THE DEVELOPMENT OF MEMS MASS SPECTROMETERS

R.R.A.Syms[1],
EEE Dept., Imperial College, London, UK

ABSTRACT

Lab-on-a-chip devices have had a major impact on analytical chemistry. Integration allowed manipulation of minute quantities of reagent, reduced dead volumes and minimised peak broadening. Integrated electrospray nozzles allowed analysis immediately after separation. By comparison, the effort devoted to mass spectrometers has been small. Although attempts were made to miniaturise most common filters, fabrication involves the formation of complex electrodes that generate precise electric fields. Consequently, mass resolution has been poor. High voltages also limited mass range, while poor sample introduction limited sensitivity. Consequently, little progress was made until recently in miniaturizing the electrospray mass spectrometer. These difficulties have been overcome. Greatly improved filters have been developed, vacuum interfaces have been constructed and bench-top ESI-MS is commercially available. This paper summarizes recent developments.

KEYWORDS

Mass Spectrometer, Mass Filter, Electrospray

INTRODUCTION

Mass spectrometry (MS) has evolved over more than a century into a highly developed field. Until recently, all mass spectrometers were bulky and expensive, apart from a small number of portable systems constructed for applications outside the laboratory, such as space exploration, explosives and drug detection, pollution monitoring and volcanology. These systems were fabricated individually, using the best available conventional workshop technologies. In the last 20 years, a sustained effort has been made to develop mass-production techniques for bench-top laboratory instruments using micro-electro-mechanical systems (MEMS) technology. In contrast to lab-on-a-chip systems, which easily outperformed conventional fluid handling by virtue of their high speed and low dead volume, the performance of early MEMS MS was poor, and unlikely to provide a challenge to state-of-the art instruments. However, recent progress has been remarkable, and instruments with useful performance are now available commercially, placing immediate analysis within reach of every laboratory chemist. The aim of this paper is to review the development of MEMS mass spectrometers.

MASS SPECTROMETER SYSTEMS

The principles of mass spectrometry are well-established [1]. A sample whose composition is to be determined (and which might exist in the solid, liquid or gas phase) is first prepared. The sample is ionized, and passed through a filter that separates the ions in time or in space, according to their mass-to-charge ratio. The separated ions are then detected using a charge counter, allowing a mass spectrum to be obtained. Mass filtering

and detection are performed at low pressure, to avoid collisions, but ionization can take place in vacuum (Fig. 1a) or at atmospheric pressure (Fig. 1b).
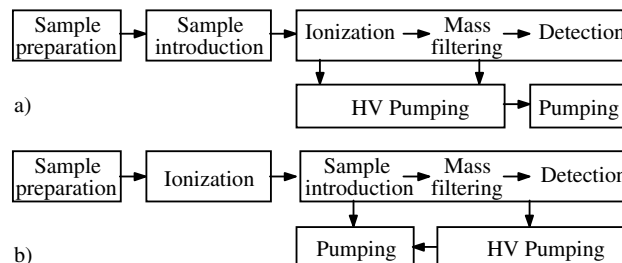

Figure 1. MS systems with ionization a) under vacuum and b) at atmospheric pressure.

Separation processes are often used to make it easier to identify the different constituents of a multi-component system, especially with gases (gas chromatography) or liquids (liquid chromatography or capillary electrophoresis) (Fig. 2a). The component of interest may also be concentrated before injection. Neutral samples may be introduced into to the vacuum system using a capillary, a permeable membrane or by solid-phase micro-extraction (Fig. 2b), and ions formed by API using a capillary, nozzle or skimmed free-jet expansion (Fig. 2c).
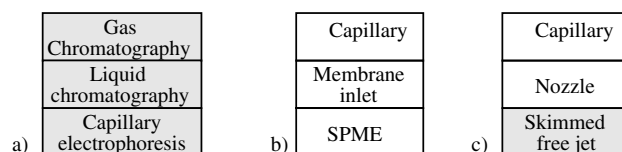

Figure 2. a) Separation methods, b) and c) sample introduction methods for neutrals and ions.

Ionization methods differ, depending on the pressure regime. In vacuum, they include hot- and cold-cathode electron-impact ionization (EI), capacitively and inductively coupled plasma ionization, photoionization (PI), and laser desorption ionization (LDI) and its matrix-enhanced derivative (MALDI) (Fig. 3a). At atmospheric pressure, available methods include electrospray ionization (ESI), LDI/MALDI and corona discharge (Fig. 3a). ESI is extensively used for liquids, because of its ability to ionize large molecules without fragmentation.
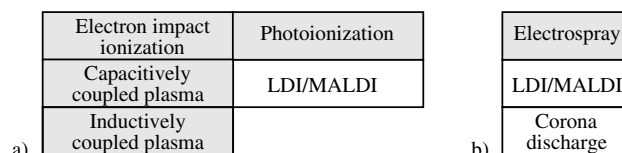

Figure 3. Methods for ionization a) under vacuum and b) at atmospheric pressure

The necessary components for EI include hot- and cold cathode electron emitters, while plasma sources require plasma chambers at intermediate pressure.

