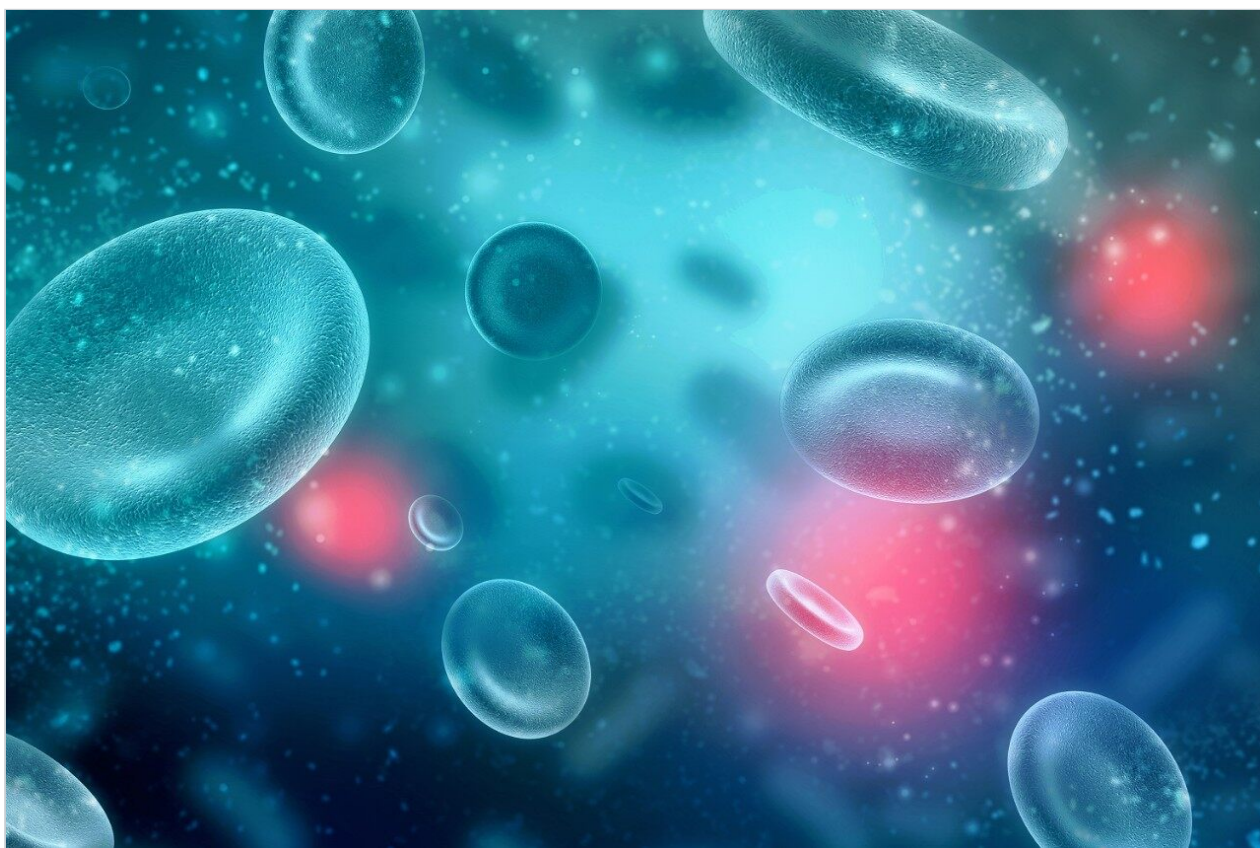


## Analysis of Antiepileptic Drugs in Plasma for Clinical Research

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### Abstract

This application note demonstrates the capabilities of the sample preparation and UPLC-MS/MS system to quantify 18 antiepileptic drugs and metabolites in plasma.

## Benefits

- Low volume, simple sample preparation
- One method for the quantification of 18 antiepileptic drugs and metabolites that cover a wide range of polarities

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## Introduction

Pharmacokinetic interactions between antiepileptic drugs are a known phenomenon, therefore an accurate quantitative method may play a role in researching the pharmacokinetic and pharmacodynamic effects of administration of antiepileptic drugs.

