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Determination of the inorganic degradation products sulfate and sulfamate in the antiepileptic drug topiramate by capillary electrophoresis

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Abstract

A capillary electrophoresis (CE) method has been developed as an alternative method for the determination of the inorganic degradation products sulfate and sulfamate in topiramate drug product and drug substance, currently performed by ion chromatography. The anions are separated in a background electrolyte containing potassium chromate and boric acid, followed by indirect UV detection. By adding tetradecyltrimethylammonium bromide to the electrolyte, analysis is performed under co-electroosmotic flow conditions. Variations in injection volumes and migration times are compensated for by use of an internal standard. The validation of the method, which was performed according to ICH guidelines (International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use) [1], comprises specificity, accuracy, linearity, precision, sensitivity and robustness. In addition, the results of an actual tablet sample analysis obtained by this CE method are statistically shown to be in close agreement with those obtained by an ion chromatographic method.

Keywords: Topiramate; Sulfate; Sulfamate

1. Introduction

Topiramate [bis-*O*-(1-methylethylidene)-fructopyranose sulfamate] is a novel anticonvulsant drug under development by the R.W. Johnson Pharmaceutical Research Institute [2,3]. Structurally distinct from other anticonvulsants in that it is a monosaccharide derivative with a sulfamate functionality (Fig. 1), topiramate has been shown to be effective for the treatment of epileptic disorders. Topiramate is marketed in numerous countries under the trade name Topamax, Topimax and Topamac.

In the solid state and under normal storage conditions topiramate is very stable, but degrades at elevated temperature and humidity to afford organic degradation products, insoluble polymeric products and the inorganic anions sulfate and sulfamate as shown in Fig. 1. Since sulfate and sulfamate are produced stoichiometrically and can be extracted quantitatively from degraded samples a stability-indicating ion chromatographic (IC) method was developed for monitoring topiramate degradation by

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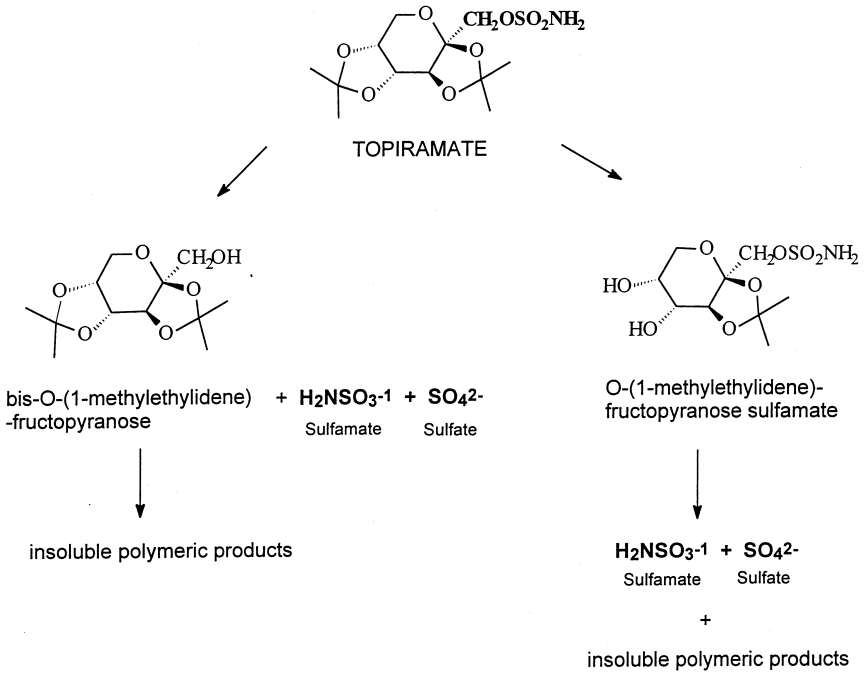

Fig. 1. Topiramate degradation pathway.

quantifying sulfate and sulfamate [4]. In order to continuously improve existing analytical methods in terms of performance, accuracy, analysis time, and costs etc., capillary electrophoresis (CE) was investigated regarding its suitability as a routine technique for monitoring topiramate degradation.

Over the last few years CE has shown a tremendous growth in its use for the analysis of small organic and inorganic ions. Since Mikkers et al. [5] described for the first time the separation of anions by electrophoresis in small tubes in 1979, several groups investigated the suitability of CE for separating and quantifying small ions [6–10]. In the meantime, this new technique named capillary ion electrophoresis (CIE) is applied e.g., in environmental analysis for the determination of anions in atmospheric aerosols [11] or raindrops [12], in food analysis (drinking water) [13] and in pharmaceutical analysis for stoichiometric testing of drug substances [14] or the determination of inorganic impurities [15].

