The History of Time-of-Flight Mass Spectrometry at VG - Micromass - Waters

Mike Morris, Jeff Brown, Martin Green, Jason Wildgoose, Steven Pringle, Kevin Giles, Waters Corporation, Wilmslow, UK.

COMPANY BACKGROUND

VG Instruments was formed in 1962 (Vacuum Generators Limited) to provide ultra-high vacuum components and systems. In 1970, VG Micromass was formed to specialise in mass spectrometry and in 1974 was fragmented into four: VG Isotopes, VG Organic, VG Quadrupoles and VG Inorganic.



VG Organic moved to Altrincham. South Manchester, UK, along with VG Data Systems. The ationale behind the epeated formation of small companies was Bernard astwell's 'Christmas card principle' : most people send Christmas cards to between

VG Analytcal Floats Road c.1990 50 and 100 people, and this

represents a natural maximum number of people with whom to associate in a company. In 1980, VG Analytical was formed, followed by VG Masslab (1984), VG Tritech (1985) and VG Biotech (1988). The ToF instruments were initially developed at the Floats Road facility.

MALDI

MALDI came to the fore following the presentations of Karas and Hillenkamp at the IMSC meeting in 1988, and commercialisation followed shortly thereafter. The first instrument from VG was the TOFSPEC, released in 1991.



This was a linear instrument with a mass resolution (M/ Δ M) of 1,500 FWHM. t was followed in 1993 with the TOFSPEC E & SE configurations incorporating reflectrons for increased resolution as well as MS/MS functionality with a

VG TOFSpec

Bradbury-Neilson ion gate to select parent and fragment ions from post-source decay. Significant enhancements in mass resolution were achieved by applying time-lag-focusing as described by Wiley-McLaren. The final floor standing MALDI

instrument was the TOFSPEC 2E in 1996 with a mass resolution o 15,000 FWHM reflectron mode. At this time systems include 96-well microtitre format sample plates for compatibility with robotic sample loaders.



VG TOFSpec 2E

In 2000 the M@LDI benchtop reflectron system was introduced. It was optimized for automated high throughput protein identification by peptide mass fingerprinting, it had a resolution of 10,000 FWHM, 1 fmol peptide sensitivity and 10 ppm mass accuracy. The





Micromass M@LDI L

M@LDI-HT version with robotic sample plate loader was able to analyse up to 4,000 samples/day. The linear version was also optimised for high-throughput analysis of bacteria or oligonucleotides. With minor enhancements, the MALDI micro was relaunched in 2002 and was the last dedicated MALDI instrument produced by the Company. The M@LDI ion source was arranged to interface with the Q-TOF Ultima[™] product MALDI micro and is still in use today on SynaptTM.

OA-TOF

In the early 1990s, the work being undertaken by the late

Mike Guilhaus at the University of New South Wales on orthogonalacceleration time-of-flight caught the attention of Bob Bateman, and became the basis of subsequent hybrid-TOF instruments. The first of these was the AutoSpec[™] oa-TOF, released in 1993, as a



VG Autospec oa-ToF

compact approach for undertaking MS-MS on sector instruments, having a much smaller footprint than the multisector and array detection MS-MS configurations.

The AutoSpec oa-TOF could be operated to generate product ions with massselection in the double-focusing sector, followed by high-energy CID prior to analysis of the fragments by the TOF. It was also possible to bypass the magnetic sector element.



AutoSpec oa-ToF (a) MS/MS mode (b) Magnet bypass mode

Q-TOF

It became clear from the development of the Autospec oa-TOF and MALDI reflectron TOFs together with an



understanding of the parameters (phase space) of ions exiting collision induced dissociation (CID) cells that a quadrupole-CID -oaTOF would be a particularly interesting geometry. The first Q-TOF, as they came to be known, was released by Micromass in 1996 with the geometry promising unrivalled full scan MSMS sensitivity. The TOF had a resolution of 5,000 FWHM and

was capable of 5 ppm RMS mass

Micromass Q-ToF

measurement accuracy and, whilst these figures might be modest by today's standards, this instrument led to an explosion of new Q-TOF instruments and geometries from both Micromass and other vendors. Over the next 2 decades

developments in oa-TOF design including folded TOF geometries (Wmode), high field orthogonal extraction, dual stage reflectrons, parallel wire grids, new detection regimes and improved phase space would take the ultimate TOF performance on Q-TOFs from a resolution of 5,000 FWHM to over 100.000



Micromass Q-ToF 2

FWHM on the recent high-performance instruments, and from a mass measurement accuracy of 5 ppm RMS to 0.5 ppm

range of



Micromass Q-ToF Ultima

applications to be achieved in benchtop configurations the first of which was the Q-TOF micro.

Further reductions in size were achieved by the removal of the quadrupole and CID cell resulting in what would come to be known as LC-TOFs. With the experimental times for a single oa-TOF experiment in the 10's-100's of microseconds range the speed of separation gives oa-TOF a unique advantage when choosing a mass analyser to couple to fast upstream separations such as those seen with ion mobility separators (IMS).

