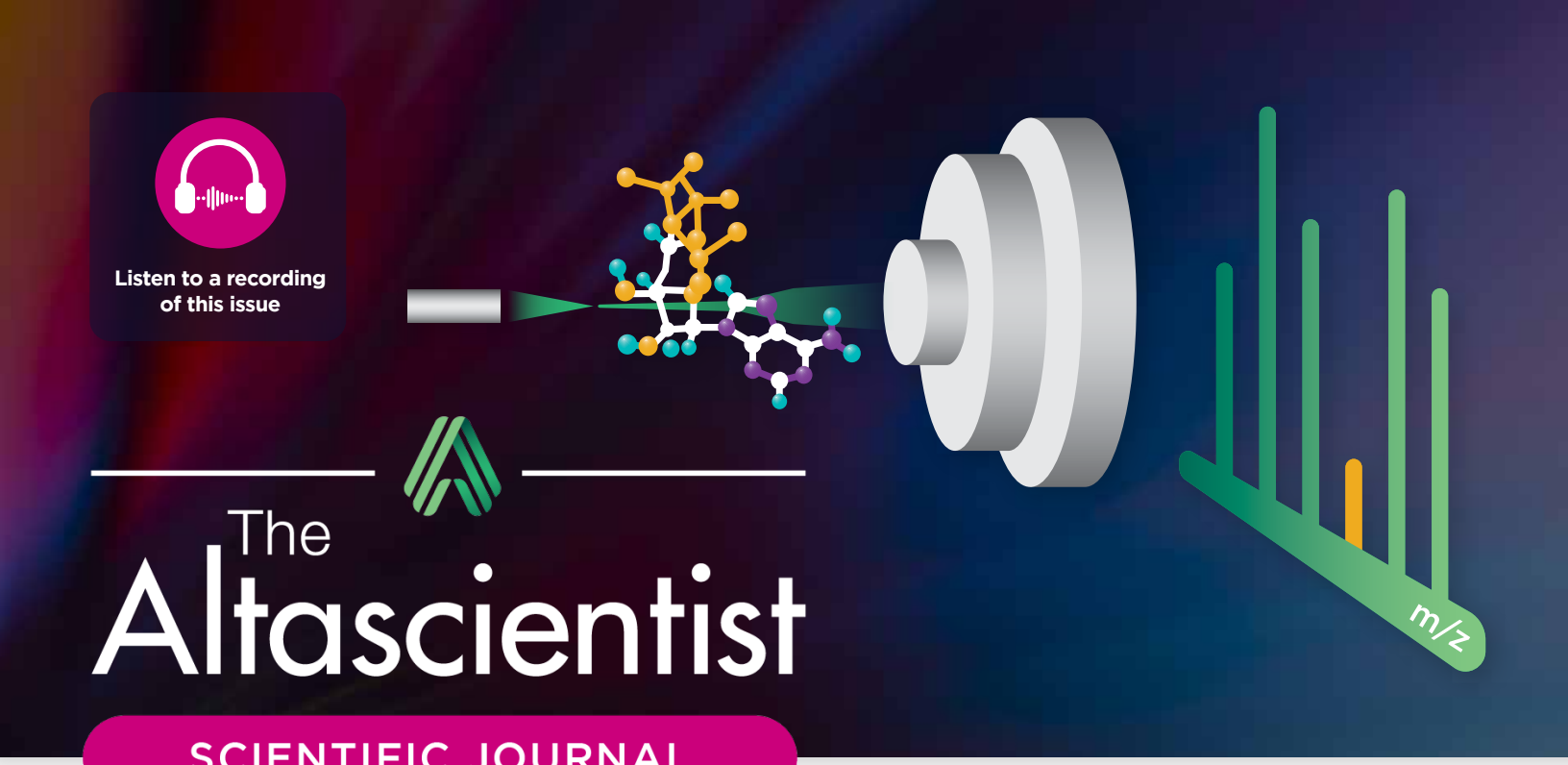

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THE EVOLUTION AND ADVANCEMENT OF LIQUID CHROMATOGRAPHY-MASS SPECTROMETRY IN DRUG DEVELOPMENT

IN THIS ISSUE

INTRODUCTION

The drug development landscape is constantly evolving, with science and technology advancing hand-in-hand to improve the essential steps of determining drug concentration profiles and the characterization of drug transformation products. The ultimate goal is to better understand drug distribution, metabolism, and pharmacokinetic characteristics, and to present regulatory bodies with a complete and comprehensive submission package driven by current guidelines.