Electrospray and its successor nanospray require fluidic channels and nozzles (Fig. 4a). Depending on whether the ions are separated in time or space, detection can involve single- or multi-channel ion counters. Simple Faraday cups may be used, or devices involving secondary electron multiplication from discrete or continuous dynodes (Fig. 4b). Scintillators and avalanche photodiodes are also used as detectors, but less often.
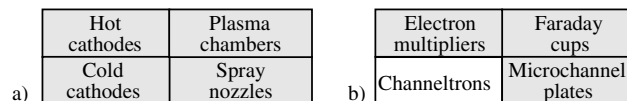
Hot cathodes	Plasma chambers		Electron multipliers	Faraday cups
Cold cathodes	Spray nozzles		Channeltrons	Microchannel plates

a)   b)

Figure 4. Components for a) ion sources and b) ion detectors.

Mass filtering involves the use of magnetic (Fig. 5a) or electric fields (Figs. 5b and 5c). However, because of the size and weight of magnets the emphasis (in both conventional and MEMS MS) is overwhelmingly on the latter. Electric fields may be static, pulsed or harmonic; components based on the first and second are used for ion focusing or gating, while the last allow quadrupole lenses, ion guides, ion traps and collision cells to be constructed.
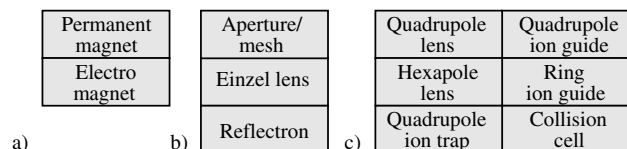
Permanent magnet		Aperture/ mesh		Quadrupole lens	Quadrupole ion guide
Electro magnet		Einzel lens		Hexapole lens	Ring ion guide
		Reflectron		Quadrupole ion trap	Collision cell

a)   b)   c)

Figure 5. Components for filters: a) magnetostatic, b) electrostatic and c) electrodynamic.

These components can be arranged to form a wide variety of mass filters, based on static fields and mixtures of pulsed and harmonically varying fields. The first include magnetic sector, electric sector and crossed-field types (Fig. 6a), the second time-of-flight (TOF) filters (Fig. 6b), and the third quadrupole filters, travelling wave filters, Fourier transform ion cyclotron resonance filters (Fig. 6c), and cylindrical, toroidal and linear ion traps (Fig. 6d). Each has different characteristics. Avoidance of any form of magnet reduces system size and weight. The use of harmonic electric fields allows guiding and trapping in two- and three-dimensional space. The quadrupole mass spectrometer allows continuous ion sampling, while TOF and trap filters only allow sampling with a low duty cycle. However, the TOF-MS allows a high mass-range to be achieved very easily.
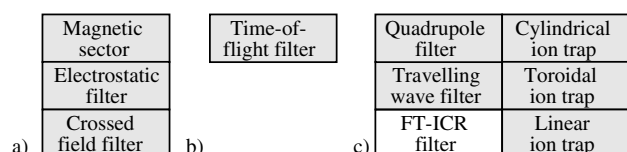
Magnetic sector		Time-of- flight filter		Quadrupole filter	Cylindrical ion trap
Electrostatic filter				Travelling wave filter	Toroidal ion trap
Crossed field filter				FT-ICR filter	Linear ion trap

a)   b)   c)

Figure 6. Mass filtering based on a) static fields, b) pulsed fields, and c) harmonically varying fields.

Filters can be combined with other components to form more complex analytical systems, in which a parent ion is selected using a first filter and then fragmented in a collision cell. The daughter ions are then examined in detail in a second filter. Provision of a detailed mass spectrum of each ion enables its precise identification, a process known as tandem-MS or MS-MS. Such systems may be based entirely on quadrupoles (the triple quadrupole or QQQ) (Fig. 7a). However, many combinations of quadrupoles, ion traps and time-of-flight filters have been developed (Fig. 7b).
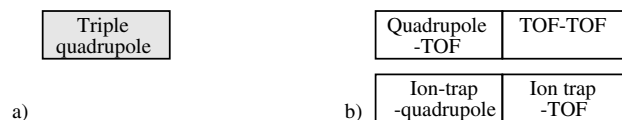
Triple quadrupole		Quadrupole -TOF	TOF-TOF
		Ion-trap -quadrupole	Ion trap -TOF

a)   b)

Figure 7. MS-MS systems based on a) quadrupoles, b) combinations of quadrupoles, traps and TOF filters.