Here we describe a clinical research method using protein precipitation of a plasma sample with internal standards. Chromatographic elution was completed within five minutes using a Waters CORTECS C<sub>8</sub> Column on an ACQUITY UPLC I-Class System followed by detection on a Xevo TQD Triple Quadrupole Mass Spectrometer utilizing polarity switching (Figure 1).



Figure 1. The Waters ACQUITY UPLC I-Class System with FTN and Xevo TQD Mass Spectrometer.

## Experimental

### Sample preparation

Plasma calibrators and quality control materials were prepared in-house using pooled human plasma supplied by BioIVT (West Sussex, UK). Concentrated stock solutions were prepared from certified powders and solutions supplied by Cambridge Bioscience (Cambridgeshire, UK), Fisher (Loughborough, UK), Sigma-Aldrich (Dorset, UK), and Toronto Research Chemicals (Ontario, Canada). Stable labelled internal standards were supplied by Cambridge Bioscience (Cambridgeshire, UK), Sigma-Aldrich (Dorset, UK), and Toronto Research Chemicals (Ontario, Canada). The calibration range was 1–100  $\mu\text{g/mL}$  for all analytes, except for oxcarbazepine, perampanel, and pregabalin (0.1–10  $\mu\text{g/mL}$ ), tiagabine (0.01–1  $\mu\text{g/mL}$ ), and valproic acid (2–200  $\mu\text{g/mL}$ ). In-house quality control samples were prepared in plasma at low, medium, and high

concentrations of 2.5, 7.5, and 40 µg/mL for 10,11-dihydro-10-hydroxycarbamazepine, carbamazepine, felbamate, gabapentin, lacosamide, lamotrigine, levetiracetam, phenobarbital, phenytoin, primidone, topiramate, and zonisamide; 0.25, 0.75, and 4 µg/mL for oxcarbazepine, perampanel, pregabalin, and retigabine; 0.025, 0.075, and 0.4 µg/mL for tiagabine; and 5, 15, and 80 µg/mL for valproic acid.

## Sample extraction

To 50 µL of sample, 200 µL of internal standard in methanol was added, containing 5 µg/mL of valproic acid-<sup>2</sup>H<sub>6</sub>, 2.5 µg/mL of carbamazepine-<sup>2</sup>H<sub>2</sub> <sup>15</sup>N, 10,11-dihydro-10- hydroxycarbamazepine-<sup>13</sup>C<sub>6</sub>, felbamate-<sup>2</sup>H<sub>4</sub>, gabapentin-<sup>2</sup>H<sub>4</sub>, lacosamide-<sup>2</sup>H<sub>6</sub>, levetiracetam-<sup>2</sup>H<sub>3</sub>, phenobarbital-<sup>2</sup>H<sub>5</sub>, phenytoin-<sup>2</sup>H<sub>10</sub>, primidone-<sup>2</sup>H<sub>5</sub>, topiramate-<sup>13</sup>C<sub>6</sub> and zonisamide-<sup>13</sup>C<sub>2</sub> <sup>15</sup>N, 0.625 µg/mL lamotrigine-<sup>13</sup>C<sub>3</sub> and oxcarbazepine-<sup>2</sup>H<sub>4</sub>, 0.5 µg/mL of perampanel-<sup>2</sup>H<sub>5</sub>, 0.25 µg/mL of pregabalin-<sup>13</sup>C<sub>3</sub> and retigabine-<sup>2</sup>H<sub>4</sub>, and 0.03125 µg/mL of tiagabine-<sup>2</sup>H<sub>6</sub>. Tubes were placed on a multi-tube vortex mixer at 2500 rpm for 30 seconds, then centrifuged for two minutes at 16,100 g. Fifty microliters (50 µL) of supernatant were transferred to a 1-mL, 96-well plate and 350 µL water added. The plate was then centrifuged at 4,696 g for two minutes prior to analysis.

