

Determination of Sulfamate and Sulfate in Topiramate by Ion Chromatography with Suppressed Conductivity Detection

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INTRODUCTION

Topiramate (Figure 1), a sulfamate-substituted monosaccharide, is an anticonvulsant drug used to treat epilepsy in children and adults.¹ Topiramate has also been used as an antidepressant and for treatment of migraine headaches. At elevated temperature and humidity, topiramate degrades to produce organic products, insoluble polymeric products, and the inorganic anions sulfamate and sulfate.² The current USP monograph specifies a limit of sulfamate and sulfate to < 0.1% in topiramate and < 0.25% in the proposed USP method for topiramate tablets.^{3,4}

Here, the authors provide a simpler approach for determining sulfamate and sulfate in topiramate than the current and proposed USP methods by using a hydroxide-selective IonPac® AS11 column with electrolytically-generated potassium hydroxide eluent and suppressed conductivity detection.

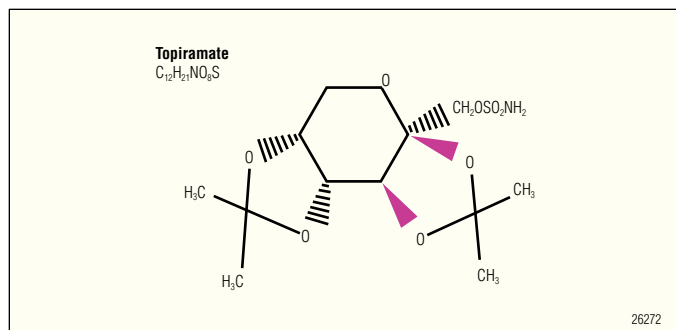


Figure 1. Chemical structure of topiramate.

EXPERIMENTAL

Dionex ICS-3000 Reagent-Free™ ion chromatography system with:

EluGen® EGC II KOH cartridge

IonPac AS11 (2 × 250 mm) column

ASRS® 300 (2 mm) suppressor operating at 24 mA in recycle mode

Chromeleon® Chromatography Data System software was used for system control and data processing

Sample Preparation

The solubility of topiramate in water is 9.8 mg/mL; therefore, topiramate was prepared at a concentration of 6 mg/mL, well below its solubility limit.

RESULTS AND DISCUSSION

The disadvantages of the current and proposed USP methods for determination of sulfamate and sulfate in topiramate include the use of manually prepared NaOH eluent, which can introduce carbonate that may cause undesirable baseline shifts, higher detection limits, and irreproducible retention times. In addition, these methods require larger injection volumes, which consume more of the pharmaceutical drug, and higher eluent flow rates, which increase disposal costs. Table 1 compares the current and proposed USP methods to the method described here.

Table 1. Comparison of Method Conditions for Determination of Sulfamate and Sulfate in Topiramate

	Current USP Method	Proposed USP Method	Method Described Here
Column	L46, 4 × 250 mm	PRP-X100, 4.6 × 150 mm	IonPac AS11, 2 × 250 mm
Eluent	Multi-Step NaOH Gradient ^a	5.8 mM <i>p</i> -Hydroxybenzoic acid/ 2.5% MeOH (pH 9.4 ± 0.5)	Multi-Step KOH Gradient ^b
Flow Rate	2 mL/min	1.5 mL/min	0.25 mL/min
Injection Volume	20 µL	70 µL	5 µL
Detection	Suppressed Conductivity	Conductivity	Suppressed Conductivity
Sample Diluent	Water/Acetonitrile (80:20)	Mobile Phase	Deionized Water

^a Manually prepared NaOH

^b Electrolytically generated KOH using DI water as the source

Table 2 summarizes linearity, limits of detection (LOD) and limits of quantitation (LOQ) for sulfamate and sulfate. Note the LOQ's for the target analytes are well below the 0.1% USP specification.

Table 2. Linearity, LOD, and LOQ for Sulfamate and Sulfate

Analyte	Range (µg/mL)	Linearity (r ²)	Limit of Detection ^a (µg/mL)	Limit of Quantitation ^b (µg/mL)
Sulfamate	0.10–1.0	0.9999	0.02	0.060
Sulfate	0.50–10	0.9995	0.005	0.01

^a S/N = 3

^b S/N = 10

^c Corresponds to 0.001% (w/w) sulfamate in 6 mg/mL topiramate

^d Corresponds to 0.0003% (w/w) sulfate in 6 mg/mL topiramate

Figure 2 shows a standard separation of 0.5 mg/mL sulfamate and 2.5 mg/mL sulfate on the AS11 column. The retention times for sulfamate and sulfate using the gradient conditions shown were approximately 6.5 min and 12 min, respectively.

