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Assay of residual organic solvents in topiramate drug substance by capillary gas chromatography*

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Abstract: The analysis of residual organic solvents (methanol, ethanol and toluene) in topiramate drug substance was investigated. Topiramate is a potent anticonvulsant drug under clinical evaluation. The drug is recrystallized from ethanol denatured by either methanol or toluene, and each residual solvent is controlled at 0.1% (w/w) level. A capillary gas chromatography (GC) method described in this manuscript utilizes a DB-WAX, 1 μm thick, 30 m × 0.53 mm i.d., column. Since topiramate is a thermally labile compound, the selection of the proper injector temperature is critical to the success of the analysis. The injector temperature was set at 120°C to prevent degradation. The initial oven temperature was set at 55°C for 8 min and programmed at a rate of 30°C min^{-1} to a final temperature of 160°C for 11 min. Helium was used as a carrier gas. The sample solvent selected was dimethylformamide pretreated with molecular sieves to remove trace amounts of alcohols that may interfere with the assay. The method was validated to be specific, linear, precise, sensitive, rugged and showed excellent recovery.

Keywords: *Methanol; ethanol; toluene; topiramate; capillary gas chromatography.*

Introduction

In this paper, a capillary gas chromatography (GC) method for the determination of methanol, ethanol toluene in a drug substance has been described. The method has been validated to be specific, linear, precise, sensitive, rugged and shows excellent spiked recovery. This method is presently used as a control method for residual solvents in topiramate drug substance for clinical use.

Topiramate (Fig. 1), a derivative of fructose, is a new anticonvulsant [1, 2] and antiepileptic drug [3] under development for the treatment of human diseases. A new class of derivatives of carbohydrates has been discovered to have such properties. The drug is recrystallized from ethanol denatured by either methanol or toluene in the manufacturing process. Though the drug is dried and most of the organic solvents evaporated, there are residual organic solvents remaining in the drug substance. The level of these residual organic solvents has to be determined and controlled.

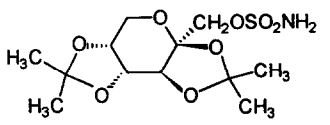

Figure 1
The structure of topiramate.

Gas chromatographic methods (including headspace GC, headspace GC–MS and capillary GC) [4–8] have been used to assay for trace amounts of volatile organic solvents in liquid and solid materials. In order to avoid the many problems associated with the headspace GC analysis of volatile organic molecules [9], an analytical method has been developed to directly inject the topiramate drug substance dissolved in dimethylformamide (DMF) into a capillary GC equipped with a flame ionization detector (FID). However, DMF is not free of trace amounts of alcohols that may interfere with the trace analysis of volatile organic solvents. Hence, it is necessary to pretreat the DMF with molecular sieves to remove the trace amount of alcohols. The DMF is filtered through an organic membrane before it can be used as a solvent for topiramate drug substance.

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Carbohydrates are thermally labile and degrade at elevated temperatures. Topiramate is no exception and degrades at moderate injector temperatures (above 150°C) to acetone and other organic species. The degradation products are detected as large peaks in the regions of methanol and ethanol, interfering with the quantitative assay of residual solvents. The method described in this manuscript minimized the degradation of topiramate by selecting an injector temperature of 120°C. By choosing the lower injector temperature, the degradation of topiramate (a carbohydrate derivative) can be decreased and the quantitation of residual organic solvents becomes feasible.

Experimental

Chemicals and reagents

Methanol is HPLC grade (Fisher Scientific, Fair Lawn, NJ, USA). Ethanol is USP grade (Pharmco Products, Inc., Bayonne, NJ, USA). Toluene and isobutanol are A.C.S. grades (Fisher Scientific, Fair Lawn, NJ, USA). Dimethylformamide is B&J Brand (Baxter Healthcare Corporation, Muskegon, MI, USA), pretreated by addition of 5 Å molecular sieves. Topiramate is from the R.W. Johnson Pharmaceutical Research Institute (Spring House, PA, USA).

Solutions

Internal standard. Ten microlitres of isobutanol are transferred into 500 ml of dimethylformamide.