## UPLC conditions

|                      |                                                                     |
|----------------------|---------------------------------------------------------------------|
| System:              | ACQUITY UPLC I-Class with Flow-Through Needle (FTN)                 |
| Needle:              | 30 µL                                                               |
| Column:              | CORTECS C <sub>8</sub> Column; 2.7 µm, 2.1 × 50 mm (p/n: 186008349) |
| Mobile phase A:      | Water + 2 mM ammonium acetate                                       |
| Mobile phase B:      | Methanol + 2 mM ammonium acetate                                    |
| Needle wash solvent: | 80% aqueous methanol + 0.1% formic acid                             |
| Purge solvent:       | 5% aqueous methanol                                                 |
| Seal wash:           | 20% aqueous methanol                                                |
| Column temp.:        | 50 °C (precolumn heater active)                                     |
| Injection volume:    | 20 µL                                                               |

Flow rate: 0.50 mL/min

Gradient elution: (see Table 1)

Run time: 5.0 minutes (5.7 minutes injection-to-injection)

| Time (min) | % Mobile phase A | % Mobile phase B | Curve   |
|------------|------------------|------------------|---------|
| Initial    | 95               | 5                | Initial |
| 0.2        | 95               | 5                | 6       |
| 1.5        | 75               | 25               | 6       |
| 2.5        | 75               | 25               | 6       |
| 4.0        | 30               | 70               | 6       |
| 4.01       | 5                | 95               | 6       |
| 4.5        | 5                | 95               | 6       |
| 4.51       | 95               | 5                | 6       |

Table 1. Chromatographic elution timetable.

## MS conditions

System: Xevo TQD

Resolution: MS1 (0.7 FWHM), MS2 (0.7 FWHM)

Acquisition mode: Multiple reaction monitoring (MRM) (see Table 2 for details)

Polarity: ESI positive ionization/ESI negative ionization (ESI+/ESI-)

Capillary: 3.5 kV (ESI+)/0.8 (ESI-)

Source temp.: 150 °C

Desolvation temp.: 500 °C

Cone gas: 100 L/hr

|                   |               |
|-------------------|---------------|
| Inter-scan delay: | 0.003 seconds |
|-------------------|---------------|

|                                        |               |
|----------------------------------------|---------------|
| Polarity/mode switch inter-scan delay: | 0.020 seconds |
|----------------------------------------|---------------|

|                      |               |
|----------------------|---------------|
| Inter-channel delay: | 0.003 seconds |
|----------------------|---------------|

