

Nota applicativa

## Exploring the Impact of Part Per Billion Mass Accuracy for Metabolite Identification using Multi Reflecting Time of Flight MS with UPLC™ Part B

---

Michael McCullagh, Martin Palmer, David Eatough, Emma Marsden-Edwards, James I. Langridge, Dale Cooper-Shepherd

Waters Corporation

---

### Abstract

Over a 24-hour period LC-MS accurate mass measurement performance in negative ion electrospray (ES-) mode has been assessed using a SELECT SERIES™ Multi Reflecting Time-of-Flight (MRT) mass spectrometer, for the identification of multiple pharmaceutical therapeutic drugs and corresponding metabolites. An RMS error of 761 part-per-billion (ppb) has been obtained for 1813 metabolite detections, along with ppb mass accuracy for MS<sup>E</sup> data independent analysis (DIA) fragment ions.

Precursor and fragment ion ppb accurate mass measurement has been obtained routinely and metabolite identification performed using stringent post detection data processing tolerances. PPB mass accuracy enhances confidence in identification of small molecule metabolite species detected for the urinary screening analysis undertaken.

The UPLC-MS<sup>E</sup> ES- non-targeted DIA assay has been performed at an acquisition rate of 10 Hz, with a system mass resolving power >200,000 FWHM. Uncompromised acquisition duty cycle at high mass resolution facilitates

---

optimum chromatographic peak fidelity and combined with ppb mass accuracy has enabled certainty in the observation of coeluting isomeric species to be attained.

Overall ppb mass accuracy and fine isotope structure characteristics observed using >200,000 FWHM system mass resolving power has facilitated the identification of metabolites of three therapeutic drugs present in a patient's urine sample, where infrequently reported metabolites have been detected.

## Benefits

### Ultimate compound identification confidence and reduced false detection rates

- Enhanced analysis efficiency
- Routine ppb mass accuracy for precursor and DIA MS<sup>E</sup> fragment ions
- Fine isotope structure can provide an additional criterion to enhance identification confidence for small molecule therapeutic drugs and metabolites
- Enhanced analyte detection in complex biological matrices using system mass resolving power >200,000 FWHM
- Uncompromised 10 Hz acquisition duty cycle to retain chromatographic peak fidelity

---

## Introduction

The SELECT SERIES MRT (Figure 1) is a state-of-the-art hybrid quadrupole MRT mass spectrometer. It provides a unique combination of high mass resolving power (200,000 FWHM), and routine ppb mass accuracy, independent of acquisition speed. High resolution mass spectrometers (HRMS) such as quadrupole time of flight mass analyzers (Q-ToF), have become more prevalent as screening tools in many research areas e.g., food and environmental analysis, natural product profiling, metabolomics, clinical, forensic toxicology, and metabolite identification, where the constituents of interest are present in complex matrices.

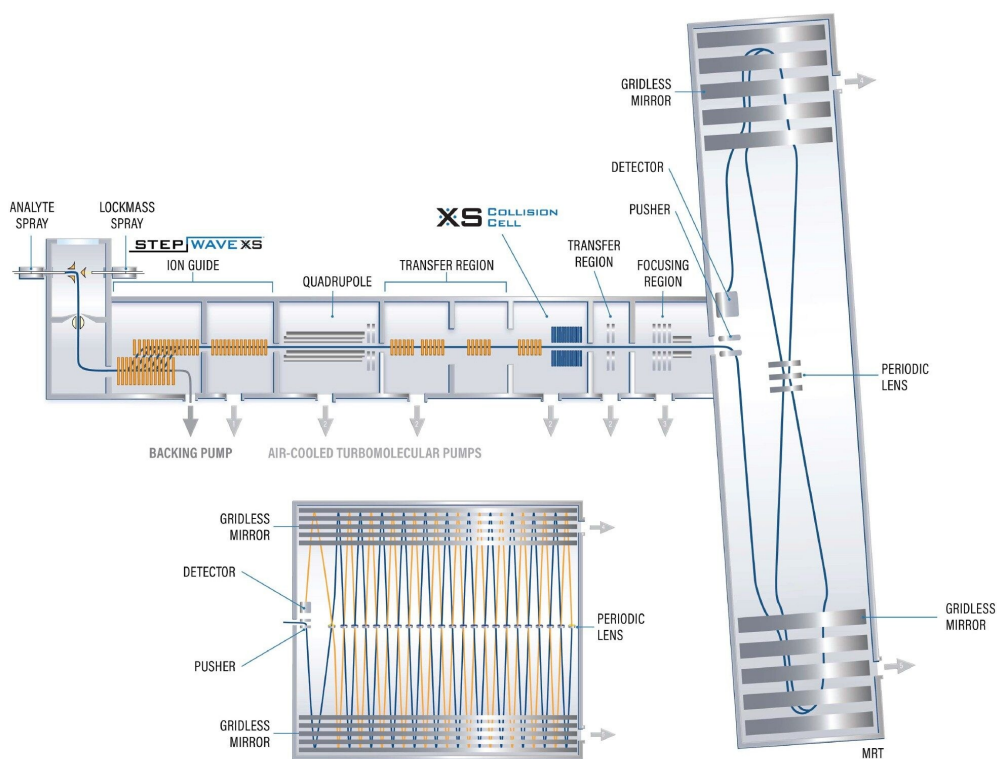


Figure 1. SELECT SERIES MRT instrument schematic.

The number of compounds screened for using targeted acquisition methodology is typically restricted and relies upon reference standards to generate characteristic MS libraries; for a targeted analytical strategy mass spectral data is not generated for unknowns. Mass spectrometry library databases (10's to 1000's of library entries) incorporating retention time, molecular formula (accurate mass), and expected product ions are used to screen for known analytes, using non-targeted acquisition strategies. Subsequently appropriate data processing filters can be applied to determine the presence of a compound in a sample and reduce the false detection rate, produced by thousands of analyte detections.<sup>1</sup> Although an analytical challenge, unbiased data acquisition is a necessity to produce complete sample characterization, whilst simultaneously performing identification of knowns and unknowns.

