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Technical Report

High-Throughput Analysis Enabled by Ultra-Fast Gradient with Nexera X4 × LCMS-8060 Series

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Abstract:

LC-MS/MS is increasingly used even in clinical testing laboratories. Such laboratories need to reduce analysis times per sample and obtain results as quickly as possible. Drug discovery and pharmacokinetic studies handle large numbers of samples, so improving analysis efficiency directly increases laboratory productivity. This article describes ultra-fast, reliable gradient analysis using the Nexera X4 ultra high performance liquid chromatograph (UHPLC) in combination with an LCMS-8060RX triple quadrupole mass spectrometer.

Keywords: Nexera X4, Ultra-fast gradient, High throughput, Multi-analyte processing

1. Background

Speeding up LC-MS/MS drug concentration measurements in biological samples is critical for pharmaceutical and clinical fields. In particular, drug discovery and pharmacokinetic studies, which handle extremely large numbers of samples, faster analysis directly increases productivity. Faster LC-MS analysis requires shorter front-end LC times. Achieving this also demands multiple instrument capabilities simultaneously, including high gradient responsiveness and reduced system volume.

2. Nexera X4 Features

Nexera X4 is a next-generation ultra high performance liquid chromatograph (UHPLC) system that builds on technologies developed for previous Shimadzu Nexera series models. In addition, cutting-edge fluid control technology, which enables exceptional solvent delivery consistency for fast analysis under ultra-high pressure conditions, provides highly reliable results.

Figure 1: Nexera X4 × LCMS-8060 Series

3. Solvent Delivery Unit that Achieves High-Speed High-Precision Gradient

The LC-40B X4 solvent delivery unit is a binary gradient pump designed specifically for the Nexera X4 that features four independently actuated plungers and a new pressure feedback mechanism. It significantly reduces pulsation effects originating from the pump by actuating each plunger independently to optimize the timing of mobile phase suction and discharge. This enables ultra-fast gradients, provides stable solvent delivery under ultra-high pressure conditions, and results in more stable baselines.

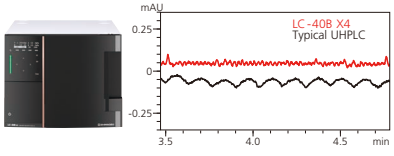

Figure 2: Baseline Fluctuation Reduction by LC-40B X4 in Nexera X4

4. Low-Capacity Design Enables Fast Gradients

Including the LC-40B X4 solvent delivery unit in the Nexera X4 successfully reduced the pump's internal volume and enabled a smaller gradient mixer. Consequently, the time required to restore gradients during ultra-fast gradient analysis can be reduced to an absolute minimum.

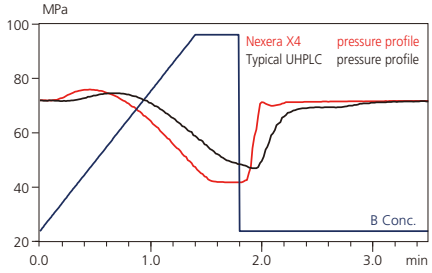

Figure 3: Comparison of Gradient Responsiveness of Typical UHPLC and Nexera X4 Systems

5. Nexflow Tubing for MS Reduces Peak Broadening during LC-MS Analysis

The Nexflow tubing for MS is a dedicated MS tubing kit, designed specifically for Nexera X4 systems, that reduces peak broadening between the column outlet and MS interface. The kit maximizes mass spectrometer performance based on the characteristically ultra-fast and high-separation performance of high-end UHPLC systems.

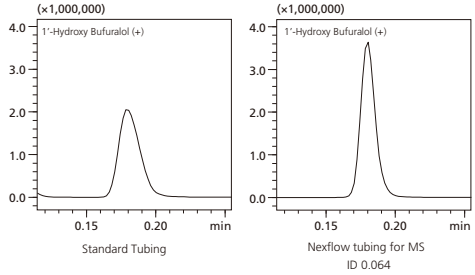

Figure 4: Examples of MS Chromatograms Obtained Using Nexflow Tubing for MS

1 Analytical & Measuring Instruments Division

6. Analysis

6.1 Target Analytes and Analytical Conditions

Target compounds are listed in Table 2 and analytical conditions are shown in Table 1.

