Quantitative Determination of Bisphosphonate Pharmaceuticals and Excipients by Capillary Ion Chromatography Mass Spectrometry

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Introduction

Bisphosphonate drugs are widely used in the treatment of bone diseases such as osteoporosis. Real-world evidence suggests that bisphosphonates can cause renal toxicity and nephrocalcinosis. Mass spectrometry (MS) is a powerful tool for quantifying bisphosphonates and their degradation products but is typically performed on high-volume, low-performance LC-MS systems. This study evaluates the potential of capillary ion chromatography (CIC) mass spectrometry (MS) for the quantitative determination of bisphosphonates and related degradation products in urine and plasma samples.

Reagents and Chemicals

Tiludronate 12.1 317 10.0–14.0 1.0
Clodronate 7.3 243 5.2–10.0 0.4
IS (citrate-d4) 5.8 195 5.2–10.0 0.2
Etidronate 6.6 205 5.2–10.0 0.4
Citrate 5.8 191 5.2–10.0 0.2
Benzoate 3.9 121 3.6–5.2 0.2

Analyte tR (min) SIM (m/z)

Table 1. Timed SIM Scan Events

Concentration: 40.00 mM

F Cl

15.0 40 mM

14.9 100 mM

8.0 100 mM

5.0 50 mM

-4.0 40mM

Eluent: Hydroxide Gradient

Eluent Source:  EGC-KOH Capillary Cartridge

Temperature: 40 °C

Columns: Dionex IonPac AS18-Fast (0.4 mm)

System:  Dionex ICS-5000 RFIC

Nebulizer Gas: Nitrogen at 65 psi

Solvent: 20 µL/min acetonitrile

Voltage: 3500 V

Probe Temp: 300 °C

Interface: Electrospray ionization (ESI)

MS Spectrometric Detector

Thermo Scientific MSQ Plus Mass Spectrometer

Table 2. Calibration and Range, Precision, and MDL

Table 3. Accuracy, Precision and Recovery

Tiludronate 41.5 3.26 83.0 497 1.28 99.4 ND 121 121
Clodronate 44.8 4.30 89.7 498 1.05 99.6 ND 134 134
Etidronate 43.4 4.27 86.8 498 2.18 99.5 424 542 117
Citrate 49.4 2.58 98.7 497 0.76 99.5 ND 102 102
Benzoate 54.2 2.75 108 499 4.71 99.9 ND 89.5 89.5

FIGURE 1. Total ion chromatograms of bisphosphonates pharmaceutics.


Conclusion

This method is applicable to the determination of bisphosphonates in a urine sample. Its analytical performance is comparable to other methods, with a lower limit of quantitation of 0.5 ng/mL for all analytes. This method is suitable for clinical and research applications, as it is rapid, sensitive, and robust. Further validation studies are ongoing to establish the method's accuracy and precision in real-world samples.