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Technical note

Ion chromatography method and validation for the determination of sulfate and sulfamate ions in topiramate drug substance and finished product

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Abstract

A stability-indicating assay method has been developed for monitoring topiramate degradation in drug substance and finished product by quantifying sulfamate and sulfate ions. Topiramate in the solid state is stable under ambient conditions but can degrade under stress conditions (elevated temperatures and humidities). This method detects and quantitates sulfamate and sulfate ions (the inorganic part of the decomposition) and in conjunction with an assay method for topiramate and its known organic degradation product provides total molar accountability. The chromatographic system consists of a sodium hydroxide gradient (2–25 m*M*) and an anion-exchange HPLC column and an anion suppressor. The analysis is complete in 30 min. The method utilizes the same sample preparation as the topiramate assay method which increases sample efficiency and throughput. The method has been validated for analysis of degraded and nondegraded topiramate drug substance and finished product. © 1998 Elsevier Science B.V.

Keywords: Sulfate; Sulfamate

1. Introduction

Topiramate is a new anticonvulsant drug developed by The R.W. Johnson Pharmaceutical Research Institute [1,2] and marketed by Ortho-McNeil Pharmaceutical. Topiramate in the solid state is stable under ambient storage conditions. However, it can degrade at elevated temperature and humidity, and produce organic degradation products, inorganic sulfamate and sulfate, as shown in Scheme 1 [3]. The bulk of the organic degradation products appear as black particles, in the drug substance and tablet samples, which are not soluble either in organic or aqueous solvents. When degraded topiramate drug substances or tablets are assayed [4], a decrease in topiramate values is observed, while no proportional amounts of organic degradation products are detectable. However, a total molar accountability was obtained for stressed samples when topiramate, its organic degradation products, sulfamate and sulfate are determined. Since sulfamate and sulfate are: (a) produced stoichiometrically during topiramate degradation; (b) stable and nonvolatile; and (c) extractable quantitatively from the degraded drug substance and drug products, they can be assayed to monitor topiramate degradation.

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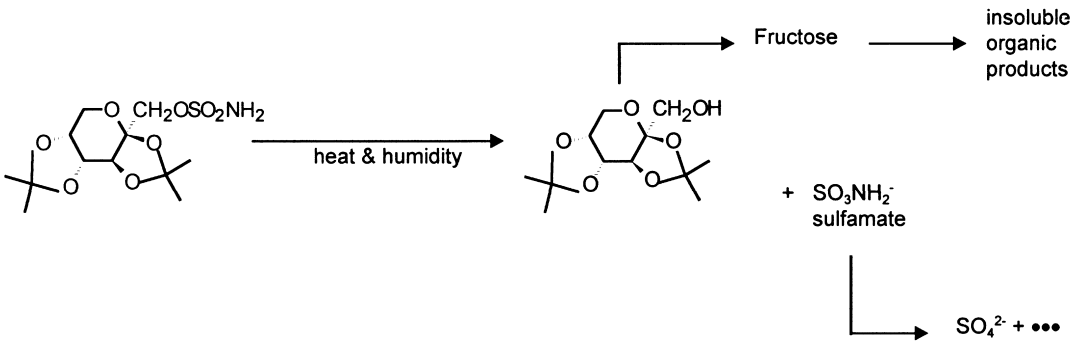

Scheme 1. Degradation of topiramate.

This paper describes an improved method to analyze sulfamate and sulfate ions in degraded topiramate compared to the original indirect UV method [3]. This method uses conductivity detection and provides better detection of sulfamate and sulfate, while also allowing for the quantitation of sulfamate in tablets that was not possible with the first method. This method takes advantage of the unique selectivity offered by ion chromatography [5]. Generally, there are significant differences in retention behavior between organic and inorganic ions, cations and anions, or monovalent and multivalent ions on ion-exchange columns. In this paper an anion-exchange column is used, therefore cations will be unretained. Anions in the sample and the mobile phase anions compete for the ionic sites on the anion-exchange column. The more strongly sample ions interact with the column the more these ions will be retained. Monovalent sulfamate and doubly charged sulfate can be separated using isocratic elution and conductivity detection. However, in order to resolve sulfamate from tablet excipients and at the same time maintain a reasonable sulfate retention time, gradient elution is required. In order to run gradient elution, an anion suppressor is used between the analytical column and the conductivity detector in order to eliminate hydroxide conductivity interference from the mobile phase. This method has been validated to be specific, linear, precise, sensitive, robust and accurate. It is presently used as a method for monitoring topiramate degradation in drug substance and tablets.

