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Enhancing ion sampling efficiency, ion transmission and detection on a triple quadrupole platform

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Introduction

Recent developments in triple quadrupole mass spectrometry have delivered higher sensitivity, lower detection limits and faster data acquisition speeds generating enhanced data quality. To further improve peak area response and higher sensitivity, the ion sampling efficiency, transmission and detection on a high-end triple quadrupole MS/MS system LCMS-8050 was modified whilst still supporting a fast polarity switching time of 5 ms and data acquisition speeds of 30,000 u/sec.

Methods

A Shimadzu LCMS-8050 high-end triple quadrupole mass spectrometer was modified to improve detection limits by changing the ion sampling device, ion guide (UF-Qarray) and vacuum efficiency. To assess the higher sensitivity of the modified MS/MS system a series of test analytes were measured using conventional gradient chromatography (Nexera X2 UHPLC system; Shimadzu Corporation, Japan) including well cited compounds. Robustness was also measured by repeatedly analyzing alprazolam spiked into human plasma following a protein crash.

Figure 1 LCMS-8060 Triple Quadrupole Mass Spectrometer.

Sample Preparation

Neat standards were initially dissolved in either acetonitrile or methanol and then diluted to working concentrations in proper solvent, for example mobile phase. For standard in human plasma matrix, standards were spiked into human plasma that had been pretreated with acetonitrile.

LC/MS/MS Analysis

All of samples except phospholipids were analyzed by the Multiple Reaction Monitoring (MRM). MRM parameters depend on compound, such as MRM transition, collision energy and ion transfer voltage, were optimized through automatic MRM optimization functionality incorporated in LabSolutions software (Shimadzu Corporation, Japan).

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Result

UF-Qarray™

Newly designed UF-Qarray optics improves ion focusing efficiency which results in higher signal intensity. It is also more effective to noise reduction compared to the previous Qarray. The new UF-Qarray is a landmark technology that combines improvements in both sensitivity and robustness to maintain high sensitivity in not only in MRM but also in scan mode.

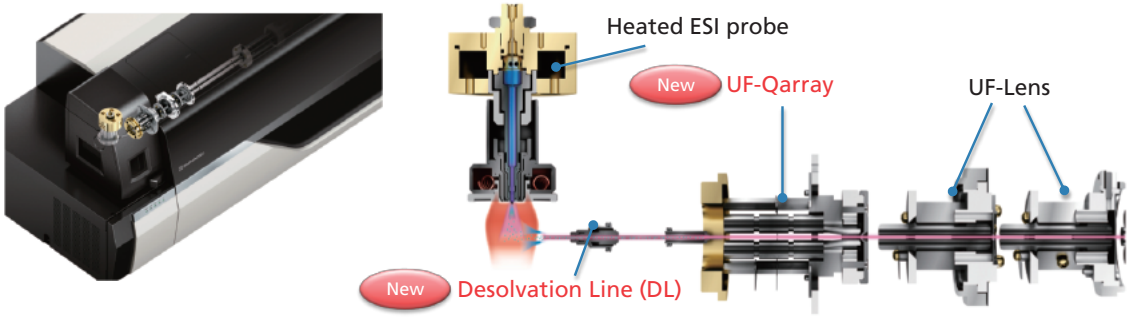

Figure 2 A cross section view of heated ESI probe and ion guide including UF-Qarray and UF-Lens.

The ion production, transmission and detection of three pesticides (fenoxaprop-ethyl, clofentezine and triclopyr) results in a meaningful increase in sensitivity compared to previous technologies. The chromatogram for each pesticide has been magnified to show the noise has not increased with a higher ion production.

