} - R_x}\right) * \left(\frac{R_{zy} - R_z}{R_y - R_{zy}}\right) \quad \text{eq. (3)}$$

One benefit of this equation is that the standard atomic weights are no longer needed, which in turn means mass bias corrections are also no longer needed. The equation only requires the raw isotopic ratios determined during the course of measurement because the mass bias would be the same for all these ratios, which means it would cancel itself out as a constant. Another benefit of this is that this equation relies only on one isotopic ratio. This means all of the other ratios can be ignored in this scenario, whereas in the single IDMS scenario they must all be taken into account to determine the standard atomic weight of the main isotope of interest. This advantage greatly decreases the number of values and their associated uncertainties that need to be included in final uncertainty calculations[20,21,23,24].

Another benefit of this technique is that the elemental concentration of the enriched spike solution is no longer required. The only additional information required in relation to the single IDMS equation are the elemental concentration of the SRM, which is a certified value that requires no extra work to obtain, and the masses and measured ratios of the extra spiked back-

spike solution being analyzed. The isotopic abundances in the back-spike are also included in this equation and not the single IDMS equation, but they were still a requirement of single IDMS to determine mass bias corrections. Eliminating the requirement of the concentration of the enriched spike and any dilutions made on it prior to spiking the sample can be very advantageous. This enriched solution is much harder to obtain certified values for and more expensive to purchase, so it is often quantified by the lab that requires it through reverse IDMS[20,23]. The biggest downside to double IDMS is that it does require more work and an extra solution. In most cases, the back-spike solution required to prepare double IDMS solutions would already be in the possession of any analyst hoping to do single IDMS because it is generally a natural abundance SRM, just like the mass bias standard required for mass bias corrections.

3 Materials and Methods

3.1. Materials

Ultratrace H_2O, Optima grade HNO_3, and Optima grade HCl (Fisher Scientific, Springfield, NJ) were used in preparation of all the acids and surrogate samples. The SIMFuel surrogate[25,26] was prepared using 10 µg/mL solutions (High Purity Standards, Charleston, SC) of all individual elements except uranium, which required using a 1000 µg/mL U solution (Inorganic Ventures, Christiansburg, VA). An isotopically enriched neodymium-150 (Oak Ridge National Laboratory, Oak Ridge, TN) solution was used as a spike. The uncertified Nd-150 spike was quantified by Multicollector ICP-MS utilizing reverse IDMS prior to use[27]. A certified natural neodymium liquid standard (SRM 3135a, National Institute of Standards and Technology, Gaithersburg, MD) was used as the back-spike and to perform mass bias measurements. The drop collector was constructed with a 1-200 µL pipette tip (VWR

International, Radnor, PA) and a 4 mL HDPE bottle (DWK Life Sciences, Milville, NJ). A custom 50-100 µm particle size Ln Resin (Eichrom Technologies, Lisle, IL) column with dimensions of 0.75 mm ID x 280 mm was utilized for this work.

3.2. Instrumentation

3.2.1 ICP-TOFMS

All mass spectrometry measurements were taken on a TOFWERK icpTOF R (Thun, Switzerland). This instrument has been thoroughly described and characterized by Hendriks, et al.[14]. The instrument was contained in a custom-built enclosure (80/20 Inc., Columbia City, IN) due to its presence in a nuclear research laboratory. The sample introduction system consisted of a 0.4 mL/min quartz nebulizer, quartz spray chamber, and a quartz torch with demountable injector. Waveforms were summed every second for qualitative experiments and every 100 milliseconds for quantitative experiments.

3.2.2 GPEC

Separations were performed using a GPEC. The first column valve (DV1 in Figure 2-2) is used for more complex separations and was bypassed for this research. This GPEC was modified from the one described in Figure 2-2 to include a fifth valve for diverting effluent away from the mass spectrometer. This diversion valve allows for separate fraction collection to avoid overwhelming or wearing out the MS detector with major matrix components that were not of interest for this work, as well as collecting samples for more accurate and precise offline measurement methods. The latter capability of this valve was not leveraged for this work because it did not fall under the scope of this research. Separations were performed at ~0.1 mL/min throughout all experiments. Gas pressure and flow were kept constant, so the only deviations in the flow were due to small changes in separation conditions.

3.2.3 Drop Collector

The novel component of this instrumental setup was devised to couple the GPEC to the ICP-TOFMS, but its use can be extended to other types of liquid chromatography including drip columns. Common laboratory consumables were used to allow for rapid and cheap replacement in the event of contamination or breakdown. The effluent from the column was directed into the top of a pipette tip, and the bottom of the tip was inserted directly into the downstream peristaltic pump tubing. The flow from the drop collector was set to 0.11 mL/min. Setting this flow rate faster than the separation flow rate of 0.1 mL/min ensured drops were pulled out faster than they formed, otherwise they had the potential to build up and overflow the collector. A poly bottle was used to hold the pipette tip and GPEC outlet tubing in place, as well as shield the effluent and internal surface of the tip from environmental contamination. The hole drilled into the bottom of the bottle was large enough for roughly half of the tip to fit through, but small enough so that the entire tip could not fall out due to its tapered shape. The result was a very snug and stable fit for the pipette tip within the bottle. The hole in the lid of the bottle was sized to match the outer diameter of the GPEC outlet tubing, again resulting in a snug and stable fit. One final hole was drilled into the side of the bottle right underneath the collar to prevent the downstream pump from creating a vacuum within the bottle that would draw liquid from the column prematurely. A drawing of the drop collector can be seen in Figure 3-1.