The detection scheme applied in CIE is either conductivity or indirect UV detection since the small ions have no chromophore allowing for direct photometric detection. In indirect UV detection a background electrolyte (BGE) is used containing an UV absorbing co-ion with an absorption maximum not interfering with the analytes. The detector measures the absence of the co-ion which is physically displaced charge-by-charge by the analyte ions resulting in negative peaks. Commonly used co-ions for anion analysis are chromate [7,8,13] or pyromellitate [9,11]. By adding a cationic surfactant such as cetyl- or tetradecyltrimethylammonium bromide (CTAB, TTAB) to the BGE the direction of the electroosmotic flow (EOF) is reversed through formation of a positively charged double layer at the inner capillary surface. The benefits of these co-EOF conditions for anion analysis are shorter analysis time and reduced dispersion due to less longitudinal diffusion.

The present report describes the development and validation of a routine CE method for monitoring the degradation products sulfate and sulfamate in both topiramate drug product and drug substance. Topiramate drug product comprises coated tablets and a sprinkle powder formulation (sugar spheres coated with the active ingredient). The validated method was applied to the determination of sulfate and

sulfamate in a number of stability samples, demonstrating the reliability of the CE method. Additionally, the results were compared statistically with the results obtained by the established IC method.

2. Experimental

2.1. Materials

All topiramate tablet and sprinkle samples as well as the topiramate drug substance were obtained from the R.W. Johnson Pharmaceutical Research Institute (Schaffhausen, Switzerland or Raritan, NJ, USA). The sodium sulfate and sulfamic acid reference standards were purchased from Aldrich (Buchs, Switzerland). Sodium chromate, TTAB, potassium nitrate and the sodium hydroxide were supplied by Fluka (Buchs, Switzerland). The boric acid was supplied by Merck (Darmstadt, Germany) and the acetonitrile (ACN) by Scharlau (Barcelona, Spain). All chemicals were of analytical grade. The reference standards were of ACS grade. Water was doubly deionized using a Barnstead NANOpure analytical grade system (Dubuque, IA, USA).

The 0.45-μm Nylon-66 sample filters were purchased from Whatman (Clifton, NJ, USA) and the filters for BGE filtration, 0.2-μm nylon N-252 filters, were purchased from Supelco (Buchs, Switzerland).

2.2. Procedures

2.2.1. Preparation of the separation buffer

Buffer stock solutions of 100 m*M* sodium chromate, 100 m*M* boric acid and 50 m*M* TTAB were prepared in doubly deionized water. The three stock solutions were mixed and diluted to a final concentration of 5 m*M* chromate, 5 m*M* boric acid and 0.5 m*M* TTAB. Using 1 *M* sodium hydroxide the buffer was titrated to pH 8.0. Before use, the buffer solution was filtered through a 0.2-μm Nylon N-252 filter and degassed for 10 min in an ultrasonic bath.

2.2.2. Preparation of the standard (STD) solution

A standard solution containing sodium sulfate (0.0123 mg/ml), sulfamic acid (0.00838 mg/ml) and potassium nitrate (I.S., 0.0496 mg/ml) was prepared. The concentration of sulfate and sulfamic acid corresponds to 0.5% and 0.25% topiramate degradation in the tablets and the sprinkles, respectively.

2.2.3. Sample preparation

2.2.3.1. *Tablets*. The volume of sample solvent and the number of tablets required per sample preparation depends on the strength of the topiramate tablets (25 mg to 400 mg). In general between 7 to 12 tablets are dissolved in 100–500 ml of ACN–water (20:80, v/v) by shaking for 1 h, followed by the addition of internal standard (I.S.) solution (25 m*M*) and filtration through a Nylon-66 membrane filter.

2.2.3.2. *Sprinkles*. The equivalent of 120 mg topiramate is dissolved in 10.0 ml of ACN–water (20:80, v/v) by shaking for 1 h, followed by the addition of 0.2 ml I.S. solution (25 m*M*) and filtration through a Nylon-66 membrane filter.

2.2.3.3. *Drug substance*. A solution of 6.0 mg topiramate/ml in ACN–water (20:80, v/v) is prepared. To 5.0 ml of this solution 0.1 ml I.S. (25 m*M*) is added.

2.2.4. Calculation

Since sulfate and sulfamate are formed stoichiometrically during topiramate degradation their content is calculated referring to the initial topiramate concentration in the tablets as mol% sulfate and sulfamate. To avoid calculation errors due to the different migration velocity of the analytes the detected peak area was corrected by the migration time. Additionally, the sulfate and sulfamate content is calculated using peak areas relative to those of the I.S., for both the reference standard and the samples ($A = A_{\mathrm{Sulf.}}/A_{\mathrm{I.S.}}$).