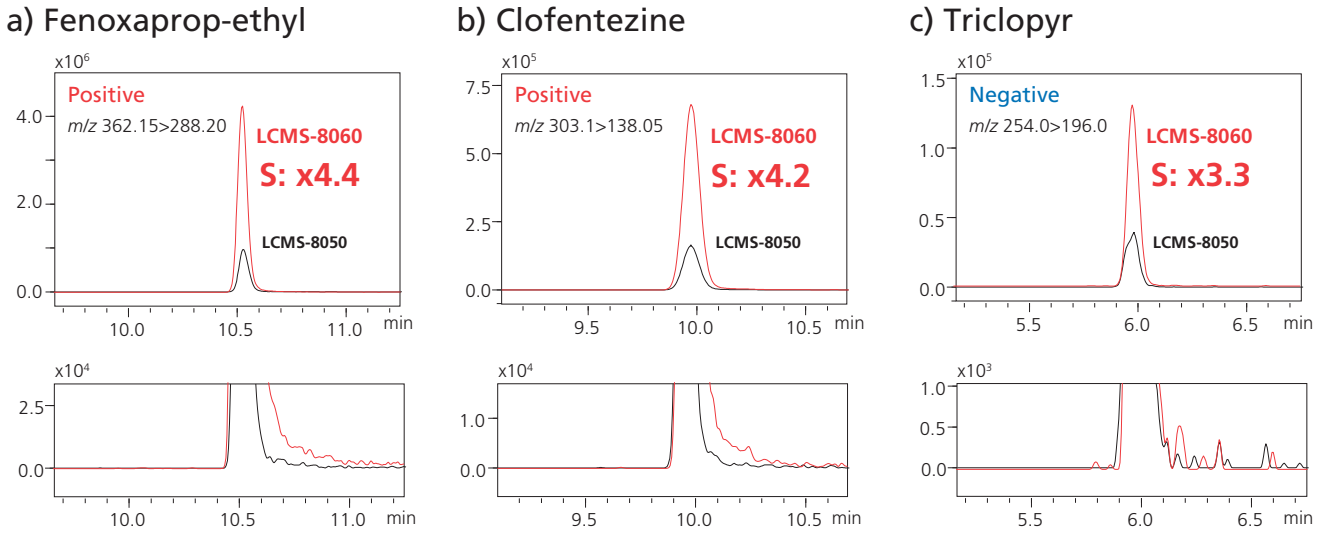

Figure 3 MRM chromatograms of three pesticides: 100 pg/mL neat standard, upper: signal comparison, lower: baseline noise comparison.

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The precursor ion scanning of phospholipids in human serum on the LCMS-8060 can detect more ion signals with greater precision and with higher confidence. With the LCMS-8060 lower levels of phosphatidylcholine could be detected in a human serum sample following a protein crash sample preparation compared to the LCMS-8050.

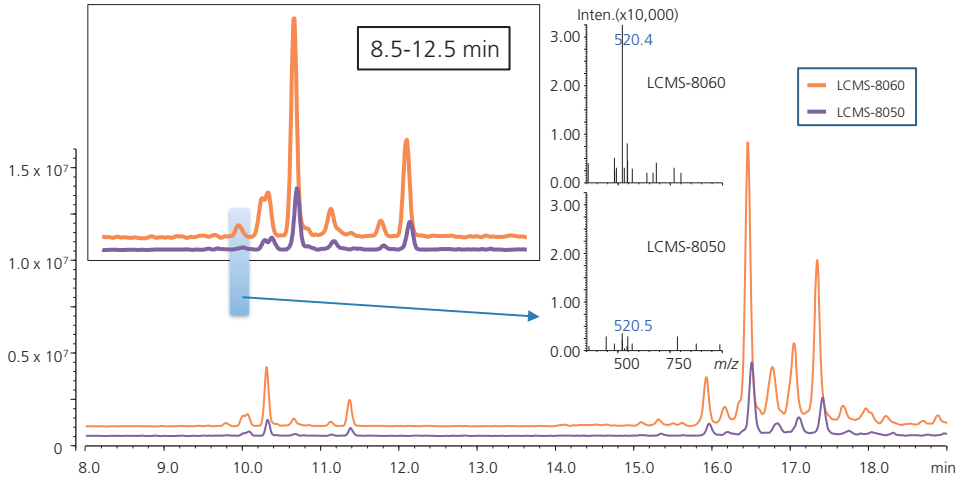

Figure 4 TIC of precursor ion scanning with *m/z* 184 by LCMS-8060 (Orange) and 8050 (Blue).