## Data management

MassLynx Software v4.2 with TargetLynx Application Manager

| Function<br>(acquisition time,<br>min) | Analyte                                                             | Polarity | Precursor<br>ion<br>( <i>m/z</i> ) | Product<br>ion<br>( <i>m/z</i> ) | Cone<br>voltage<br>(V) | Collision<br>energy<br>(eV) | Dwell<br>time<br>(s) |
|----------------------------------------|---------------------------------------------------------------------|----------|------------------------------------|----------------------------------|------------------------|-----------------------------|----------------------|
| 1 (0.65–1.65)                          | Pregabalin (Quan)                                                   | ESI+     | 160.05                             | 142.1                            | 24                     | 10                          | 0.015                |
|                                        | Pregabalin (Qual)                                                   | ESI+     | 160.05                             | 97.1                             | 24                     | 16                          | 0.015                |
|                                        | Pregabalin- <sup>13</sup> C <sub>3</sub>                            | ESI+     | 163.1                              | 145.1                            | 24                     | 10                          | 0.015                |
|                                        | Levetiracetam (Quan)                                                | ESI+     | 171.1                              | 126.1                            | 14                     | 14                          | 0.015                |
|                                        | Levetiracetam (Qual)                                                | ESI+     | 171.1                              | 69.1                             | 14                     | 28                          | 0.015                |
|                                        | Gabapentin (Quan)                                                   | ESI+     | 172.1                              | 154.1                            | 24                     | 14                          | 0.015                |
|                                        | Gabapentin (Qual)                                                   | ESI+     | 172.1                              | 55.1                             | 24                     | 20                          | 0.015                |
|                                        | Levetiracetam- <sup>2</sup> H <sub>3</sub>                          | ESI+     | 174.1                              | 129.1                            | 14                     | 14                          | 0.015                |
|                                        | Gabapentin- <sup>2</sup> H <sub>4</sub>                             | ESI+     | 176.1                              | 158.1                            | 24                     | 14                          | 0.015                |
|                                        | Zonisamide (Quan)                                                   | ESI+     | 212.95                             | 132.1                            | 28                     | 14                          | 0.015                |
|                                        | Zonisamide (Qual)                                                   | ESI+     | 212.95                             | 77.1                             | 28                     | 30                          | 0.015                |
|                                        | Zonisamide- <sup>13</sup> C <sub>2</sub> <sup>15</sup> N            | ESI+     | 215.95                             | 134.1                            | 28                     | 14                          | 0.015                |
| 2 (1.65–2.22)                          | Primidone (Quan)                                                    | ESI+     | 219.1                              | 162.1                            | 24                     | 12                          | 0.010                |
|                                        | Primidone (Qual)                                                    | ESI+     | 219.1                              | 91.1                             | 24                     | 32                          | 0.010                |
|                                        | Primidone- <sup>2</sup> H <sub>5</sub>                              | ESI+     | 224.1                              | 167.1                            | 24                     | 12                          | 0.015                |
|                                        | Felbamate (Quan)                                                    | ESI+     | 239.1                              | 178.1                            | 14                     | 8                           | 0.010                |
|                                        | Felbamate (Qual)                                                    | ESI+     | 239.1                              | 117.1                            | 14                     | 18                          | 0.010                |
|                                        | Felbamate- <sup>2</sup> H <sub>4</sub>                              | ESI+     | 243.1                              | 182.1                            | 14                     | 8                           | 0.010                |
|                                        | Lacosamide (Quan)                                                   | ESI+     | 251.1                              | 91.1                             | 20                     | 18                          | 0.010                |
|                                        | Lacosamide (Qual)                                                   | ESI+     | 251.1                              | 74.1                             | 20                     | 22                          | 0.010                |
|                                        | Lacosamide- <sup>2</sup> H <sub>3</sub>                             | ESI+     | 254.1                              | 91.1                             | 20                     | 18                          | 0.015                |
|                                        | Lamotrigine (Quan)                                                  | ESI+     | 255.95                             | 211.1                            | 50                     | 24                          | 0.015                |
|                                        | Lamotrigine (Qual)                                                  | ESI+     | 255.95                             | 145.1                            | 50                     | 38                          | 0.015                |
|                                        | Lamotrigine- <sup>13</sup> C <sub>3</sub>                           | ESI+     | 258.95                             | 214.1                            | 50                     | 24                          | 0.025                |
| 3 (2.12–2.50)                          | Phenobarbital (Quan)                                                | ESI-     | 231.1                              | 42.0                             | 28                     | 14                          | 0.075                |