2. Experimental

2.1. Chemicals and reagents

Acetonitrile was HPLC grade (Fisher Scientific, Fair Lawn, NJ, USA). Water was deionized or distilled, 18 MΩ or better. Sodium sulfate was ACS grade (Fisher Scientific, Fair Lawn, NJ, USA). Sulfamic acid was 99+% (Aldrich Chemical Company, Milwaukee, WI, USA). Sodium hydroxide solution, 50% w/w (Fisher Scientific, Fair Lawn, NJ, USA).

2.2. Solutions

2.2.1. Mobile phase A

Water deionized or distilled (18 MΩ or better).

2.2.2. Mobile phase B

2.6 ml of sodium hydroxide solution (50% w/w) was added per 1 l of water (18 MΩ or better) (50 m*M* NaOH solution). Before adding the sodium hydroxide, the water was made free of carbon dioxide by helium sparging for 30 min.

2.2.3. Sample solvent

Acetonitrile–water, 20:80, v/v.

2.2.4. Standard stock solution

Approx. 42.7 mg sulfamic acid and 62.5 mg sodium sulfate was accurately weighed into a 100 ml

volumetric flask and dissolved in and diluted to volume with water.

2.2.5. 0.5 mol% standard solution

5.0 ml of the standard stock solution was accurately transferred by a pipette into a 25 ml volumetric flask and diluted to volume with sample solvent (5 mol%). Then 2.5 ml of this 5 mol% solution was accurately transferred by a pipette into a 25 ml volumetric flask and diluted to volume with sample solvent (corresponding to 0.5% topiramate degradation: 0.00854 mg/ml sulfamic acid and 0.0125 mg/ml sodium sulfate).

2.2.6. Sensitivity solution

5.0 ml of the 0.5 mol% standard solution was transferred by a pipette into a 25 ml volumetric flask and diluted to volume with sample solvent (corresponding to 0.1% topiramate degradation).

2.2.7. Sample preparation

Topiramate drug substance was diluted or tablets were extracted with sample solvent to a final concentration of approx. 6 mg/ml. When a stock sample solution was needed the concentration was equal to or less than 12 mg/ml topiramate. Tablet samples were shaken for 1 h and the final solution filtered through a 0.2 μm Nylon-66 Whatman syringeless filter device (Whatman LabSales, Hillsboro, OR, USA), discarding the first 3 ml of the filtrate and using the remainder for the analysis.

2.3. Procedures

The instrumentation used was a Waters liquid chromatographic system (Model 600E pump, model 715 autosampler) (Waters Corporation, Milford, MA, USA) and a Dionex pulsed electrochemical detector (PED) (Dionex Corporation, Sunnyvale, CA, USA) equipped with an anion self-regenerating suppressor (4 mm). The detector was operated in the conductivity mode and the anion self-regenerating suppressor was operated in the autosuppression recycle mode. The analog range of the detector was set at 300 μS. The detector signal was fed into a Hewlett-Packard LAS 1000 computer system. The instrument parameters described below were set up to determine the sulfamate and sulfate.

The guard column was a Dionex, Ion Pac AG5A-5μ 5 cm×4.0 mm. The analytical column was a Dionex, Ion Pac AS5A-5μ 15 cm×4.0 mm. The flow-rate was 1.0 ml/min with the initial gradient condition of 4% mobile phase B. The mobile phase composition was changed linearly to 50% B in 2 min. The conditions were held constant till 15 min after injection and then linearly returned to the initial conditions in 1 min. The total run time was 30 min. The column temperature was ambient. The injection volume was 20 μl. The retention times were 6 min for sulfamate and 17 min for sulfate.

