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Technical Report

Technical Background for the LCMS-2050, a Compact Mass Detector for LC

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Abstract:

The LCMS-2050 single quadrupole mass spectrometer is highly compact in size, yet provides both high-speed and high-sensitivity analysis. Shimadzu's technology has been condensed into an instrument miniaturized to the utmost. In the pursuit of flawless usability, the LCMS-2050 mass spectrometer combines ease of use as an LC detector with excellent MS performance. This article will introduce the basic feature of a mass spectrometer, its advantages as an MS detector, and the impressive features of the LCMS-2050.

Keywords: LC, LC-MS, LC/MS, ESI, APCI, Quadrupole, High-speed analysis, Durability

1. LC-MS

Liquid chromatography (LC) is an analysis method in which samples are passed through a column; the sample compounds are retained to different extents by the column, separating them temporally; and these are detected as changes in an electrical signal when passed through a detector. The retention time within the column is determined by the chemical properties of the compound, so the compounds can be identified by their retention times. In addition, in general, the strength of the detector signal is proportional to the concentration of the compound, so this is used to quantify the amount of compound within the sample.

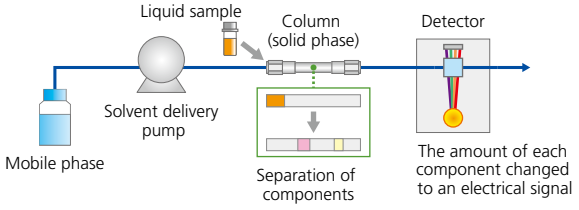
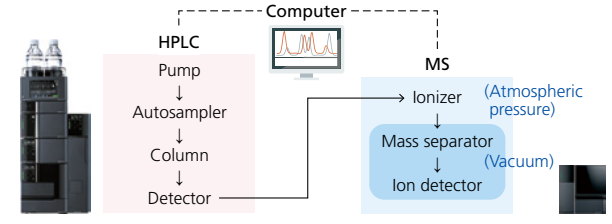


Fig. 1 Overview of HPLC Analysis

A mass spectrometer (MS) is an instrument that ionizes compounds, measures the ratio of their mass to charge (*m/z*), and obtains mass information (mass spectrum). Connecting an LC and MS in series makes it possible to analyze samples efficiently by combining the benefits of LC and MS. A mass spectrometer designed for this configuration is referred to as an LC-MS.

In an analysis using an LC-MS, mass spectra are obtained every several hundred millimeters corresponding to the elution of the compounds via LC. The data obtained is displayed as a Total Ion Current Chromatogram (TICC), in which the total value for the intensity of all the ions measured is plotted versus the LC retention times, or as a mass chromatogram (MC), in which specific *m/z* ion intensities are plotted. Fig. 3 shows examples of a chromatogram and MS spectrum from an MS detector.

With an LC alone, the peaks of components with similar retention times are inadvertently detected as overlapping, which prevents accurate analysis. However, with an LC-MS, the components are separated into individual peaks by drawing a mass chromatogram corresponding to their molecular weights. This is particularly useful when analyzing specific compounds contained in highly complex samples such as food products and biological samples. An analysis can be established easily even if separation by the column is incomplete, which reduces the labor involved in analytical method development and speeds up the process.



Basic Configuration of an LC

(1) **Pump**:	Delivers the mobile phase
(2) **Autosampler**:	Injects the samples
(3) **Column**:	Separates the components within the sample
(4) **Detector**:	Detects the separated components

Basic Configuration of an MS

(1) **Ionizer**:	Ionizes the components
(2) **Mass separator**:	Separates components by the difference in the mass charge ratio (*m/z*)
(3) **Ion detector**:	Detects the separated ions

Fig. 2 Basic Configuration of an LC-MS

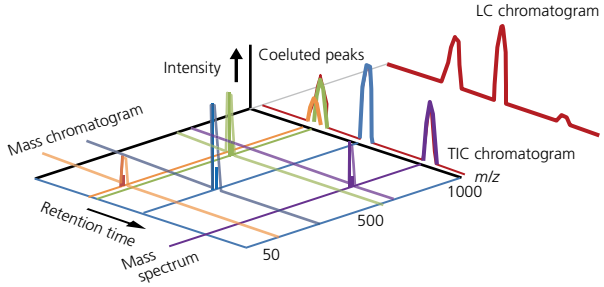


Fig. 3 Mass Chromatogram and Mass Spectrum Obtained by a Mass Spectrometer

1 Analytical & Measuring Instruments Division

2. Principles behind a Mass Spectrometer

2-1. Overview of Mass Spectrometers

Mass spectrometers ionize compounds and pass the ions through specific electric fields in order to detect them separately depending on the *m/z* of the ions. These instruments consist of an ionization unit, a mass separator, and an ion detector.