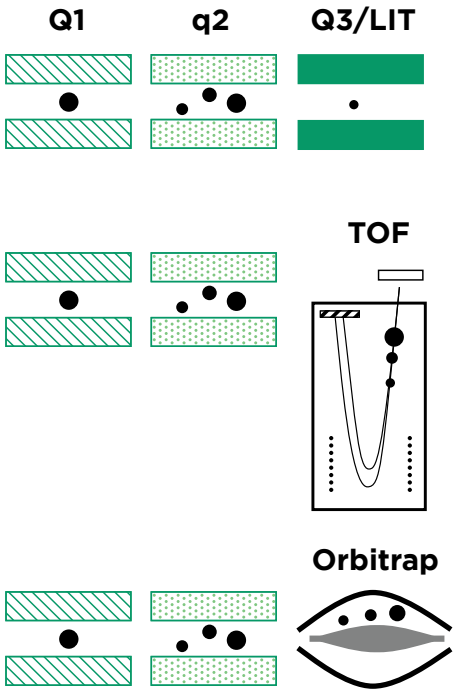
To this end, liquid chromatography (LC) coupled with mass spectrometry (MS) via an atmospheric pressure ionization (API) interface is a well-established analytical approach to support each phase of drug development, from early discovery through to clinical studies.

The ubiquitous leveraging of LC-MS may largely be attributed to the following characteristics: (i) high sensitivity with broad dynamic range and selectivity from interferences, particularly when incorporating a tandem mass spectrometric (i.e., MS/MS) approach, (ii) a near-universal and thermodynamically favorable electrospray ionization process which facilitates the transport of analyte ions from the condensed state of LC into the gas phase for MS detection, and (iii) the ability to support multiplexing capabilities due to rapid MS/MS scanning and chromatographic separation.

The mainstream adoption of the LC-MS approach for the support of drug development initiatives originated in the early 1990s, pioneered by the triple-stage quadrupole (QqQ) platform. To this day, the QqQ architecture remains the gold standard for drug quantitation in biological fluids due to the unique nature by which MS/MS is performed.

Specifically, and as outlined in Figure 1, ionized precursor ions with a targeted mass-to-charge ratio (*m/z*) are transmitted through the first resolving quadrupole (Q_1) and axially accelerated into a collision cell (q) containing an inert gas (N_2 or Ar). The resulting collision-induced fragmentation leads to the production of progeny ions whose profile represents a fingerprint unique to that of the selected precursor. Progeny ions of a specific *m/z* can then be transmitted from the collision cell through the third resolving quadrupole (Q_3) for detection. The scan function representing precursor ion selection with subsequent collision-induced dissociation and detection of a specific progeny ion is often referred to as multiple (or selected) reaction monitoring (MRM or SRM, respectively), and is single-handedly responsible for the mainstream adoption of the QqQ platform for quantitative mass spectrometry.

Figure 1. Function of commonly used mass spectrometers in MS/MS acquisition modes. These instruments can select a precursor in the first quadrupole, fragment it in the collision cell, and record the fragment in the last mass analyzer, which can be either a quadrupole, time-of-flight, (ToF) or Orbitrap™ spectrometer.



Over the years, advancements in LC-MS technology have been required to meet the ever-increasing complexities of assay demands. At the 12th Workshop on Recent Issues in Bioanalysis (WRIB), a panel discussion focused on the topic of integrating new technology into bioanalytical workflows. Below is an excerpt from the published summary:

> *As drug discovery advances more novel therapeutic molecules, bioanalytical technologies and capabilities need to keep pace, particularly where measurements cross the threshold from drug discovery into drug development. Requests to support new modalities like gene therapies and chimeric antigen receptor (CAR) T cells may require assessment of PK using unconventional approaches as well as pharmacodynamic end points or more functional assay readouts.*
>
> *New modalities and the continued need for increased sensitivity are driving the development of many new technologies. In concert, there is a strong industry ambition to deliver better translational end points from the research and clinical development phases. This is pushing technologies originally conceived for discovery research activities toward the regulated world to complement the measurements from HPLC–MS/MS and LBA. The current outsourcing paradigm sees CRO at the forefront of this technology onslaught into drug development... as an industry we need to remain inventive, extending (where possible) the applicability of established technologies that are already accepted by regulatory bodies, but be innovative highlighting the unmet need in current technologies early so that the transition from drug research to drug development is seamless.*[1]

In the following sections, we describe the numerous benefits of incorporating a stable isotope labelled internal standard for quantitative LC-MS, and detail recent advances in MS technology. Several case studies are presented, which exemplify novel bioanalytical workflows that are required to meet the challenges faced in both non-clinical and clinical development, across a variety of drug classes.