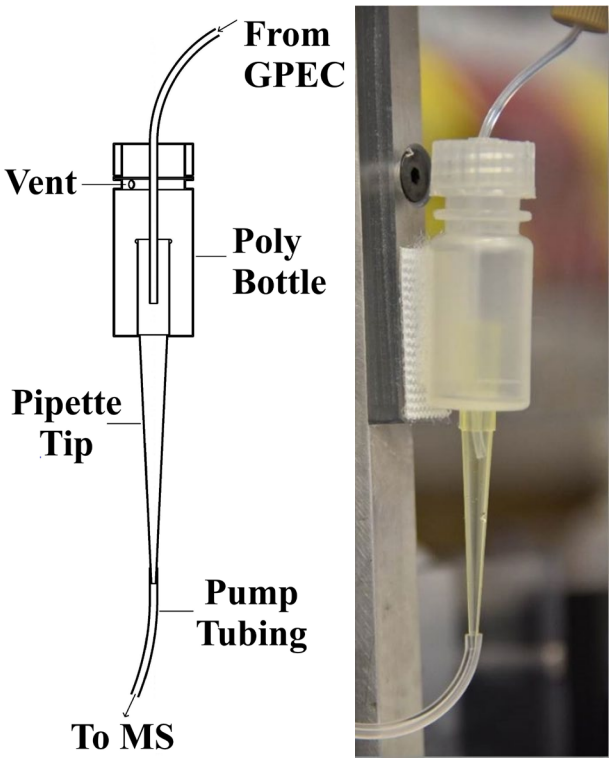

Figure 3-1: On-line drop collector

3.2.4 Flowing Rinse with Internal Standard

The effluent mixed with a flowing rinse via a Y-connector downstream from the drop collector before introduction into the mass spectrometer. The flowing rinse served to wash out the spray chamber between the injection of each drop of effluent. The rinse was controlled by the same peristaltic pump as the effluent. However, a larger inner diameter pump tubing was used to provide a rinse flow of 2.2 mL/min to aid in quick rinsing of the spray chamber between the injection of drops. The flowing rinse contained 10 ng/g of holmium-165 internal standard. The internal standard was added to monitor the drop size consistency and potential issues with the sample introduction system.

3.3. Preparation of the SIMFuel Surrogate Sample

The separation chosen to demonstrate the developed method is often employed to

separate neodymium and samarium isobars so that nuclear fuel burn-up calculations can be performed using neodymium isotope concentrations[28]. Considering this, a surrogate nuclear fuel sample was prepared and tested. The ratios of analytes in the surrogate sample were taken from the SIMFuel described elsewhere[25,26]. A stock solution with higher than required concentrations was prepared, and dilutions of this stock solution were analyzed. The isotopic abundances within each element could not be made to match that of a real fuel sample due to the lack of certified fission produced standards. The concentrations of the elements in the stock surrogate sample are reported in Table 3-1. The uncertainty in the neodymium concentration was calculated for quantification purposes using GUM Workbench (Metro Data, Braunschweig, Germany).

Table 3-1: Surrogate sample composition. Surrogate fuel sample elemental concentrations. Wt % values were obtained from SIMFuel results reported elsewhere[25,26]. The µg/g values were calculated based on the standard solution concentrations and masses of aliquots used.

Element	wt %	µg/g
U	95.55	176.5
Nd	0.71	1.34 ± 0.01
Ce	0.42	0.781
La	0.21	0.385
Pr	0.2	0.368
Sm	0.14	0.256
Y	0.08	0.148
Eu	0.02	0.0344
Gd	0.03	0.0539
Ba	0.33	0.612
Sr	0.13	0.238
Te	0.08	0.146
Mo	0.59	1.09
Ru	0.54	0.993
Rh	0.07	0.126
Pd	0.27	0.491
Zr	0.63	1.16

3.4. Qualitative Experiments

Initial experiments were designed to demonstrate the qualitative aspects of the method. A

1:35 dilution of the surrogate sample was made using water as the diluent to bring the HNO_3 concentration down to 0.05 M so the lanthanides would be retained on the Ln Resin. After loading the sample onto the column, the majority of the elements in the surrogate sample were eluted from the column with 1 mL of 0.05 M HNO_3. Early lanthanide separation was then evaluated during a 2.5 mL injection of 0.20 M HCl. Of particular interest was the separation of neodymium and samarium for quantitative experiments. The column was stripped of any remaining lanthanides with 1 mL of 2.5 M HCl and reconditioned with 0.05 M HNO_3. The scheme was then repeated, increasing the HCl molarity by 0.01 each test and finishing with 0.30 M HCl (i.e., 0.21, 0.22, 0.23 M, etc.). All other matrix elements were monitored for informational purposes but are not reported here. The ICP-TOFMS data was background corrected using Igor Pro.

The sample injection and data collection were each started manually and separately. This made it necessary to determine a time zero for each separation. The start of the first marked drop in the Ho-165 internal standard signal was used to determine time zero for each elution, because the introduction of effluent drops into the internal standard-containing flowing rinse stream noticeably diluted the internal standard and lowered its signal. Some disruption to the signal can be seen prior to this drop due to pressure changes at the Y-connector when the effluent drops begin to mix with the flowing rinse. This drop in signal can be seen in Figure 3-2. To account for GPEC flow discrepancies from one separation to the next, an end time was also determined by evaluating where each injection ended in the data sets. The resultant start and end time for each elution gave a specific amount of data points for each one. The number of data points was not equivalent for each eluent in these experiments, but two factors overcame these deviations. First, drop size was consistent for a given eluent unless an outside factor was allowed to interfere. This

aspect was carefully controlled to give the most consistent drop volumes possible. As a result, each drop was only carried away once it reached the proper size and fell into the bottom of the collector. The rate of drop formation was consistent for a given eluent. This was monitored by watching the internal standard signal for deviations from its regular periodic cycles. An example of this cyclic signal is shown in Figure 3-2.