2.4. Calculations

Since there is always a sulfate interference peak present in the sample solvent, the peak areas of sulfate in the standard and sample have to be corrected by subtracting away the sulfate interference peak area in the sample solvent (average area of 6 injections) in order to quantitate sulfate accurately.

3. Results and discussion

3.1. Specificity

Sulfamate and sulfate are well resolved from background peaks arising from sample solvent, tablet excipients and from each other. A chromatogram of a 0.5 mol% standard solution is reported in Fig. 1 to illustrate the separation obtained with this method. A chromatogram of a typical tablet placebo is presented in Fig. 2 to illustrate the elution time of the excipient peaks, these excipient peaks have been identified [6] and are labeled. The broad rise in the chromatograms baseline from 2 to 8 min is due to the acetonitrile in the sample solvent. The baseline rise at approx. 10 min is due to the gradient profile. These baseline effects do not impede quantitation of the peaks of interest.

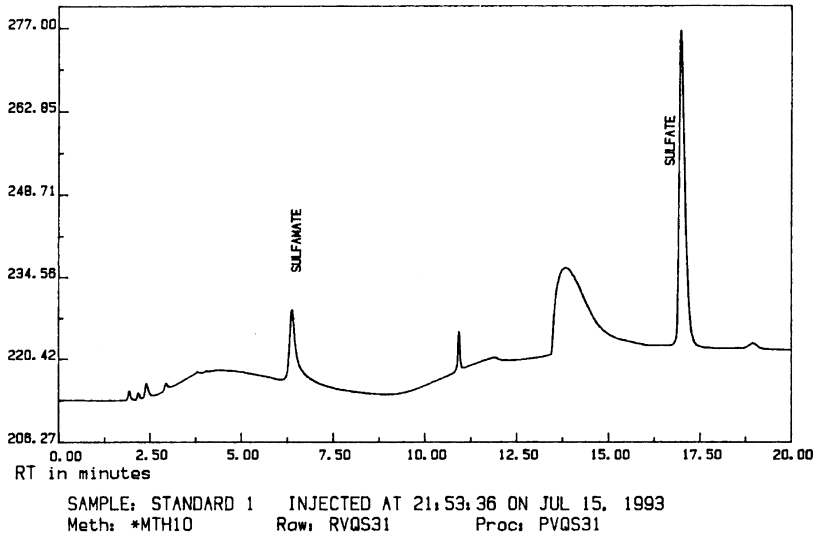

Fig. 1. Chromatogram of a 0.5 mol% standard solution of sulfamate and sulfate.

3.2. Stability-indicating

The stability-indicating ability of the method was determined by assaying routine stability samples of topiramate tablets. The data provided in Table 1 demonstrate that a complete molar accountability can be obtained by assaying topiramate and its organic degradation products, along with sulfamate and sulfate ions.

3.3. Linearity

The plots of peak area vs. ng of sulfamic acid (12.5 ng to 9375 ng corresponding to 0.04 to 27.31