Utilizing an unbiased data acquisition strategy such as DIA where all precursor and fragment ions are acquired, facilitates a representative profile of whole sample composition to be attained. Although DIA MS<sup>E</sup> acquisition is not as selective as MS/MS or DDA strategies, the MS<sup>E</sup> specificity is enhanced using the MRT system resolving

power >200,000 FWHM.<sup>2</sup> High mass resolution enhances ion selectivity of analytes in complex matrices, subsequently providing high mass accuracy and detectability which in turn enhances analyte identification confidence. Fragment ions can be mass resolved from coeluting isobaric matrix components. As a result, retention time aligned precursor/fragment ions with high mass accuracy are observed, facilitating reliable CID spectral interpretation. The number of possible elemental compositions generated with ppb high mass accuracy data is reduced and consequently there is a high degree of confidence in analyte identification. MRT routine ppb mass accuracy performance results in high quality mass spectrometry data, facilitating a high degree of credence in analyte elemental compositions generated in non-targeted screening workflows. In conjunction with fine isotope structure, enhanced mass accuracy specificity can be utilized to improve identification certainty in research areas involving small molecules, such as metabolite identification.

A non-targeted urinary screen of a healthy human volunteer has previously been performed, using an ES+ metabolite identification workflow, with Ultra Performance LC™ coupled to a SELECT SERIES MRT (system resolution >200,000 FWHM).[waters apps note: [720007896](#), April 2023] Naproxen, carbamazepine, acetaminophen therapeutic drugs, and metabolites, were identified. To illustrate the comprehensive benefits of high mass resolution performance a comparative ES- non-targeted urinary screen is presented.

---

## Experimental

### Sample Description

Human urine sample diluted 10:1 (H<sub>2</sub>O)

Carbamazepine dosage: 2 x 200 mg tablets.

Acetaminophen dosage: 2 x 500 mg tablets.

Naproxen dosage: 1 x 500 mg tablet.

Sample time points: 0, 2, 4, and 6 hours after medication was administered.

### LC Conditions

LC system:

Waters™ ACQUITY UPLC I-Class

Premier chromatograph

Column:	ACQUITY UPLC HSS T3 C <sub>18</sub> (100 mm x 2.1 mm, 1.8 µm) Column
Column temperature:	40 °C
Sample temperature:	4 °C
Injection volume:	5 µL
Flow rate:	0.5 mL/min
Mobile phase A:	Water (containing 0.1% formic acid v/v)
Mobile phase B:	Acetonitrile (containing 0.1% formic acid v/v)

## Gradient Table

Time (min)	Flow (mL/min)	%A	%B	Curve
0.0	0.5 mL/min	99	1	initial
1.0	0.5 mL/min	99	1	6
3.0	0.5 mL/min	85	15	6
6.0	0.5 mL/min	50	50	6
9.0	0.5 mL/min	5	95	6
10.0	0.5 mL/min	5	95	6
10.1	0.5 mL/min	99	1	6
12.0	0.5 mL/min	99	1	6

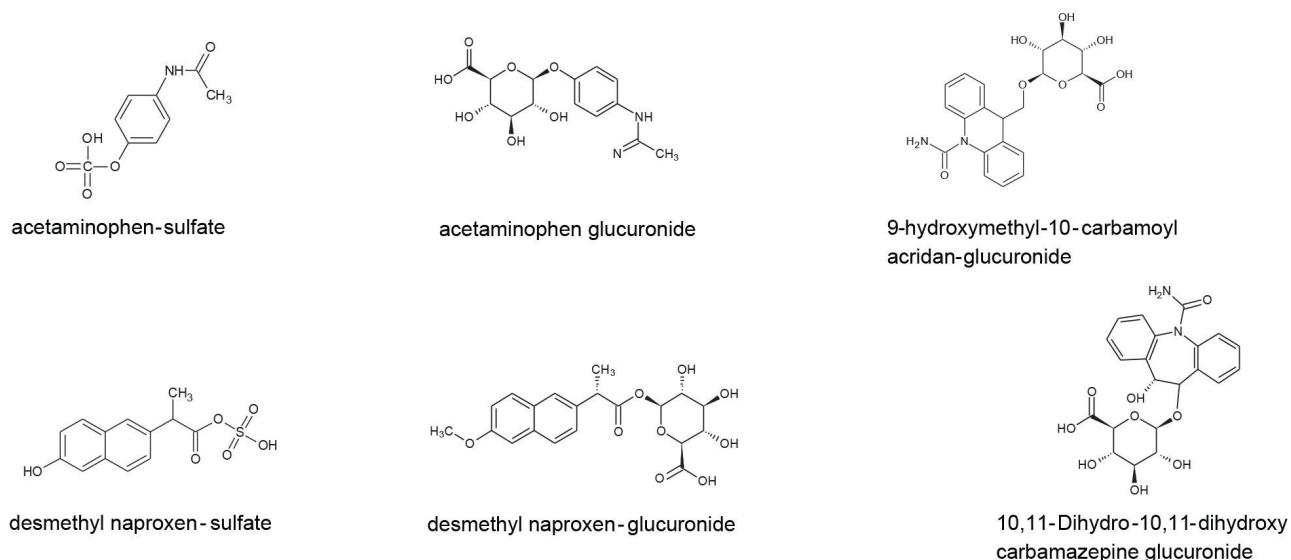
## MS Conditions

Acquisition:	ES-
--------------	-----

Capillary voltage:	1 kV
Desolvation temperature:	500 °C
Source temperature:	120 °C
Cone voltage:	20V
MS <sup>E</sup> Collision energy ramp:	15-45 eV
Mass range:	<i>m/z</i> 50–2400
Acquisition rate:	10 Hz
Acquisition/Processing software:	MassLynx v4.2 SCN1026 and waters_connect™ 3.1.0.243

---

## Results and Discussion



*Figure 2. Example metabolites identified for a UPLC-MS<sup>E</sup> ES- human urinary screen, for therapeutic drugs acetaminophen, carbamazepine and naproxen using a metabolite identification workflow.*

Publication of the FDA MIST guidelines in 2008 initiated major changes in experimental strategies employed within the pharmaceutical industry, to identify, quantify and improve metabolite coverage.<sup>4</sup> For drug candidates developed in pharmaceutical discovery and development, formation of reactive and potentially toxic metabolites during metabolism is a continuing challenge. In the case of the formation of acyl or ester glucuronidation which have an association with drug toxicity, has led to instances of drug withdrawal.<sup>5</sup> Metabolite identification is an important part of the drug development process where the metabolic fate of a drug molecule is investigated. Time efficient clinical/nonclinical studies to generate biotransformation identification with certainty is essential. Mass spectrometry techniques with high specificity are required for structural elucidation. Here we describe the use of ACQUITY Ultra Performance LC coupled with a SELECT SERIES MRT, for the LC-MS analysis of drug metabolites. A urinary screen of a healthy human volunteer has been performed to identify therapeutic drugs and metabolites, using a metabolite identification workflow with LC-MS (resolving power >200,000 FWHM). Performing UPLC-MS<sup>E</sup> ES+ and UPLC-MS<sup>E</sup> ES- provides a route to comprehensive analysis to characterize knowns and unknowns.