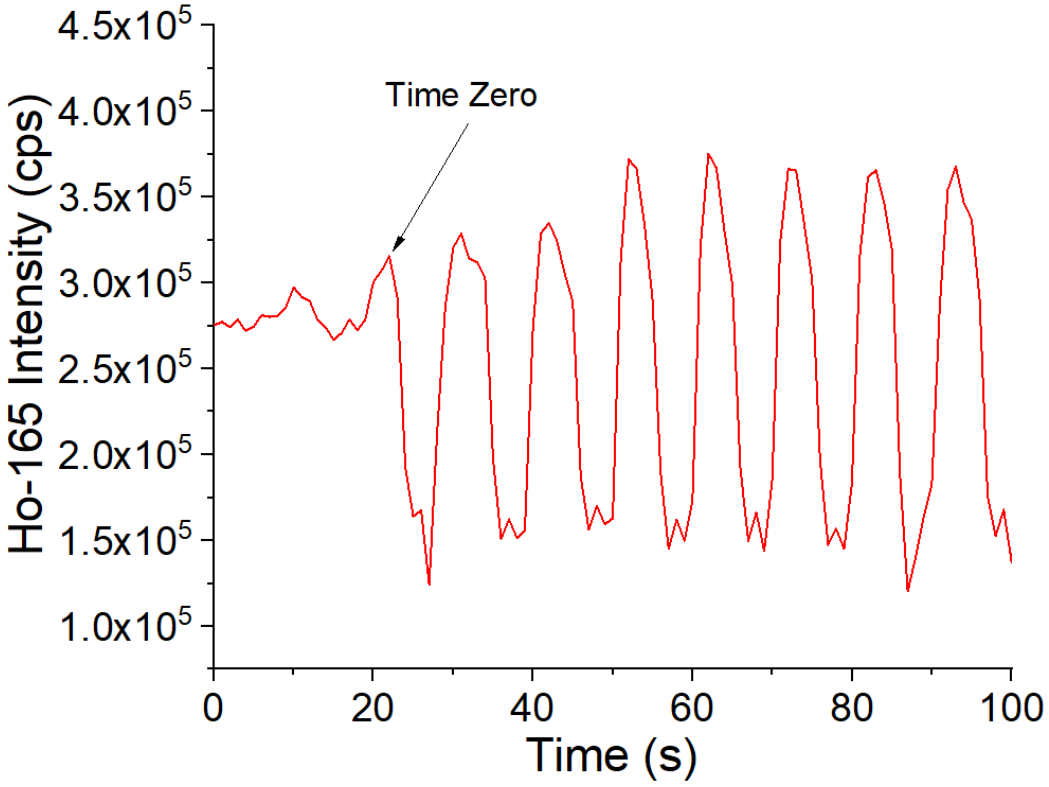

Figure 3-2: Ho-165 internal standard signal used to monitor the system for sample introduction issues, time zero, end times for injections, and consistency of drop sizes.

Second, the effluent flow is regulated by a steady peristaltic pump downstream from the drop collector. These two factors together essentially create a new MS sample introduction system by turning the GPEC effluent stream into a consistent series of same size microinjections. Because each elution was the same volume and the start and end time for each injection was able to be determined from the data, it was possible to plot eluate volume vs intensity for all analytes

of interest.

The void volume, or volume of the mobile phase, was easily measured directly due to the quantitative recovery of liquid from the GPEC. First, a 5% HNO_3 solution was used to fill a 250 µL sample loop. The 250 µL was then driven out of the GPEC with argon with the column bypassed, and the collected solution was weighed to obtain an accurate density on the solution used for the next step. Then, the packed Ln Resin column was filled, emptied, and a mass was obtained on the amount of 5% HNO_3 it held. The resulting mass of 5% HNO_3 was converted to the void volume using the density of the solution. The peak elution was determined in these plots by searching for respective maximum intensity values using Microsoft Excel and recording the corresponding eluate volume to peak maximum from the x-axis at that point. The k' values, defined as number of free column volumes to peak elution of the analyte of interest, were then calculated as reported by Horwitz, et al.[29].

While a more rigorous treatment of this data is possible (e.g., integrating the signal from each drop to determine peak elution rather than picking the drop with the maximum intensity value), it was not undertaken because the effort required was not expected to alter these qualitative results in a significant way. However, this is a quick and easy way to generate eluent concentration vs k' plots for the separation conditions that real samples would be subjected to.

3.5. Quantitative Experiments

After determining the best eluent for the desired separation, two quantitative experiments were performed to determine the total Nd concentration and isotopic abundances in the surrogate fuel sample. This eluent was also run through the system to collect blank signals for determination of the limit of quantification (LOQ) of each analyte. The LOQ was estimated as

3.3 times the limit of detection (LOD), while the LOD was estimated as the mean of the blank plus three times the standard deviation of the blank.

The dropwise nature of the analysis made external calibration of the mass spectrometer impossible. However, it is well known that an internal calibration method, such as IDMS, provides more accurate and precise measurements[20,21]. Experiments were designed so that single and double IDMS results could be evaluated. Double IDMS only requires one isotopic ratio from the samples for quantification of total Nd. Ln Resin is known to show difficulty fully resolving Ce-142/Nd-142 isobars in dilute hydrochloric acid[30,31]. However, double IDMS results will not be affected by this isobaric interference if 142 m/z is not chosen as one of the signals used in the equation. Likewise, single IDMS results will not be affected by this interference. In the analysis of fission produced neodymium in nuclear samples, Nd-142 results are not included and its contribution to the standard values and sample results are subtracted as needed. This is due to Nd-142 being essentially nonexistent in these samples[28,32].

While there are several ratios that can be chosen for IDMS of neodymium and evaluated for mass bias correction accuracy, the 150/144 ratio was chosen for this work due to the use of an enriched Nd-150 spike solution (92.730 wt % Nd-150) and the high natural abundance of the Nd-144 isotope. Moreover, the double IDMS results will be based entirely on this ratio, so ensuring its accuracy is of the utmost importance. Each experiment was bracketed by mass bias standard (SRM 3135a) analyses to determine the mass bias correction factors for each isotopic ratio. The Russell equation[33] was used with the mean 150/144 results from the certified standard runs as the basis for the mass bias corrections. Between mass bias analyses, each run consisted of an unspiked surrogate sample to obtain Nd isotopic composition, a Nd-150 spiked surrogate sample for total Nd, and a spiked back-spike to complete the double IDMS equation.

The transient nature of the signal necessitated the use of a suitable quantification method. The linear regression slope (LRS) technique was chosen, in part, due to the signal frequently moving in and out of the background range. One of the benefits of LRS is that removal of points at or near background is not necessary for LRS quantification to work well[17]. In fact, it has been reported that these points are necessary for LRS to provide precise results[19]. Data points where either isotope was below the LOQ were removed and the results were compared with full data sets to ensure this held true for this type of data. Other methods of quantification were considered, but the sheer amount of data and number of drops to analyze made integrating the peak from each drop impractical. Moreover, LRS has been shown to perform well in LC-MS applications[18,34].

Along with quantification of full data sets, individual drops from various regions of the Nd elution peak were selected to determine how well quantification could be performed on them in both runs. This analysis was performed on the data sets with the points below the LOQ's removed because these data sets made it easier to see where some drops ended and others began, and these data sets included sufficient points near background to give precise results. Each drop contained roughly 90 data points in its respective LRS plot. The less intense drops contained slightly fewer points due to background levels being fully reached between drops. A drop from both the spiked and unspiked surrogate samples were required for the IDMS equations. Drops were selected based on the intensity of the Nd-144 signal in each. The first drop to reach 1k, 2k, 5k, 10k, 20k, 50k, and peak cps, as well as the last to reach each of those intensities in the unspiked and spiked samples were chosen and paired up for this analysis. This is best represented in Figure 3-3.

