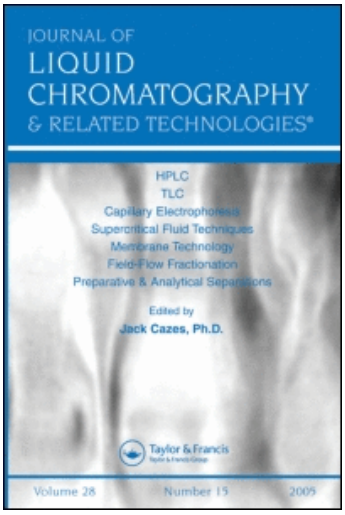

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DETERMINATION OF SULFAMATE AND SULFATE AS DEGRADATION PRODUCTS IN AN ANTIEPILEPTIC DRUG USING ION CHROMATOGRAPHY AND INDIRECT UV DETECTION

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ABSTRACT

Topiramate (bis-O-(1-methylethylidene)-fructopyranose sulfamate) is a potent antiepileptic drug currently in phase III clinical trials. Sulfamate and sulfate have been found to be two stoichiometrically formed degradation products in topiramate. An ion chromatographic method with indirect UV detection has been developed to assay sulfamate and/or sulfate in topiramate drug substance and formulated products. When used in combination with an HPLC assay method, this method is stability-indicating and can be used as a regulatory method.

INTRODUCTION

Traditionally carbohydrates and derivatives are not considered good candidates for pharmacological development. In the last few years, however, new evidence of pharmacological activity for some carbohydrates has excited many scientists in the pharmaceutical industry. Currently, carbohydrates are being investigated by pharmaceutical companies and academic institutes alike in many therapeutic areas including rheumatoid arthritis, ulcer, tumor, tissue

repair, cardiovascular, and inflammatory diseases [1-3]. Topiramate, a sulfamate derivative of fructose developed by the R.W. Johnson Pharmaceutical Research Institute, is a potent antiepileptic drug currently in Phase III clinical trials [4].

In the process of developing regulatory analytical methodology, the analytical chemists faced several problems that have been proven to be very interesting and challenging. Like most other carbohydrates, topiramate and most related impurities do not have a chromophore active above 190 nm. This limits the choices of detection techniques if an HPLC method needs to be developed. Also, topiramate, the process impurities and degradation products cover a wide range of polarity. This makes it very difficult to select the right column, elution mode and mobile phase which is compatible with the detector. Another problem was to achieve mass balance in the stability studies. Insoluble residues were formed in some stability samples and mass balance was not observed for those samples using conventional HPLC or capillary GC methods by assaying the major and organic degradation products.

This paper describes a simple ion chromatographic method which is stability-indicating when used in combination with an HPLC assay method.

EXPERIMENTAL

Materials

Topiramate drug substance was prepared by the R.W. Johnson Pharmaceutical Research Institute as previously reported [4]. HPLC grade methanol and water were used to prepare the mobile phase. *p*-Hydroxybenzoic acid was obtained from Sigma (St. Louis, Missouri).

Apparatus

An HPLC system consisting of a Waters 600E pump, a WISP 712 automatic injector and an Applied Biosystems 783A programmable UV detector was used. Data acquisition was done using a Hewlett Packard 3357 laboratory automation system via a 18652A A/D converter.

HPLC Conditions

The method utilizes a polymer based anion-exchange column (PRP-X100, 10 μm particle size, 15 cm x 4.6 mm I. D.) purchased from Hamilton (Reno,

Nevada) and indirect UV detection at 310 nm [5]. The mobile phase was a mixture of 5.8 mM *p*-hydroxybenzoic acid and 2.5% methanol and was adjusted to pH 9.4 ± 0.1 using sodium hydroxide. All analyses were performed isocratically at 40 °C ± 0.1 with a flow rate of 1.5 mL/min. The injection volume was 100 µL.