Performing a LC-MS urinary screening of a healthy volunteer patient, therapeutics drugs acetaminophen (analgesic), naproxen (nonsteroidal anti-inflammatory) and carbamazepine (anticonvulsant) were identified in

the time course point samples (2, 4, and 6 hours post dose). Presented in Figure 2 are example metabolites identified using UPLC ES- and Figure 3 shows an example of an MRT-LC-MS ES- chromatographic complexity obtained at 10 Hz for the analysis of the biologically complex human urine sample. Using the extracted mass chromatogram of carbamazepine-N-glucuronide as an example, 19 data points are obtained across a 3.6 second base peak width. The corresponding continuum mass spectrum is shown in Figure 3 (II), where mass resolution  $>189,000$  FWHM was obtained at  $m/z$  411. The data illustrates UPLC ES- DIA analyses can be performed across the mass range, where at low  $m/z$ , duty cycle is not compromised to retain high mass resolving power and chromatographic fidelity is retained.

The therapeutic drugs discussed herein, ionize preferentially using ES+. However, using ES-, additional metabolite confirmation and discovery can be attained where ES+ and ES- metabolite screening assays are performed. In addition to improved ionization efficiency, for example in the case of phase II glucuronide and sulfate conjugates. Importantly identification confidence is enhanced where ES+ and ES- ppb mass accuracy is obtained routinely. As shown in Table 1, RMS mass measurement error for acetaminophen sulfate (882 ppb), acetylcysteine acetaminophen (740 ppb) and acetaminophen glucuronide (773 ppb) have been attained over a 24-hour period, for repeat analysis of the human urine time course point samples. Overall, an RMS error of 761 ppb (detections  $N=1813$ ), has been obtained for the metabolites shown in Table 1, which are comprised of small molecules between  $m/z$  150 and  $m/z$  427.



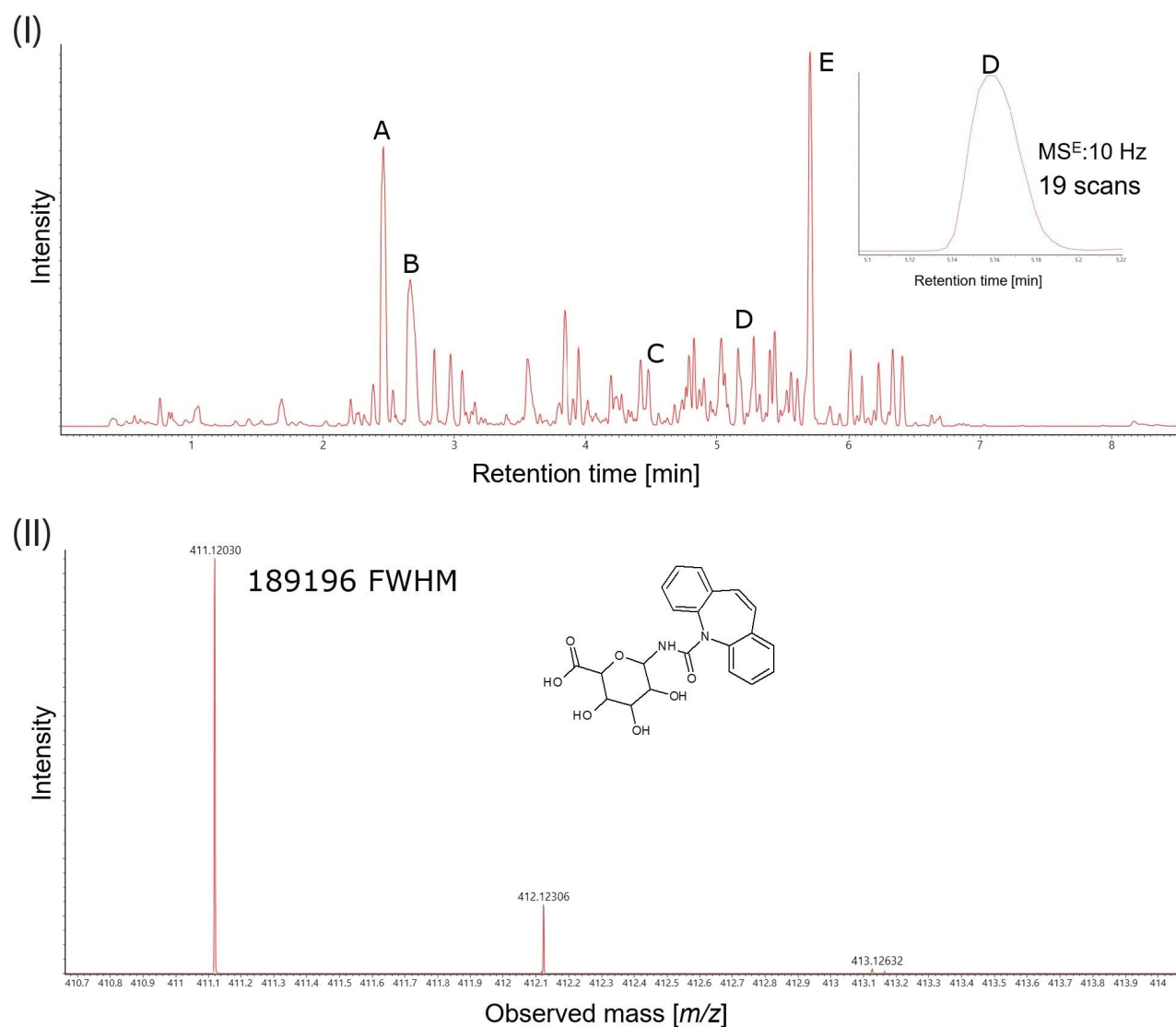


Figure 3. MRT-LC-MS ES- expanded base peak ion chromatogram for the analysis of therapeutic xenobiotics and metabolites identified in the urine of a healthy volunteer patient. a) acetaminophen glucuronide, b) acetaminophen sulfate, c) carbamazepine-O-glucuronide, d) carbamazepine-N-glucuronide, and E) naproxen glucuronide. Inset expanded extracted mass chromatogram of carbamazepine-N-glucuronide. II)  $m/z$  411  $[M-H]^-$  mass spectrum of carbamazepine-N-glucuronide.