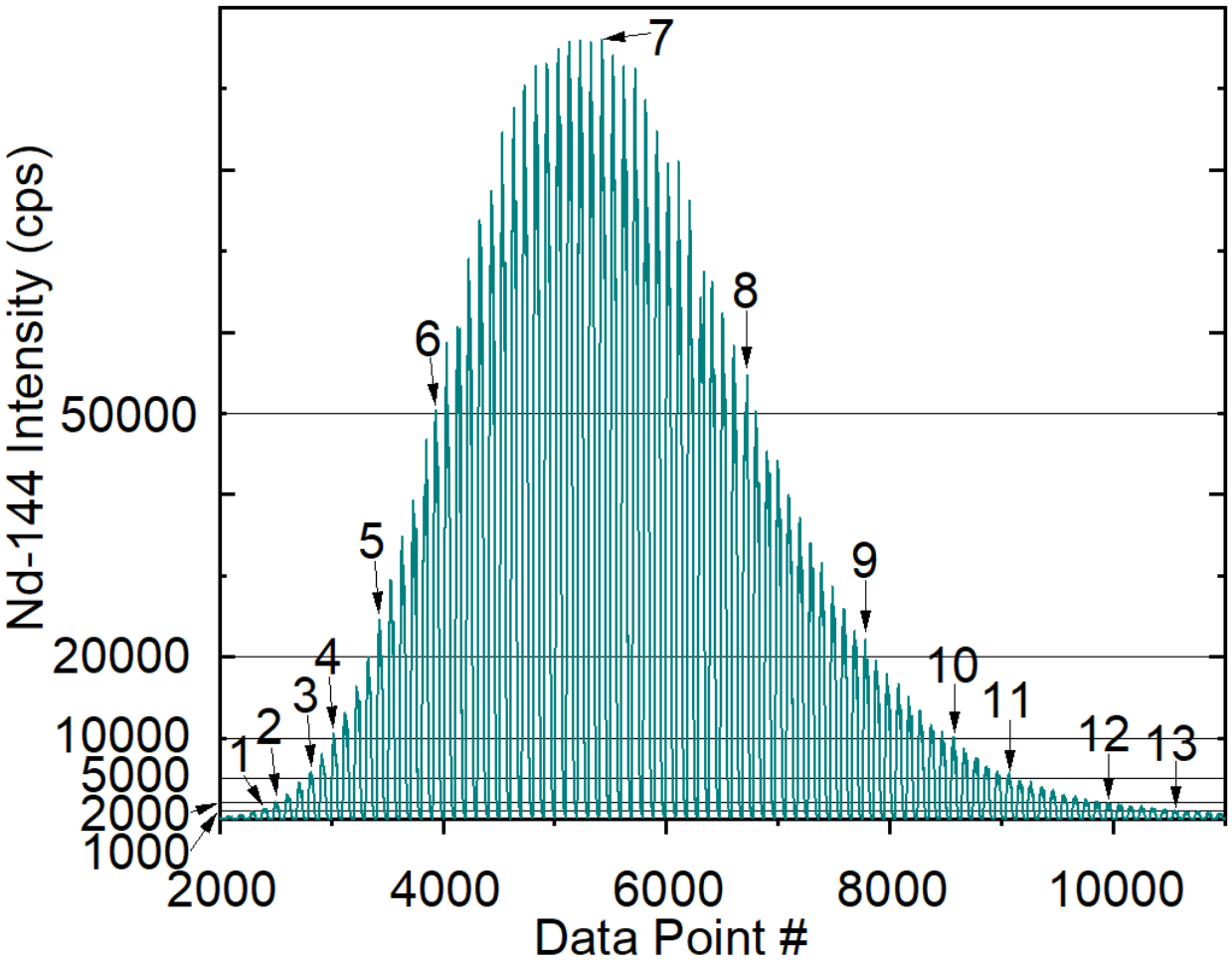

Figure 3-3: Nd-144 elution data showing how drops were selected for dropwise analysis. Data shown was taken from run A spiked surrogate sample separation.

Drops were not selected from the mass bias or spiked back-spike data sets because they are standard samples. Selecting anything less than the entire data set would never be required because there are no overlapping peaks to avoid like there could be in samples with isobaric interferences.

All uncertainties for quantitative results were calculated using GUM Workbench.

4 Results and Discussion

4.1. Qualitative Results

The chromatograms generated using this system look much like they would in a continuous flow system except the peaks are broken into several smaller sections. This is represented in Figure 4-1.