THE CASE FOR STABLE ISOTOPE LABELLED INTERNAL STANDARDS (SLIS) FOR LC-MS QUANTITATION

Since analytical measurements have a degree of uncertainty derived from sample extraction, chromatography and detection, quantitation leverages an internal standard added in equal amounts to all samples at the start of processing, with the aim of having it mirror everything that can happen to the analyte. Rather than the detector measuring the absolute response of the analyte, it measures the relative response of the analyte to the internal standard. In practice, however, when the internal standard is not chemically identical to the target analyte, it can behave differently. Measurement uncertainty can be mitigated, but not fully compensated.

In using MS detection, an isotopic analog of the analyte (the most common labels include ^{2}H, ^{13}C or ^{15}N) can be distinguished by mass-to-charge ratio (*m/z*), and its physicochemical properties are identical, hypothetically compensating fully for uncertainty at every analytical stage. This is particularly relevant for ionization, since unwanted species that chromatographically co-elute with analytes can impact the electrospray process (e.g., change in charge-state distribution or droplet surface tension), causing a change in predicted response. This phenomenon, coined "matrix effect", can be caused by salts, fats (especially phospholipids), and other interferences of differing proton affinity. Matrix effects cannot be wholly compensated with use of an analog internal standard, and measurement uncertainly can actually increase since analyte and internal standard may suffer from independent and unrelated matrix effects (e.g., signal for one may be enhanced while the other is decreased, or vice versa).

In contrast, use of SLIS that co-elutes exactly with the analyte will be subject to identical matrix effects, and ionization efficiency will be equally impacted such that the peak area response ratio (i.e., analyte response/SLIS response) is conserved relative to the absence of matrix effect.

Five key factors to consider when selecting a suitable internal standard include:

(i) low residual contamination from unlabelled molecule

(ii) optimal mass difference between analyte and its SLIS to avoid naturally occurring isotopic contribution of the former to the latter

(iii) minimal isotope effects that can lead to unwanted chromatographic separation between analyte and SLIS when too many labels are incorporated

(iv) labelled sites, ideally on the MS/MS fragments of interest

(v) stability during extraction (e.g., avoid ^{2}H labels adjacent to carbonyl groups that may be susceptible to proton-deuterium exchange); ^{13}C tends to be preferable to ^{2}H in order to avoid label scrambling.

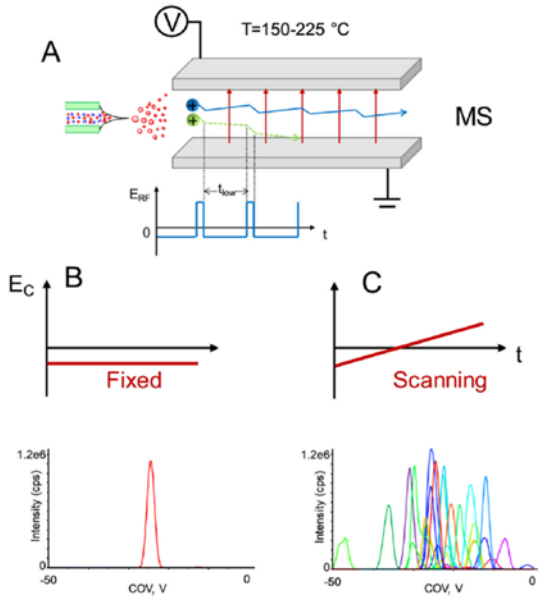
RECENT INNOVATIONS IN MASS SPECTROMETRY

QqQ Advancements: Ion Mobility and Linear Ion Trap Modalities

While recent advancements in QqQ raw sensitivity and rapid scan speeds are noteworthy and predicted to improve with each generation of instrument design, matrix interference from biological extracts and/or elevated baseline response can still represent a formidable challenge in achieving lower limits of quantitation (LLOQ). Considerable effort has been made to improve the selectivity to discriminate analytes from background signal, two recent examples of which include differential mobility spectrometry (DMS) and operation of Q_3 in a QqQ configuration as a linear ion trap (LIT), the latter allowing an additional stage of fragmentation often referred to as MS/MS/MS, or MRM^3.

In the LC-DMS-MS/MS approach, the ion mobility cell is interfaced between the ion source and sampling orifice of the mass spectrometer; the separation of ions occurs based upon differences in migration rates under alternating low- and high-field waveform amplitudes (Figure 2). Ion clustering with an introduced chemical modifier occurs in low fields with alternating declustering events in high fields, amplifying the distinction between the mobility of targeted ion from interfering species, the magnitude of which depends on differences in molecular cross section. This unique orthogonal mode of separation derived from differential migration, when coupled with the MRM scan function of the QqQ, promises a reduction in baseline noise, thereby improving signal-to-noise ratio and achievable detection limits. In furthering the elimination of co-extracted interferences by DMS, the burden associated with exhaustive sample preparation and complex chromatographic separation can often be lessened—and costs reduced.