|                                        | Phenobarbital (Qual)                                                | ESI-     | 231.1                              | 188.1                            | 28                     | 10                          | 0.075                |
|                                        | Phenobarbital- <sup>2</sup> H <sub>5</sub>                          | ESI-     | 236.1                              | 42.0                             | 28                     | 14                          | 0.075                |
| 4 (2.50–3.10)                          | Valproic acid                                                       | ESI-     | 143.0                              | 143.1                            | 30                     | 5                           | 0.015                |
|                                        | Valproic acid- <sup>2</sup> H <sub>8</sub>                          | ESI-     | 149.0                              | 149.1                            | 30                     | 5                           | 0.015                |
| 5 (2.50–3.10)                          | 10,11-dihydro-10-hydroxycarbamazepine (Quan)                        | ESI+     | 255.1                              | 194.1                            | 16                     | 18                          | 0.025                |
|                                        | 10,11-dihydro-10-hydroxycarbamazepine (Qual)                        | ESI+     | 255.1                              | 179.1                            | 16                     | 32                          | 0.025                |
|                                        | 10,11-dihydro-10-hydroxycarbamazepine- <sup>13</sup> C <sub>6</sub> | ESI+     | 261.1                              | 200.1                            | 16                     | 18                          | 0.025                |
|                                        | Topiramate (Quan)                                                   | ESI+     | 340.1                              | 264.1                            | 30                     | 8                           | 0.025                |
|                                        | Topiramate (Qual)                                                   | ESI+     | 340.1                              | 184.1                            | 30                     | 18                          | 0.025                |
|                                        | Topiramate- <sup>13</sup> C <sub>6</sub>                            | ESI+     | 340.1                              | 270.1                            | 30                     | 8                           | 0.025                |
| 6 (3.10–3.50)                          | Oxcarbazepine (Quan)                                                | ESI+     | 253.1                              | 180.1                            | 30                     | 30                          | 0.050                |
|                                        | Oxcarbazepine (Qual)                                                | ESI+     | 253.1                              | 208.1                            | 30                     | 20                          | 0.050                |
|                                        | Oxcarbazepine- <sup>2</sup> H <sub>4</sub>                          | ESI+     | 257.1                              | 184.1                            | 30                     | 30                          | 0.050                |
| 7 (3.50–3.85)                          | Carbamazepine (Quan)                                                | ESI+     | 237.1                              | 179.1                            | 34                     | 34                          | 0.020                |
|                                        | Carbamazepine (Qual)                                                | ESI+     | 237.1                              | 165.1                            | 34                     | 34                          | 0.020                |
|                                        | Carbamazepine- <sup>2</sup> H <sub>2</sub> <sup>15</sup> N          | ESI+     | 240.1                              | 181.1                            | 34                     | 34                          | 0.030                |
|                                        | Phenytoin (Quan)                                                    | ESI+     | 253.1                              | 104.1                            | 28                     | 34                          | 0.005                |
|                                        | Phenytoin (Qual)                                                    | ESI+     | 253.1                              | 182.1                            | 28                     | 16                          | 0.005                |
|                                        | Phenytoin- <sup>2</sup> H <sub>10</sub>                             | ESI+     | 263.1                              | 109.1                            | 28                     | 34                          | 0.005                |
|                                        | Retigabine (Quan)                                                   | ESI+     | 304.1                              | 109.1                            | 34                     | 34                          | 0.015                |
|                                        | Retigabine (Qual)                                                   | ESI+     | 304.1                              | 230.1                            | 34                     | 18                          | 0.015                |
|                                        | Retigabine- <sup>2</sup> H <sub>4</sub>                             | ESI+     | 308.1                              | 113.1                            | 34                     | 34                          | 0.025                |
| 8 (3.85–4.20)                          | Perampanel (Quan)                                                   | ESI+     | 350.1                              | 219.1                            | 60                     | 34                          | 0.015                |
|                                        | Perampanel (Qual)                                                   | ESI+     | 350.1                              | 247.1                            | 60                     | 26                          | 0.015                |
|                                        | Perampanel- <sup>2</sup> H <sub>5</sub>                             | ESI+     | 355.1                              | 220.1                            | 60                     | 34                          | 0.015                |
|                                        | Tiagabine (Quan)                                                    | ESI+     | 376.1                              | 111.1                            | 40                     | 36                          | 0.010                |
|                                        | Tiagabine (Qual)                                                    | ESI+     | 376.1                              | 247.1                            | 40                     | 20                          | 0.010                |
|                                        | Tiagabine- <sup>2</sup> H <sub>8</sub>                              | ESI+     | 382.1                              | 114.1                            | 40                     | 36                          | 0.010                |