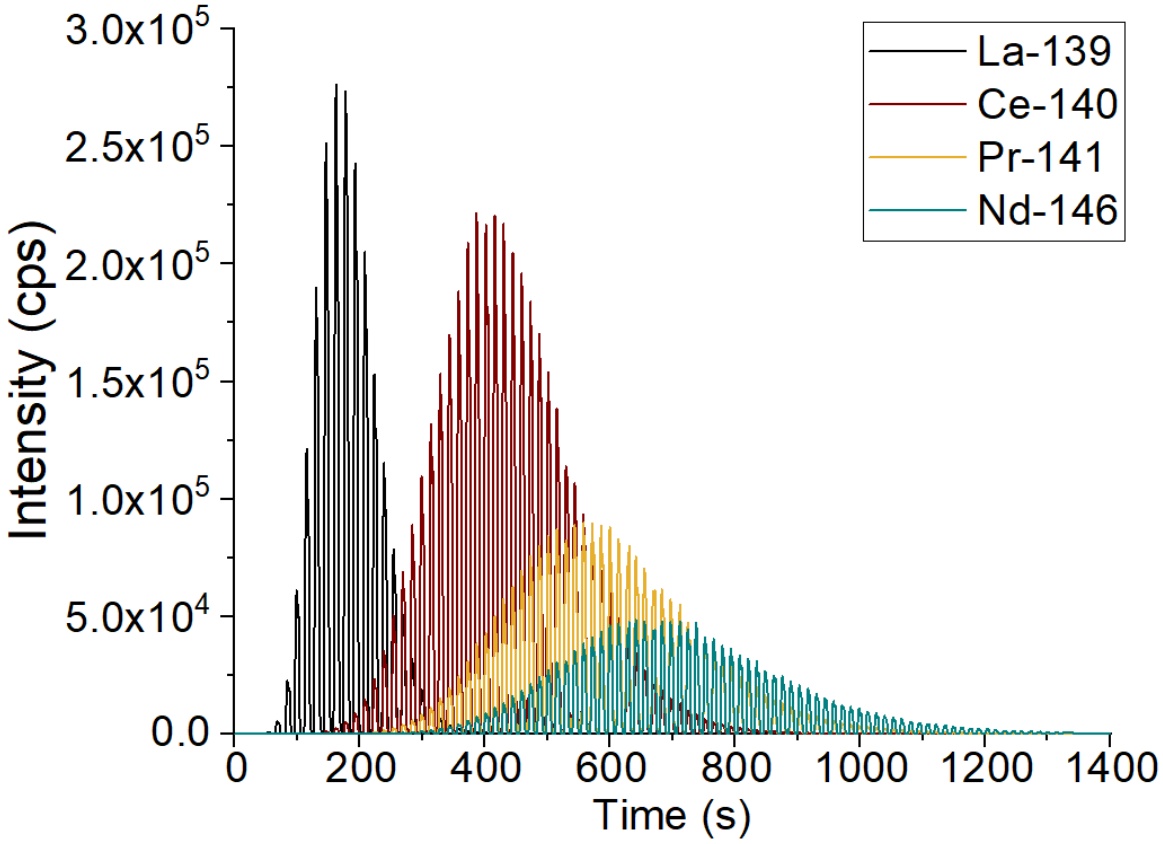

Figure 4-1: Early lanthanide elution from Ln resin using 0.20 M HCl

Evaluation of the data for the series of eluents tested showed that a complete resolution of the neodymium and samarium peaks was not possible for any of them under the conditions of the experiments. Only the lowest two concentration tested, 0.20 and 0.21 M HCl (see Figure 4-2), did not show any samarium breakthrough during the 2.5 mL elutions.

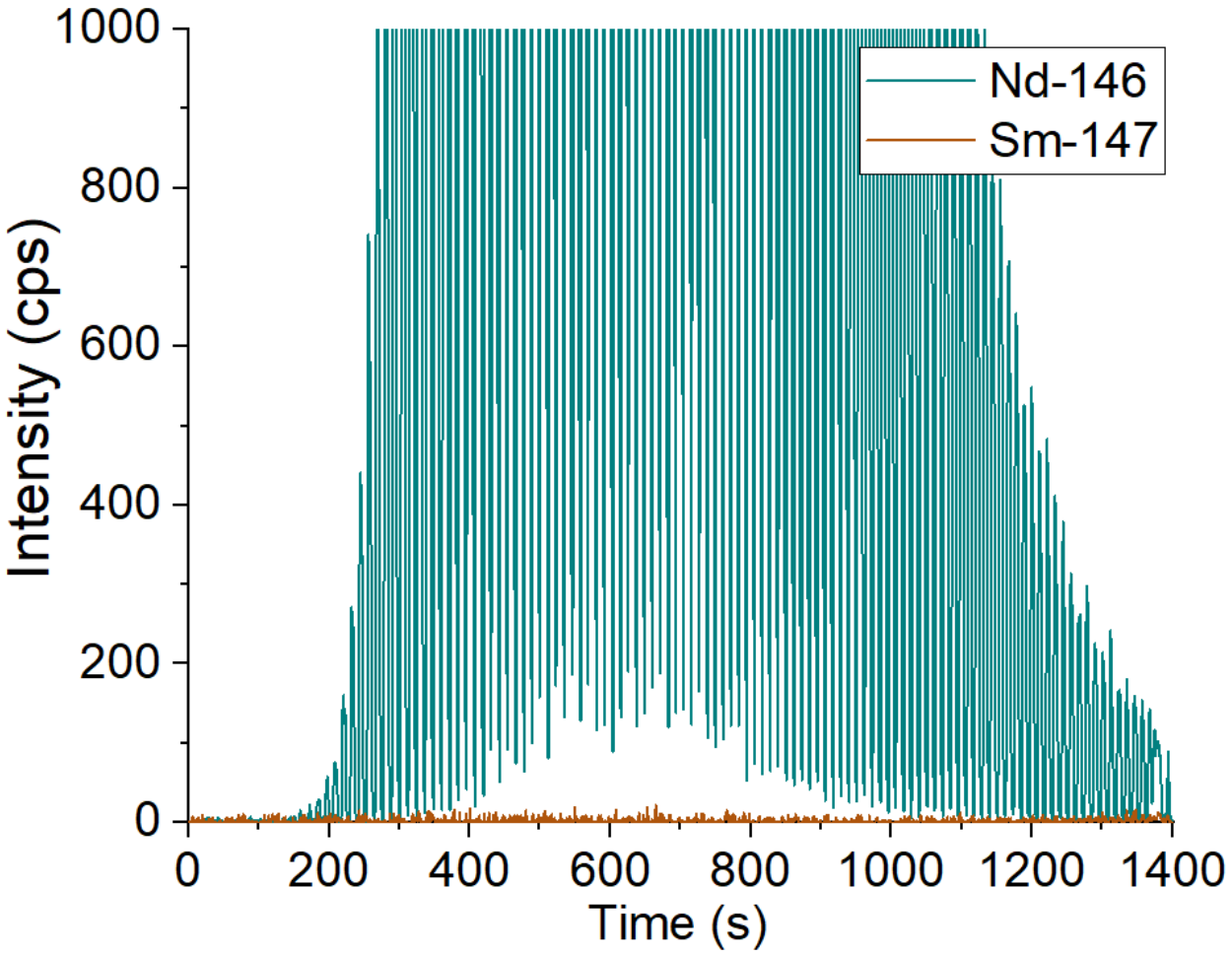

Figure 4-2: Chromatogram showing the entirety of the elution and no Sm breakthrough using 0.21 M HCl and Ln Resin GPEC column

Any of the eluents tested could have been used because quantification could have been stopped as soon as samarium levels reached above their limits of detection. However, for the purposes of this demonstration and to limit any column fractionation effects [35], 0.21 M HCl was used. This eluent provided a full set of samarium-free data throughout the entire 2.5 mL elution, and 0.21 M HCl recovered a bit more of the total neodymium than the same volume of 0.20 M HCl would have.

Figure 4-1 and the eluent concentration vs k' plot for the column and reagents tested, shown in Figure 4-3, give good graphical representations of why attempting to completely

resolve Ce, Pr, and Nd using this resin and dilute hydrochloric acid is not ideal. The tailing of these peaks on this resin is rather significant. Additionally, the k' values are very similar and the trendlines for these three elements are essentially parallel. This means that adjusting concentrations within this range does little to resolve the peaks, and instead only has a significant effect on how soon the elements elute.

