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Short communication

A novel compact mass detection platform for the open access (OA) environment in drug discovery and early development

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ABSTRACT

A new 'compact mass detector' co-developed with an instrument manufacturer (Waters Corporation) as an interface for liquid chromatography (LC), specifically Ultra-high performance LC® (UPLC® or UHPLC) analysis was evaluated as a potential new Open Access (OA) LC–MS platform in the Drug Discovery and Early Development space. This new compact mass detector based platform was envisioned to provide increased reliability and speed while exhibiting significant cost, noise, and footprint reductions. The new detector was evaluated in batch mode (typically 1–3 samples per run) to monitor reactions and check purity, as well as in High Throughput Screening (HTS) mode to run 24, 48, and 96 well plates. The latter workflows focused on screening catalysis conditions, process optimization, and library work. The objective of this investigation was to assess the performance, reliability, and flexibility of the compact mass detector in the OA setting for a variety of applications. The compact mass detector results were compared to those obtained by current OA LC–MS systems, and the capabilities and benefits of the compact mass detector in the open access setting for chemists in the drug discovery and development space are demonstrated.

1. Introduction

Mass spectrometry is an essential tool for supporting research across the biopharmaceutical industry [1–3]. Historically, MS experimentation was carried out by highly-trained analytical chemists using sophisticated instrumentation and complex software packages making it less than optimal for efficiently supporting fast-paced synthetic research programs. Until recently most of the mass spectrometers on the market were expensive, possessed a large footprint, and required skilled-operation thereby prohibiting widespread deployment within synthetic chemistry laboratories. In recent years however, much focus has been placed on bringing mini-MS instrumentation or compact mass detectors that mimic the simplicity of a UV detector [4–6] to market. As MS instrumentation has become more robust and easier to use, MS experimentation has become more mainstream with primary analysis and interpretation responsibilities falling onto non-experts with consultation and advanced experimentation provided by analytical MS experts as needed. Open access liquid chromatography–mass spectrometry (OA LC–MS) networks are one such area where these compact mass detectors could be extremely impactful, as there are large quantities of synthesized samples and substantial numbers of potential "non-expert" end-users.

As described in the paper by Coddington et al. [7] in 2003, a walk-up non-expert instrument must have the following criteria: robustness, ease of use, chromatographic and mass spectral fidelity, long LC column life, and exceptional uptime. Chromatography and mass spectrometry instrumentation quickly improved through the early 2000s with shorter chromatography analysis times, enhanced resolution and detection limit, and faster data acquisition scan speeds to match the peak widths associated with UHPLC chromatography. As a result, "walk-up" or open access (OA) LC–MS environments have seen tremendous growth in the biopharmaceutical and other industries. In fact, dedicated OA software packages are now available from many of the leading instrument manufacturers (e.g., Waters Corporation OpenLynx, MassLynx; Agilent EasyAccess; Bruker Compass OpenAccess; Shimadzu Scientific

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Instruments Open Solutions and QuantAnalytics). Using these OA LC–MS systems, chemists routinely obtain molecular weight information of their samples, monitor reaction progress, and carry out purity assessments of intermediates and products. Automated sample analyses are rapidly conducted by use of short LC columns and fast gradients with typical analysis times of 2 min or less. As the LC–MS instrument performance had exceeded the basic needs of the discovery space, it was determined the next step was not additional features, but rather improvement in the more physical aspects of the instrument along with simplification of the user interface.

Whether in the drug discovery space or early development stage, OA LC–MS systems are now critical analytical tools used by bench chemists on a daily basis to drive research [8,9]. Therefore, incorporation of a "robust" compact mass detector into existing OA platforms would deliver significant improvements in efficiency and cost. Implementing novel technology into the everyday workflow of a pharmaceutical research environment must however be carefully planned out. Any disruptions caused by reductions in throughput, lack of system robustness, or difficulties related to the 'ease of use' would be readily identified by researchers and extremely detrimental. As such, assessments of the compact mass detector in 'applied use' scenarios were essential to properly evaluate the compact mass detector with regards to these potential concerns. A small subset of discovery chemists was enlisted to test the compact mass detector in 'real world' pharmaceutical applications by monitoring reactions and evaluating compound purities over an extended period of time. Comparisons of the compact mass detector to that of the traditional mass spectrometers currently employed were performed during this assessment period. Experiments using commercially available reference compounds, quantitation studies, and some HTS applications were conducted to evaluate and compare the baseline performance of the compact mass detector. The results of these studies were used to determine the overall feasibility, robustness, and flexibility of this novel technology within an OA environment as set forth by the co-development collaboration between Merck and Waters Corporation.