MEMS MASS SPECTROMETERS

Construction of MEMS mass spectrometer systems typically involves replacement of conventional sample introduction systems, ion sources, mass filters or ion detectors with smaller and more precise micro-fabricated components. Although MEMS vacuum pumps have been investigated, it is safe to say that both the pumping system and vacuum enclosure are likely to remain conventional devices for the foreseeable future.

The range of MEMS fabrication processes that has been used includes methods for patterning and material deposition (Fig. 8a) and etching, large-scale structuring and assembly (Fig. 8b). The challenge has been to adapt these processes to the particular requirements of MS systems, which typically involve some combination of large size, high precision, high RF voltage, high DC voltage, and gas-tight or liquid-tight assembly. The most successful developments have used 'three-dimensional' processes such as wafer bonding, deep reactive ion etching and assembly, in addition to 'two-dimensional' processes such as lithography, deposition and etching.
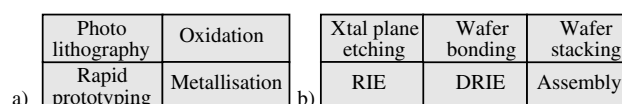
Photo lithography	Oxidation		Xtal plane etching	Wafer bonding	Wafer stacking
Rapid prototyping	Metallisation		RIE	DRIE	Assembly

a)   b)

Figure 8. MEMS fabrication: a) patterning and deposition, b) structuring and assembly.

Out of all the components needed for a miniature MS system, attention has overwhelmingly been paid to the electrospray source. The obvious explanation is that this represented the simplest fabrication problem, because almost any open-ended fluidic channel with a suitable electrical contact can emit a spray. This convenient property placed its construction within the capability of most chemistry departments. Furthermore, useful results (such as analysis immediately after separation) could be obtained directly, and the potential for combination with lab-on-a-chip components was obvious. Consequently, papers on this topic number several hundred [2-7].

The focus on miniaturization of ESI sources did, however, ignore an inconvenient truth: by far the largest component of the analytical chain was the mass spectrometer itself, often involving extremely large floor pumps in addition to the visible instrument. Progress in this area was much slower. Possible explanations include

the lack of a viable strategy for miniaturization, the complexity of complete system development, and a market structure based on relatively small numbers of instruments with very high performance.

Miniaturization of all major mass filter types has now been attempted, except FT-ICR-MS. Examples include:

1. Magnetic filters   [8-10]
2. Electrostatic filters   [11-12]
3. Crossed field filters   [13-16]
4. Time-of-flight filters   [17-19]
5. Travelling wave filters   [20-21]
6. Quadrupole filters   [22-25]
7. Cylindrical ion traps   [26-31]
8. Toroidal ion traps   [32-34]
9. Linear ion traps   [35-40]

Most designs involve complex electrode arrangements to control ion motion over long paths, and hence occupying (by MEMS standards) relatively large volumes. Consequently, the main difficulty has been to develop processes that can define suitably large electrodes with sufficient precision. Often, approximations to the desired structure are used. These either include replacement of an exact equipotential surface with an approximation, or with a set of planar electrodes held at controlled potentials.

In addition, many micro-fabricated sources and detectors have been developed, including:

10. EI sources with hot cathodes   [17]
11. EI sources with cold cathodes [41-45]
12. Plasma ion sources   [46-50]
13. Photoionization sources   [17]
14. Array-type ion detectors   [51-54]

The above are described in several reviews [55-57].

MEMS QUADRUPOLES

MEMS quadrupole development at Imperial College began in 1995 with a collaboration with Liverpool University. At the time, many common microfabrication methods were less developed, and construction was based on the older crystal plane etching techniques used to form optical fibre connectors. Etching and re-oxidation of entire Si wavers was used to batch-fabricate 30 mm long dies containing V-grooves capable of mounting 0.5 mm dia cylindrical electrode rods made of metallised glass, together with larger spacer rods (Fig. 9a,b) [58-61]. Mass spectra were obtained using EI (Fig. 9c), providing valuable proof that sufficient ion flux could be obtained from such a small device.
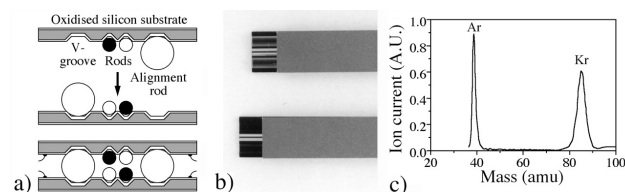

Figure 9. Quadrupole filter fabricated by crystal plane etching: a) schematic, b) device and c) mass spectrum.