2-2. Ionizer

In LC/MS, there are mainly two ionization methods used: Electrospray Ionization (ESI) and Atmospheric Pressure Chemical Ionization (APCI). These are classified as soft ionization methods, and have the advantage of minimal energy transfer due to ionization, which means that the molecules are not decomposed by ionization. Molecular weight information for the compounds is easily obtained from the ions observed.

With ESI, high voltage is applied to the eluate from the column, producing charged droplets. The electrostatic repulsion force produced by the charge accelerates the splitting into smaller droplets and further desolvating, until finally the ions of the compound with charge are released in the gas phase. Spraying a so-called nebulizer gas enables efficient desolvating and ionizing even if the LC solvent flowrate is high.

In APCI, the eluate from the column is vaporized by the nebulizer gas and high temperatures, after which ions are produced by the corona discharge produced by a needle to which a high voltage is applied. Even analyte compounds that are hard to ionize directly can be ionized chemically through mutual interaction with the ionized solvent.

Fig. 4 shows an overview of these ionization methods, and Fig. 5 shows which compounds can be ionized respectively.

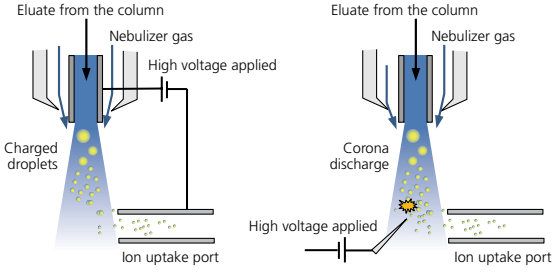


Fig. 4 Schematic Diagram of the Ionizer
(Left: ESI Method; Right: APCI Method)

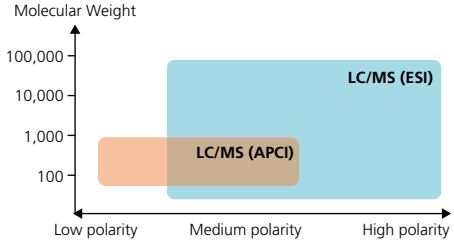


Fig. 5 Ionization Method and Applicable Compounds

2-3. Mass Separator

Ions with different *m/z* ratios differ little by little in their behavior in electric fields and magnetic fields. In a mass separator, ions are separated using this difference in behavior. There are various techniques for ion separation. However, the most widely used, and the one with which the LCMS-2050 is equipped, is called the quadrupole type. A quadrupole consists of four rods. Identical high-frequency voltage is applied to the 2 rods opposite each other. The ions are injected into the gap between the quadrupoles, and pass through while vibrating due to the electric field applied by the rods. At this point, the *m/z* ratio of the ions that pass through stably changes depending on the voltage. In other words, by adjusting the voltage, it is possible to select the ions passed through.

If the voltage applied to the rods is fixed at a specific value, it is possible to detect with high sensitivity only those ions with the corresponding *m/z* ratios. (Selected Ion Monitoring: SIM Mode) Scanning the voltage will scan for a wide range of *m/z* ratios, enabling a mass spectrum to be obtained. (SCAN Mode)

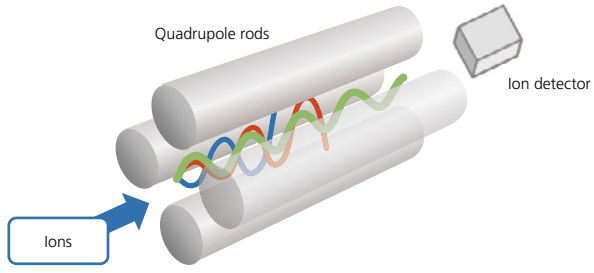


Fig. 6 Schematic Diagram of the Quadrupole Type Mass Separator and the Ion Detector

3. Features of the LCMS-2050

3-1. User-Friendly LC Detector

The design of the LCMS-2050 mass spectrometer is fully integrated with that of the Nexera™ series, and it is easy for LC users to operate, so it can easily be treated as an LC detector. It is the same size as other LC units, so it can be incorporated within systems. (Fig. 7) The LCMS-2050 can start an analysis 6 minutes after vacuum startup, so preparation for analysis can be completed during the LC setup.