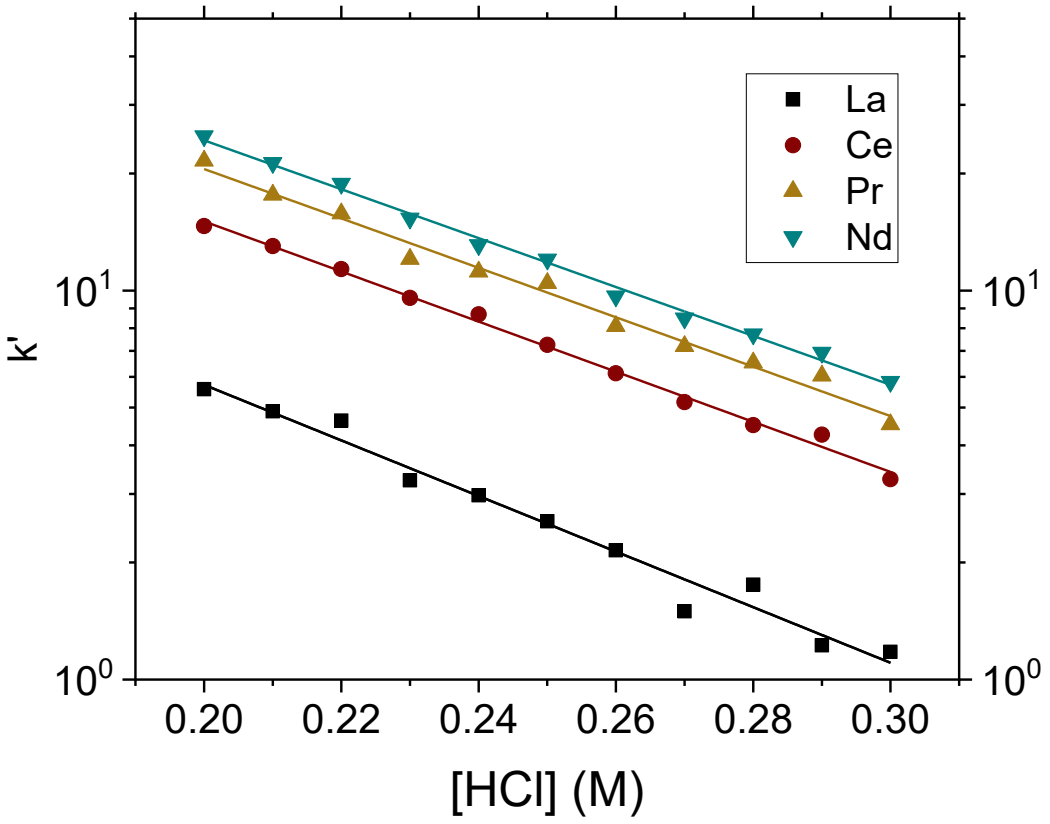

Figure 4-3: Concentration vs k' plot for elution of early lanthanides from Ln resin in dilute hydrochloric acid

The plot in Figure 4-3 is a good way to represent all the chromatographic data for all the eluents tested in one condensed plot, rather than making eleven chromatograms similar to the one in Figure 4-1.

4.2. Quantitative Results

4.2.1 Single IDMS

It was necessary to remove all 142 m/z signals from the results and all Nd-142 contribution to the total Nd concentration of the surrogate sample to perform single IDMS, as explained above. Doing so results in an expected concentration of 0.982 ± 0.01 µg/g Nd. The single IDMS results were 0.9647 ± 0.0118 µg/g and 0.9627 ± 0.0118 µg/g Nd for runs A and B, respectively. The error bars from both results overlap with the error bars of the expected value for total Nd. Removing all points from the LRS plots where either isotope was below the LOQ and applying the single IDMS equation again produced values of 0.9621 ± 0.0118 µg/g and 0.9611 ± 0.0118 µg/g Nd for runs A and B, respectively. These values still fell within the range of expected concentrations, albeit just barely. Removing these points ultimately made the results worse, as indicated by Epov et al.[19], but in this case they were changed by <0.2%.

4.2.2 Double IDMS

The two runs of the sample sets on separate days gave double IDMS results of 1.343 ± 0.008 µg/g and 1.340 ± 0.008 µg/g Nd, both within the 1.34 ± 0.01 µg/g calculated concentration and associated uncertainty of the surrogate sample. Removing the data points below the LOQ's and performing the double IDMS calculations again resulted in an identical result for the first run and a difference of only +0.001 µg/g for the second run. The exclusion of these points did not alter the double IDMS result the same way it did the single IDMS result. This lessened effect is likely do to the greatly decreased number of isotopic ratio results that are ultimately used in the double IDMS equation. This result confirmed that this extra work is not necessary for LRS quantification of data produced using this method.

4.2.3 Isotopic Ratios

Isotopic ratio results obtained from the mass bias corrected unspiked surrogate samples are reported in Table 4-1. Isotopic ratio results were also determined after removing the points below the LOQ, and these results are shown in Table 4-2.

Table 4-1: Results and % errors of mass bias corrected isotopic ratios. Percent errors are relative to the natural Nd isotopic abundances.

Isotopic Composition Results					
Ratio	Expected	Run A	% Error	Run B	% Error
143/144	0.5116	0.5068	-0.9296	0.5069	-0.9101
145/144	0.3485	0.3441	-1.255	0.3437	-1.370
146/144	0.7223	0.7194	-0.3998	0.7202	-0.2890
148/144	0.2419	0.2387	-1.310	0.2391	-1.145
150/144	0.2369	0.2344	-1.060	0.2352	-0.7221

Table 4-2: Results and % errors of mass bias corrected isotopic ratios with data points below the LOQ excluded. Percent errors are relative to the natural Nd isotopic abundances.

>LOQ Data Only Isotopic Composition Results					
Ratio	Expected	Run A	% Error	Run B	% Error2
143/144	0.5116	0.5066	-0.9687	0.5067	-0.9492
145/144	0.3485	0.3440	-1.284	0.3437	-1.370
146/144	0.7223	0.7197	-0.3582	0.7205	-0.2475
148/144	0.2419	0.2387	-1.310	0.2392	-1.104
150/144	0.2369	0.2345	-1.018	0.2354	-0.6377

Once again, removal of the points that were below the LOQ did not alter the results to any appreciable degree. None of the % errors were found to be >1.5% for any of the results.

4.2.4 Dropwise IDMS Results

The dropwise data analysis was surprisingly accurate. As expected, the uncertainties were much larger for drops with lower Nd intensities. In most cases, the values and their respective uncertainties encompassed the calculated total Nd value in the surrogate sample. All the double

IDMS results that failed in run A were drops that only reached 1k, 2k, or 5k Nd-144 cps. The results for run A can be seen in Figure 4-4.