Confidence in therapeutic drug xenobiotics and metabolite identification, is further enhanced where DIA fragment ions are generated using  $MS^E$  and resolved from matrix interference. In Figure 4 an example of 10 Hz

UPLC MRT ES- precursor and fragment ion spectra obtained for [acetaminophen sulfate - H]<sup>-</sup> is presented with measurement error between -58 ppb (*m/z* 150) and 28 ppb (*m/z* 230). Sub 1ppm mass accuracy is observed for fragment ion *m/z* 80, where mass resolution >115,000 FWHM at 10 Hz is attained respectively. Alongside routine precursor/fragment ion ppb mass accuracy, characteristic fine isotope structure also provides an additional identification criterion, as illustrated for the [M-H]<sup>-</sup> A+1 and A+2 isotopes of acetaminophen sulfate (see Figure 4 (II)).

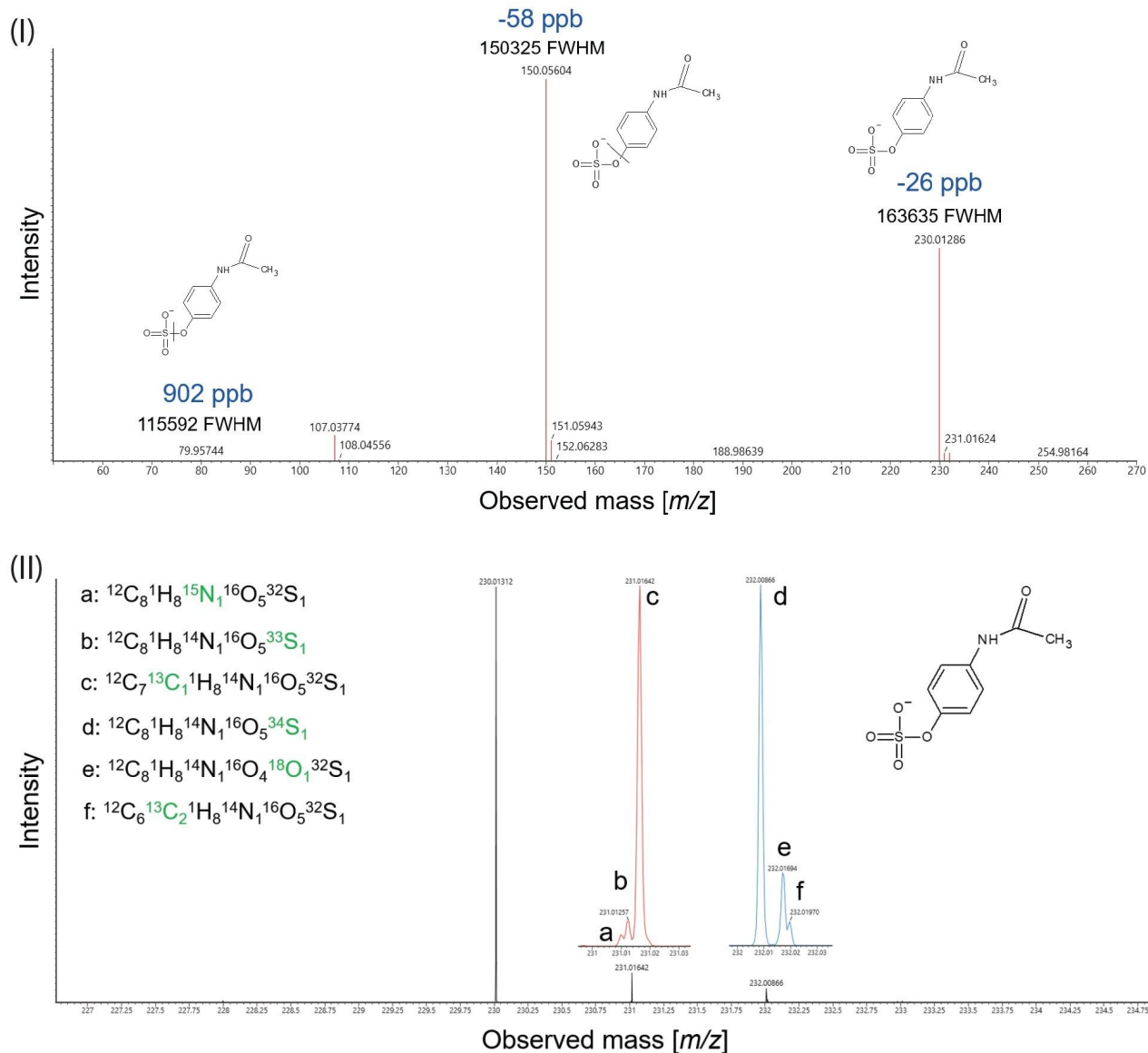


Figure 4. I) 10 Hz UPLC MRT ES- precursor and fragment ion spectra obtained for [acetaminophen sulfate -H]<sup>-</sup>. II) [Acetaminophen sulfate -H]<sup>-</sup> confirmatory fine isotope structure obtained using 10 Hz UPLC MRT ES-.

In the case of Naproxen, using ES+ chromatographic peak shape characterization 1-β-O and 2, 3, 4-O isomeric acyl glucuronide ES+ [M+Na]<sup>+</sup> species were observed at  $t_r$  = 5.59, 5.69/5.73 (coeluting) and 5.86 minutes, corresponding [M-H]<sup>-</sup> species have been detected routinely with ppb mass accuracy, providing additional identification confidence.<sup>6,7</sup> For these species greater ES- ionization efficiency has enabled an additional

isomeric naproxen acyl glucuronide species to be identified at 5.95 minutes, with an RMS mass measurement error of 744 ppb. Also, ppb mass accuracy for the observed fragment ions reinforces certainty in the identification of the unknown isomeric entity (see Figure 5).

