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Short communication

Evaluation of a compact mass spectrometer for routine support of pharmaceutical chemistry

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ABSTRACT

The suitability of a recently introduced inexpensive, compact mass spectrometer detector is evaluated for supporting pharmaceutical chemistry investigations. While high performance/high cost MS detectors dominate the marketplace, there is growing recognition of the need for a small, inexpensive MS detector with reduced capabilities for supporting synthetic chemistry investigations, where reduced sensitivity and unit mass resolution are often suitable for solving routine problems. In this study, the fundamental performance characteristics of the recently introduced Advion compact mass spectrometer were evaluated, investigating the use of the instrument for routine product and impurity identification, reaction monitoring, evaluation of potential genotoxic impurities and study of high molecular weight biomolecules. In general, the results of the evaluation show this compact and inexpensive mass spectrometer to be well suited for providing reliable support for pharmaceutical chemistry investigations, with sub-nanogram limit of detection and impurity identification below 0.1% being possible in some instance.

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1. Introduction

In recent years mass spectrometry (MS) data has become increasingly essential for carrying out drug discovery and development [1–3]. While many of the applications that rely on MS require high resolution/high cost instruments (*e.g.* proteomics, lipidomics, glycomics, *etc.*), MS support for routine synthetic chemistry applications is often quite straightforward by comparison, suggesting that MS instruments with reduced capabilities [4–6], could be sufficient fit-for-purpose tools for supporting pharmaceutical chemistry research. However, until very recently, major instrument vendors had concentrated on the development of high-end mass spectrometers, ignoring the need for smaller, less expensive, fit-for-purpose mass spectrometers with pared down capabilities that would be more suitable for supporting synthetic chemistry research.

Recently the results of a collaboration on the development of a miniaturized MS detector specifically targeted for supporting synthetic chemistry investigations has been reported, in which a compact (35 cm × 18 cm × 60 cm) chip-based, inexpensive (<$50,000) MS detector was shown to have acceptable performance for some synthetic chemistry workflows [7]. The miniaturized MS is capable of ionizing a range of compounds of general interest to process chemists. Although the sensitivity is somewhat reduced relative to conventional MS instruments, it is sufficient for some analysis to support synthetic chemistry, where sample is generally abundant and unit mass resolution is often sufficient. The detector sensitivity in the selected ion monitoring (SIM) mode was found fairly good, allowing trace-level detection of known components at the parts per million levels.

In this study the utility of the recently introduced Advion Compact MS for providing reliable support for pharmaceutical chemistry is investigated. The Advion system is a compact version of a conventional single quadrupole MS instrument. The system contains an external rough pump and like the chip-based MS system, is priced in the <$50,000 range, an important feature when considering a more widespread rollout to the large numbers of industrial synthetic chemists. While at 66 cm × 28 cm × 56 cm, the Advion instrument is smaller than conventional MS instruments, it is approximately twice as big as the chip-based system. In the article a series of studies have been conducted, including evaluation the performance characteristics of the Advion compact MS, comparing with the previously studied chip-based MS system and with conventional low-end MS instruments in current use for supporting synthetic chemistry applications, and various applications such as reaction monitoring, production identification, PGI evaluation, impurity identification, and largest molecules.

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2. Experimental

2.1. Instrumentation

The test system consists of an Agilent 1290 UHPLC system coupled to an Advion expression Compact MS detector. The Advion system (Advion Inc., Ithaca, NY, USA) was first introduced at 2012 Pittcon, and designed for in-hood use for synthetic chemists. The system contains an external rough pump, conventional ESI ion source, and single quadrupole MS detector in a vertical layout. The calibration vials, load/inject valve and API inlet are located on the front of the unit for easy access. The interface was coupled to a passive splitter delivering a flow of approximately 0.2 mL/min to the ion source (an approximately 3:1 split ratio). The comparison instruments were comprised of an HPLC system coupled to a conventional single quad mass spectrometer (Agilent LC/MSD, Agilent Technologies, Palo Alto, CA, USA) or a chip-based Microsaic MiD 3500 mass selective detector (Microsaic Systems Ltd., Woking GU21 5BX, UK). Comparison of specifications of three MS detectors were shown in Supplementary Materials Table S1. The Microsasic miniature MS still has the distinguished advantage in terms of footprint. All three instruments are not offering MS/MS capability for characterization of the analytes, and comparing to a conventional MS system, the major drawbacks of both compact/mini MS are lacking the ability to cycle through different acquisition modes within a single run, and have a smaller mass range.