Table 1: Nexera X4 and LCMS-8060RX Analytical Conditions

HPLC conditions	
System	: Nexera X4
Column	: Shim-pack Scepter™ C18 *1 (20 mm × 2.1 mm I.D., 1.9 µm)
Temperature	: 40 ˚C
Injection volume	: 1 µL (15 µL Sample loop)
Mobile phases	: A 0.05 % formic acid in Water B Acetonitrile
Flow rate	: 0.6 ml/min
Time program	: B conc. 25 % (0.00 min) → 60 % (0.10 min) → 90 % (0.30-0.45 min) → 25 % (0.46-0.60 min)
MS conditions	
System	: LCMS-8060RX
Ionization	: ESI, Positive and Negative mode
Interface voltage	: ±1.0kV
Mode	: MRM
Nebulizing gas flow	: 3 L/min
Heating gas flow	: 15 L/min
Interface temp.	: 400 ˚C
DL temp.	: 200 ˚C
Block heater temp.	: 400 ˚C
Drying gas flow	: 5 L/min

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6.2 Ultra-Fast Analysis of CYP-related compounds

The chromatograms obtained are shown in Figure 5. This analysis was performed with a measurement time setting of only 0.6 minutes (36 seconds), which achieved separation in an extremely short time.

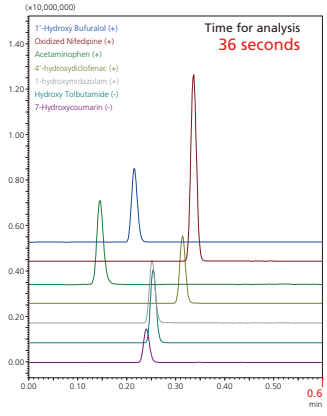

Figure 5: Chromatograms from Ultra-Fast LC-MS/MS Analysis of 7 Types of CYP-related compounds

6.3 Evaluation of Retention Time and Area Reproducibility

The target compounds are listed in Table 2. Retention time reproducibility was a very good 0.2 %RSD, confirming that analytical stability was maintained even under fast gradient conditions. In addition, the LCMS-8060 series features Shimadzu's proprietary UFswitching™ high-voltage power supply technology, enabling ultra-fast 5 msec switching between positive and negative ionization modes. This mechanism enables rapid switching between positive and negative polarities, ensuring sharp peaks without loss of ion intensity and maintaining excellent quantitative accuracy, even when multiple peaks elute simultaneously (Figure 6). The reproducibility of peak area values for target compounds was also evaluated for this article, which indicated an excellent 5 %RSD result.

Table 2: List of Target Compounds

Compound	Polarity	*m/z*	Retention time (min)	RT %RSD	Area	Area %RSD
1'-Hydroxy Bufuralol	(+)	256.10>238.10	0.214	0.14	2485474	2.37
Oxidized Nifedipine	(+)	345.10>284.10	0.337	0.11	6510872	2.82
Acetaminophen	(+)	152.10>110.00	0.146	0.10	708714	2.87
4'-hydroxydiclofenac	(+)	312.00>231.10	0.315	0.11	399563	4.22
1-hydroxymidazolam	(+)	342.10>324.10	0.251	0.20	2066492	3.15
Hydroxy Tolbutamide	(-)	285.10>186.00	0.254	0.20	445907	4.14
7-Hydroxycoumarin	(-)	161.00>133.10	0.240	0.10	64490	4.90

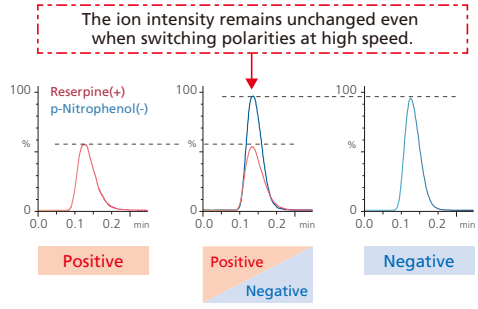

Figure 6: Comparison of Measurements Using High-Speed Positive/ Negative Ion Switching (5 msec) and Separate Positive and Negative Ion Modes

7. Conclusions

- Due to the four independently actuated plungers and a pressure feedback mechanism, the LC-40B X4 offers consistent solvent delivery and a stable baseline under ultra-high pressure conditions.
- The Nexera X4 reduces gradient delay during ultra-fast gradient analysis by reducing the system volume.
- Combining Nexera X4's superior fast gradient capability with UFswitching of the triple quadrupole mass spectrometer delivers a next-generation LC-MS solution offering speed and reliability.

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