2.3. Capillary electrophoresis

CE analyses were performed on a HP^{3D}CE system (Hewlett-Packard, Waldbronn, Germany), equipped with a diode-array detector. Separations were carried out in fused-silica capillaries (Composite Metal Services, The Chase Hallow, UK) of 48.5 cm (effective length 40.0 cm)×50 μm I.D.×375 μm O.D., at 25°C. Samples were injected hydro-

dynamically at 50 mbar for 7 s, corresponding to an injection volume of 11.1 nl. During separation irregular fluctuations in the current occur due to the sample composition resulting in additional migration time shifts. For this reason separations were performed at a constant current of −11 μA. The polarity was reversed with the injection taking place at the cathodic end and the detection at the anodic end of the capillary. Indirect UV detection at 272 nm was applied.

New capillaries were rinsed with BGE for 15 min, followed by preconditioning at −20 kV for another 15 min. Between the runs the capillary was rinsed for 5 min with the BGE. The BGE in the separation vials was replaced after every fourth run. After about 100–120 injections the capillaries had to be replaced.

3. Results and discussion

A CE method was developed to quantitate the level of sulfate and sulfamate in topiramate drug product and drug substance. Since sulfate and sulfamate do not contain a chromophore, indirect UV detection was used by adding an UV absorbing carrier electrolyte ion to the separation buffer. The molar absorptivity of the carrier electrolyte ion should be high in order to ensure high sensitivity. Additionally, its concentration has to be such that it guarantees a high dynamic range, a background absorbance falling within the linear range of the detector and a low level of baseline noise [16]. Another very important aspect regarding the selection of an appropriate carrier electrolyte ion is its electrophoretic mobility which should match with that of the analyte ions. Under these conditions electrophoretic dispersion becomes negligible resulting in nearly Gaussian peak forms [16].

For the present application, chromate was chosen as the carrier electrolyte ion because its electrophoretic mobility of $-81.1 \cdot 10^{-9}$ m^2 V^{-1} s^{-1} is very close to that of the sulfate ion with $-79.5 \cdot 10^{-9}$ m^2 V^{-1} s^{-1} [17], and its molar absorptivity with $\varepsilon =$ 3180 l mol^{-1} cm^{-1} was found to be sufficient. Among the cationic surfactants investigated for the present application, such as TTAB, CTAB and cetyltrimethylammonium hydroxide, addition of 0.5 m*M* TTAB to the BGE lead to the most stable migration times for sulfate and sulfamate. Addition of TTAB higher than 0.5 m*M* resulted in the formation of insoluble complexes with chromate resulting in turbid buffer solutions.

The migration time of sulfate and sulfamate showed unsatisfactory reproducibility due to matrix effects of the drug product excipients which caused gradual alteration of the capillary surface and therefore a change in the EOF. Rinsing the capillary with sodium hydroxide after each run resulted in a significantly decreased separation performance due to destruction of the positively charged double layer formed by the TTAB. However, adding an internal standard to the sample solution and calculating both the migration time and the peak area relatively to the internal standard, resulted in improved migration time reproducibility and injection precision. As demonstrated in Table 1 the positive effect of the internal standard addition is more significant in case of the migration time reproducibility. Regular replenishment of the separation buffer and working at constant current instead of constant voltage also improved the run-to-run reproducibility.

To prove the suitability of the present CE method for its intended use as an stability indicating assay for topiramate by monitoring the sulfate and sulfamate levels, the CE method was validated according to the ICH guidelines [1] for both drug product and drug substance. For monitoring degradation of topiramate, sulfate–sulfamate values in the range of 0.5 mol% are of special interest since this value corresponds to the specification of the drug. The concentration range in the individual validation steps was therefore chosen accordingly.

3.1. Specificity

Fig. 2 shows the separation of a 0.5 mol% standard solution, containing sulfate, sulfamate and potassium nitrate as internal standard. As expected the three anions were well resolved with the sulfate ion migrating in front of the nitrate and the sulfamate ion due to its higher electrophoretic mobility [17]. By comparing the electropherograms obtained from the analysis of a reference standard and a placebo, it is demonstrated that no interference of the analyte anions with peaks generated by the excipients, other

Table 1
R.S.D.s for migration times and peak areas of a 0.5 mol% standard solution and a topiramate tablet and a sprinkle solution spiked with 0.5 mol% standard