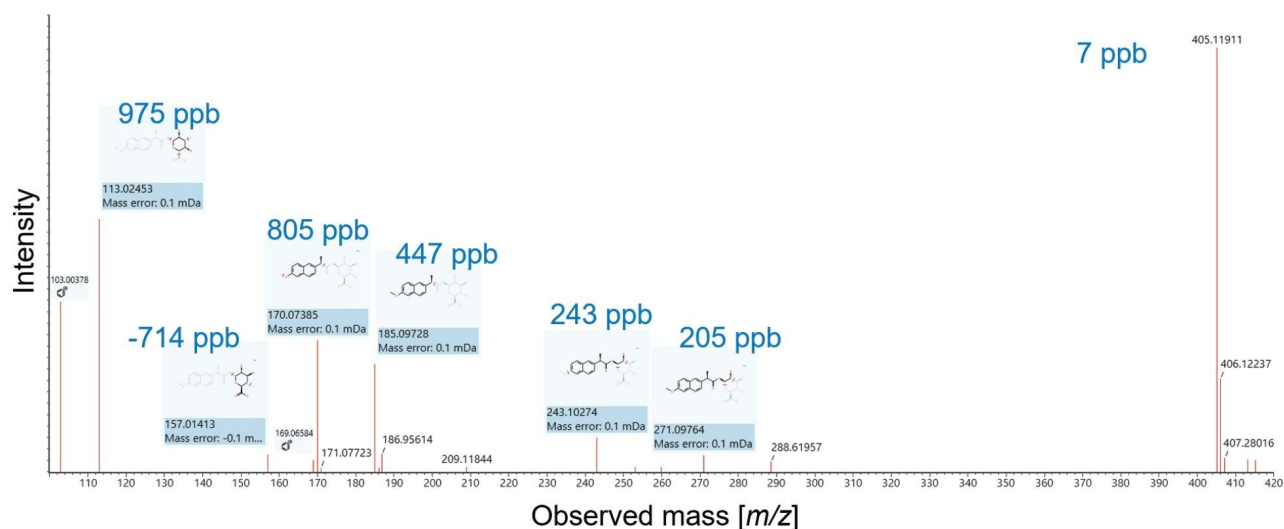


Figure 5. 10 Hz UPLC MRT ES- precursor and fragment ion spectra obtained for  $[naproxen\ glucuronide-H]^-$ .

Desmethyl naproxen glucuronide  $[M-H]^-$  species corresponding to the ES+  $[M+Na]^+$  have been detected, which is observed at  $t_r$  4.83 minutes, and identification was determined with a precursor ion RMS mass measurement error of 950 ppb. It has been reported that 95% (85% are naproxen glucuronide or 6-O-desmethyly naproxen glucuronide) of orally administered naproxen and its metabolites are recovered in urine.<sup>8</sup> Absence of a free naproxen hydroxyl group determines that naproxen sulfation is not observed. Although not commonly reported, sulfation of 6-O-desmethyl naproxen is observed. It accounts for 11% of dose and desmethyl naproxen sulfate ( $[M-H]^-$   $m/z$  295) has been identified at  $t_r$  4.75 minutes, where mass accuracy of 21 ppb is illustrated (see Figure 6 (I)).<sup>9</sup> The metabolite identification is confirmed with a high degree of confidence, where product ions  $m/z$  171 ( $m/z$  261 ppb) and  $m/z$  143 (28 ppb) have been determined. Additionally characteristic fine isotope structure provides another identification criterion (see Figure 6 (III)).<sup>10,11</sup> In the DIA fragment spectrum illustrated in Figure 6, a peak at  $m/z$  331 is observed, this peak also has fine isotope structure indicative of a species with an elemental composition inclusive of sulfur (shown in Figure 6 (III)). Using ES- metabolite identification workflow, it was determined that a phase II sulfonated biotransformation product of carbamazepine had been observed. Such metabolites are also not commonly reported, however at  $t_r$  4.75 minutes the precursor ion  $m/z$  331 (68 ppb) and

fragment ions ( $m/z$  251 (216 ppb)/ $m/z$  208 (68 ppb) are observed.<sup>12-16</sup> The routine and reproducible attainment of ppb mass accuracy precursor and fragment ion spectra obtained provides additional support for proposed identification of a carbamazepine hydroxy sulfate metabolite. From Figure 6, it can be seen, using DIA with sub ppm mass accuracy there is correlation of the respective fragment ions of desmethyl naproxen sulfate and carbamazepine hydroxy sulfate species, illustrating highly specific data has been obtained using a DIA acquisition strategy.

Finally, the observed time course response profile is indicative of a true biotransformation, where observed biotransformation species are not detected in time course point T0 or exhibit a different response than the latter time course points analyzed. To assess ES- assay robustness and mass accuracy, the experiments performed comprised replicate injections of solvent blank (N=3), post dose time course points 0, 2, 4, and 6 hours, with repeat data set analyses carried out continuously over a 24-hour period. In Figure 7 we illustrate reproducibility via the metabolism trend plots of therapeutic xenobiotics identified, acetaminophen, carbamazepine-O-glucuronide, and naproxen.