Figure 2. In the LC-DMS-MS/MS experiment, the SCIEX SelexION differential ion mobility cell is placed between the ion source probe and MS sampling orifice (A), operating at atmospheric pressure in the presence of an auxiliary flow of nitrogen gas. Modifiers (e.g., iso-propanol) can be added to the nitrogen gas in order to enhance selectivity by increasing the differences in mobility between analyte and interference through a series of clustering/declustering events controlled by the application of a square waveform. The DMS cell can be operated at a fixed compensation voltage (CoV) acting as a selectivity filter (B), or with variable CoV in a scanning mode offering an additional gas-phase separation dimension with increased peak capacity (C).



An alternative means to achieve enhanced selectivity is offered by implementation of the LIT for an additional stage of fragmentation via MRM^3 (Figure 1), typically prompted by high baseline or persistent interference observed during MRM analysis where the chosen transition is simply not discriminating enough to isolate a primary fragment from other ions of similar *m/z*. To generate additional selectivity in these instances, a primary fragment ion originating from the collision cell is isolated in Q3 operated as a LIT, and then dissociated by resonance excitation using an applied single-frequency waveform in the presence of a pulsed collision gas. The new array of secondary fragments is then scanned out to the detector. By selecting a primary fragment and a subsequent secondary fragment that exclusively characterizes the analyte, a unique ion stream is created, enabling abstraction from the milieu of other components in the sample, with each fragmentation step providing an additional dimension of selectivity. Since all secondary fragment ions are scanned out of the LIT, an extracted ion chromatogram can be derived by summing several *m/z* species, potentially increasing overall sensitivity.

High-Resolution Accurate Mass Spectrometry

Although the QqQ remains the pillar for quantitation when operated in MRM mode, the applicability of high-resolution accurate mass spectrometry (HRAMS) has become increasingly important, especially for large molecule quantitation given the complexity of matrix extracts, exemplified by proteolytically digested samples often used in a surrogate peptide approach. Although the QqQ demonstrates rapid scan rates at high sensitivity and specificity, the relatively low-resolution measurement of *m/z* may fail to differentiate analyte response from nominally isobaric background interference. In contrast, HRAMS allows discrimination against interference by the accurate mass assignment of either precursor ion or progeny ion, with success largely dictated by analyte molecular weight, effective instrument resolution and the stability of mass calibration. High-resolving power can make the difference between detecting and not detecting low-concentration analytes due to the masking effect of isobaric interferences.

The two primary MS architectures used for quantitation by accurate mass determination at high-resolving power incorporate either time-of-flight (ToF) or Orbitrap™ technologies, as outlined in Figure 1. In the ToF experiment, a targeted precursor *m/z* is transmitted through Q1 and fragmented in the collision cell, with the entire progeny ion mass distribution then pulsed through a ToF analyzer with subsequent measurement of flight time. Flight time resolutions on the order of 25 ps translate to achievable mass resolutions between 20,000 and 35,000, depending on the implemented scan function; mass spectral resolution in this context is defined as $m/\Delta m_{FWHM}$, where FWHM represents full width at half maximum.

In order to derive product ion selectivity, a mass extraction window (MEW) is used to construct extracted ion chromatograms, optimized to within the practical limits tolerable for a given mass resolution. Predictably, analyte signal-to-noise ratio increases as the MEW decreases until the peak reaches the practical MEW limit, ideally 10 to 25 mDa. The reproducibility of the MEW is reliant upon mass stability being maintained throughout the analysis, with accuracy of mass measurement typically <3 ppm error.

The Orbitrap™ is an ion trap mass analyzer that consists of two outer electrodes and a central electrode, which enable it to act as both an analyzer and detector (Figure 1). Ions entering the Orbitrap™ are captured through electrodynamic squeezing, after which they oscillate around the central electrode and between the two outer electrodes. Different ions oscillate at different frequencies, resulting in their separation. By measuring the oscillation frequencies induced by ions on the outer electrodes, the mass spectra of the ions are acquired using image current detection. In contrast to ToF measurement, the Orbitrap™ offers much higher resolution (up to 500,000 FWHM) and improved mass accuracy (<1 ppm error).

CASE STUDIES HIGHLIGHTING NOVEL ADVANCED QUANTITATIVE LC-MS WORKFLOWS

Dried Blood Microsampling

While recent advancements in device technologies supporting dried blood microsampling (DBS) have eliminated the sampling volume bias due to hematocrit (Ht) level, the inherent challenges associated with low volume collection still remain. For example, only 10 µL of capillary blood is collected when using the Capitainer® qDBS device or Neoteryx's lowest volume Mitra® Volumetric Absorptive Microsampling (VAMS®) substrate, while <3 µL is supported by Trajan's hemaPEN®.