	Standard (mean of $n=10$)		Spiked tablets (mean of $n=10$)		Spiked sprinkles (mean of $n=10$)	
	Sulfate	Sulfamate	Sulfate	Sulfamate	Sulfate	Sulfamate
t_m	1.62	2.13	1.67	2.25	1.65	2.21
R.S.D. (%)	0.7	1.2	2.2	3.2	0.2	0.2
t_m ratio	0.977	1.29	0.976	1.32	0.976	1.31
R.S.D. (%)	0.07	0.6	0.07	0.9	0.03	0.09
Peak area	$3.02\cdot10^{-2}$	$1.95\cdot10^{-2}$	$3.77\cdot10^{-2}$	$2.26\cdot10^{-2}$	$4.32\cdot10^{-2}$	$2.09\cdot10^{-2}$
R.S.D. (%)	2.2	4.3	2.2	3.8	1.2	3.6
Peak area ratio	0.366	0.238	0.452	0.270	0.464	0.225
R.S.D. (%)	1.5	4.2	1.5	2.6	1.3	3.1

t_m ratio$=t_{mSulf.}/t_{mI.S.}$, peak area ratio$=A_{Sulf.}/A_{I.S.}$.

than sulfate itself, occurred (Fig. 2). Beside the analyte anions also chloride and carbonate were identified in the sample solution. The carbonate peak which was found to be a system peak caused by contamination of the carrier electrolyte with carbonate, can be either positive or negative [18]. In Fig. 3 it is demonstrated that even in sample solutions of heavily degraded topiramate tablets containing very high amounts of sulfate, good resolution of both the sulfate/I.S. peak pair ($R=2.02$) and the sulfate/chloride peak pair ($R=1.12$) is achieved and no interference with other peaks occurs. For the topiramate sprinkle formulation, a separation pattern very similar to that of the tablets was obtained (data not shown).

3.2. Linearity

The linearity of the detection system was investigated for a concentration range of 0–10.0 mol% sulfate and sulfamate, corresponding to 0–10.0% topiramate degradation. The plot of the peak area

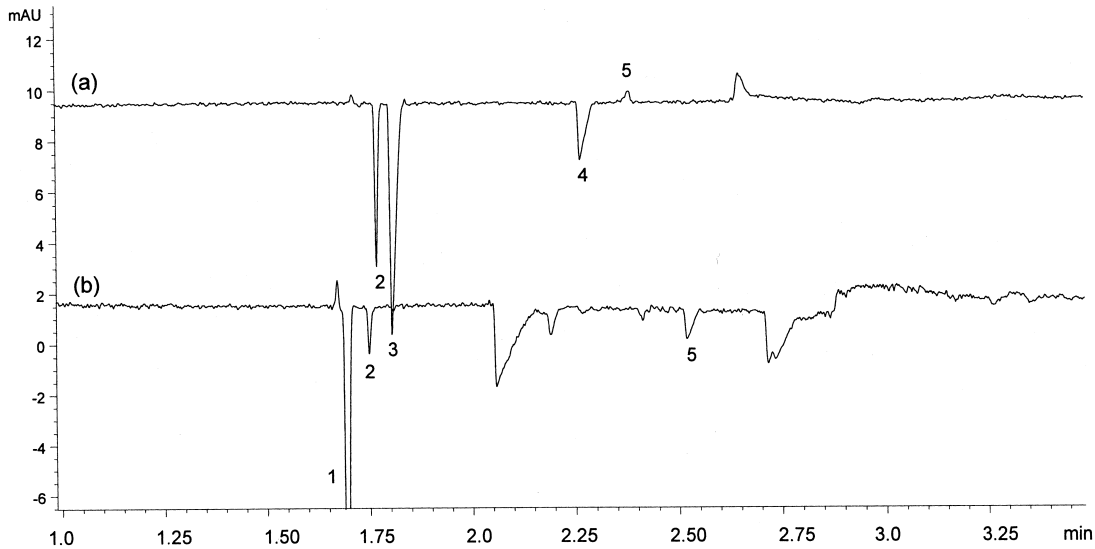

Fig. 2. Electropherograms for a 0.5 mol% reference standard (a) and a placebo (b). Separation conditions are as indicated in Section 2.3. Peaks: 1=chloride, 2=sulfate, 3=I.S., 4=sulfamate, 5=carbonate.