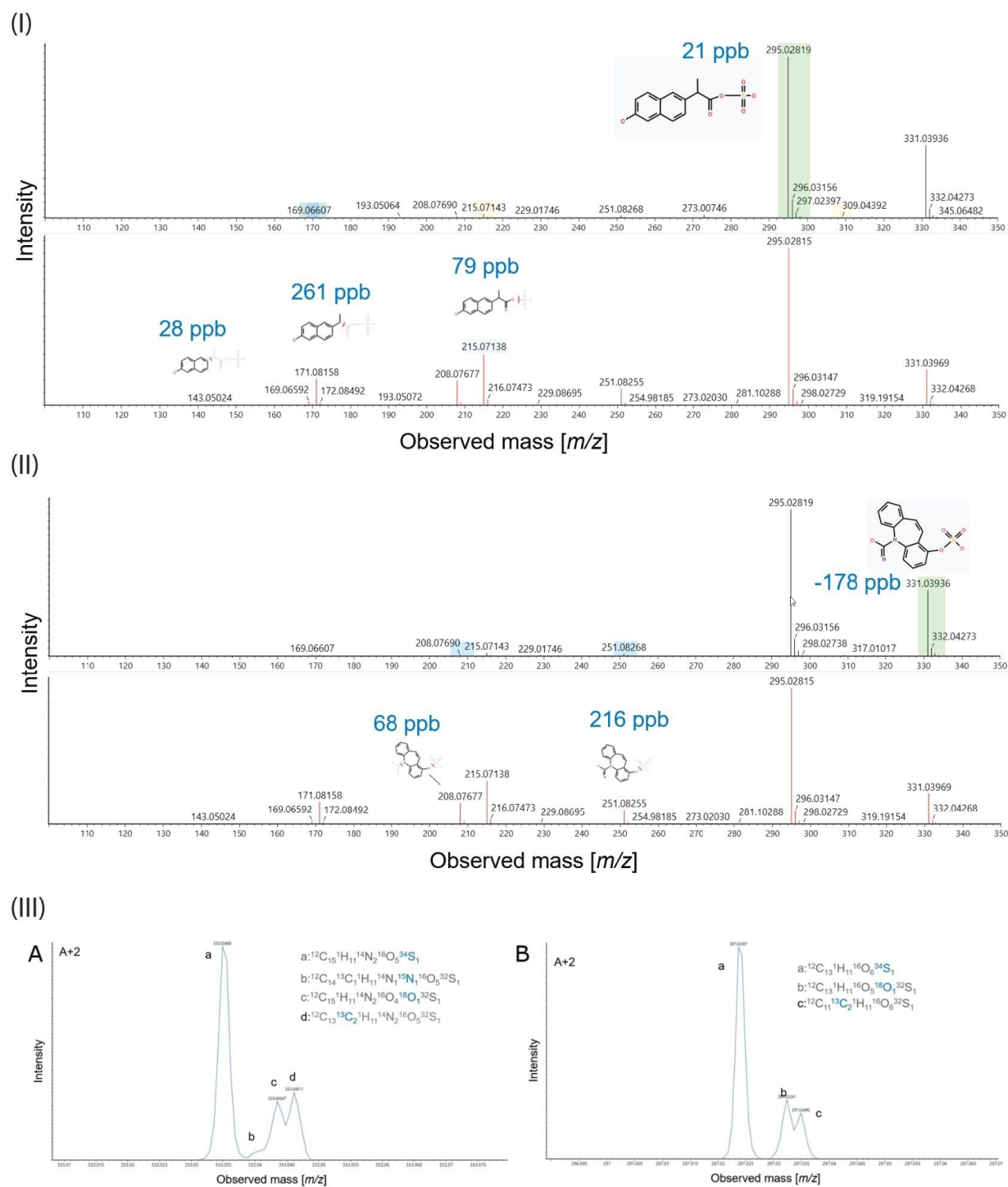


Figure 6. ES- data independent analysis precursor and fragment ion spectra obtained for coeluting I) [desmethyl

---

*naproxen sulfate - H]<sup>-</sup> and II) [carbamazepine-O-sulfate - H]<sup>-</sup>. III) (A) carbamazepine-O-sulphate<sup>-</sup> and (B) desmethyl naproxen sulfate confirmatory A+2 fine isotope structure obtained using 10 Hz UPLC MRT ES-.*