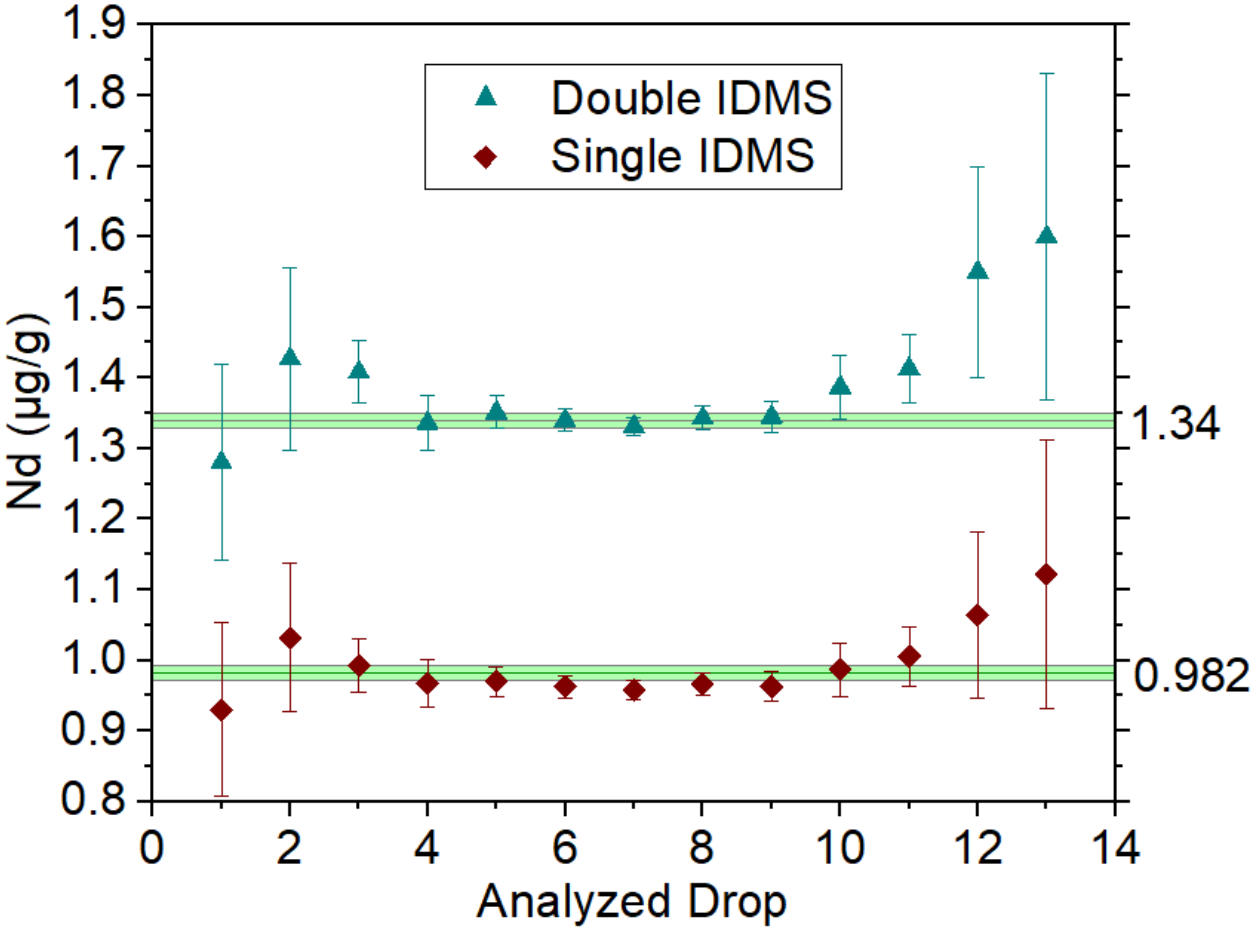

Figure 4-4: Single and double IDMS results for Nd totals in run A. See Figure 3-3 to relate the analyzed drop numbers to the region of the elution peak evaluated.

Natural Nd-150 is only about a quarter as abundant as Nd-144, so the intensities of the Nd-150 component of the calculations were only about 25% as high as the Nd-144 signals that were used to determine which drops to analyze. This helps to explain the large uncertainties in the slopes obtained from the LRS plots of the less concentrated drops and the erroneous results.

On the other hand, all the drops tested from the second run gave results that fell within the expected range except for one seemingly anomalous double IDMS result at >20k cps Nd-144

in the tail side of the peak. The results for run B are plotted in Figure 4-5.

