Perspective

Drug Testing and Analysis

Received: 11 July 2011 Revised: 25 July 2011 Accepted: 26 July 2011 Published online in Wiley Online Library: 28 February 2012

(wileyonlinelibrary.com) DOI 10.1002/dta.344

Recent instrumental progress in mass spectrometry: advancing resolution, accuracy, and speed of drug detection

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Fast and unequivocal drug detection is of considerable importance in numerous fields of analytical chemistry, and today mass spectrometry-based approaches are often the method of choice due to their sensitive and specific nature. Mass spectrometry is in constant flux with innovations and thus supports the development of new, complementary assays for rapid determination of drugs and toxins as well as their metabolic products in clinical, forensic, and doping control laboratories. Examples of such innovations that have greatly aided the worldwide bioanalytical efforts are the modern improvements in ion trap, for example, Fourier transform-ion cyclotron resonance (FT-ICR) mass spectrometer - Orbitrap, and time-of-flight (TOF) mass analyzers when coupled with sensitive ionization techniques such as electrospray ionization. In this perspective, the utility of state-of-the-art mass spectrometers and recent instrumental developments such as new and/or improved hybrid analyzers are discussed and selected applications presented. Copyright © 2012 John Wiley & Sons, Ltd.

Keywords: Orbitrap; Q-Exactive; triple-TOF; IMS-MS(/MS); FT-ICR

Introduction

Because of their particular value in research and routine testing, mass spectrometers with high resolving power and accurate mass measurement capabilities have been sought-after by mass spectrometrists since the development of Mattauch and Herzog's double-focusing magnetic analyzer in 1934.[1] With the availability of soft ionization techniques such as electrospray ionization (ESI), high resolution-high accuracy mass spectrometry (HRMS) has become even more attractive, for example, to determine molecular masses and elemental formulae, which is of particular value for multiply charged macromolecules.[2] Furthermore, the increasing demand for speed, comprehensiveness, cost-efficiency, and sensitivity in modern drug analysis[3–5] is an important driving force for the constant improvements of existing equipment or for entirely new innovations. Examples of such developments include high mass accuracy with adequate stability over time, MS/MS or MS^n capability, fast polarity switching, fast scan rates, simultaneous targeted and untargeted analysis with (semi)-automatic and intelligent recording of product ion spectra (information-/data-dependent analysis), and additional separation capabilities such as ion mobility spectrometry (IMS). Moreover, computational and bio-informatic tools must be available for processing and data-mining of the massive amounts of raw data generated within a single acquisition in such analyses.

The ideal analytical instrument would combine all of these features. Technically, these capabilities exist; however, several of them are not (yet) compatible, and today's state-of-the-art mass spectrometers provide many but not all of the desired features (Table 1). This short overview will present and contrast properties and advantages/disadvantages of modern hybrid mass spectrometers and illustrate their utility in drug analysis.

Orbitrap-based analyzers

The first report on the analytical application of a mass spectrometer employing Orbitrap mass analysis was published by its inventor Alexander Makarov in 2000.[6] This paper outlined the construction of an instrument capable of resolving *m/z* signals with a resolution >150 000 and a mass measurement uncertainty of 5 ppm or less, with the observed peak resolution predominantly limited only by the scan speed. These findings were soon followed by several publications on the hyphenation of the Orbitrap mass analyzer to ESI by means of a linear ion trap (LIT). This hybrid mass spectrometer provided an analytical instrument of great utility for sensitive and specific measurements in different areas of analytical chemistry.[7,8] Naturally, this new LIT-Orbitrap instrument was immediately implemented for drug analysis,[9] and proved readily applicable to high throughput and targeted detection assays for drug testing purposes.[10,11] The usual limitations regarding low-mass cut-off associated with ion-trapping devices in MS^n experiments were overcome in recent generations

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Table 1. Comparison of instrument characteristics