RMS, whilst simultaneously increasing the sensitivity by over two orders of magnitude. Whilst these improvements increased the ultimate performance that Q-TOF instruments were capable of they also improved the performance versus instrument size envelope allowing designs that were fit for purpose for a



Micromass Q-ToF Premier



LCT

The LCT was launched in 1997 and was a benchtop oa-ToF 'V' geometry system capable of 50 ppm RMS mass accuracy with an external calibration and 5 ppm with internal LockMass at a mass resolution of 5,000 FWHM

The LCT Premier was launched in 2003 at ASMS in Montreal, and was designed for routine application in natural product identification, drug metabolism, impurity analysis, compound



ntact protein analysis. This instrument incorporated ion unnel source optics piving a x10 increase in

screening, and

Micromass LCT - with 'V' optics

sensitivity, and also improved oa-ToF performance featuring sub-3 ppm RMS with in-built LockMass correction. The ToF now included a high-resolution, 12,000 FWHM, mode of operation with 'W' geometry optics mode, and a 'V' mode of operation delivering 6,000 FWHM with the option of fast



Micromass LCT Premier with 'W' optics

positive/negative switching. The LCT Premier XE launched in 2006 at ASMS in Seattle, this had an increased resolution of 15,000 FWHM in 'W' mode and faster polarity switching.

GCT

Following the success of the LCT for high-resolution accurate mass measurement using LC and atmospheric pressure



ionisation, work began to interface

Micromass GCT

Gas Chromatography and Electron Impact ionisation (EI) to the orthogonal ToF analyser. The GCT was released in 1998 featuring EI, CI and Field Ionisation (FI) ion sources at 5.000 FWHM resolution and ±5 ppm mass accuracy, and was capable of the fast acquisition

speeds required for integration with Gas Chromatography but also offered solids probe introduction. The very soft ionisation afforded by FI allowed acquisition of molecular ion, accurate mass measurements for thermally labile compounds such as organometallics as well as finding application in oil analysis for hydrocarbon analysis.

In 2005 the GCT Premier was released adding Field Desorption (FD) and a fully automated robotic solids probe (DCI) option for open access operation. The GCT Premier boasted 7.000 FWHM resolution and increased quantitative dynamic range up to four orders of magnitude.

The GCT product line was discontinued in 2012.



The Xevo G2 Q-Tof, launched at 2010 at ASMS in Salt Lake City, introduced a higher performance oa-Tof with two resolution modes of >22,500 FWHM and >10,000 FWHM, T-Wave source optics and the QuanTof[™] ADC

REFERENCES:



Waters THE SCIENCE OF WHAT'S POSSIBLE.

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2000	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	
@LD	[ToF		M@LDI micro												
ст			LCT Premier					LCT Premier XE			G2 ToF		G2-S ToF		
	GCT			GCT Premier				G	GCT Premier XE						
				Q-ToF micro					Xevo Q-ToF		G2 Q-	32 Q-ToF		G2-S Q-ToF	
	Q-ToF Ultima			Q-ToF Premier											
	Q-ToF API US						Syn	Synapt		Synapt	: G2 S		napt G2-S		

Waters THE SCIENCE OF WHAT'S POSSIBLE.



Micromass GCT Premier

BENCHTOP Q-TOF

Launched in 2001, the Q-Tof micro was a guadrupole-oa-Tof tandem instrument with a 4kDa resolving quadrupole and oa-ToF resolution of 5,000 FWHM capable of 5 ppm RMS mass accuracy with an internal

standard. Sensitivities were in the fmol range for peptides. Micromass Q-ToF micro The Xevo[™] Q-ToF. launched in

2009, introduced a powerful benchtop system in a small footprint, with a redesigned two-stage reflectron ToF providing >10,000 FWHM mass resolution and better than 3 ppm RMS

mass accuracy. This the first Waters ToF instrument to include the Universal Source Architecture.



Xevo Q-ToF

(1) R H Bateman in K R Jennings (Ed.) A History of European Mass Spectrometry, IM Publications, (2012).

based detector system. Mass accuracy was better than 1 ppm RMS. Two years later the Xevo G2-S was made its debut in Vancouver at ASMS in 2012. New to this system was the StepWave^{IM} ion guide giving a x4 boost in sensitivity at an increased resolution of 32,500 FWHM and x20 at 22.500 FWHM.



SYNAPT

Through the 1990s the combination of ion mobility (IM) with mass spectrometry began to gather momentum as a number of key research groups pushed the technology for investigations of biomolecules. In particular, the work of David Clemmer in the late 90s sparked interest at Waters towards application of the technology to enhance MS performance. After a slow burn, the first IM-enabled MS from a major manufacturer was launched in 2006, the Synapt HDMS. This featured a quadrupole-IM-ToF geometry and the newly

developed travelling wave IM technology. This modest mobility resolution (~10) instrument paved the way for broader uptake and application of IM-MS, providing a number of unique acquisition modes along with the more general benefits of increased peak capacity and

determination of collision crosssection values

Waters Synapt afforded by the separation. In 2009 a second generation instrument, the Synapt G2 was introduced with the mobility resolution increased to around 40, a maximum mass resolution increase from 17,500 to 40,000 FWHM and a new, higher dynamic range ADC-based

detection system. In 2011 high transmission

Synapt G2-S

source transfer ion optics were implemented to produce the Synapt G2-S with 25x increase in sensitivity. The Synapt G2-Si was released in 2013 with enhanced informatics and workflows for IM acquisitions and an increased mass resolution of 50,000 FWHM.

Waters, Micromass, Q-TOF Ultima, Synapt, AutoSpec, Xevo, QuanToF and StepWave are Trademarks of Waters Technologies Corporation.