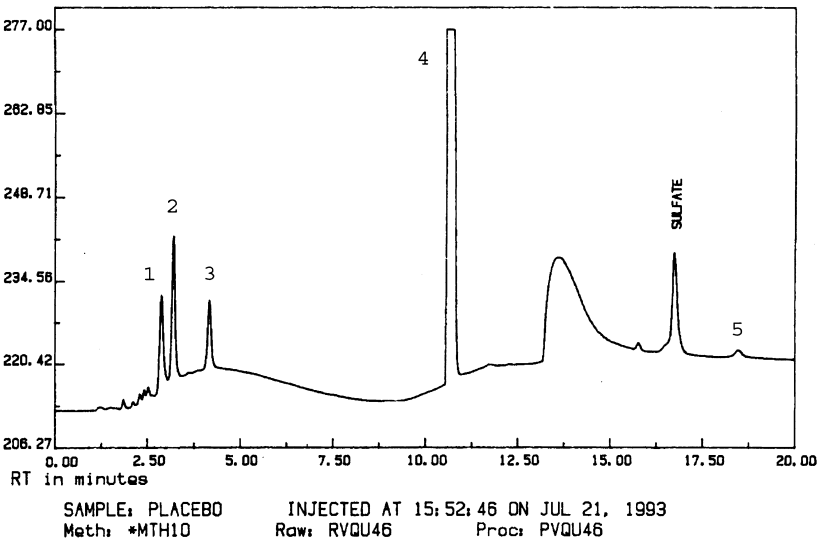

Fig. 2. Chromatogram of a typical placebo tablet (100 mg). Excipient peak identification: (1) lactate; (2) glycolate; (3) formate; (4) chloride; (5) oxalate.

Table 1
Mol% sulfamate and sulfate from degraded topiramate tablets

Strength of tablets conditions (°C/time)	100 mg 40/12 mo Mol%	200 mg 40/14 mo	300 mg 40/17 mo	400 mg 40/12 mo
Assay method for inorganics				
Sulfamate[a]	<0.1	<0.1	<0.1	<0.1
Sulfate[a]	3.32	3.31	1.70	1.38
Assay method for organics				
RWJ-36638[c]	NA	0.0	0.0	NA
RWJ-34826[c]	0.0	0.06	0.1	0.0
Topiramate	97.6	97.0	98.0	99.3
Total (topiramate+sulfamate and sulfate)[b]	100.9	100.3	99.7	100.7
Initial assay%	101.3	100.2	100.7	100.6

[a] Average assay values
[b] Value reported as 'less than' are not included.
[c] RWJ-36638 and RWJ-34826 are numbered designations for impurities.
NA: Not Available.

mol%) and sodium sulfate (49.98 ng to 14 992.5 ng or 0.1 to 29.85 mol%) injected gave a seemingly linear response with a coefficient of determination of 0.9997 and 0.9995 for sulfamic acid and sodium sulfate, respectively. However, as has been reported in the literature [7,8] and demonstrated by residual plots, the detector response is systematically skewed. For this reason a narrow concentration range with a standard chosen in the middle of this range was used to reduce errors due to nonlinear response.

3.4. Precision

The relative standard deviation (R.S.D.) was determined to be 1.11% for sulfamate and 1.47% for sulfate for 10 injections of a 0.5 mol% standard solution. The typical sample solvent background contains sulfate interference peak at a low level of 0.07 mol%. The R.S.D. of sulfate for 6 injections of a sample solvent blank was 4.90%. Precision was not run on actual tablet samples because not enough degraded tablets were available.

3.5. Sensitivity

The limit of detection was determined experimentally ($S/N=3$) to be 0.02 mol% for sulfamate (the baseline noise was taken by measuring the average peak-to-valley fluctuation over a period of time of a chromatogram of a 0.02 mol% standard). A limit of detection for sulfate could not be calculated because of the interference peak in the sample solvent. The experimentally verified limit of quantitation (arbitrarily defined as having an accuracy of better than 80% with a precision of 10% or better for 6 replicate injections) was 0.05 mol% for sulfamate and 0.1 mol% for sulfate.

3.6. Ruggedness

Method parameters were modified to study ruggedness, the variations used and the system suitability results obtained. All of the modified conditions (column, initial gradient conditions, flow-rate and column temperature) resulted in satisfactory chromatography and system suitability requirements (precision, sensitivity) were met. However, the retention time of sulfamate is sensitive to the initial mobile-phase composition. It is important to keep the sulfamate peak away from the topiramate tablet excipient and sample solvent interference peaks by maintaining a sufficient retention time for sulfamate (minimum 4.4 min).