However, difficulties were identified with RF heating of the semiconducting substrate, which caused the electrodes to detach. Consequently, the mass range was limited to around 100 atomic mass units (a.m.u.). The substrate also acted as a nearby ground plane, distorting the local electric field. The mass resolution was therefore several a.m.u., preventing exact elemental determination. Although quadrupole arrays (Fig. 10a) and quadrupoles with entrance and exit optics in the form of 1D einzel lenses (Fig. 10b, c) were also constructed, [62] the technique was abandoned. However, results were encouraging enough to form a spin-out at Imperial, Microsaic Systems.
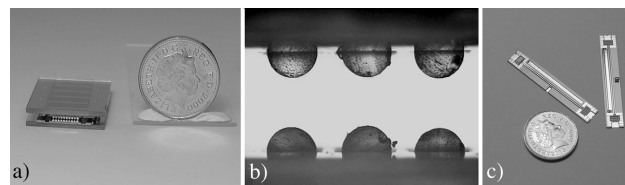

Figure 10: V-groove etched components: a) array-type QMS, b) einzel lens, c) quadrupole with integrated lens.

At the time, bonded silicon-on-insulator (BSOI) was becoming available and appeared to offer the solutions to electrical isolation and rod mounting. New designs involving pairs of stacked substrates were therefore developed (Fig. 11a,b). These incorporated entrance and exit optics and sprung mounts for metal electrodes (again, derived from optical fibre components). Greatly improved spectra were obtained, with a mass range increased to 400 a.m.u and a resolution approaching 1 a.m.u. (Fig. 11c) [63]. This performance was high enough to allow development of two MS systems with MEMS quadrupoles (portable and bench-top mass spectrometers, respectively, with EI sources and SPME interfaces) [64].
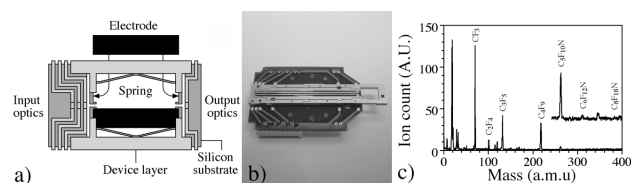

Figure 11. BSOI MEMS quadrupole: a) schematic, b) device and c) mass spectrum of PFTBA.

Once again, careful study revealed intrinsic limitations: residual RF heating (due to the limited thickness of oxide interlayer) and distortion of the RF field (due to fringe fields of the highly-constrained and asymmetric entrance and exit optics) [65]. A third-generation design was therefore developed, based on pairs of substrates formed using anodically bonded silicon-on-glass. This process was much more flexible, and allowed incorporation of RF-only (Brubaker) prefilters to improve input and/or output coupling (Fig. 12 a,b). Mass range was immediately improved to 1200 a.m.u. (Fig. 12c), comparable to conventional quadrupoles. The mass resolution of early devices again approached 1 a.m.u. and has since been improved [66].
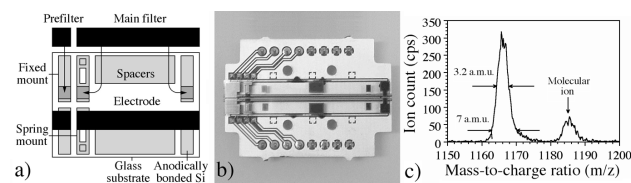

Figure 12. Silicon-on-glass quadrupole: a) schematic, b) device and c) spectrum of tris(perfluoroheptyl)-s-triazine.

MEMS ESI-MS

The availability of improved quadrupole filters suggested the possibility of constructing more advanced mass spectrometer systems such as an ESI-MS. However, two additional components were required: a nanospray ion source and a device for ion transport from atmospheric pressure into vacuum.

Although many integrated nanospray sources have been developed, their planar format often introduces difficulties in coupling to other equipment, which is typically capillary-based. Furthermore, such sources often offer limited ion current, due to the lack of a nebuliser, while the use of the mass spectrometer as the extraction electrode renders the spray highly unpredictable. A more reliable source based on a standard nanospray capillary needle and with all the features necessary for spray generation, gaseous nebulisation and desolvation was therefore developed. A stacked, two-chip assembly was again used. To sustain the high voltages ($\approx$ 1 kV) needed for spray generation, the substrate was a thick-layer of photopatterned SU-8 epoxy resist, while the capillary mount, coaxial nebuliser and ion extraction electrode were formed using a combination of crystal plane and deep reactive ion etching (Fig. 13a, b). Spray could then be obtained entirely independently of any mass spectrometer, with the source effectively acting as a stand-alone ion gun (Fig. 13c) [67].
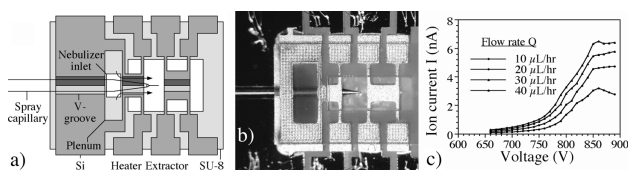

Figure 13. MEMS nanospray source: a) schematic, b) device and c) I-V characteristics at different flow rates.