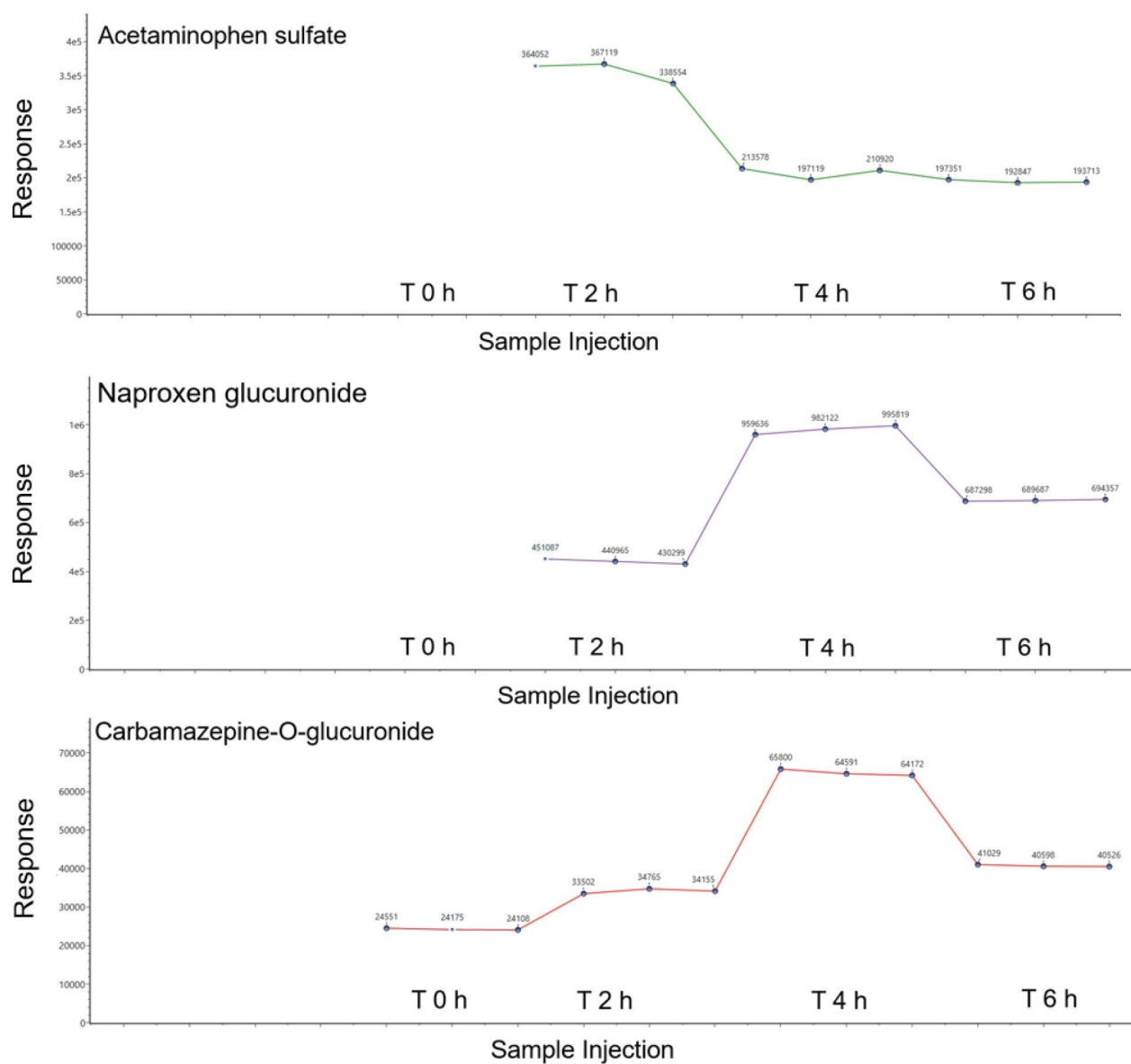


Figure 7. 10 Hz UPLC MRT ES- metabolism response trend plots (post dose time course points 0, 2, 4, and 6 hours) for therapeutic drug metabolites identified in a human urine sample using a metabolite identification workflow.



Therapeutic xenobiotic/metabolite	Adduct	m/z	RMS error ppb	Retention time (t <sub>r</sub> )/minutes
Acetaminophen sulfate	[M-H] <sup>-</sup>	230.01287	882	2.72
Acetaminophen glucuronide	[M-H] <sup>-</sup>	326.08814	773	2.40
Acetaminophen acetyl cysteine	[M-H] <sup>-</sup>	311.07072	740	3.53
Acetaminophen sulfate	[M-H] <sup>-</sup>	230.01287	928	2.55
10,11-dihydroxy carbamazepine glucuronide	[M-H] <sup>-</sup>	443.10960	585	4.32
Carbamazepine-N-glucuronide	[M-H] <sup>-</sup>	411.11977	719	5.16
carbamazepine-10,11-epoxide-N-glucuronide	[M-H] <sup>-</sup>	427.11469	716	4.73
Hydroxy 9-hydroxymethyl-10-carbamoyl acridan-O-glucuronide	[M-H] <sup>-</sup>	445.12525	654	4.02
10,11-Dihydro-10,11-dihydroxy Carbamazepine glucuronide	[M-H] <sup>-</sup>	445.12525	709	4.42
9-hydroxymethyl-10-carbamoyl acridan-O-glucuronide	[M-H] <sup>-</sup>	429.13034	664	5.03
carbamazepine-O-glucuronide 1	[M-H] <sup>-</sup>	427.11469	745	4.18
carbamazepine-O-glucuronide 2	[M-H] <sup>-</sup>	427.11469	687	4.24
carbamazepine-O-glucuronide 3	[M-H] <sup>-</sup>	427.11469	641	4.47
carbamazepine-O-glucuronide 4	[M-H] <sup>-</sup>	427.11469	791	4.88
carbamazepine-hydroxy-sulfate 1	[M-H] <sup>-</sup>	331.03942	784	4.62
carbamazepine-hydroxy-sulfate 2	[M-H] <sup>-</sup>	331.03942	814	4.75
carbamazepine-hydroxy-sulfate 3	[M-H] <sup>-</sup>	331.03942	865	5.24
Naproxen glucuronide 1	[M-H] <sup>-</sup>	405.11911	663	5.59
Naproxen glucuronide 2/3*	[M-H] <sup>-</sup>	405.11911	540	5.68/5.73
Naproxen glucuronide 4	[M-H] <sup>-</sup>	405.11911	734	5.85
Naproxen glucuronide 5	[M-H] <sup>-</sup>	405.11911	744	5.95
Desmethyl naproxen glucuronide	[M-H] <sup>-</sup>	391.10346	950	4.83
Desmethyl naproxen sulfate	[M-H] <sup>-</sup>	295.02818	866	4.75

Table 1. RMS accurate mass measurement obtained for detection of therapeutic xenobiotics and metabolites for analyses performed over a period of 24 hours using UPLC ES-.

## Conclusion

Routine ppb mass accuracy has been attained for precursor and fragment ions when performing a complex

urinary non-targeted screening analysis using LC-MS negative ion electrospray at 10 Hz, which encompassed a system resolving power of >200,000 FWHM. Achieving RMS 754 ppb level mass accuracy over a 24-hour period has enabled confident identification of major and minor metabolites of a combination of therapeutic drugs, in the urine samples of a volunteer patient. Overall, the high- resolving power ppb mass measurement performance illustrated, reduces the number of potential elemental compositions determined for small molecule identification, which is substantially beneficial when dealing with knowns and unknowns. In the case of naproxen, five O-glucuronide species were identified, although not all fully resolved, the fifth identification could be made with certainty where isomeric chromatographic fidelity was retained at 10 Hz duty cycle. Combined with precursor/fragment ion ppb mass accuracy, confidence could be had from the informatics metabolite workflow assignment. In this complex analysis fine isotope structure has proven to be an invaluable and additional identification criterion, acquired characteristic isotopologue profiles have been compared to the theoretical. This has added confidence to metabolite identification, as illustrated for the identification of phase II metabolite desmethyl naproxen sulfate coeluting with a sulfonate hydroxy carbamazepine biotransformation species. These identifications illustrate the interdependent correlation between data quality and informatics solutions output, ppb mass measurement for DIA precursor ion and fragment ions providing a high degree of specificity for non-targeted analytical acquisition strategies. Transformative mass measurement resulting from greater mass resolving power affords the opportunity to improve informatics output and moreover study efficiency, in the drug discovery and development process. High resolving power mass spectrometry facilitates implementation of more stringent informatics data processing filters, enhancing credence in the identification of parent drug, metabolite precursor, expected fragment ions, and in-silico fragment ions.