Minimal DBS volumes coupled with an inability to derive a meaningful concentration factor upon extraction often translates to a strong requirement for MS sensitivity, more so for those analytes exhibiting low recovery. As several microsampling applications support multi-analyte detection (e.g., therapeutic drug monitoring), rapid MS scan speeds are required to provide the chromatographic sampling rate necessary to meet precision and accuracy requirements for quantitation, without concomitant losses in sensitivity.

Below, we describe two DBS case studies illustrating the benefits of modern MS.

Anti-Epileptic Drug Panel

LC-MS assays for anti-epileptic drug (AED) panels are often required in clinical trials for new AEDs. In pediatric populations, current venous blood sampling is invasive, and an alternative microsampling strategy is extremely attractive. Both the Mitra® VAMS® and the Capitainer® qDBS device were evaluated in combination with MS detection leveraging the SCIEX 6500+ TripleQuad system.

The AED panel consisted of 15 target analytes chromatographed within a six-minute run time, and it was necessary to incorporate an advanced *scheduled* MRM (sMRM) scan function for all 30 transitions (target analyte + SLIS). In order to achieve suitable sampling rates, 150 milliseconds of scan time was applied to each sMRM window, the duration of which was 30 seconds; in several instances, more than two MRM transitions were required for each scan window due to multiple co-eluting AEDs.

Coupled with sMRM, rapid polarity cycling of the ion source was required to optimize sensitivity since some of the AEDs only ionized as negatively charged ions by electrospray. Since polarity cycling with the 6500+ is extremely rapid (10 milliseconds), there was insignificant impact on sampling rate. The duty cycle for each sMRM window was thus sufficient to confer a minimum of 15 data points across each chromatographic peak, allowing accurate and precise quantitation. 100-fold extract dilution factor could be leveraged to negate matrix effect while accelerating sample preparation throughput due to the extensive sensitivity of the 6500+, even when combining sMRM and polarity cycling.

COVID-19 Neutralizing Monoclonal Antibody

The COVID-19 pandemic and the speed at which the coronavirus spread emphasized the urgency to identify and develop new therapies. Bamlanivimab, a neutralizing monoclonal antibody developed by Eli Lilly, was designed to block attachment of SARS-CoV-2 to the spike glycoprotein, thereby preventing entry into human cells. In this large molecule microsampling case study, the applicability of dried blood Mitra® VAMS® coupled with hybrid LC-MS/MS was evaluated for the quantitation of bamlanivimab.

In this approach, human whole blood fortified with bamlanivimab was sampled onto 10 µL Mitra® tips. Addition of mild detergents and chelators to the desorption buffer significantly improved recovery of the antibody from the Mitra® substrate when coupled with impact-assisted extraction. Bamlanivimab was affinity purified using protein G coupled with magnetic beads followed by digestion with trypsin, and monitoring of a bamlanivimab-specific peptide from the CDR variable domain. Data was acquired by LC-MRM on a SCIEX Triple Quad 5500.

The performance of the assay was similar to the blood derived serum method in terms of linearity, specificity, precision, and accuracy over an analytical range from 5.00 to 250 µg/mL. Quantitation of the monoclonal antibody from Mitra® dried blood samples was unaffected by blood hematocrit levels between 25% and 55%. The stability of the biotherapeutic was demonstrated at different storage temperatures (ambient, 37 °C, and 50 °C).

Differential Mobility Spectrometry

As the majority of reported DMS applications support qualitative analysis, the quantitative attributes of the SCIEX SelexION DMS when coupled to the 6500+ were investigated to gauge potential improvements in assay performance and overall suitability for regulated bioanalysis, defined as the successful validation of a method incorporating an LC-DMS-MS/MS workflow. The urinary biomarkers of tobacco exposure, N-nitrosonornicotine (NNN) and 4-methylnitroamino-1-3-pyridyl-1-butanol (NNAL) were chosen as analytical probes given:

(i) their low molecular weight in a large chemical space, generating significant selectivity challenges

(ii) the requirement for extremely low but toxicologically relevant 200 fg/mL detection limits

(iii) poor MS/MS specificity due to formation of a primary fragment ion resulting from loss of only the nitroso functionality

(iv) literature reports of highly concentrated extracts (60- to 400-fold) resulting in 35% to 60% ionization suppression with concomitant high-chemical baseline noise and co-extracted interferences, a tripartite effect ultimately throttling achievable detection limits

Through rigorous optimization of the DMS separation and compensation voltages, in combination with the introduction of ethanol as chemical modifier to further discriminate analyte from co-extracted interferences and high-chemical background noise through selective clustering-declustering events, it was possible to achieve a reproducible and validatable 200 fg/mL detection limit (15 fg on-column) with an average signal to-noise ratio of 20:1. The extreme sensitivity of the 6500+ coupled with the orthogonal level of selectivity imparted by the DMS separation translated to only a fivefold extract concentration factor being required to attain the targeted LOQ, essentially eliminating previously reported sensitivity losses due to ionization suppression as a result of over-concentrating interferences.