System	Scan speed	Resolution	Mass range	Sensitivity	Polarity switching	Investment and operating costs
Orbitrap	+	+++	+	++	yes	++
TOF	+++	++	+++	++	no	++
Magnetic sector	+	+	+	++	no	+
FT-ICR	+	++++	+	+	no	+++

of commercially available Orbitrap-based mass spectrometers by addition of a multipole collision cell. As a result, product ion mass spectra comparable to conventional (triple quadrupole) collision-induced dissociation (CID) instruments were obtained. More recently, a new inexpensive benchtop Orbitrap system performs dissociation of all ions entering the mass spectrometer simultaneously in a dedicated collision cell rather than by resonance activation of isolated ions in the preceding LIT. Numerous drug-screening methods were established allowing for combined targeted and non-targeted analysis of relevant substances and metabolites.[3,12–14] Important recent technical improvements of Orbitrap-based mass spectrometers include the availability of high resolving power combined with scan-to-scan polarity switching, which cannot be achieved by other HRMS techniques. The major technical limitations of Orbitraps are predominantly the slow scan speed and the resulting difficulty of performing 'simultaneous' acquisition experiments in different scan modes, when fast LC gradients (and narrow HPLC peaks) are employed. These limitations have been overcome recently with the introduction of a quadrupole mass filter preceding the C-trap and the collision cell combined with improved fast Fourier Transform (FFT) algorithms. The current generation hybrid Orbitrap has shown to provide the speed, resolution, and sensitivity required in modern drug-testing laboratories, by offering resolving powers of 140 000 (FWHM @ *m/z* 400) at acquisition rates of 1 Hz in addition to precursor ion selection via quadrupole, which prevents the risk of overfilling the C-trap/Orbitrap with irrelevant ions. By improving and fine-tuning the Orbitrap technology further, recently launched systems offer resolving powers of $>$ 240 000. This has been achieved using slightly modified electrode geometry, resulting in a so-called high-field Orbitrap with a thicker central electrode for a higher field strength and higher resolution. A maximum resolution of up to 600 000 has been proposed as technically feasible with this device, which will possibly rival FT-ICR systems in selected applications.[15]

Time-of-flight-based analyzers

The era of time-of-flight (TOF) mass spectrometry began in the mid-1940s with the prototype of 'a pulsed mass spectrometer with time dispersion' by W.E. Stephens,[16] followed by improved TOF instruments in 1948[17] and 1953.[18] While early linear TOF mass spectrometers allowed only for mass resolving powers considerably below 1000, technical advances (especially the introduction of the reflector technique) eventually resulted in mass analyzers capable of resolving ions with a resolution between 10 000 and 20 000.[19] The main advantages of TOF-based analyzers include the ability of generating data very fast, high resolution/high accuracy mass data, and the (theoretically) unlimited *m/z* range. These capabilities are of great importance for interfacing TOF analyzers to ultra-fast ion-separation devices such as IMS. Compared to Orbitrap or FT-ICR mass spectrometers, the resolving power achieved by TOF-MS has been significantly lower until recently. Improvements in flight path length and new ion optics ensuring high ion transmissions, however, have resulted in modern TOF-based mass spectrometers with resolving powers of up to 100 000 and scan rates of 200 Hz.[20] Modern commercial reflectron TOF instruments with a flight path length of 2.5–3 m are able to provide mass resolving powers between 35 000 and 60 000.[21,22] This performance in combination with fast acquisition rates of up to 100 Hz allows multiple (targeted) MS/MS experiments even when very fast separations are utilized as seen for ultra-high performance liquid chromatography (UHPLC). By employing spiral ion trajectories, TOF[23] and TOF/TOF instruments [24] with 17 m flight path and transmission efficiencies of 100% have been reported. The extra-long flight path length via figure-eight ion trajectories resulted in measured mass resolutions of up to 60 000, which allowed mono-isotopic precursor ion selection at *m/z* 2500 in a TOF/TOF design. In a similar fashion, a TOF design referred to as 'folded flight path'[20,25] enabled a resolving power of 100 000 and acquisition rates of 200 spectra per second.