To couple the ion stream into the vacuum system, a differentially pumped silicon interface was developed. This structure was formed from two stacked BSOI dies, which were in turn attached to a flange for mounting on the vacuum chamber. The outer die provided an entrance capillary and an internal electrostatic lens, while the inner die provided an exit capillary, an intermediate vacuum chamber and pumping ports (Fig. 14a,b). The combination approximates the skimmed free-jet expansion used in cluster beam and mass spectrometer systems. The intermediate chamber is relatively shallow, however, so that only a low Mach number is attained. Despite this, the three components above (the nanospray source, vacuum interface and quadrupole) allow ESI-MS spectra to be routinely obtained using MEMS parts for the three steps of ion generation, transport into vacuum and mass filtering (Fig. 14c) [68].
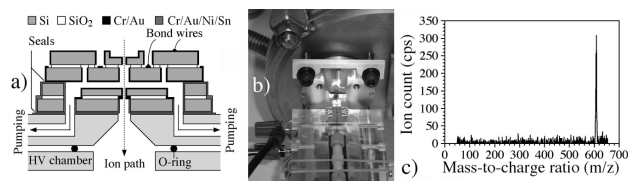

Figure 14. MEMS vacuum interface: a) schematic, b) device under test and c) ESI-MS spectrum of reserpine.

The system was commercialized in 2012 as the Microsaic 3500 MiD, the first MEMS-based ESI-MS. The MEMS components are fabricated in batches (Fig. 15a), and are considered as identical consumables that are directly exchangeable to minimize service downtime. The entire instrument, including all pumps and the computer, is contained in a single enclosure that may conveniently be accommodated at the basis of an instrument stack (Fig. 15b). The system is capable of detecting eluents from a high-performance liquid chromatography (HP-LC) system (Fig. 15c). The limit of detection for reserpine is 5 ng on-column (1 pg of which is passed to the spray source). The mass range is m/z = 100-800 a.m.u., and each spectrum is typically acquired at a rate of 1 scan per second [69].
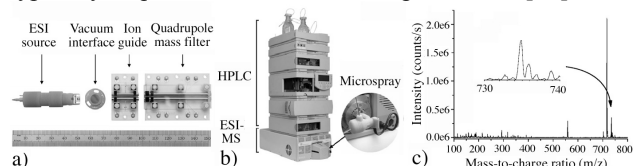

Figure 15. Microsaic 3500 MiD ESI-MS: a) MEMS components, b) system and c) mass spectrum of erythromycin.

CONCLUSIONS

Despite a long gestation, MEMS-based mass spectrometry is now a reality. While there are necessarily trade-offs in sensitivity, mass range and mass resolution involved firstly in miniaturization and secondly in approximation of the structures used for ion control using available materials and fabrication methods, it is now possible to obtain mass spectra of sufficient quality for many purposes using MEMS components. This advance may be transformative. For decades, size and cost have limited the use of mass spectrometry, particularly in the pharmaceutical industry. Laboratory chemists have been forced to submit samples to a centralized service for analysis. The wider availability of benchtop instruments at much lower cost will allow considerably more rapid feedback, particularly on the progress of crucial reactions, and the availability of mass-produced, identical 'plug-and'-play' replacement components will allow a reduction in the downtime and expense of servicing.

ACKNOWLEDGEMENTS

REFERENCES

[1] E. De Hoffmann, J. Charette, V. Stroobant "Mass spectrometry: Principles and applications" John Wiley and Sons, Chichester, 1996.

[2] R. Ramsey, J. Ramsey "Generating electrospray from microchip devices using electroosmotic pumping" *Anal. Chem.* vol. 69, pp. 1174-1178, 1997.

[3] L. Licklider, X.Q. Wang, et al. "A micromachined

chip-based electrospray source for mass spectrometry" *Anal Chem.* vol. 72, pp. 367-75, 2000.

[4] G.A. Schultz, T.N. Corso, S.J. Prosser, et al. "A fully integrated monolithic microchip electrospray device for mass spectrometry" *Anal. Chem.* vol. 72, pp. 4058-4063, 2000.

[5] P. Griss, J. Melin, J.Sjödahl et al. "Development of micromachined hollow tips for protein analysis based on nanoelectrospray ionization mass spectrometry" *J. Micromech. Microeng.* vol. 12, pp. 682-687, 2002.