Bioequivalence

Liquid chromatography with tandem mass spectrometry is the standard technology implemented for bioequivalence studies, an important part of generic drug development in the pharmaceutical clinical research field. Generic and brand name medications have identical active ingredients, and their formulations must demonstrate indistinguishable bioequivalence to attain market approval. The alignment of pharmacokinetic measurements (e.g., AUC and C_{max}) must follow regulatory guidance for the generic product to be bioequivalent to that of the original.

In the current bioequivalence case study for the determination of furosemide in human plasma, chemical background noise prevented adequate detection of the targeted LOQ (5 ng/mL) when using LC-MRM on the QqQ platform. Therefore, the advanced and highly selective scan functions represented by DMS-MRM and MRM^3 were evaluated to mitigate baseline noise.

In standard MRM mode scanning four candidate progeny ions, the LOQ was indistinguishable from background response due to augmented chemical noise derived largely from the mobile phase (Figure 3). In contrast, MRM^3 offered enhanced selectivity via reduction of chemical noise, but an LOQ of only 150 ng/mL was attained due to poor second order LIT fragmentation efficiency. An adequate signal-to-noise ratio was achieved at the required LOQ when leveraging DMS-MS/MS (Figure 4). When standard LIT-MRM^3 fails, *in-source* collision induced dissociation (CID) of the parent ion to generate an initial fragment ion represents an alternative approach, achieved with an increase in declustering potential. The in-source derived fragment ion is then selected in Q1 and further fragmented in the collision cell, producing a *pseudo*-MRM^3 transition. Although not always successful due to an absence of parent-ion selectivity, in the case of furosemide, *in-source* CID resulted in successful detection of the LOQ (Figure 5), producing a validatable assay in human plasma.

Figure 3. Representative chromatograms of furosemide LOQ at 5 ng/mL in human plasma using LC-MRM .

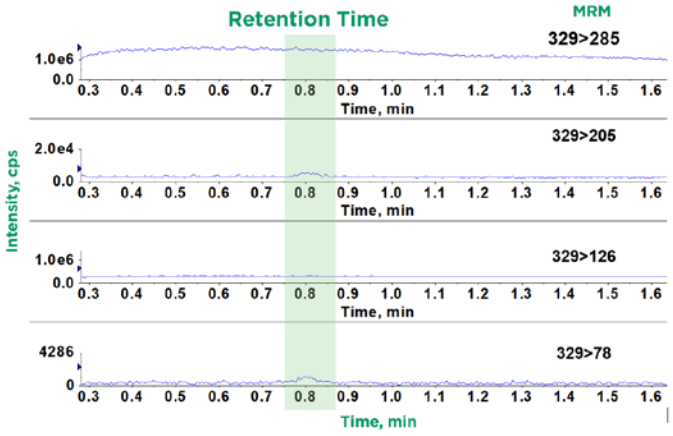


Figure 4. Furosemide LOQ in human plasma by LC-DMS-MS/MS monitoring *m/z* 329 > 285.

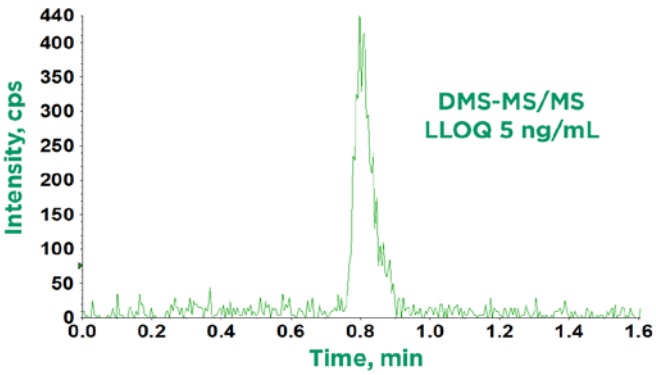
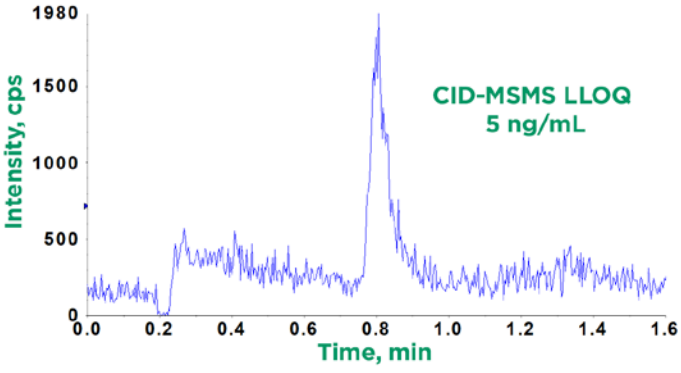


Figure 5. Furosemide LOQ in human plasma by in-source CID-MRM monitoring *m/z* 285 > 205.