Table 2. Guideline MRM parameters for analytes and internal standards used in this study.

g/mL of 10,11-dihydro-10-hydroxycarbamazepine, carbamazepine, felbamate, gabapentin, lacosamide, lamotrigine, levetiracetam, phenobarbital, phenytoin, primidone, topiramate, and zonisamide; 10 µg/mL of oxcarbazepine, perampanel, pregabalin, and retigabine; 1 µg/mL of tiagabine; and 200 µg/mL of valproic acid.

Figure 2 shows an example chromatogram for the analysis of the 18 antiepileptic drugs and metabolites.

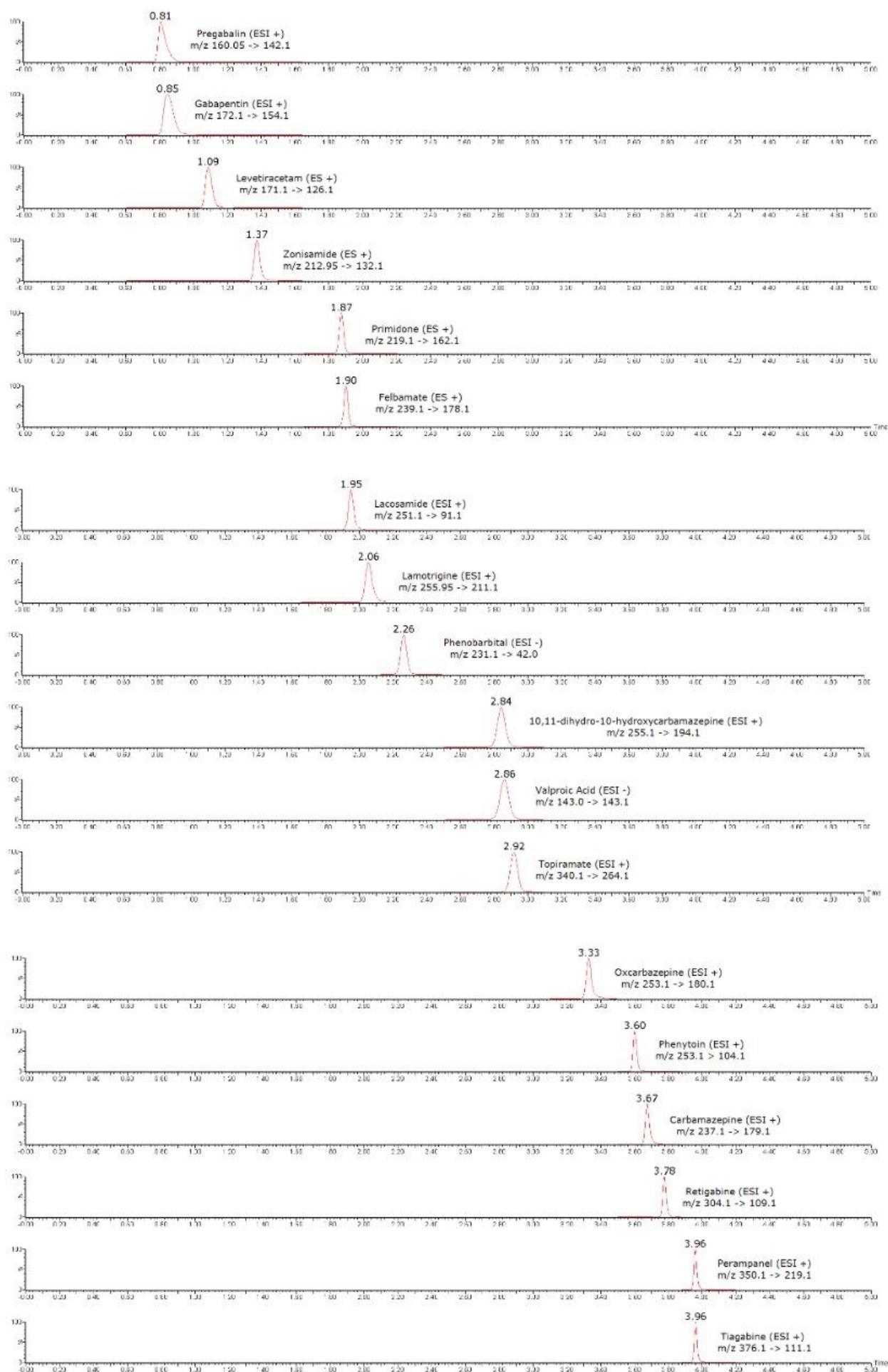


Figure 2. Chromatogram showing the analysis of antiepileptic drugs using the ACQUITY UPLC I-Class/Xevo TQD IVD

g/mL for phenobarbital, topiramate, and zonisamide, when low and high pools were mixed in known ratios over the range. Linear fits were used to construct calibration lines. Carbamazepine, 10,11-dihydro-10-hydroxycarbamazepine, felbamate, gabapentin, lacosamide, lamotrigine, levetiracetam, phenytoin, and primidone were determined to have quadratic fits over 0.752–130 µg/mL. Similarly, oxcarbazepine, perampanel, pregabalin, and retigabine were quadratic over 0.0752–13.0 µg/mL; tiagabine over 0.00752–1.30 µg/mL; and valproic acid over 1.5–260 µg/mL. Quadratic fits were used to construct calibration lines.