Fig. 7 LCMS-2050

Fig. 8 shows the Operating Window for the LCMS-2050. Operations and data analysis can be performed using the LabSolutions™ control software, the same as for LC. LC/MS analysis can be performed simply by setting the measurement time, mass range, and sampling rate, so it can be used in the same way as a PDA detector that sets the measurement time, wavelength range, and sampling rate.

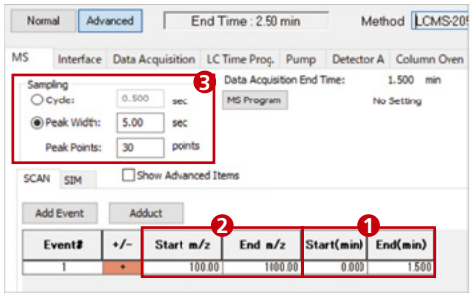


Fig. 8 LCMS-2050 Parameter Settings Window

Fig. 9 shows the configuration of the LCMS-2050. The ionizer is at the front, and the mass separator and ion detector are inside. The ionizer is also arranged with an ionization unit for autotuning that automatically performs sensitivity adjustments, resolution adjustments, and mass calibration in order to maintain instrument status. The instrument can be adjusted without replacing the piping, so instrument status is always optimal during use.

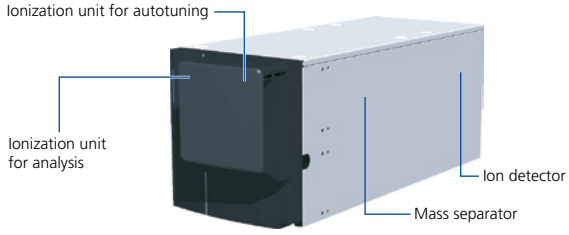


Fig. 9 LCMS-2050 Instrument Configuration

3-2. Wide Mass Range

Thanks to the quadrupole rods machined and assembled with high precision, the LCMS-2050 can detect *m/z* ratios up to a value of 2,000. Fig. 10 shows an example of the analysis of polyethylene glycols with different chain lengths. It is evident that isomer peaks can be separated even for high molecular weight compounds.

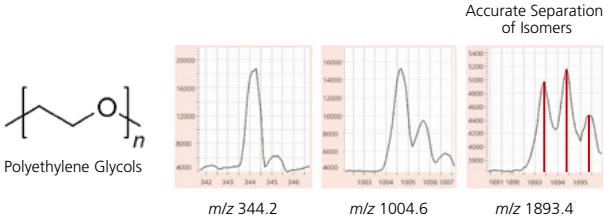


Fig. 10 Mass Spectrum for Polyethylene Glycols

3-3. Wide Ionization Range

The LCMS-2050 is equipped with an ionization unit (DUIS: Dual Ion Source) that provides both ESI and APCI functionality. Thanks to Shimadzu's proprietary DUIS technology, a wide range of compounds can now be analyzed in a single analysis when conventionally, ESI and APCI would have been separately required. Figs. 11 and 12 show schematic diagrams of the LCMS-2050 ionizer.

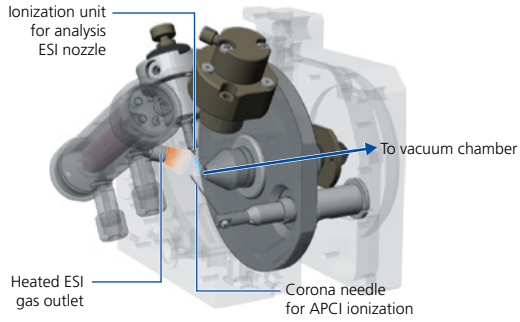


Fig. 11 Configuration of the LCMS-2050 Ionizer

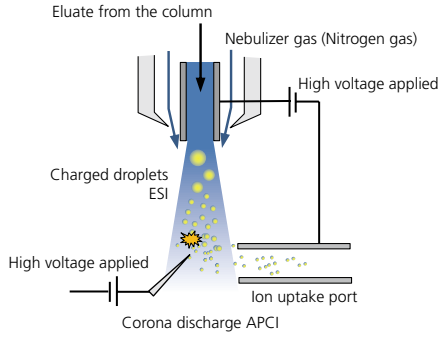


Fig. 12 Schematic Diagram of the LCMS-2050 Ionizer (ESI/APCI)

Fig. 13 shows the mass chromatograms for 2 compounds measured with ESI and DUIS. Simetryn is measured with good sensitivity using ESI, but quintozene is a low polarity compound, so it cannot be measured using ESI. When measured with DUIS, both of these compounds were detected with good sensitivity.