The ppb mass accuracy performance of 10 Hz UPLC-MRT- MS<sup>E</sup> has been shown in the context of a metabolite identification workflow, where duty cycle facilitating chromatographic fidelity and routine ppb mass accuracy affords the opportunity to enhance identification confidence in many small molecule application areas.<sup>17-19</sup>

---

## References

1. Schymanski EL, Jeon J, Gulde R, Fenner K, Ruff M, Singer HP, Hollender J. Identifying Small Molecules via High Resolution Mass Spectrometry: Communicating Confidence. *Environ. Sci. Technol.* 2014, **48** (4), 2097–2098.
2. Cooper-Shepherd DA, Wildgoose J, Kozlov B, Johnson WJ, Tyldesley-Worster R, Palmer ME, Hoyes JB,

- McCullagh M, Jones E, Tonge R, Marsden-Edwards E, Nixon P, Verenchikov A, Langridge JI. Novel Hybrid Quadrupole-Multireflecting Time-of-Flight Mass Spectrometry System. *J Am Soc Mass Spectrom*. 2023 Feb 1;34(2):264–272.
3. McCullagh M, Palmer M, Marsden-Edwards E, Cooper-Shepherd D and James Langridge, Exploring the Impact of Part Per Billion Mass Accuracy for Metabolite Identification using Multi Reflecting Time-Of-Flight MS with UPLC Part A. Waters application note [720007896](#), April 2023.
  4. FDA, US. "Guidance for industry: safety testing of drug metabolites." *Center for Drug Evaluation and Research, Rockville, MD, USA* (2008).
  5. Bradshaw PR, Athersuch TJ, Stachulski AV, Wilson ID. Acyl glucuronide reactivity in perspective, *Drug Discovery Today*, Volume 25, Issue 9, 2020, Pages 1639–1650.
  6. Mortensen RW, Corcoran O, Cornett C, Sidelmann UG, Troke J, Lindon JC, Nicholson JK, Hansen SH. LC-1H NMR used for determination of the elution order of S-naproxen glucuronide isomers in two isocratic reversed-phase LC-systems. *J Pharm Biomed Anal*. 2001 Jan;24(3):477–85.
  7. Higton D , Wilson ID, Vissers JPC , Plumb RS. An automated method to study the rapid intramolecular transacylation of drug acyl glucuronides using Cyclic Ion Mobility Spectrometry-Mass Spectrometry Waters Corporation Poster: [PSTR135089718](#) < [https://www.waters.com/webassets/cms/library/docs/2021asms\\_higton\\_acylglucuronide.pdf](https://www.waters.com/webassets/cms/library/docs/2021asms_higton_acylglucuronide.pdf)> .
  8. Falany CN, Ström P, Swedmark S. Sulphation of o-desmethylnaproxen and related compounds by human cytosolic sulfotransferases. *Br J Clin Pharmacol*. 2005 Dec;60(6):632–40.
  9. Kiang CH, Lee C, Kushinsky S. Isolation and identification of 6- desmethylnaproxen sulfate as a new metabolite of naproxen in human plasma. *Drug Metab Dispos* 1989; 17: 43–8.
  10. Nagao T, Yukihiro D, Fujimura Y, *et al*. Power of isotopic fine structure for unambiguous determination of metabolite elemental compositions: in silico evaluation and metabolomic application. *Anal Chim Acta*. 2014;813:70–76.
  11. Ipsen A. Efficient calculation of exact fine structure isotope patterns via the multidimensional Fourier transform. *Anal Chem*. 2014;86(11):5316–5322.
  12. Lertratanangkoon K and Horning M G. Metabolism of carbamazepine. *Drug Metabolism and*

Disposition January 1982, 10 (1) 1–10.

13. Bahlmann A, Brack W, Schneider RJ, Krauss M. Carbamazepine and its metabolites in wastewater: Analytical pitfalls and occurrence in Germany and Portugal. *Water Res.* 2014 Jun 15;57:104–14. doi: 10.1016/j.watres.2014.03.022. Epub 2014 Mar 19. PMID: 24704908.
14. Richter WJ, Kriemler P, Faigle JW. (1978). Newer Aspects of the Biotransformation of Carbamazepine: Structural Characterization of Highly Polar Metabolites. In: Frigerio, A. (eds) *Recent Developments in Mass Spectrometry in Biochemistry and Medicine*. Springer, Boston, MA. [https://doi.org/10.1007/978-1-4613-3991-5\\_1](https://doi.org/10.1007/978-1-4613-3991-5_1)
15. Russell JL, Spiller HA, Baker DD. Markedly elevated carbamazepine-10,11-epoxide/carbamazepine ratio in a fatal carbamazepine ingestion, *Case Rep. Med.* 2015 (2015), 369707.
16. Kerr BM, Thummel KE, Wurden CJ, Klein SM, Kroetz DL, Gonzalez FJ, Levy R, Human liver carbamazepine metabolism: Role of CYP3A4 and CYP2C8 in 10,11-epoxide formation, *Biochemical Pharmacology*, Volume 47, Issue 11, 1994, Pages 1969–1979, ISSN 0006–2952.
17. Batucan NSP, Tremblay LA, Northcott GL, Matthaei CD. Medicating the environment? A critical review on the risks of carbamazepine, diclofenac and ibuprofen to aquatic organisms, *Environmental Advances*, Volume 7, 2022, 100164.
18. Gago-Ferrero p, Bletsou AA, Damalas DE, Aalizadeh R, Alygizakis NA, Singer HP, Hollender J, Thomaidis NS. Wide-scope target screening of >2000 emerging contaminants in wastewater samples with UPLC-Q-ToF-HRMS/MS and smart evaluation of its performance through the validation of 195 selected representative analytes. *Journal of Hazardous Materials*, Volume 387, 2020, 121712.
19. Carere M, Polesello S, Kase R, Gawlik BM. (2015). The Emerging Contaminants in the Context of the EU Water Framework Directive. In: Petrovic M, Sabater S, Elosegi A, Barceló, D. (eds) *Emerging Contaminants in River Ecosystems. The Handbook of Environmental Chemistry*, vol 46. *Springer, Cham*.

---

## Featured Products

[ACQUITY UPLC I-Class PLUS System <https://www.waters.com/134613317>](https://www.waters.com/134613317)

---

[SELECT SERIES MRT <https://www.waters.com/waters/nav.htm?cid=135082877>](https://www.waters.com/waters/nav.htm?cid=135082877)

[MassLynx MS Software <https://www.waters.com/513662>](https://www.waters.com/513662)

[waters\\_connect <https://www.waters.com/waters/nav.htm?cid=135040165>](https://www.waters.com/waters/nav.htm?cid=135040165)

720007889, April 2023



© 2024 Waters Corporation. All Rights Reserved.

[Condizioni d'uso](#) [Informativa sulla privacy](#) [Marchi di fabbrica](#) [Opportunità professionali](#)  
[Informativa legale e relativa alla privacy](#) [Cookie](#) [Preferenze cookie](#)