Matrix effects were evaluated at low (QC1) and high (QC3) concentrations in plasma (n=6) taken as a percentage of extracted solvent samples spiked to equivalent concentrations. Calculations using analyte:internal standard response ratio indicated compensation for signal enhancement by the internal standard (Table 5).

| Analyte                               | Spiked concentration (µg/mL) | Matrix factor based on peak area mean (range) | Matrix factor based on response mean (range) |
|---------------------------------------|------------------------------|-----------------------------------------------|----------------------------------------------|
| 10,11-dihydro-10-hydroxycarbamazepine | 2.5                          | 1.01 (1.00–1.02)                              | 1.00 (0.99–1.01)                             |
|                                       | 40                           | 1.00 (0.98–1.01)                              | 1.01 (1.00–1.03)                             |
| Carbamazepine                         | 2.5                          | 1.00 (0.98–1.02)                              | 1.00 (0.99–1.00)                             |
|                                       | 40                           | 1.00 (0.97–1.02)                              | 1.01 (1.01–1.02)                             |
| Felbamate                             | 2.5                          | 0.98 (0.98–0.99)                              | 0.97 (0.95–0.98)                             |
|                                       | 40                           | 0.99 (0.97–1.00)                              | 1.00 (0.98–1.04)                             |
| Gabapentin                            | 2.5                          | 0.98 (0.97–0.99)                              | 0.99 (0.98–1.00)                             |
|                                       | 40                           | 0.99 (0.97–1.01)                              | 1.02 (0.99–1.06)                             |
| Lacosamide                            | 2.5                          | 0.99 (0.98–1.00)                              | 0.99 (0.97–1.01)                             |
|                                       | 40                           | 1.00 (0.99–1.00)                              | 1.00 (0.99–1.01)                             |
| Lamotrigine                           | 2.5                          | 1.02 (0.98–1.06)                              | 1.01 (0.97–1.02)                             |
|                                       | 40                           | 1.00 (0.98–1.01)                              | 1.01 (1.01–1.02)                             |
| Levetiracetam                         | 2.5                          | 0.99 (0.98–1.00)                              | 0.98 (0.95–1.01)                             |
|                                       | 40                           | 1.00 (0.98–1.01)                              | 1.00 (0.99–1.03)                             |
| Oxcarbazepine                         | 0.25                         | 0.98 (0.91–1.01)                              | 0.99 (0.97–1.01)                             |
|                                       | 4                            | 0.98 (0.94–0.99)                              | 1.01 (0.99–1.03)                             |
| Perampanel                            | 0.25                         | 0.83 (0.79–0.87)                              | 0.96 (0.95–0.99)                             |
|                                       | 4                            | 0.89 (0.85–0.92)                              | 1.01 (0.99–1.02)                             |
| Phenobarbital                         | 2.5                          | 0.97 (0.90–1.12)                              | 0.97 (0.91–1.09)                             |
|                                       | 40                           | 0.98 (0.95–1.00)                              | 1.03 (1.01–1.06)                             |
| Phenytoin                             | 2.5                          | 0.95 (0.92–1.01)                              | 0.99 (0.96–1.05)                             |
|                                       | 40                           | 0.97 (0.97–0.98)                              | 1.01 (0.98–1.03)                             |
| Pregabalin                            | 0.25                         | 0.99 (0.91–1.03)                              | 0.99 (0.90–1.03)                             |
|                                       | 4                            | 0.99 (0.96–1.02)                              | 1.03 (1.00–1.05)                             |
| Primidone                             | 2.5                          | 1.00 (1.00–1.00)                              | 0.99 (0.97–1.01)                             |
|                                       | 40                           | 1.00 (0.99–1.02)                              | 1.03 (1.01–1.05)                             |
| Retigabine                            | 0.25                         | 1.37 (1.32–1.44)                              | 0.94 (0.91–1.03)                             |
|                                       | 4                            | 1.17 (1.12–1.21)                              | 0.91 (0.88–0.96)                             |
| Tiagabine                             | 0.025                        | 1.02 (0.98–1.08)                              | 0.94 (0.87–1.01)                             |
|                                       | 0.4                          | 1.05 (1.02–1.09)                              | 1.00 (0.95–1.05)                             |
| Topiramate                            | 2.5                          | 1.00 (0.99–1.01)                              | 0.98 (0.97–1.00)                             |
|                                       | 40                           | 1.00 (0.99–1.00)                              | 1.01 (0.99–1.02)                             |
| Valproic acid                         | 5                            | 1.01 (0.96–1.04)                              | 0.99 (0.95–1.03)                             |
|                                       | 80                           | 1.00 (0.99–1.02)                              | 1.02 (1.00–1.03)                             |
| Zonisamide                            | 2.5                          | 0.99 (0.98–1.00)                              | 0.99 (0.96–1.01)                             |
|                                       | 40                           | 0.99 (0.98–1.00)                              | 1.02 (1.01–1.04)                             |