2. Materials and methods

2.1. Instrumentation

A mass spectrometer consists of a single quadrupole in which electrical potentials of RF and DC are applied to opposite pairs of a linear array of four parallel cylindrical rods, where ions are separated by mass-to-charge (m/z) ratios and filtered depending on their trajectory in the oscillating electrical fields which are applied to the cylindrical rods. This research explores a novel technology typically utilized in higher-end triple quadrupole mass spectrometers but employed with a thought-free user interface design to easily attain electrospray based nominal mass measurements. The concepts of tuning parameters, manual calibrations, and various ionization choices have been eliminated to facilitate a fit-for-purpose practicality of providing masses for a detected analyte analogous in workflow and visual outputs of a simple UV detector and wavelength determination. For this reason, the instrument will be referred to as a mass detector due to the streamlined approach and simplified user-interface when compared to those user-inputs required for a traditional mass spectrometer. The size comparison of the mass detector, to that of a traditional mass spectrometer further lend itself to being defined as a compact mass detector, since the footprint is more comparable to that of an optical detector. The compact mass detector design utilizes dual off-axis ion guides for elimination of neutral noise to provide increased detection limit and robustness. The design incorporates a conjoined stacked ring ion guide and second stage quadrupole ion guide (Fig. 1). The design reduces contamination, which contributes to improvement in method robustness where complex matrices are being analyzed.

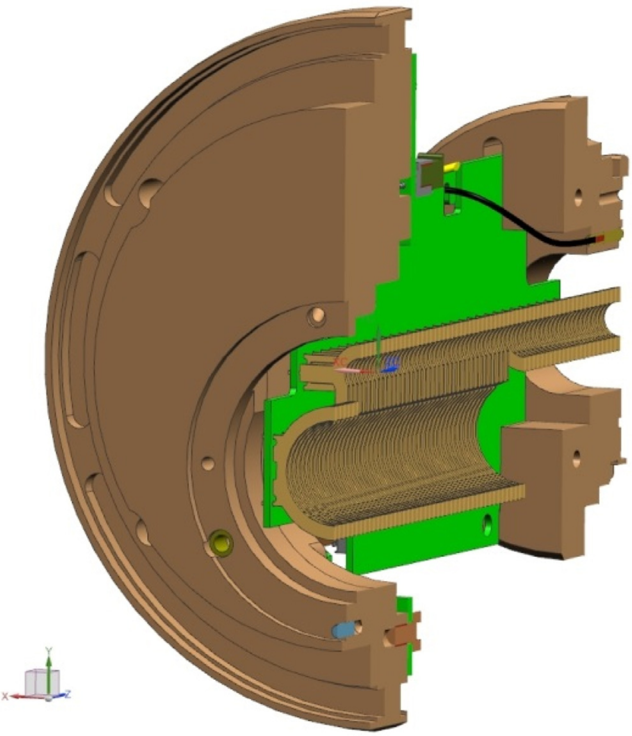

Fig. 1. Cross-sectional view of the compact mass detector ion guide and analyzer technology (compliments of Waters Corporation).

2.2. Open access instrument configurations

Experiments were performed using ACQUITY H-Class UPLC and ACQUITY 'Classic' UPLC instrumentation (Waters Corporation, Milford, Massachusetts, USA). The ACQUITY H-Class was configured with a sample organizer for increased sample capacity required during high throughput screening assessments. Each UPLC configuration was coupled with a Waters QDa compact mass detector. An ACQUITY SQD (Waters Corporation) mass spectrometer coupled to the UPLC configurations was used as the traditional mass spectrometer for comparative assessments. MassLynx Open Access OpenLynx 4.1 (Waters, Milford) application manager software was used to enable walk-up functionality and data visualization. The UPLC systems were configured with ACQUITY BEH C_{18} columns (1.0 mm × 50 mm; 1.7 μm) on both the ACQUITY H-Class and on the ACQUITY *Classic* UPLC. Each column compartment was maintained at 50 °C. The ACQUITY H-Class automatically metered the mobile phase for a linear gradient elution composition of 95:5 to 5:95 (0.05% TFA/water: 0.05% TFA/acetonitrile) over 2.0 min. The ACQUITY '*Classic*' UPLC used a linear gradient method composition of 95:5 to 5:95 (0.05% TFA/water: 0.05%TFA in acetonitrile). The flow rate was maintained at 0.3 mL/min. The injection volume of each sample was 1.0 μL.

2.3. Chemicals

Acetonitrile and methanol (LC/MS Optima Grade) were obtained from Fisher Scientific (FairLawn, NJ, USA). Sulfadimethoxine, terfenadine, verapamil, leucine-enkephalin, 2-fluro-5-trifluromethoxy phenyl acetic acid and L-1-BOC-nipecotic acid were obtained from Sigma–Aldrich (St. Louis, MO, USA). Human insulin was obtained from FUJIFILM Diosynth Biotechnologies (Morrisville, NC, USA). (R)-