Highest Sensitivity: Quantitation of Verapamil

LCMS-8060 has successfully detected 100 ag of verapamil in plasma with pretty good peak appearance and excellent reproducibility as well as the developed method has achieved excellent linearity with very wide dynamic range from 0.1 pg/mL to 50 ng/mL.

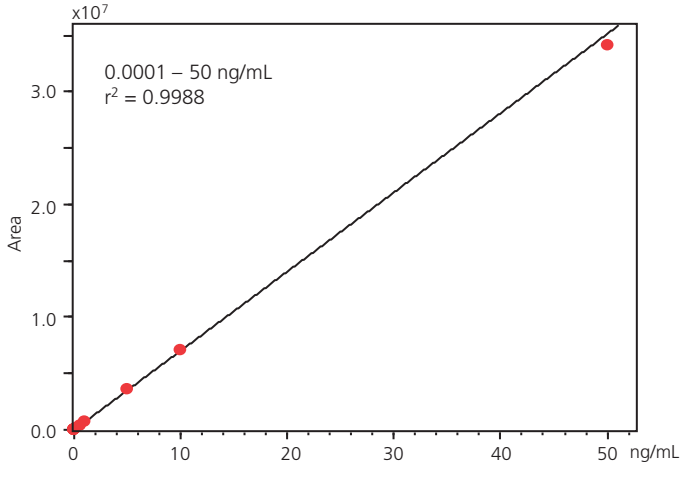

Figure 5 Calibration curve for Verapamil.

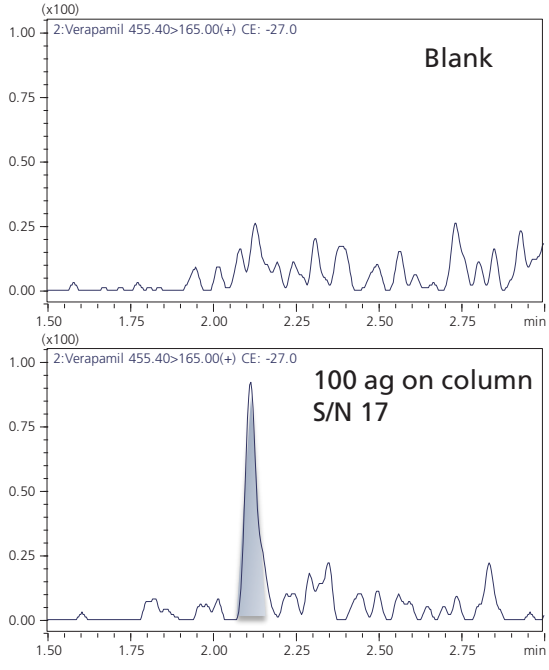

Figure 6 MRM chromatograms of Verapamil.

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Table1 Precision and Accuracy of Verapamil.

Actual Conc. (ng/mL)	Calculated Conc. (ng/mL)	AreaRSD (%, n=3)	Accuracy (%)
0.0001	0.000100	2.97	100.3
0.0005	0.000508	6.15	101.7
0.001	0.000942	5.32	94.3
0.005	0.00491	3.54	98.9
0.01	0.00949	2.94	95.0
0.05	0.0511	2.14	102.4
0.1	0.0996	1.18	99.8
0.5	0.522	0.63	104.5
1	1.01	0.26	100.8
5	5.28	0.43	105.6
10	10.0	0.60	100.0
50	48.8	0.33	97.8

Table 2 IDL for Verapamil.

Compound	Amount measured	Replicates	%RSD	t (99%)	IDL
Verapamil	100 ag	n = 10	5.08	2.821	14.3 ag

Fastest Speed: Simultaneous analysis of 105 pesticides

The LCMS-8060 uses UF Technologies to switch polarity in 5 msec. Using a polarity switching time of 5 msec has a profound influence on the dwell time and the options to generate high quality data and confident results.

Figure 8 shows MRM chromatograms of 105 pesticides (300 pg/mL each) using a polarity switching speed of 5 msec and a sampling window of 65 compounds in 400 msec loop times. To achieve a data sampling rate of 20 data points per compound, a dwell time of 2 msec was used to precisely detect and quantitate each compound.