3.7. Solution stability

In order to demonstrate that the samples and standards are stable during the normal chromatographic analysis time, the stability of the sample and standard solutions was determined. The solutions

Table 2
Recovery of sulfamate and sulfate (in mole%) from degraded topiramate tablets using various extraction times

Strength of tablets:	100 mg		200 mg		300 mg		400 mg	
Conditions (°C/time):	40/12 mo		40/14 mo		40/17 mo		40/12 mo	
Extraction time for sulfamate								
1 h	<0.1	<0.1	<0.1	<0.1	<0.1	<0.1	<0.1	<0.1
24 h	<0.1	<0.1	<0.1	<0.1	<0.1	<0.1	<0.1	<0.1
Extraction time for sulfate								
1 h	3.18	3.46	3.78	2.84[b]	1.63	1.77	1.38	1.38
24 h	3.27	3.42	3.78	2.87	1.63	1.81	1.39	1.36
Topiramate assay%								
	97.6		97.0		98.0		99.3	
Total% [Topiramate+(average of sulfamate and sulfate at 1 h extraction)][c]								
	100.9		100.3		99.7		100.7	
Initial Assay%	101.3		100.2		100.7		100.6	

[a] The quantitation limit of sulfamate is 0.1 mole%.
[b] Each analysis was done on a sample of one tablet because of a lack of degraded samples. When using a small sample size such as this, variation in the data generated is expected.
[c] Value reported as 'less than' are not included.

(standard solutions and solutions of degraded topiramate tablets stored in glass volumetric flasks) were determined to be stable for 6 days when kept at room temperature on an open bench (approx. 26°C). There was no difference between the initial values and the values at 6 days.

3.8. Recovery

The recovery was determined by analysing degraded tablet samples as a function of extraction time and by examining tablet samples spiked with various amounts of sulfamate and sulfate. Table 2 shows the effect of extraction time on the sulfamate and sulfate values for several degraded topiramate tablets. The extraction time varied from 1 h to 24 h and did not effect the assay values. Therefore, 1 h of extraction time is used in this method. The experimental recovery of spiked samples for sulfamate and sulfate was 103.4 and 103.3%, respectively. These data are the mean of many spiking experiments performed at many levels over the range 0.24–1.0%.

3.9. Improvements over existing methods

This method has many advantages over the original indirect UV method. First this method is capable of quantitating sulfamate in addition to sulfate. This is accomplished by using gradient elution which separates the sulfamate from the tablet excipient peaks, sulfamate could not be separated from table excipients with an isocratic system. The original method was not capable of quantitating sulfamate for tablet samples. This method has much better precision than the original method. The precision of the original method was over 5.5% while the precision of this method was under 1.5% for both sulfamate and sulfate. The limit of quantitation of this method is at least 3 times more sensitive than the original method.

4. Conclusion

The results of these studies demonstrate that this method is specific, linear over the specified range, precise, sensitive and robust. This method is suitable for the analysis of sulfamate and sulfate ions in topiramate tablets topiramate sprinkle formulation, and drug substance.

References

[1] R.J. Rangel, J.K. Penry, B.J. Wilder, A. Riela, B.L. Neurology 38 (1988) 234.

[2] A.B. Reitz, R.W. Tuman, C.S. Marchione, A.D. Jordan, C.R. Bowden, B.E. Maryanoff, J. Med. Chem. 32 (1989) 2110–2116.
[3] W. Li, T.M. Rossi, J. Chromatography 18(5) (1995) 917–923.
[4] PRI Assay methods, The Robert Wood Johnson Pharmaceutical Research Institute.
[5] L.R. Snyder, J.J. Kirkland, Introduction To Modern Liquid Chromatography, Chapter 10, 2nd ed., Wiley-Interscience, New York, 1979.
[6] X. Xiang, C. Ko, H.Y. Guh, Anal. Chem. 68 (1996) 3726–3731.
[7] A. Gameito, M.C. Goncalves, A.S. Fermino, Port. Electrochem. Acta 10 (1992) 49–61 (Engl.).
[8] D. Midgley, R.L. Raymond, Talanta 36 (12) (1989) 1277–1283 (Engl.).