Stock standard. One millilitre of methanol and toluene and 2.5 ml of ethanol are accurately transferred by a pipette into a 100 ml volumetric flask and diluted to volume with internal standard solution. Then, 1.0 ml of this mixture solution is transferred into a 100-ml volumetric flask and diluted to volume with internal standard solution.

Standard. 12.5 ml of stock solution are transferred by pipette into a 100-ml volumetric flask and diluted to volume with internal standard solution [0.098% methanol, 0.108% toluene, 0.246% ethanol (w/w) relative to topiramate].

Procedures

Column conditioning. The column was preconditioned for 2 h at 200°C. A Hewlett-Packard 5880A gas chromatograph with a FID was used. The GC detector signal was fed into a Hewlett-Packard LAS 1000 computer system. The instrument parameters described below were set up to determine the residual solvents.

Column: DB-wax 1 μm film thickness 30 m × 0.53 mm (maximum temperature 240°C; J & W). Injection liner: a narrow straight glass linear (78 × 2 mm i.d.) packed tightly with silanized glass wool (upper 1/4 not packed). Injector temperature: 120°C. Detector temperature: FID, 250°C. Column temperature: 55°C initial for 8 min; rate, 30°C min^{-1}; final temperature 160°C for 11 min. Gases: carrier, helium; head pressure, 4 psi; flow, 6 ml min^{-1}; split flow, 6 ml min^{-1}; make-up gas, nitrogen 30 ml min^{-1}; detector, hydrogen 40 ml min^{-1}; air 400 ml min^{-1}. Injection volume: 2.0 μl. Run time: 22.5 min. Retention times: methanol, 2.3 min; ethanol, 2.7 min; toluene, 4.6 min; isobutanol, 6.2 min.

Sample preparation. About 40 mg of sample was weighed into a 1-dram bottle and 4.0 ml of internal standard solution was accurately pipetted into the bottle. The bottle was sealed with a cap lined with Teflon® or other liner that did not cause interference in the chromatography. The bottle was shaken well to dissolve the contents.

Calculations

The concentration of residual solvent was calculated from:

$$\% \text{ Solvent} = \frac{Au}{As} \times \frac{Als}{Alu} \times \frac{D}{Wu} \times f \times 4 \times 100, \quad (1)$$

where Au = area of solvent peak in the sample; As = area of solvent peak in the standard; Alu = area of the internal standard peak in the sample; Als = area of the internal standard peak in the standard; D = density of solvent standard (mg ml^{-1}), 786.6 for methanol, 787 for ethanol, and 866 for toluene; Wu = sample weight (mg); f = dilution factor = 0.0000125 for methanol and toluene, and 0.0000313 for ethanol; and 4 = sample solution volume (ml).

Results and Discussion

Specificity

Ethanol, methanol and toluene were well

resolved from the internal standard (isobutanol), the sample solvent, DMF, and each other. A chromatogram of a standard solution prepared according to the assay procedure is reported in Fig. 2 to illustrate the separation obtained with this method [0.098% methanol, 0.246% ethanol and 0.108% toluene (w/w) relative to topiramate]. A chromatogram of a topiramate sample is presented in Fig. 3 [0.09% ethanol and 0.01% toluene (w/w)]. A chromatogram of DMF solvent contaminated with trace quantities of methanol is presented in Fig. 4. Figure 5 shows the chromatogram of the same DMF solvent after the molecular sieves treatment. The molecular sieves helped to absorb the methanol and other impurities that elute later in the chromatogram. The sample solvent used was checked before preparing samples to make sure there were no peaks that would interfere with the assay.

Linearity

The plots of peak area ratio versus concentration of methanol (0.5–40 μg ml^{-1}), ethanol (1–100 μg ml^{-1}) and toluene (0.5–50 μg ml^{-1}) injected was linear with a correlation coefficient of 0.999 or better and intersected the *y*-axis near the origin, indicating that the response is linear from 0.005 to 0.4% for methanol and toluene and from 0.1 to 1.0% for ethanol (w/w) of the amount of topiramate specified to be injected in this method.

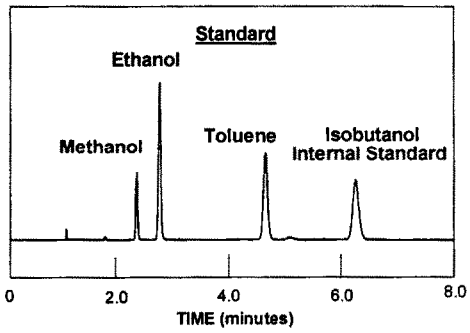

Figure 2
A chromatogram of standard solvents.