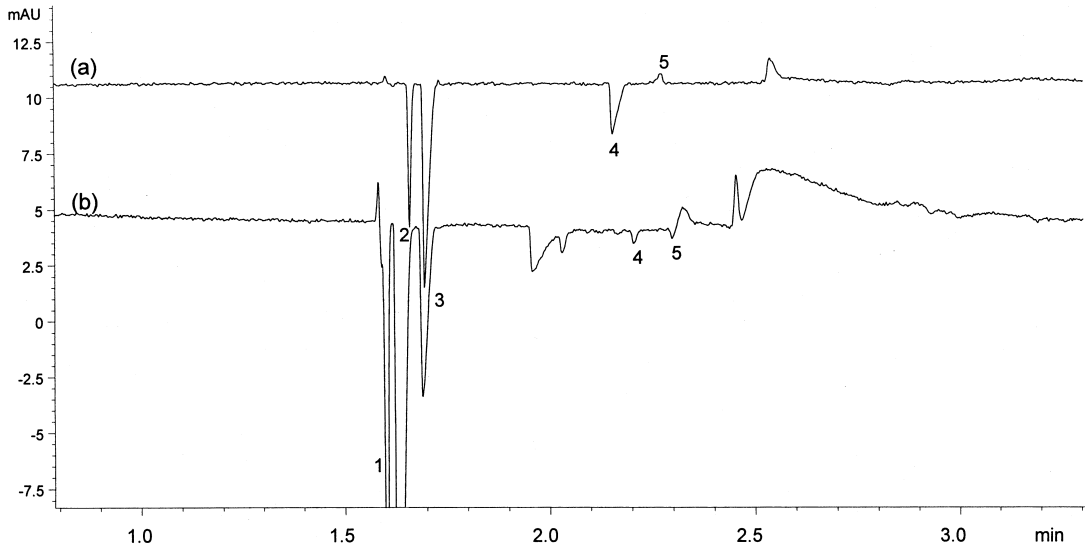

Fig. 3. Electropherograms for a 0.5 mol% reference standard (a) and a heavily degraded topiramate tablet containing 6.0 mol% sulfate (b). Separation conditions and peak numbering as in Fig. 2.

versus mol% sulfate showed a good linear behavior with a squared linear correlation coefficient of 0.9999 and an insignificant *y*-intercept counting for only 2.1% of the response of the 0.5 mol% calibration standard (Fig. 4). The plot of the response factor Rf (Rf=peak area/concentration) versus concentration revealed an upward drift in response in the concentration range below 0.25 mol% sulfate (Fig. 4). However, even the 0.1 mol% standard deviated only 10% from the 0.5 mol% calibration standard, which was found to be acceptable. The same good linear behavior could be demonstrated for the sulfamate ion with a squared correlation coefficient of 0.9993 and deviations from the response of the 0.5 mol% calibration standard below 10%, even for the 0.05 mol% standard.

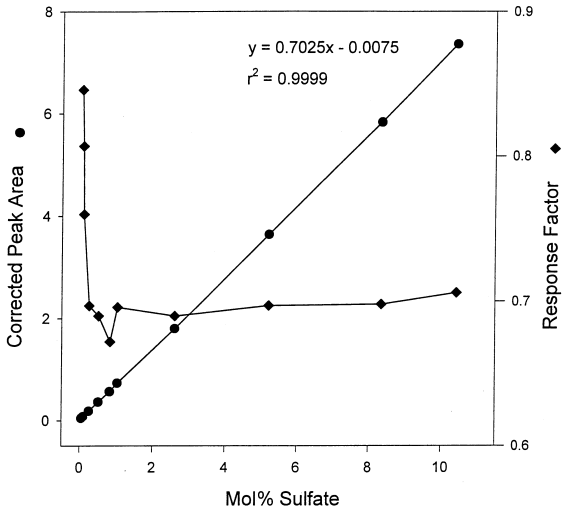

Fig. 4. Sulfate linearity plot and plot of sulfate response factors from 0.05–10.0 mol%.

Referring to the present linearity data, an one-point calibration against a 0.5 mol% reference standard was applied to both less and heavily degraded topiramate drug product and drug substance containing low and high concentrations of sulfate and sulfamate.

3.3. Precision

The injection precision, determined by 10 subsequent injections of a 0.5 mol% reference standard solution, was found to have a relative standard deviation (R.S.D.) of 1.5% and 4.2% for sulfate and sulfamate, respectively. Similar values were found for tablet and sprinkle solutions spiked with reference standard (Table 1).

To assess the repeatability of the method the same drug product or drug substance samples were pre-

Table 2
Repeatability

	Tablets (n=5)	Sprinkles (n=8)	Drug substance (n=8)
Sulfate (mol%)	0.33	0.11	0.35
R.S.D. (%)	4.7	13.7	7.2
Sulfamate (mol%)			0.05
R.S.D. (%)			17.8

pared five and eight times, respectively, and assayed. In the tablets and the sprinkles only sulfate was identified whilst in the drug substance electropherograms a small sulfamate peak occurred. As demonstrated in Table 2, the repeatability showed R.S.D.s of about 5–14% for tablets, sprinkles and drug substance. In the drug substance a sulfamate content of 0.05 mol%, which is below the limit of quantitation (LOQ), was determined with a precision of 17.8% R.S.D. (Table 2).

To investigate the intermediate precision the same samples were assayed by two different analysts. Each analyst used his/her own capillaries, buffer solutions and standard solutions. In two sequences both non-degraded tablets with low sulfate contents (stored at ambient conditions) and degraded tablets with high sulfate contents (stored at 30°C/60% rel. humidity for 36 months) were assayed. The results generated by the two analysts (see Table 3), were found to be in close agreement even for the very low sulfamate contents. Calculating the total R.S.D. for these results the intermediate precision for the sulfate determination was found to be 12.2%/20.0% for the non-degraded and 4.5%/4.3% for the degraded tablets. The sulfamate contents were determined with an intermediate precision of 8.2%/15.8%.