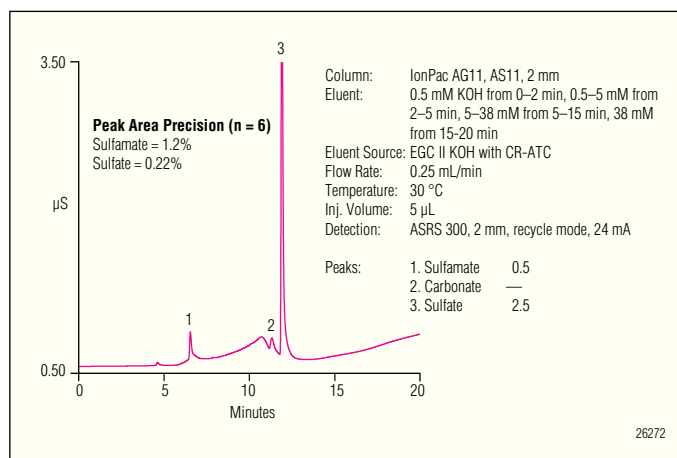


Figure 2. Separation of sulfamate and sulfate on the IonPac AS11 column.

Figure 3 compares the separation of a topiramate sample to the same sample spiked with known concentrations of sulfamate and sulfate.

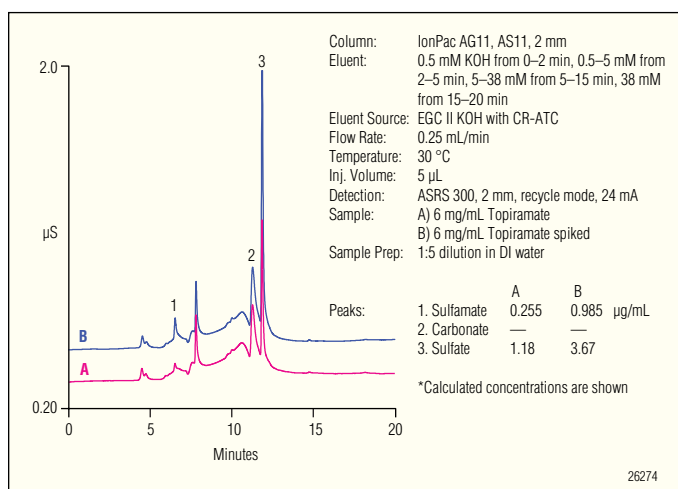


Figure 3. Separation of sulfamate and sulfate in A) topiramate and B) spiked topiramate sample.

Accuracy and Precision

The precision of standard injections containing 0.5 µg/mL sulfamate and 2.5 µg/mL sulfate (n=6) was 1.2% and 0.22%, respectively. For the sample spiked with known concentrations of sulfamate and sulfate, the average recoveries were 104.5% and 102.8%, respectively (Figure 3).

Table 3. Results for the Determination of Sulfamate and Sulfate in Topiramate

Analyte	n	Amount Found ^a (µg/mL)	% of Topiramate ^b	Peak Area RSD	Amount Added (µg/mL)	% Recovery
Sulfamate	6	0.255	0.004	2.46	0.140	104.5
Sulfate	6	1.18	0.019	0.64	0.486	102.8

^a The sample was diluted 1:5. The amount shown was calculated with the dilution factor.

^b % of sulfamate and sulfate in 6 mg/mL topiramate. The USP limit is <0.1% each for sulfamate and sulfate.

Sample Stability

The stability of topiramate was investigated over five consecutive days at temperatures of 25 °C, 4 °C, and 60 °C. Storage at 4 °C and 25 °C produced no change in sulfamate and sulfate concentrations. Storage at 60 °C caused the sulfamate concentration to increase by 8.5% and the sulfate concentration to increase by 0.18% in a 6 mg/mL topiramate solution over five consecutive days. This indicates that topiramate is unstable at high temperatures, which is consistent with the current literature on this compound.

Figure 4 demonstrates the degradation of topiramate when stored at 60 °C for five consecutive days which indicates this compound is not stable under these conditions. In addition to the significant increase in the concentrations of sulfate and sulfamate, several unidentified compounds were also observed.

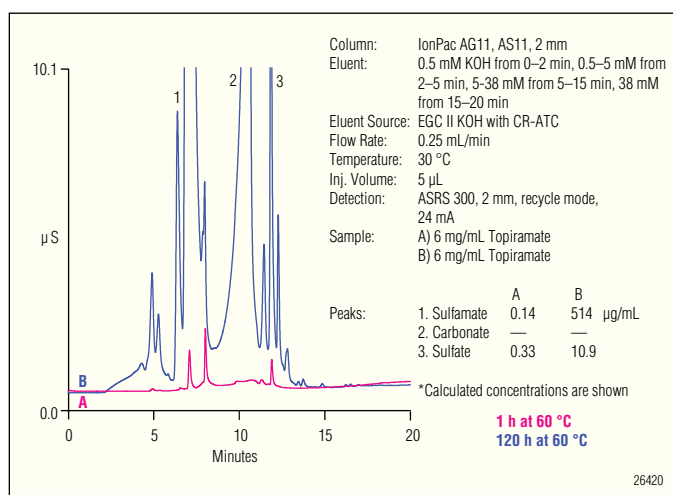


Figure 4. Degradation of topiramate at elevated temperature.

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CONCLUSIONS

The method described here demonstrates the ability to determine sulfamate and sulfate in topiramate using electrolytically generated potassium hydroxide eluent with the IonPac AS11 column and suppressed conductivity detection. This method represents an improved approach over the current and proposed USP methods because it does not require manual preparation of eluents, it uses a lower amount of sample, and reduces waste disposal. The use of the RFIC™ system enhances the automation and ease-of-use, which can improve inter- and intra-laboratory reproducibility.

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