Table 5. Matrix factor summary.

Potential interference from endogenous compounds (albumin, bilirubin, cholesterol, triglycerides, and uric acid) spiked at high concentrations was assessed by determining the recovery (n=3) from low and high pooled plasma samples (QC1 and QC3 concentrations). Recoveries ranged from 85.1–112.8%. A substance was deemed to interfere if a recovery range of 85–115% was exceeded. Additionally, full chromatographic resolution of the metabolite carbamazepine epoxide from isobaric oxcarbazepine was established.

LGC (Greater London, UK) provided serum external quality assurance samples for accuracy testing, except for oxcarbazepine and retigabine, which were not included in the schemes. All samples passed the criteria of the scheme, with mean deviations  $\leq 10.6\%$  from assigned concentrations. Results are presented in Table 6.

| Analyte                               | Scheme range (µg/mL) | Number of samples tested | Waters mean % deviation from scheme assigned value |
|---------------------------------------|----------------------|--------------------------|----------------------------------------------------|
| 10,11-dihydro-10-hydroxycarbamazepine | 0–40.76              | 10                       | 0.7                                                |
| Carbamazepine                         | 0–38.00              | 30                       | -2.0                                               |
| Felbamate                             | 0–102.49             | 10                       | 10.6                                               |
| Gabapentin                            | 0–37.75              | 10                       | -2.2                                               |
| Lacosamide                            | 0–23.87              | 10                       | 7.0                                                |
| Lamotrigine                           | 0–34.68              | 30                       | -0.3                                               |
| Levetiracetam                         | 0–100.00             | 10                       | 0.9                                                |
| Oxcarbazepine                         | N/A                  | N/A                      | N/A                                                |
| Perampanel                            | 0–0.592              | 10                       | -0.8                                               |
| Phenobarbital                         | 0–55.00              | 30                       | -6.1                                               |
| Phenytoin                             | 0–36.00              | 30                       | 5.4                                                |
| Pregabalin                            | 0–73.06              | 10                       | -6.3                                               |
| Primidone                             | 0–35.15              | 30                       | 0.6                                                |
| Retigabine                            | N/A                  | N/A                      | N/A                                                |
| Tiagabine                             | 0–0.2723             | 10                       | -4.4                                               |
| Topiramate                            | 0–39.3               | 10                       | 0.7                                                |
| Valproic acid                         | 0–213.5              | 30                       | 1.4                                                |
| Zonisamide                            | 0–48.36              | 10                       | -2.6                                               |

Table 6. Accuracy summary (N/A = not available).

## Conclusion

The developed method for clinical research demonstrates the capabilities of the sample preparation and UPLC-MS/MS system to quantify 18 antiepileptic drugs and metabolites in plasma. The method demonstrated excellent performance characteristics, including precision and agreement with an external quality assurance scheme, with neither system carryover nor significant matrix effects.

## Featured Products

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

Xevo TQD Triple Quadrupole Mass Spectrometry <<https://www.waters.com/134608730>>

MassLynx MS Software <<https://www.waters.com/513662>>

TargetLynx <<https://www.waters.com/513791>>