[6] T. Sikanen, S. Franssila, T.J. Kauppila et al. "Microchip technology in mass spectrometry" *Mass Spectrom. Rev.* vol. 29, pp. 351-391, 2009.

[7] P.R. Chiarot, R.B. Mrad "An overview of electrospray applications in MEMS and microfluidic systems" *J. Microelectromech. Syst.* vol. 20, pp. 1241-1249, 2011.

[8] M.P. Sinha, A.D. Tomassian "Development of a miniaturized, lightweight magnetic-sector for a field-portable mass spectrograph" *Rev. Sci. Inst.* vol. 62, pp. 2618-2620, 1991.

[9] C. Sun "Microengineered mass spectrometer with novel electron source" *Proc. 43rd AVS Nat. Symp.*, 1996.

[10] Gilchrist K.H., Bower C.A., Lueck M.R., et al. "A novel ion source and detector for a miniature mass spectrometer" *Proc. IEEE Sensors 2007*, pp 1372-1375, 2007.

[11] R.E. Stalder, S. Boumsellek, T.R. Van Zandt et al. "Micromachined array of electrostatic energy analyzers for charged particles" *J. Vac. Sci. Tech. A* vol. 12, pp. 2554-2558, 1994.

[12] C.L. Enloe, L.H. Krause, R.K. Haaland et al. "Miniaturized electrostatic analyser manufactured using photolithographic etching" *Rev. Sci. Instrum.* vol. 74, pp. 1192-1195, 2003.

[13] J.A. Diaz, C.F. Giese, W.R. Gentry "Sub-miniature E x B sector-field mass spectrometer" *J. Am. Soc. Mass Spectrom.* vol. 12, pp. 619-632, 2001.

[14] C.B. Freidhoff "Mass spectrograph on a chip" *Proc. 1997 IEEE Aerospace Conference*, pp. 32, 1997.

[15] C.B. Freidhoff, R.M. Young, S. Sriram, et al. "Chemical sensing using non-optical microelectro-mechanical systems" *J. Vac. Sci. Tech. A* vol. 17, pp. 2300-2307, 1999.

[16] N. Sillon, R. Baptist "Micromachined mass spectrometer" *Sensors and Actuators B* vol. 83, pp. 129-137, 2002.

[17] H.J. Yoon, J.H. Kim, et al. "Fabrication of a novel micro time-of-flight mass spectrometer" *Sensors and Actuators A* vol. 97-8, pp. 441-447, 2002.

[18] E. Wapelhorst, J.P. Hauschild, J. Muller "Complex MEMS: a fully integrated TOF micro mass spectrometer" *Sensors and Actuators A* vol. 138, pp. 22-27, 2007.

[19] J. Fox, R. Saini, K.Tsui, et al. "Microelectro-mechanical system assembled ion optics: an advance to miniaturization and assembly of electron and ion optics" *Rev. Sci. Instrum.* vol. 80, 093302, 2009.

[20] P. Siebert, G. Petzold, A. Hellenbart, et al. "Surface microstructure/miniature mass spectrometer: processing and applications" *Appl. Phys. A* vol. 67,

pp. 155-160, 1998.

[21] J. Hauschild, E. Wapelhorst, J. Müller "The novel synchronous ion shield mass analyzer" *J. Mass Spectrom.* vol. 44, pp. 1330-1337, 2009.

[22] D. Wiberg, M. Hecht, R. Brennan, et al. "A LIGA fabricated quadrupole array for mass spectroscopy" *Proc. HARMST '97*, Madison, WI, June, 1997

[23] D. Wiberg, N.V. Myung, B. Eyre, et al. "LIGA fabricated two-dimensional quadrupole array and scroll pump for miniature gas chromatograph/mass spectrometer" *SPIE Proc.* 4878, pp. 8-13, 2003.

[24] L.F. Velasquez-Garcia, K. Cheung, A.L. Akinwande "An application of 3D MEMS packaging: out-of-plane quadrupole mass filters" *J. Microelectromech. Syst.* vol. 17, pp. 1430-1438, 2008.

[25] K. Cheung, L.F. Velasquez-Garcia, A.I. Akinwande "Chip-scale quadrupole mass filters for portable mass spectrometry" *J. Microelectromech. Syst.* vol. 19, pp. 469-483, 2010.

[26] R.G., Brewer, R.G. Devoe, R. Kallenbach "Planar ion microtraps" *Phys. Rev. A* vol. 46, pp. R6781-R6784, 1992.

[27] O. Kornienko, P.T.A. Reilly, W.B. Whitten et al. "Micro ion trap mass spectrometry" *Rapid Comm. in Mass Spectrom.* vol. 13, pp. 50-53, 1999.