Sample Preparation

For drug substance, accurately weigh about 40.0 mg sample into a 0.5 oz bottle. Pipette 10.0 mL of mobile phase into the bottle and shake for one hour. Visually inspect each sample solution. If insoluble particles are found in the solution, filter the sample through a 0.45 µm Nylon 66 Whatman filter (Clifton, NJ), discarding the first 5 mL of filtrate.

For tablets (100 mg strength), place 10 tablets into a 250 mL volumetric flask. Add 200 mL of mobile phase into the flask and shake for one hour. Dilute to volume with mobile phase and shake well. Filter each diluted sample through a 0.45 µm Nylon 66 Whatman filter, discarding the first 5 mL of filtrate.

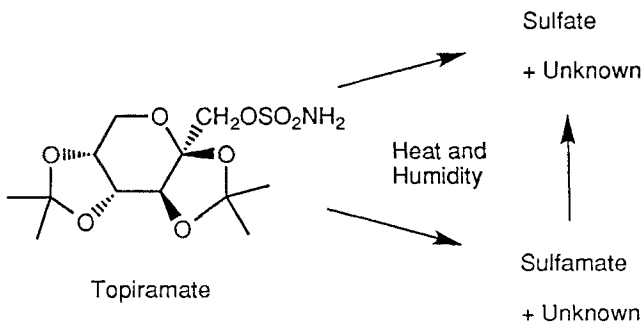
RESULT AND DISCUSSION

The method was validated for monitoring sulfate in topiramate tablets and sulfamate and sulfate in topiramate drug substance. Validation studies, including specificity, solution stability-indicating ability, recovery, linearity, precision, sensitivity, and ruggedness, were performed. The results are summarized in Table 1.

Topiramate (Scheme 1) in the solid state is very stable at ambient temperature. In fact, several batches of topiramate have been stored at room temperature for several years with no noticeable degradation detected. At elevated temperatures , however, degradation was observed for drug substance and formulated products. Interestingly, when degraded samples were assayed by a reversed-phase HPLC method [6], a decrease in topiramate assay values was observed, but no proportional amount of degradation products could be detected. Meanwhile, insoluble black particles were found in the degraded samples. An elemental analysis was performed for one of the degraded samples and the result indicated that black carbon was present which implied that a mass balance would not be achieved by assaying topiramate and the organic moieties of the

Table 1: Selected Method Validation Results

Specificity -	Specificity of this method is determined by resolving sulfamate and/or sulfate from system peaks
Linearity -	The assay response was linear from 0.25 to 18.8 mole percent for sulfate and 0.25 to 6.3 mole percent for sulfamate
Precision -	The method precision (ten replicates), expressed as relative standard deviation (RSD%), was 6.1% for sulfamate at the 0.7 mole percent level and 5.8% for sulfate at the 1.5 mole percent level.
Sensitivity-	The limit of detection was determined to be 0.1 mole percent for both sulfamate and sulfate (signal/noise = 2). The limit of quantitation was determined to be 0.3 mole percent for sulfamate and sulfate with an RSD% $\leq$ 10%.
Solution Stability -	Sample solutions are stable at ambient temperatures for 2 days
Recovery -	The recovery of sulfamate and sulfate from degraded drug substance samples and the recovery of sulfate from degraded tablet samples, both contained insoluble black particles, was determined by exhaustive extraction followed by IC analysis. A range of extraction times from 1 hour to 22 hours was studies and did not affect the recovery.
Ruggedness -	Data generated to study the method ruggedness indicate that the method is rugged. Mobile phase composition and pH, column temperature and length were varied.



Scheme 1. Topiramate Degradation

degradation products. In probe stability studies, it was found that the degraded drug substance and tablets contained considerable amount of acids. For example, a 10 mg/mL suspension of topiramate drug substance sample stressed at 90 °C and uncontrolled humidity for about 19 hours had a pH of 1.9. The initial pH for undegraded samples was about 6. Based on literature references [7] and the above observations, we proposed a degradation pathway for topiramate in Scheme 1. The simplified scheme is used to develop an analytical strategy rather than to describe topiramate degradation.