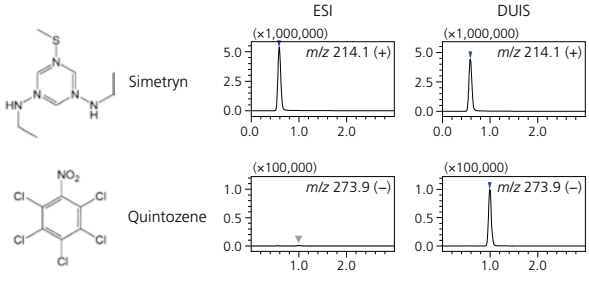


Fig. 13 Mass Chromatograms for Simetryn (Top) and Quintozene (Bottom), Measured with ESI and DUIS

3-4. High-Speed Data Collection

In order to measure a chromatogram correctly, a sufficient number of data points, normally about 10 to 20 points, is required for each peak. If the number of data points is insufficient, the shape of the original peak cannot be reproduced, which leads to variance in the quantitative results. (Fig. 14) To perform measurements with a high degree of repeatability, it is necessary to speed up data collection, reducing the cycle time.

The main contributor to shortening the cycle time with LC/MS is the capacity to scan a wide range of mass values in a short time (high-speed scan performance). In order to measure both positive ions and negative ions, the system must switch quickly between positive and negative ion modes. The LCMS-2050 is equipped with UFscanning™ and UFswitching™, so the same LC-MS unit provides the world's fastest scanning at 15,000 u/sec, and a 10 msec positive/negative ionization mode switching time. The technology for controlling high voltages quickly and accurately, cultivated by Shimadzu through the Ultra Fast Mass Spectrometry (UFMS) series, is also demonstrated in this compact LC-MS.

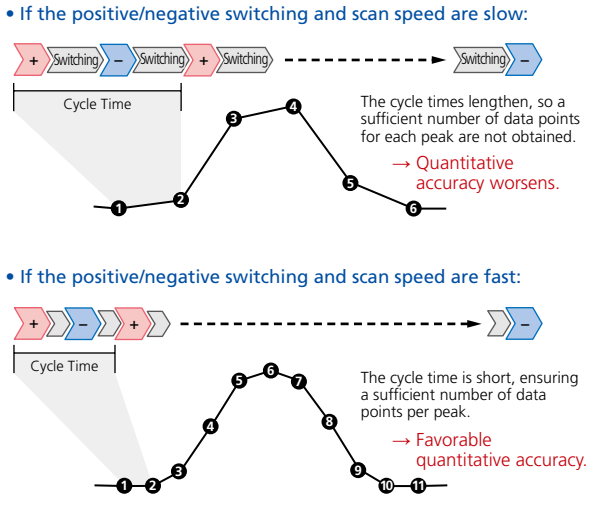


Fig. 14 Relationship between Cycle Time and Data Points

3-5. High Sensitivity and Impressive Dynamic Range

Mass spectrometers are generally capable of high sensitivity measurements, and the sensitivity of the LCMS-2050 does not disappoint even though it is compact. In a sensitivity test using reserpine, favorable area value repeatability was obtained with 1 pg measurements. (Fig. 15) Further, the system is capable of quantitative analysis across a wide dynamic range from 0.1 to 1,000 pg (4 digits).

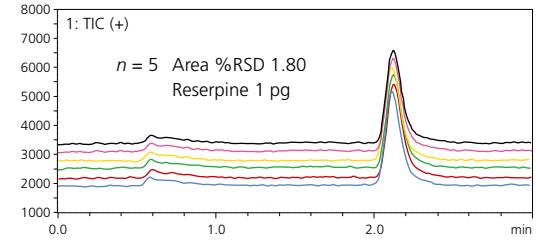


Fig. 15 MS Chromatogram for 1 pg Reserpine

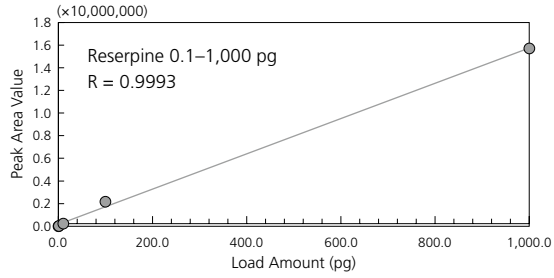


Fig. 16 Calibration Curve for Reserpine (0.1 to 1,000 pg)

3-6. Impressive Long Term Stability and Robustness

In LC/MS measurements, the stability and robustness of the instrument are very important. The long-term stability of peak intensity and mass accuracy is directly related to usability and improved productivity.