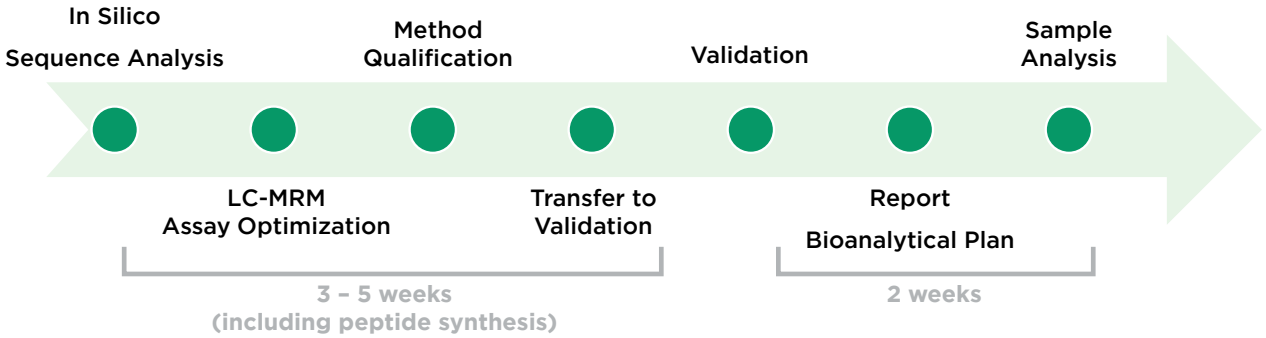


Large Molecule Bioanalysis

In recent years, the increasing importance of large molecule therapeutics has been coupled with advancements in LC-MS technology and sample preparation workflows. Compared with small molecule applications, the quantification of peptides and proteins poses unique challenges, such as dissemination of the ion current among multiple charge states and the multiple progeny ions formed upon fragmentation. Typically, large molecules are analyzed using LBAs. Mass spectrometry has several attributes that make it an important complement to LBAs for protein analysis. In addition to unparalleled specificity, MS can achieve high precision in complex matrices using stable isotope labelled (SIL) internal standards.

Currently, there are two common approaches for MS-based targeted quantitation of peptides and proteins. The bottom-up approach involves the enzymatic cleavage of a protein into small peptides followed by LC-MRM analysis of one or more proteolytic peptides, also called signature or surrogate peptides. Signature peptides are chosen based on a specific region of interest in a target protein, or simply a unique sequence without homology to other non-target proteins. Unlike LBA methods, the bottom-up LC-MS workflow does not rely on specific reagents such as antigens or anti-idiotypic antibodies, and time for development is shorter. As an example, the surrogate peptide approach was recently used at Altasciences to rapidly develop and validate a multiplex method for the quantification of bamlanivimab and etesevimab, a dual monoclonal antibody therapy developed by Eli Lilly for emergency use against mild-to-moderate COVID-19 infections. The high specificity of the MS through the selected surrogate peptides, as well as the non-reliance of the method on critical reagents, were key for the rapid development (Figure 6) and validation of this multiplexed assay to support ongoing clinical trials.

Figure 6. Assay development timeline from kick-off to sample analysis.



The second approach, known as top-down, refers to the analysis of an intact target molecule. This approach can overcome the shortcomings of the bottom-up approach, such as ability to detect degradation products and post-translational modifications (PTMs). Top-down methods commonly use high-resolution MS (HRMS) to achieve specificity and are ideally applied in full scan mode to smaller proteins of 10 to 20kDa. In comparison to LBA, the drawbacks of LC-MS large molecule quantitation assays are low sensitivity, extensive sample preparation, and relatively low throughput. To this end, immunoaffinity (IA) enrichment has been successfully applied to MS analysis. This workflow, often referred to as hybrid methods, utilizes affinity capture to deliver selective enrichment of the analytes and removal of background. Together, these factors account for the sensitivity advantage over conventional LC-MS methods for peptide and protein bioanalysis.

Recent work at Altasciences coupled nanoflow-LC to HRAMS (Orbitrap™) to detect drug-induced dystrophin protein levels (0.002% in striated muscle) in patient muscle biopsies as a measure for Duchenne muscular dystrophy. By leveraging the increased ionization efficiency of dystrophin peptides following nanoflow separation and the enhanced specificity from the Orbitrap™, the method can detect very low levels of dystrophin with an LOQ equal to 1% of dystrophin in normal control cells in 50 µg total muscle protein extract.[2]

The adoption of LC-MS over the past decade for the quantitation of large molecules has been driven by improved MS sensitivity and resolution/accuracy, the ability of LC to resolve and measure complex mixtures, new immunoaffinity workflows and increased robustness of low-flow LC methods.