The ability for rapid generation of high resolution/high accuracy mass spectra has made TOF analyzers the first choice for hyphenation to fast ion separation devices (e.g. IMS). A commercial geometry for such a quadrupole-ion mobility-TOF setup utilizes a 'travelling waveform ion mobility spectrometry' technique,[26] the potential of which has recently been demonstrated for drug testing.[27] In principle, the additional separation dimension from IMS supports unambiguous drug detection by providing supplementary drift times in addition to traditionally acquired information (chromatographic retention time, accurate masses, diagnostic product ions, etc.). Various methods using TOF and QqTOF mass spectrometers have been published,[20,28,29] and future aspects will encompass combined targeted and non-targeted analyses for which rapid analyzers are invaluable tools.

FT-ICR-based analyzers

Fourier transform ion cyclotron resonance (FT-ICR) mass spectrometry was first developed in 1974 by Mel Comisarow and Alan Marshall.[30–32] Despite the increasing competition from Orbitrap and TOF analyzers, this instrument remains the highest performing mass analyzer in terms of mass resolving power and mass accuracy today. As many of the performance parameters of FT-ICR scale with magnetic field strength,[33,34] including mass resolving power, mass accuracy, measurement speed and dynamic range, instruments with magnets up to 18 Tesla field strength are now commercially available. Mass resolving powers of $>$1 000 000 and ppb level mass accuracies are routinely available. Until a few years ago, it was true that if one wanted to investigate the most difficult problems demanded of complex biological systems, then the *only* instrument of choice was the FT-ICR. In proteomics, for example, tens of thousands of peptides can be resolved and masses measured in a single

run using FT-ICR, allowing rapid analysis of complete proteomes without the need for primary structure analysis.[35] FT-ICR is equally applied to complex sample mixtures from other fields of research such as metabolomics, pharmaceutical, and environmental studies or the petroleum industry. Breitling *et al*. described an interesting example, where a mass resolving power of 1 000 000 was required to distinguish two small molecule metabolites at *m/z* 405 ($C_{16}H_{15}O_8$ *versus* $C_{17}H_{27}NO_2S_4$).[36]

Over the past decade, a series of technical advances such as efficient ion transport-and-storage devices have increased the ease-of-use characteristics of FTICR and enabled straightforward hyphenation with liquid chromatography using electrospray ionization.[37] Modern FT-ICR systems are almost always of a hybrid design – for example, Qq-FT-ICR or LIT-FT-ICR – allowing pre-accumulation of ions in multi-pole lenses preceding the FTICR cell and external low-energy CID experiments. In particular, the commercial LIT-FT-ICR design significantly increased the user-friendliness by allowing method development to be performed in the same way as with most other mass spectrometers, i.e. the MS or MS/MS method can be first developed and optimized on the linear ion-trap (which has its own detector) and then the capability of FT-ICR is added by switching into high-resolution mode, thus obtaining high resolution and accurate masses.[38] All these technical developments allowed FT-ICR to be applied to problems that are far beyond the intrinsic capabilities of any other mass spectrometer designs.[29]

FT-ICR is no longer the dominating high resolution instrument, however, thanks to the capabilities of Orbitrap mass spectrometers and new TOF designs. Orbitraps now approach the performance of lower magnetic field strength FT-ICR instrument (i.e. 7 Tesla). As a result, of the three major instrument companies producing competitive commercial FT-ICR systems five years ago, only one company remains involved in future developments for FT-ICR.