As an accelerated test in order to evaluate the robustness of the LCMS-2050, a 3,000 ng/µL solution was injected 1 µL at a time consecutively for 10,000 cycles over five days. This is equivalent to 15 months of operation in a usage environment in which 1,000 ng/µL are routinely analyzed. (100 analyses/day, 20 days/month) In this accelerated test, 10 ng/µL of propranolol was measured in each standardized injection, and the stability of the peak area value with respect to instrument contamination was evaluated.

The results obtained showed a favorable RSD of 8.5 % with respect to the peak area value when measured in SCAN mode. Fig. 18 shows the measurement procedures.

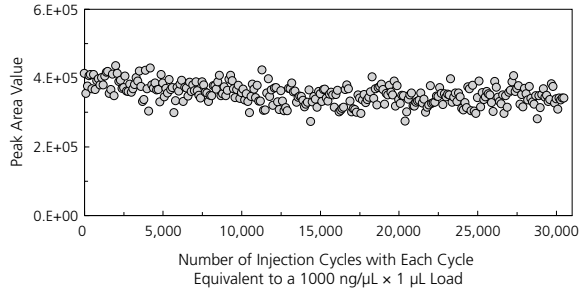


Fig. 17 Peak Area Value for a 10 ng/µL Propranolol Solution for Each Load Cycle

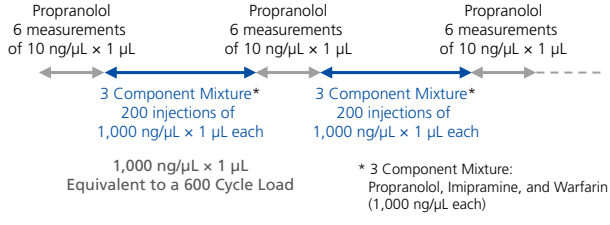


Fig. 18 Measurement Procedures for the Stability Test

Table 1 shows the *m/z* for 10 ng/µL propranolol measured every 6,000 injection cycles of a 1,000 ng/µL solution as the load amount. Throughout the five days of testing, the measured *m/z* remained within 0.1 u of the true value (260.17), indicating impressive mass stability.

Table 1 *m/z* Ratio for Propranolol Measured Every 6,000 Load Cycles

Load Amount	*m/z*	Deviation from True Value
0 cycles	260.14	−0.03
6,000 cycles	260.11	−0.06
12,000 cycles	260.12	−0.05
18,000 cycles	260.13	−0.04
24,000 cycles	260.14	−0.02
30,000 cycles	260.12	−0.05

The LCMS-2050 implements 3 contamination preventive measures to enable robust analysis.

1. A clog-resistant design has been adopted (patented technology) in which the vacuum exhaust system is optimized to ensure that the vacuum inside the instrument is maintained despite increasing the size of the ion uptake port.
2. The heated ESI gas vaporizes contaminants, eliminating them. Furthermore, spraying towards the top of the ion uptake port is designed to promote ionization while preventing contaminants from entering into the MS vacuum. (Patent Pending)
3. If a large amount of ions is injected into the mass analyzer such as when analyzing high concentration samples or highly contaminated samples, the precision quadrupole rods could become contaminated. In such cases, the ions are retained by the quadrupole rods, causing the sensitivity to drop. With the LCMS-2050, the voltage applied to the quadrupole rods is controlled so as to remove retained ions. This enables stable, contamination-resistant analysis.

In addition, if the ion uptake port becomes clogged, the ion uptake parts can be replaced without compromising the vacuum, so instrument downtime is minimized.

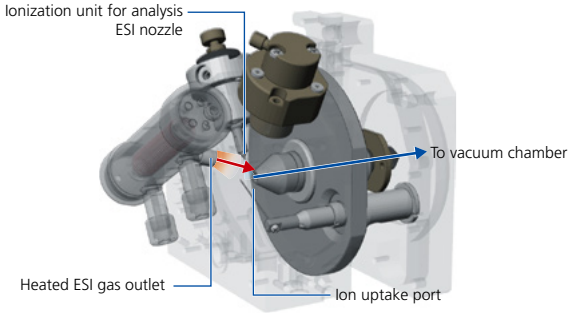


Fig. 19 Interior of the LCMS-2050 Ionizer

4. Summary

The LCMS-2050 is a highly versatile mass spectrometer that inherits and consolidates Shimadzu's accumulated technology within its compact body. It provides new value including enhanced mass range, ionization methods, and speed, while optimizing usability and robustness for LC users.

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