3.4. Sensitivity

According to the European Pharmacopeia [19], the limit of detection (LOD) was calculated as signal-to-noise (S/N)=$2H/h_n$, with H being the height of the peak of interest and h_n the peak-to-peak baseline noise. As illustrated in Fig. 5 the LOD was determined to be 0.01 mol% (0.25 μg/ml) for sulfate and 0.025 mol% (0.42 μg/ml) for sulfamate with a ratio S/N of 3.

The LOQ was defined as the minimum amount quantified with ≤10% R.S.D. (for n=10 injections) and an accuracy of ≥80%. Under these conditions the LOQ was determined to be 0.05 mol% for sulfate and 0.1 mol% for sulfamate as shown in Table 4. Because of the non-linear behavior of the sulfate calibration curve below 0.1 mol%, the LOQ for sulfate was also defined as 0.1% topiramate degradation.

3.5. Accuracy

For determination of accuracy, topiramate tablets and sprinkles of various strengths were spiked with increasing amounts of sulfate and sulfamate (0.1–2.0 mol% for tablets, 0.1–0.75 mol% for sprinkles) and analyzed according to the present method. The average recovery in the topiramate tablets, assayed against a 0.5 mol% reference standard was 107.0% (100.2–114.0%) for sulfate and 102.3% (96.6–110.2%) for sulfamate. For the sprinkle capsules the

Table 3
Intermediate precision

Tablet strength	Mol% sulfate		R.S.D. (%)		Intermediate precision (%)
	Analyst 1	Analyst 2	Analyst 1	Analyst 2	
50 mg (n=6)	0.10	0.11	9.7	13.2	12.2
200 mg (n=6)	0.10	0.08	17.0	14.7	20.0
100 mg (n=3)	3.61	3.33	1.9	1.2	4.5
100 mg (n=2)	0.81	0.77			4.3
	Mol% sulfamate				
100 mg (n=3)	0.068	0.060	5.3	5.8	8.2
100 mg (n=2)	0.059	0.048			15.8

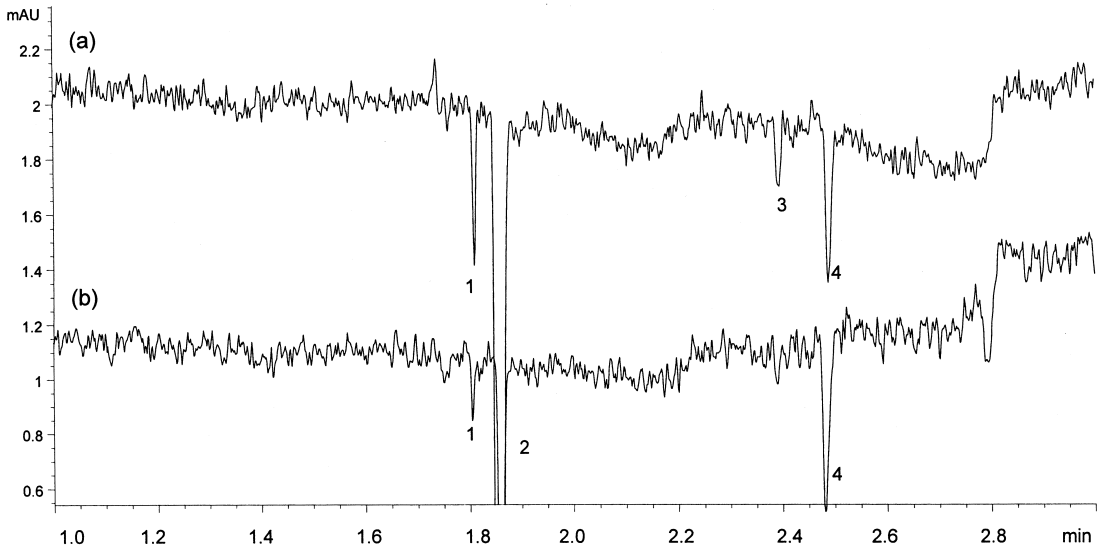

Fig. 5. Separation of a 0.025 mol% (a) and a 0.01 mol% (b) reference standard solution. CE conditions are as indicated in Section 2.3. Peaks: 1=sulfate, 2=I.S., 3=sulfamate, 4=carbonate.

average recovery assayed against a 0.25 mol% reference standard was 96.0% (89.5–103.6%) for sulfate and 100.4% (94.9–109.0%) for sulfamate. The plot of spiked mol% sulfate and sulfamate against the assayed mol% showed a good linear response with squared linear correlation coefficients of 0.998.