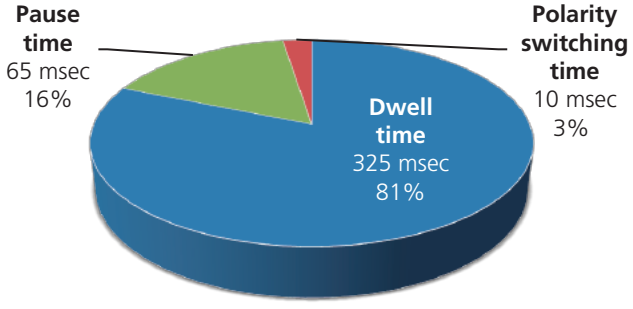

Figure 7 Ratio of dwell time, pause and polarity switching time in 400 msec of loop time when 65 of MRMs are simultaneouly monitored.

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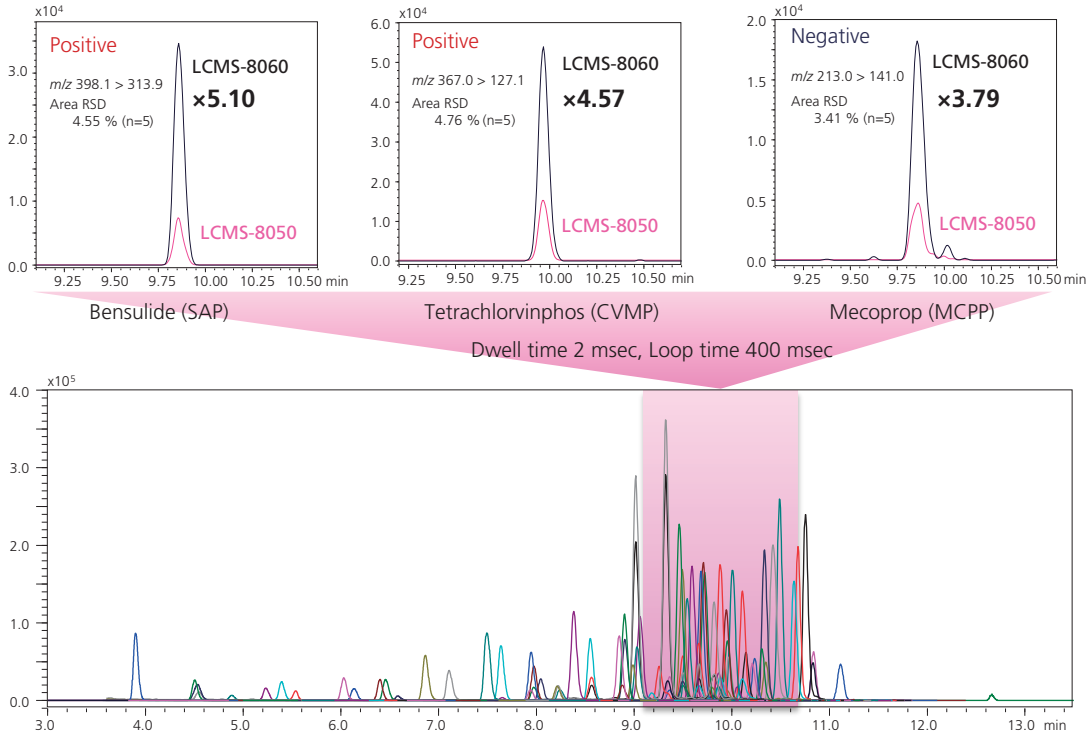

Figure 8 MRM chromatograms of 105 pesticides (300 pg/mL each).

Outstanding Durability: Alprazolam in human plasma

Desolvation is facilitated and contamination from droplets entering the mass spectrometer is prevented due to the synergies between the heated ESI in the ionization unit, the high-temperature heating block, the heated DL and the drying gas. Furthermore, thanks to the highly effective ion focusing of the newly developed ion guide (UF-Qarray), performance degradation due to electrode contamination can be reduced. The robustness of the modified ion optics was also assessed by injecting 2400 samples of alprazolam spiked into protein-precipitated human plasma extracts over a 6 day period (over 400 samples were injected each day). The RSD of peak area response was around 5% over this test period, using a deuterated internal standard (alprazolam-d5) the RSD was around 3%. As part of the robustness test the vacuum system was vented to model a transient power failure with no effect on signal response or baseline noise level.