In addition to the superior resolving power and mass accuracy, FT-ICR has several inherent advantages over other high resolution mass spectrometers, however. For example, precursor ion selection in the FT-ICR cell can be performed with high resolution, which is extremely useful for subsequent MS/MS analyses of complex sample mixtures. After trapping the ions in the FT-ICR cell and precursor ion isolation, various ion-activation techniques, including sustained off-resonance irradiation (SORI), infrared multiphoton dissociation (IRMPD) and electron-capture dissociation (ECD), can be used to generate product ions in the FT-ICR cell. In addition, Schaub *et al*. recently described [39] a novel ion storage optics in a 14.5 Tesla instrument that utilizes an additional octapole between LIT and FT-ICR cell to increase the number of ions that can be delivered to the FT-ICR cell. This instrument also features automatic gain control to precisely select the number of ions measured in each scan.[39]

FT-ICR analyzers have been successfully coupled to many different ion sources, including electrospray, atmospheric pressure chemical ionization (APCI), and matri-assisted laser desorption ionization (MALDI) but also more recent developments such as automated chip-based nanospray (Nanomate),[40] atmospheric-pressure photoionization (APPI),[41] direct analysis in real time (DART),[42] and desorption electrospray ionization (DESI).[43] As well, imaging mass spectrometry of biological tissue samples have been successfully implemented using MALDI-FT-ICR instruments.[44,45] FT-ICR shows clear advantages over other mass spectrometers in these applications because of its ability to resolve isobaric ions and its ability to identify analytes.[45] Of note for the present overview is a recent study on the MALDI-FT-ICR imaging analysis of drugs and metabolites in tissue [46] and on MALDI-FTICR analysis of methamphetamine incorporated into hair.[47]

In sports drug application, Thevi *et al*. proposed FT-ICR for analysis of synthetic insulins such as the 4-fold charged Novolog Aspart and Glulisine Apidra.[48] Even with a resolving power of 100 000 as obtained from an Orbitrap instrument, the resolution of the multiply charged species of these two variants was not possible. The authors demonstrated that a theoretical resolving power of 500 000 as available from FT-ICR is required to differentiate these two compounds using full scan MS only.

Finally, efforts are currently under way to build the first 21 Tesla FT-ICR instrument in Allan Marshall's laboratory at the National High Magnetic Field Laboratory in Tallahassee, Florida.[49] This instrument will see application in two areas where FT-ICR is expected to continue its dominance over other high resolution designs, top-down proteomics, and petroleum analysis.

Conclusions

Ultra-high resolution MS technology has advanced at an amazingly rapid rate over the past years. While FT-ICR dominated this field only 10 years ago, Orbitrap and novel TOF designs – introduced only in the last few years – have quickly found full implementation in many different laboratories and areas of science. These instruments are increasingly suited to combine technical capabilities and data acquisition modes into a single experiment or a set of simultaneous experiments and have the potential to form the basis for a future universal, multi-purpose mass spectrometer. Selective scan modes such as precursor ion scan or neutral loss scan from triple quadrupole MS would have been clearly on the list of desirable features for such a universal instrument only a few years ago; however, the information gained from accurate mass data in MS and MS/MS modes easily outweighs the benefits of these scan modes.

In our opinion, a single multipurpose instrument would offer the following features: it must be able to provide accurate mass data in MS and MS/MS modes with mass measurement uncertainties at 1 ppm or less to allow single elemental formula assignments. Secondly, it must be able to provide linked precursor/product ion information (MS^n) for comprehensive mapping of genealogical links in fragmentation reactions. This can be readily achieved in hybrid instruments using a first stage linear ion-trap. It is also available directly in the FT-ICR cell via SORI. Finally, it must be fast enough to allow hyphenation with modern chromatography techniques such as UHPLC to analyze relatively narrow chromatographic peaks (commonly between 3 and 6 s wide), or signals from gas phase separation techniques such as IMS, where duty cycle times in the low millisecond range are required.

Instruments with many of the described requirements are already available. It will be interesting to see whether latest generation Orbitrap and TOF instruments will rival triple quadrupole instruments in terms of precision, accuracy and ruggedness in quantitative analyses, which, if successful, would truly create a single purpose universal mass spectrometer.

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