3.6. Comparison of CE and IC results

To further investigate the accuracy of the CE method, topiramate sample solutions were analyzed using the present CE method and a well established IC method, currently in use for stability and release testing of topiramate. The comparison study was performed with non-degraded, slightly degraded and heavily degraded topiramate tablets, sprinkles and drug substance. The mol% sulfate determined by the two methods are presented graphically in Fig. 6, with Fig. 6a showing the range from 0.05–0.8 mol% sulfate and Fig. 6b showing the whole range of samples investigated (up to 5.0 mol%). The results generated by CE and IC are in good agreement, expressed by the very linear relationship ($y=1.033x-0.012$) with a slope of close to 1, a negligible y-intercept and a squared correlation coefficient of 0.999.

Unlike in CE, in IC a sulfate peak is generated during sample solvent injection and analysis. For calculations, the background sulfate has to be subtracted from the sample sulfate peak areas, making the results less accurate, especially in the concentration range around the LOQ.

However, the results of the CE and the IC experiments were statistically evaluated for correlation by the paired t-test. This test is a means to prove that the differences between two sets of data, i.e., generated by applying two independent analytical procedures, are not significant [20]. The differences of the CE and the IC results for each sample were used to calculate the t-value. The paired t-test did not show statistically significant differences between the sulfate contents determined by the two independent methods. Since the sulfamate levels in all the sam-

Table 4
Limit of quantitation

Sample	Theoretical (mol%)	Assay (mol%)	Accuracy (%)	R.S.D. (%) ($n=10$)
Sulfate	0.051	0.060	117.6	5.9
Sulfate	0.102	0.112	109.8	4.2
Sulfamate	0.051	0.052	102.0	12.5
Sulfamate	0.102	0.104	102.0	6.1

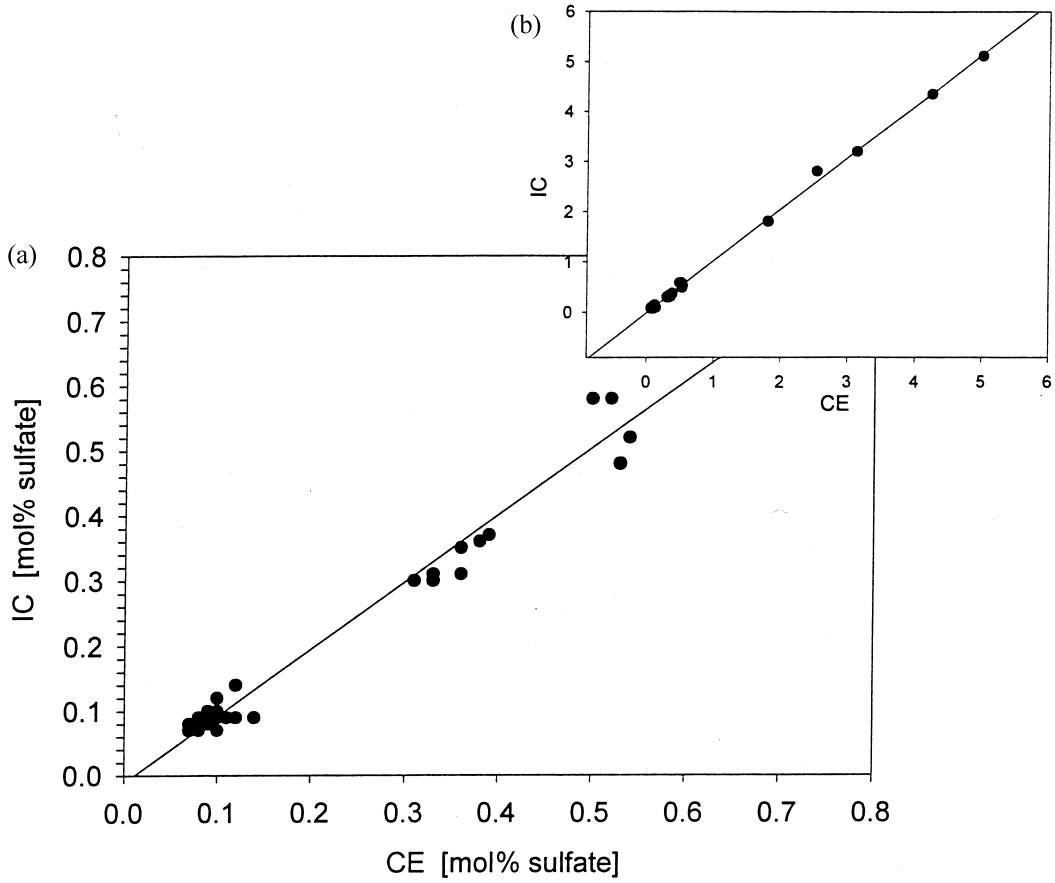

Fig. 6. Mol% sulfate determined in topiramate drug product with CE and IC. (a) Shows the range from 0.05–0.8 mol% and (b) from 0.05–5.0 mol% sulfate. CE separation conditions are as indicated in Section 2.3. IC separation conditions: column, Ion Pac AS5A 5 μm (Dionex); eluent, NaOH gradient from 2–25 m*M* NaOH within 15 min; flow-rate, 1.0 ml/min; detection, conductivity with anion self-regenerating suppressor.