Degradation studies were carried out to confirm the proposed scheme. Topiramate drug substances were stressed at 70 and 90 °C and uncontrolled relative humidity. Samples pulled at different time points were assayed for sulfamate and sulfate using this ion chromatographic method and for topiramate remainings using a reversed-phase HPLC method [6]. The results are presented in Table 2. Sulfamate and sulfate were detected in the drug substance samples stressed at 90 °C after 11 hours. At 15 hours, the concentration of sulfamate reached a maximum of 5.7% (mole) then started decreasing whereas the concentration of sulfate increased steadily as topiramate assay values decreased. A similar pattern was observed for samples stressed at 70 °C except that the maximum concentration of sulfamate was only 1.3% (mole) observed at 120 and 144 hours.

The mass balance (recovery) data are also presented in Table 2. For the 90 °C samples, the total recovery decreased with time and was 71.0% when about 44.1 % topiramate was degraded. The lack of total recovery with these samples indicated a possibility of several parallel degradation reactions for topiramate at this temperature. The degradation reactions may generate sulfamate, sulfate, black carbon and some unknown organic degradation products to which the sulfamate functionality was still attached. Therefore, Scheme 1 is not a complete description for topiramate degradation at 90 °C. For the 70 °C samples, the improved recovery (96.6% - 98.3%) was time-independent and acceptable for practical purposes. The best recovery results were observed for three batches of degraded topiramate tablets which had been stored in three different containers at 40 °C for 9 months. Different amounts of desiccant were present in two of those containers. These samples were analyzed using this method for sulfamate and sulfate. The method had to be modified to assay sulfamate because of interference from the excipients [8]. It is interesting that

Table 2: Weight Percent Assay Values for Topiramate and Degradation Products Observed in Stressed Drug Substance and Tablets

	Stress Cond. °C/hour	Sulfamate (mole%)	Sulfate (mole%)	Topiramate (%)	Recovery (%)
Drug Substance					
	90/7	0.0	0.0	100.4	100.4
	90/11	0.4	0.2	98.7	99.3
	90/13	2.0	0.5	91.6	94.1
	90/15	5.7	3.5	72.1	81.3
	90/17	4.0	11.1	55.9	71.0
	70/120	1.3	2.0	93.9	97.2
	70/144	1.3	6.4	90.0	97.7
	70/168	0.6	9.7	86.3	96.6
	70/192	0.5	10.4	87.4	98.3
	70/240	0.9	13.8	83.1	97.8
Tablets					
	40/9 month[a]	N/A	13.4	86.3	99.7
	40/9 month[b]	N/A	7.3	93.0	100.3
	40/9 month[c]	N/A	0.7	100.7	101.4

a - No desiccant in container
b - 1 g desiccant in container
c - 10 g desiccant in container

only sulfate was detected in these samples. and that the stability of topiramate is related to the amount of desiccant present in the containers.

In summary, for topiramate drug substance and tablets exposed to elevated temperatures ($\leq$70 °C), sulfamate and/or sulfate are the stoichiometrically formed degradation products. Therefore, the assay of sulfamate and/or sulfate is equivalent to assaying the total organic moieties of degradation products that do not contain sulfur. This strategy takes advantage

of the fact that sulfamate and sulfate are stable and nonvolatile chemical entities, while the disadvantage is that two assay methods are needed (one for the active drug and one for the degradation products) for the release testing and stability monitoring of the drug substance and tablets. Currently at the R. W. Johnson Pharmaceutical Research Institute, this strategy has been incorporated into the official stability testing program for topiramate. Many drug substance and tablet samples stressed at 40 or 50 °C have been assayed. Good mass balance has been observed for all samples assayed.

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