2.2. Chemicals, reagents and HPLC method

All commercial chemicals used were of analytical grade. Acetonitrile (HPLC Grade) was purchased from Fisher Scientific (Fair Lawn, NJ, USA). Ammonium formate (NH_4HCO_2), formic acid, insulin chain B MS standard and angiotensin II MS standard were purchased from Sigma–Aldrich (St. Louis, MO, USA). Ultrapure water was obtained from a Milli-Q Gradient A10 from Millipore (Bedford, MA, USA). The HPLC method condition comprised a Waters BEH C18 (100 mm × 2.1 mm, 1.7 μm) (Waters Corp., Milford, MA, USA) column with mobile phase of A: 2 mM NH_4HCO_2 in H_2O (pH = 3.5, adjusted by formic acid) and B: 2 mM NH_4HCO_2 in 90% Acetonitrile and 10% H_2O (pH* = 3.5, adjusted by formic acid), and a gradient elution of 10–90% B in 8 min (1 min post; 40 °C; 1uL injection; 0.6 mL/min).

3. Results and discussion

The fundamental performance characteristics of the compact MS system were evaluated first. The sensitivity and linearity of the Compact MS was investigated using a typical active pharmaceutical ingredient (API) from Merck Research Laboratories in the positive ion mode using both full scan mode and selected ion monitoring (SIM) of the corresponding molecular ions (*m*/*z* 562), with tuning for the optimal signal intensity. The results (presented in Supplementary Materials, Fig. S1) show adequate performance of the compact MS for low level detection in both the scan mode and the SIM mode.

The linearity of detector response for the Compact MS was demonstrated using API concentrations from 0.5 μg/mL to 50 μg/mL, which represents a concentration range of importance for quantifying minor impurities. Fig. S1D shows the calibration curve for standard solutions of the test compound. The instrument offers two orders of magnitude linearity with an R-squared value of 0.9997 determined for the test analytes, comparable to a conventional system. It should be noted that LOD and linearity will be compound dependent, but our experience with the pharmaceutically relevant samples suggests that these range is fairly typical.

Next, the utility of the Compact MS system for confirming product identity, reaction monitoring and in-process analysis was investigated. While the confirmation of product identity can be relatively straightforward for high yielding reactions with few side products, MS detection shows its greatest value in troubleshooting problematic reactions. The example shown in Fig. 1 is a case in point. Attempted reduction of a nitrile to a primary amine afforded no peak at the anticipated mass of the desired product (*m*/*z* 213). The major peak in the reaction was identified as starting material (*m*/*z* 209), and MS revealed that the smaller, early eluting peak showed *m*/*z* 211, presumably coming from the incompletely reacted imine intermediate. These results quickly provided a window of understanding on an unsuccessful reaction,

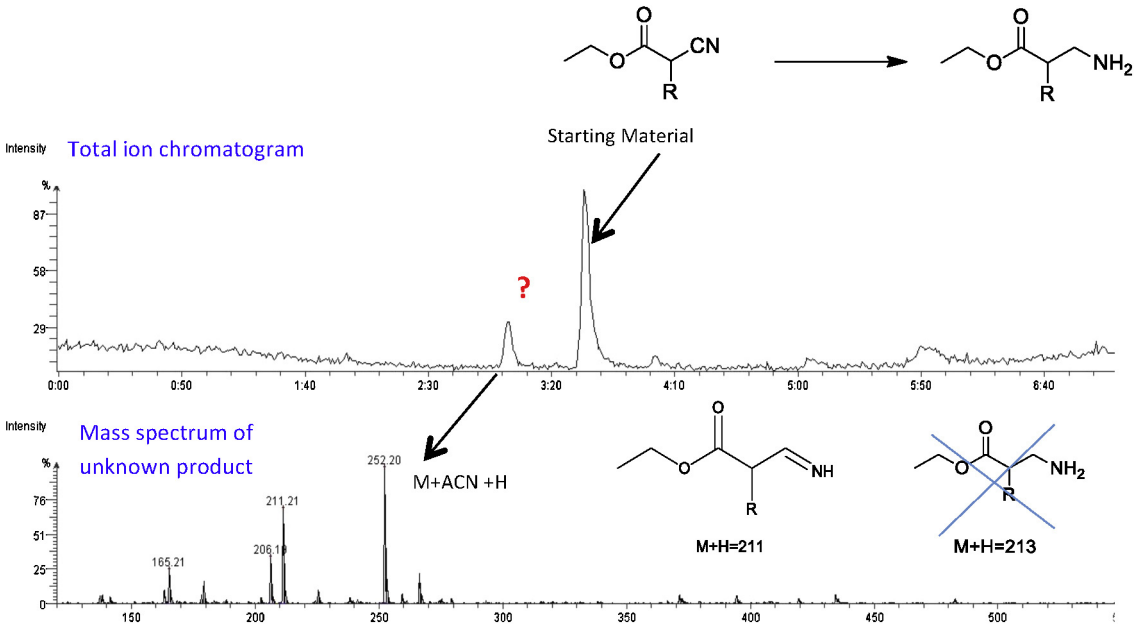

Fig. 1. Use of compact MS detector for synthetic reaction product confirmation. Top: total ion chromatogram; bottom: MS spectrum of minor peak; conditions: full scan positive mode; scan range 100–1000 *m*/*z*; scan time: 0.3 s; step: 0.2; capillary voltage: 350 V; capillary temp: 275 °C; source voltage: 25 V offset, 25 V gain.

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