Oligonucleotides

Oligonucleotides are an emerging therapeutic option to target a wide range of indications that are challenging to treat, particularly those caused by genetic mutations. They are short synthetic DNA or RNA sequences that can regulate gene expression by binding to complementary sequences of mRNA in target cells. Sub-types include antisense oligonucleotides (ASOs), aptamer RNAs, and RNA interference (RNAi) oligonucleotides. Chemical modifications of oligonucleotides and advancements in drug delivery have improved drug stability and potency, reducing the requirements for quantity of drug per dose, and total number of doses. Several oligonucleotide drugs have been licensed in the last five years, and many others are currently in different phases of drug development.

For quantitative bioanalysis of ASOs, two of the most commonly leveraged analytical approaches include ligand binding assays based on hybridization and chromatographic assays with MRM detection. Hybridization-based assays are recognized for high sensitivity (< sub- ng/mL concentration) and MS-based assays for specificity and the ability to discriminate closely related analogs (e.g., *n*-1 and *n*-2 metabolites). To overcome the limitations of each platform, the two techniques have been combined into a hybridization LC-MRM approach that isolates the target oligonucleotide using hybridization with LC-MRM detection.[3]

The hybridization step relies on a full-length biotinylated complementary probe for ASO extraction. Sample preparation including binding, washing, and elution steps can be fully automated using a Thermo Scientific™ KingFisher™ Flex magnetic sample processor (Figure 7) to achieve high throughput and reproducibility. Although reversed-phase chromatography leveraging ion-pairing agents offers optimal separation capacity for the resolution of *n*-1 and *n*-2 metabolites, ionization efficiency by ESI is compromised. Consequently, highly sensitive QqQ platforms such as the SCIEX Triple Quad 6500+ operated in MRM mode are used to quantify ASO progeny ions. This novel workflow has successfully been applied towards method qualification/validation of an ASO drug candidate (ASO-001) in NHP serum, cerebrospinal fluid (CSF) and tissues in the range of 0.500 to 500 ng/mL.

CONCLUSION

With the ever-increasing fervor of drug development and resulting introduction of new chemical entities of inherently complex design, bioanalytical challenges can be significant, from achieving ultra-low detection limits to supporting high-throughput multiplexing. It is therefore critical that sponsors partner with a CRO that understands how to actively leverage the most recent advancements in LC-MS technology as applied to regulated bioanalysis, thereby ensuring an alignment of capabilities for supporting each drug development milestone.

Ideally positioned to deliver the crucial data needed for novel drug development, Altasciences' bioanalytical scientists possess extensive expertise in both non-clinical and clinical applications with a deep understanding of the complexities involved in the bioanalysis of small molecule and biologic development, both GLP and non-GLP.

As exemplified by the case studies in this edition of *The Altascientist*, including the resources below, we are your partner of choice. We seamlessly integrate the latest LC-MS advancements into our scientific workflows, ensuring accurate and precise data delivery to support each and every client's drug development program.

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ALTASCIENCES' RESOURCES

Webinars

Quantitation of Passive Immunotherapeutic Agents for COVID-19 by LC-MS

Differential Mobility Spectrometry Tandem Mass Spectrometry

A New Dimension by Differential Mobility Spectrometry

Patient Centricity and the Evolving Role of Microsampling

Fact Sheets

Bioanalysis of Biologics Using Mass Spectrometry

Bioanalysis of Small Molecules Using Mass Spectrometry

Posters

Quantitation of the COVID-19 Neutralizing Antibody Bamlanivimab* Using Mitra® Microsampling and Mass Spectrometry

Development of a Surrogate Cerebrospinal Fluid Matrix for Quantitative Analysis of Antisense Oligonucleotides by Hybridization LC-MS/MS

Webpage

Bioanalytical Solutions

Infographic

Selecting the Right Platform for Your Molecule

ABOUT ALTASCIENCES

Altasciences is an integrated drug development solution company offering pharmaceutical and biotechnology companies a proven, flexible approach to preclinical and clinical pharmacology studies, including formulation, manufacturing, and analytical services. For over 25 years, Altasciences has been partnering with sponsors to help support educated, faster, and more complete early drug development decisions. Altasciences' integrated, full-service solutions include preclinical safety testing, clinical pharmacology and proof of concept, bioanalysis, program management, medical writing, biostatistics, clinical monitoring, and data management, all customizable to specific sponsor requirements. Altasciences helps sponsors get better drugs to the people who need them, faster.

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CONTACT US

altasciences.com | contact@altasciences.com | Tel: 514 246-4191

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