ples investigated were below the LOQ (<0.1 mol%), the sulfamate data were not statistically evaluated. The results of the paired *t*-test confirm the suitability of the present CE method for monitoring topiramate degradation.

3.7. Robustness

For robustness evaluation the univariate approach [21] was applied, which involves a systematic variation of each parameter sequentially. The parameters investigated are the injection time, the temperature of the capillary, the buffer pH, the chromate concentration and the detection wavelength (Table 5). Resolution of the sulfate/I.S. peak pair and the signal-to-noise ratio of the sulfamate peak were used as indicators. The parameters were varied 5–30% below and above the value set in the method, whereas only slight changes were made in the wavelength testing since 254 nm and 280 nm represent the wavelengths usually available in single-wavelength detectors.

Variations in pH, chromate concentration and injection volumes resulted in variations in resolution of about 5–10% (Table 5). In each case the sulfate/nitrate peak pair was at least baseline separated with a resolution of $\geq$1.5. Variations (especially decrease) in the capillary temperature showed a more pronounced effect on the resolution. This might be due to temperature depended changes in the chromate–

Table 5
Robustness testing

Factor	Level			Resolution[a]		
	−1	0[b]	1	−1	0[b]	1
Injection time (mbar s)	250	350	450	1.95	1.73	1.50
Capillary temperature (°C)	20	25	30	1.44	1.87	1.65
Buffer pH	7.5	8.0	8.5	1.96	1.85	1.64
Chromate concentration (m*M*)	4	5	6	1.87	1.79	1.62
				S/*N*		
Detection wavelength (nm)	254	272	280	20.0	24.6	22.6

[a] Resolution was calculated by the tangent method.
[b] Level 0=value set in the method.

dichromate equilibrium influencing the separation performance. A change in the detection wavelength to 254 nm and 280 nm, respectively, showed only an insignificant decrease in sensitivity as obvious from the signal-to-noise ratios in Table 5. However, a 10% variation in the detection wavelength resulted in a 2–3 fold decrease in sensitivity.

3.8. CE specific validation aspects

In principal the criteria for method validation applied to CE are similar to those applied to other analytical separation techniques such as high-performance liquid chromatography (HPLC). However, there are some factors which need to be considered in CE that are different from the HPLC validation criteria and which are discussed in this section.

Since the quality of the fused-silica capillaries might change from batch to batch, the present application was performed on capillaries of two different batches. No significant variations were observed regarding the migration time and the resolution of the analytes. Due to electrolysis effects pH changes and deterioration of the separation buffer may occur. Therefore the peak area precision for sulfate and sulfamate was checked for ten subsequent injections without buffer replenishment and with replenishment after every fourth run. While for sulfate no difference in the peak area precision was observed, R.S.D.s of 3.6% and 5.8% with and without replenishment, respectively, were found for sulfamate. Therefore, periodic buffer replenishment is applied in the present application. The stability of the separation electrolyte was also investigated and the capillary preconditioning procedure optimized during the validation process.

4. Conclusions

A CE method with indirect UV detection was developed for monitoring the inorganic degradation products sulfate and sulfamate in topiramate drug product and drug substance. The extensive method validation showed good levels of performance in terms of specificity, linearity, accuracy, precision, LOD and LOQ and robustness. With a linear range of 0.1–10.0 mol% and average recoveries of 96–107%, a specified range of 0.1–10.0 mol% for sulfate and sulfamate was defined for the present method. The statistical comparison (*t*-test) of the CE results with those obtained by a well established IC method did not show significant differences proving the reliability of the results generated using the CE method.

The described method is being submitted to regulatory authorities for the approval for the routine testing of topiramate. The advantage of the CE procedure over the IC method currently in use is its extended linear range, allowing for the analysis of both non- and heavily degraded topiramate drug product without requiring additional dilution steps. The run time is reduced by a factor of three in case of CE, allowing for a much higher sample throughput, a very important aspect in today's routine test labs. Additionally, in CE substraction of background sulfate is not necessary, making the calculations simpler and the results more accurate. In sum, the

CE procedure showed to be less complex and more rugged compared to the IC method.

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