[28] M.G. Blain, L.S. Riter, D. Cruz, et al. "Towards the hand-held mass spectrometer: design considerations, simulation, and fabrication of micrometer-scaled cylindrical ion traps" *Int. J. Mass Spect.* vol. 236, pp. 91-104, 2004.

[29] S. Pau, C.S. Pai, Y.L. Low, et al. "Microfabricated quadrupole ion trap for mass spectrometer applications" *Phys. Rev. Lett.* vol. 96, 120801, 2006.

[30] F.H.W. van Amerom, et al. "Microfabrication of cylindrical ion trap mass spectrometer arrays for handheld chemical analyzers" *Chem. Eng. Comm.* vol. 195, pp. 98-114, 2008.

[31] A.Chaudhary, F.H.W. van Amerom, R.T. Short "Development of microfabricated cylindrical ion trap mass spectrometer arrays" *J. Microelectromech. Syst.* vol. 18, pp. 442-448, 2009.

[32] D.E. Austin, M. Wang, S.E. Tolley, et al. "Halo ion trap mass spectrometer" *Anal. Chem.* vol. 79, pp. 2927-2932, 2007.

[33] Z. Zhang, Y. Peng, B.J. Hansen, et al. "Paul trap mass analyzer consisting of opposing microfabricated electrode plates" *Anal. Chem.* vol. 81, pp. 5241-4248, 2009.

[34] Y. Peng, B.J. Hansen, H. Quist, et al. "Coaxial ion trap mass spectrometer: concentric toroidal and quadrupolar trapping regions" *Anal. Chem.* vol. 83, pp. 5578-5584, 2011.

[35] M.J. Madsen, W.K. Hensinger, D. Stick, et al. "Planar ion trap geometry for microfabrication" *Appl. Phys. B-Lasers* vol. O78, pp. 639-651, 2004.

[36] M. Yu, M. Fico, S. Kothari, et al. "Polymer-based ion trap chemical sensor" *IEEE Sensors J.* vol. 6, pp. 1429-1434, 2006.

[37] M. Debatin, M. Kröner, et al. "Planar multipole ion trap" *Phys. Rev. A* vol. 77, 033422, 2008.

[38] M. Fico, J. Maas, S.A. Smith, et al. "Circular arrays of polymer-based miniature rectilinear ion traps"

Analyst 134, pp. 1338-1347, 2009.

[39] A.T. Clare, L. Gao, B. Brkic, et al. "Linear ion trap fabricated using rapid manufacturing technology" *J. Am. Soc. Mass Spectrom.* vol. 21, pp. 317-322, 2010.

[40] J.D. Maas, P.I. Hendricks, Z. Ouyang, et al. "Miniature monolithic rectilinear ion trap arrays by stereolithography on printed circuit board" *J. Microelectromech. Syst.* vol. 19, pp. 951-959, 2010.

[41] T.E. Felter "Cold cathode field emitter array on a quadrupole mass spectrometer: route to miniaturization" *J. Vac. Sci Tech. B* vol. 17, pp. 1993-1996, 1999.

[42] O. Kornienko, P.T.A. Reilly, W.B. Whitten, et al. "Field-emission cold-cathode EI source for a microscale ion trap mass spectrometer" *Anal. Chem.* vol. 72, pp. 559-562, 2000.

[43] H.J. Yoon, S.H. Song, et al. "Fabrication of an ion source using carbon nanoparticle field emitters for a micro time-of-flight mass spectrometer" *Proc. Transducers '07*, pp. 1067-1070, 2007.

[44] C.A. Bower, K.H. Gilchrist et al. "On-chip electron-impact ion source using carbon nanotube field emitters" *Appl. Phys. Lett.* vol. 90, 124102, 2007.

[45] K. Han, Y. Lee, D. Jun, et al. "Field emission ion source using a carbon nanotube array for micro time-of-flight mass spectrometer" *Japn. J. Appl. Phys.* vol 50, 06GM04, 2011.

[46] J.W. Frame "Microdischarge devices fabricated on silicon" *Appl. Phys. Lett.* vol. 71, pp. 1165-1167, 1997.

[47] J.A. Hopwood "A microfabricated inductively coupled plasma" *J. Microelectromech. Syst.* vol. 9, pp. 309-313, 2000.

[48] A. Bass, C. Chevalier, M.W. Blades "A capacitatively coupled microplasma (CCμP) formed in a channel in a quartz wafer" *J. Anal. At. Spectrom.* vol. 16, 9190921, 2001.

[49] J. Hopwood, F. Iza, S. Coy, et al. "A microfabricated atmospheric pressure microplasma source operating in air" *J. Phys. D. Appl. Phys.* vol. 38, pp. 1698-1703, 2005.