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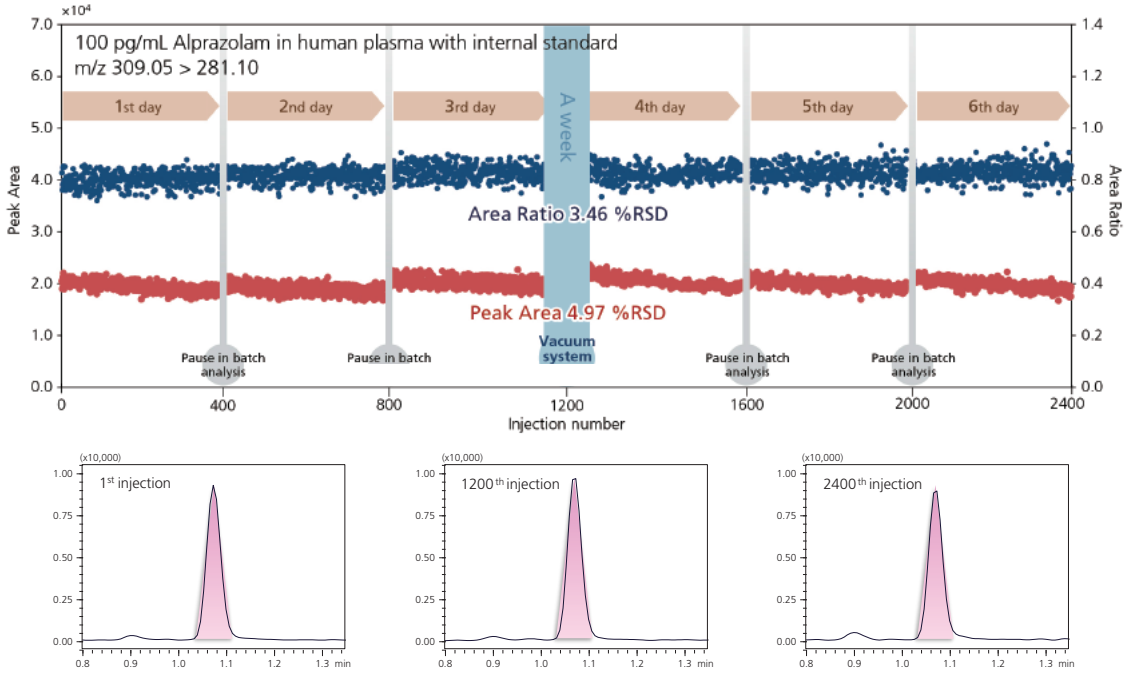

Figure 9 Long term stability study on LCMS-8060. (lower) MRM chromatograms for the 1st, 1200th and 2400th measurements of Alprazolam.

Table 3 Intra-day and inter-day variations on LCMS-8060.

Compound	%RSD							inter-day variation		
	1st day	2nd day	3rd day	4th day	5th day	6th day	Averaege	the former 3 days	the latter 3 days	total 6 days
Alprazolam	5.04	4.94	5.06	5.38	4.55	4.83	4.97	3.19	1.63	2.74
Alprazolam-d5 (ISTD)	5.04	4.68	5.48	5.31	4.26	4.91	4.95	2.62	1.89	2.18
Area ratio	3.48	3.11	3.48	3.44	3.71	3.54	3.46	1.79	0.26	1.40

Conclusions

- Development of ion introduction and ion transmission has brought significant improvements in sensitivity for a triple quadrupole mass spectrometer.
- With a data acquisition scan speed of 30,000 u/sec and a polarity switching time of 5 msec the LCMS-8060 brings new levels of data quality and confidence at the highest sensitivity.
- The LCMS-8060 provides highly reliable data even for the long, continuous analysis of matrix-matched samples such as biological and food samples.

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