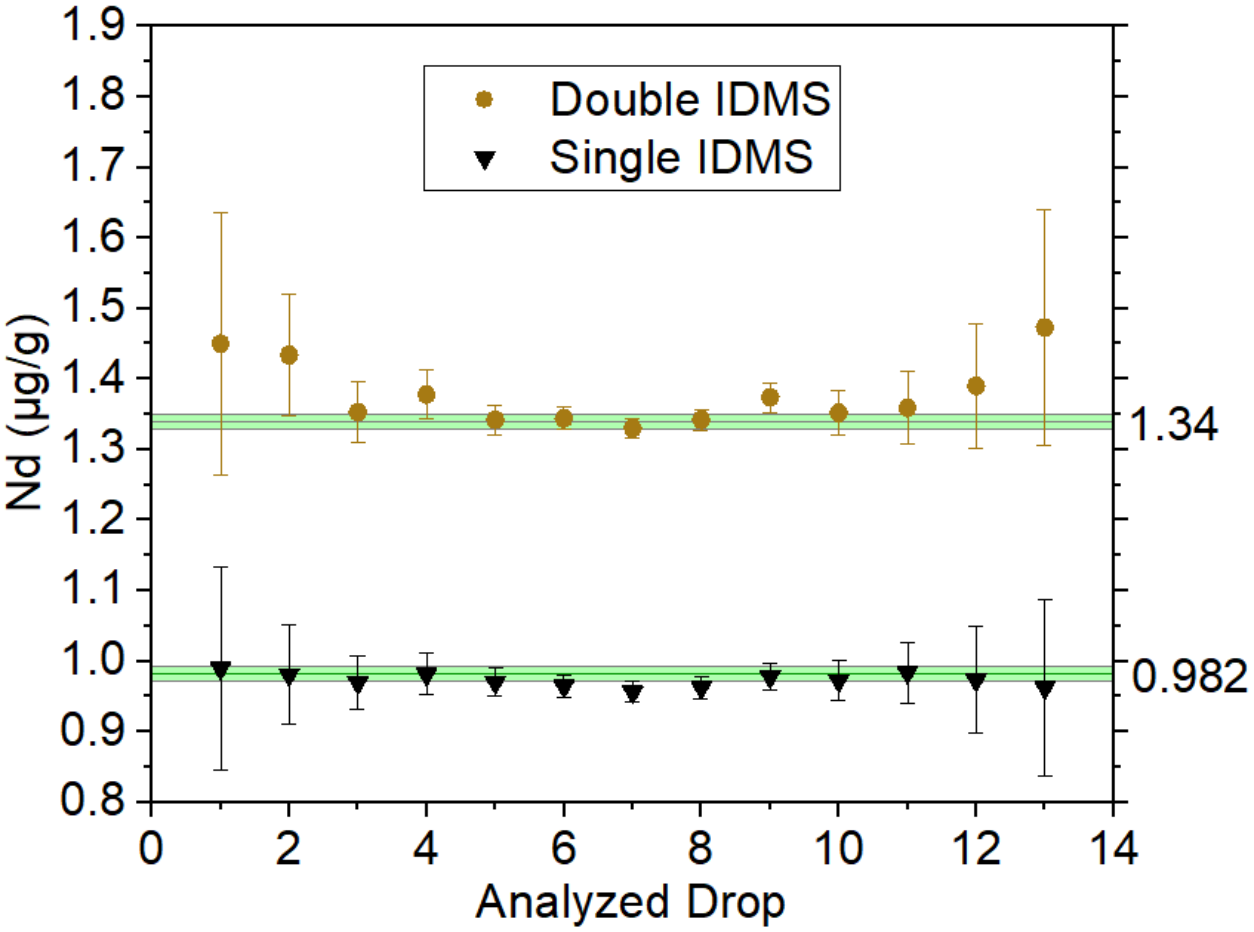

Figure 4-5: Single and double IDMS results for Nd totals in run A. See Figure 3-3 to relate the analyzed drop numbers to the region of the elution peak evaluated.

The isotopic ratios obtained from each drop with >10k cps Nd-144 were nearly all under 3% error, with the only three (out of 70) exceptions being from the lowest intensity drops in this group. The ratios obtained from the less concentrated drops contained much more uncertainty, as expected. From the selection of drops analyzed, the >10k cps Nd-144 seems to be a cutoff point where accurate and precise values can be measured. The percent errors of these analyses can be seen in Table 4-3 and Table 4-4 for run A and run B, respectively. The measured results were omitted from the tables.

Table 4-3: Percent error values for the evaluation of mass bias corrected isotopic ratios obtained from run A.

Dropwise Analysis Isotopic Ratio Results -Run A							
Ratio	>1k cps Front	>2k cps Front	>5k cps Front	>10k cps Front	>20k cps Front	>50k cps Front	Peak cps
143/144	-18.48	-8.084	-0.1086	-3.021	-1.751	-1.321	-1.008
145/144	-18.24	-4.957	1.442	-0.7388	-0.2797	-1.628	-1.399
146/144	-6.658	-3.750	0.02941	-1.120	-0.06751	0.1263	-0.5521
148/144	-20.99	-2.137	-0.6901	0.2195	-1.641	-2.344	-2.096
150/144	-13.98	-3.424	-0.04671	0.2488	-1.566	-1.229	-1.018
Ratio	>1k cps Tail	>2k cps Tail	>5k cps Tail	>10k cps Tail	>20k cps Tail	>50k cps Tail	
143/144	-11.37	-6.071	-2.044	0.08687	-0.2454	-0.6755	
145/144	-20.57	-6.277	-5.617	1.356	-0.5954	-1.026	
146/144	-14.78	-3.653	-0.7874	-0.8013	-0.9951	-0.1644	
148/144	0.05413	-3.129	1.708	-2.220	0.4676	-0.7728	
150/144	2.106	-1.651	-0.1311	-0.004502	-1.904	-0.7643	

Table 4-4: Percent error values for the evaluation of mass bias corrected isotopic ratios obtained from run B.

Dropwise Analysis Isotopic Ratio Results - Run B							
Ratio	>1k cps Front	>2k cps Front	>5k cps Front	>10k cps Front	>20k cps Front	>50k cps Front	Peak cps
143/144	-7.439	-2.083	-2.357	-0.7537	-1.438	-1.086	-0.4018
145/144	-8.860	1.959	2.389	-3.608	-2.260	-2.489	-0.8536
146/144	-0.8013	-0.4552	-1.410	-1.314	-0.3721	-1.037	-0.4275
148/144	-10.82	-3.502	0.2609	-1.889	0.09548	-2.220	-0.9381
150/144	-8.278	-1.229	-4.141	-0.6799	0.2910	-1.735	-0.2578
Ratio	>1k cps Tail	>2k cps Tail	>5k cps Tail	>10k cps Tail	>20k cps Tail	>50k cps Tail	
143/144	-4.077	-3.862	-2.728	0.06733	-0.4605	-0.8905	
145/144	-7.913	-8.831	0.3516	-3.092	-0.2223	-1.772	
146/144	-2.726	0.1817	0.8739	-1.632	-0.3859	-0.2613	
148/144	-4.742	-3.253	-1.848	-1.641	-0.1526	-0.9381	
150/144	-12.63	-8.615	1.431	-2.031	-0.4688	-0.04671	

5 Conclusion

The developed dropwise sample introduction method coupled with ICP-TOFMS provides advantages to separation method development, real-time separation monitoring, and rapid quantification of even the smallest samples. The on-line drop collection apparatus is easily accessible to any analytical laboratory without incurring significant costs. It is also easily

replaced in the case of breakdown or contamination concerns. The pipette tip can be popped out and replaced between each analysis in a matter of seconds.

While this work utilized the GPEC, the drop collector is easily modified for other types of LC including gravity driven drip columns. The break in flow that the drop collector provides could easily be leveraged for coupling separations with slower flow rates than the ideal flow rates for the mass spectrometer or low analyte concentrations. Other types of ICP-MS could be leveraged as well to suit the needs of the analysis. However, the speed of the ICP-TOFMS would be ideal for the dropwise analysis because more data points can be obtained during the short injections.

The accuracy and precision of a transient signal method, such as this one, could never reach that of a steady signal measurement. Even so, the results of this method have shown that quantification is possible and passable for analyses that do not require the extra rigor of off-line methods. The results from the dropwise analysis indicated that the isotopic and elemental total results from single drops that reached >10k cps Nd-144 showed a minimal increase in uncertainties compared to the results obtained from evaluating the entire Nd peak. This information could be applied to LC-MS applications where only a region of the peak of interest is isobar free.

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