[50] J.-P. Hauschild, E. Wapelhorst, J. Müller "Mass spectra measured by a fully integrated MEMS mass spectrometer" *Int. J. Mass Spectrom.* vol. 264, pp. 53-60, 2007.

[51] R.B. Darling, A.A. Scheidemann, K.N. Bhat, et al. "Micromachined Faraday cup array using deep reactive ion etching" *Sensors and Actuators A* vol. 95, pp. 84-93, 2002.

[52] M.P. Sinha, M. Wadsworth "Miniature focal plane mass spectrometer with 1000-pixel modified-CCD detector array for direct ion measurement" *Rev. Sci. Instrum.* vol. 76, 025103, 2005.

[53] C.A. Bower, K.H. Gilchrist, M.R. Lueck et al. "Microfabrication of fine-pitch high aspect ratio Faraday cup arrays in silicon" *Sensors and Actuators A* vol. 137, pp. 296-301, 2007.

[54] O. Hadjar, W.K. Fowler, G. Kibelka, et al. "Preliminary demonstration of an IonCCD as an alternative pixelated anode for direct MCP readout in a compact MS-based detector" *J. Am. Soc. Mass Spectrom.* vol. 23, pp. 418-424, 2012.

[55] E.R. Badman, R.G. Cooks "Special feature: Perspective - miniature mass analysers" *J. Mass. Spectrom.* vol. 35, pp. 659-671, 2000.

[56] Z. Ouyang, R.G. Cooks "Miniature mass spectrometers" *Ann. Rev. Anal. Chem.* vol. 2, pp. 10.1-10.28, 2009.

[57] R.R.A. Syms "Advances in microfabricated mass filters" *Anal. Bioanal. Chem.* vol. 393, pp. 427-429, 2009.

[58] R.R.A. Syms, T.J. Tate, M.M. Ahmad, et al. "Design of a microengineered quadrupole electrostatic lens" *IEEE Trans. Electron Dev.* vol. 45, pp. 2304-2311, 1998.

[59] R.R.A Syms, T.J. Tate, M.M. Ahmad, et al. "Fabrication of a microengineered quadrupole electrostatic lens" *Elect. Lett.* vol. 32, pp. 2094-2095, 1996.

[60] S. Taylor, J.J. Tunstall, R.R.A. Syms, et al. "Initial results for a quadrupole mass spectrometer with a silicon micromachined mass filter" *Elect. Lett.* vol. 34, pp. 546-547, 1998.

[61] S. Taylor, J.J. Tunstall, J.H. Leck, et al. "Performance improvements for a miniature quadrupole with a micromachined mass filter" *Vacuum* vol. 53, pp. 203-206, 1999.

[62] R.R.A. Syms, L. Michelutti, M.M. Ahmad "Two-dimensional microfabricated electrostatic einzel lens" *Sensors and Actuators A* vol. 107, pp. 285-295, 2003.

[63] M. Geear, R.R.A. Syms, S. Wright, A.S Holmes "Monolithic MEMS quadrupole mass spectrometers by deep silicon etching" *J. Microelectromech. Syst.* vol. 14, pp. 1156-1166, 2005.

[64] A. Malcolm, S. Wright, R.R.A. Syms, et al. "Miniature mass spectrometer systems based on a microengineered quadrupole filter" *Anal. Chem.* vol. 82, pp. 1751-1758, 2010.

[65] S. Wright, R.R.A. Syms, S. O'Prey, et al. "Comparison of ion coupling strategies for a microengineered quadrupole mass spectrometer" *J. Am. Soc. Mass Spectrom.* vol. 20, pp. 146-156, 2009.

[66] S. Wright, S.O. O'Prey, R.R.A. Syms, et al. "Microfabricated quadrupole mass spectrometer with a Brubaker prefilter" *J. Microelectromech. Syst.* vol. 19, pp. 325-337, 2010.

[67] R.R.A. Syms, H. Zou, M. Bardwell, at al. "Microengineered alignment bench for a nanospray ionisation source" *J. Micromech. Microeng.* vol. 17, pp. 1567-1574, 2007.

[68] S. Wright, R.R.A. Syms, R.W. Moseley, et al. "MEMS-based nanospray ionisation mass spectrometer" *J. Microelectromech. Syst.* vol. 19, pp. 1430-1443, 2010.

[69] A. Malcolm, S. Wright, R.R.A. Syms, et al. "A miniature mass spectrometer for liquid chromatography applications" *Rapid Comm. in Mass Spectrom.* vol. 25, pp. 3281-3288, 2011.

CONTACT

*R.R.A.Syms, tel: +44-207-594-6203:
r.syms@imperial.ac.uk