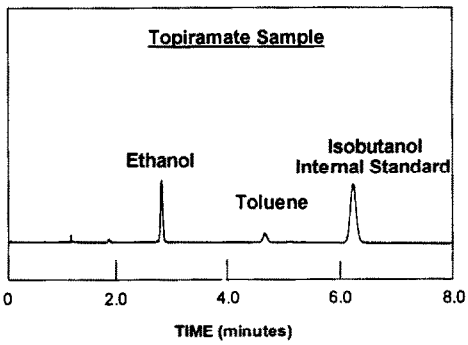

Figure 3
A chromatogram of a topiramate sample.

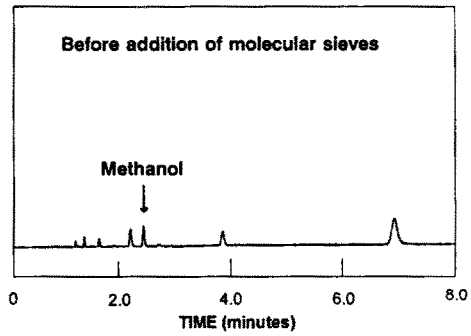

Figure 4
A chromatogram of DMF solvent before addition of molecular sieves.

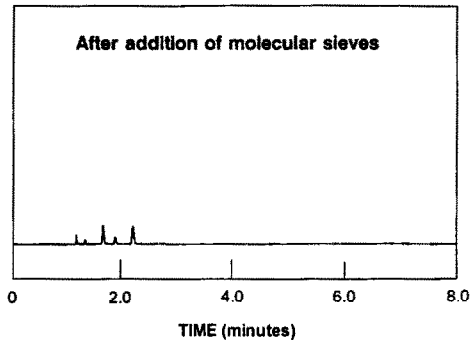

Figure 5
A chromatogram of DMF solvent after addition of molecular sieves.

Precision

The relative standard deviation (RSD) was determined to be 0.70% for methanol, 0.91% for ethanol and 0.88% for toluene (Table 1) for 10 injections of a standard solution [0.098% methanol, 0.246% ethanol and 0.108% toluene (w/w)], demonstrating acceptable precision for the chromatographic system. The method precision was also found to be acceptable. The RSD was determined to be 5.69% (Table 2) for ethanol and 3.51% for toluene for 10 weighings of a topiramate drug substance which contained 0.09% ethanol (w/w) and 0.01% toluene (w/w).

Sensitivity

The limit of detection was determined experimentally (S/N = 2) to be at 0.002% [the

Table 1
Precision of peak area ratios of 10 replicate injections of a standard solution

Injection no.	Methanol Peak area ratio	Ethanol Peak area ratio	Toluene Peak area ratio
1	0.290799	0.904611	0.882118
2	0.286373	0.900309	0.867345
3	0.289514	0.899275	0.872979
4	0.292008	0.897446	0.868747
5	0.285980	0.901955	0.865366
6	0.289436	0.903687	0.870302
7	0.290718	0.919542	0.884953
8	0.291708	0.917753	0.867014
9	0.288871	0.909936	0.863717
10	0.290292	0.916716	0.861391
Mean =	0.289570	0.907123	0.870393
RSD (%) =	0.70	0.91	0.88

Table 2
Precision of 10 replicate determinations of ethanol and toluene in a sample of topiramate drug substance*

Weighing	Ethanol (%)	Toluene (%)
1	0.0956	0.0126
2	0.0889	0.0118
3	0.0938	0.0122
4	0.0922	0.0118
5	0.1088	0.0130
6	0.0926	0.0122
7	0.0908	0.0118
8	0.0944	0.0120
9	0.0956	0.0128
10	0.0941	0.0122
Mean =	0.0947	0.0122
RSD (%) =	5.69	3.51

*Topiramate drug substance contains 0.09% ethanol and 0.01% toluene.

Table 3
Limit of quantitation based on 10 replicate injections of methanol, ethanol and toluene at the 0.005% level

	% Assay		
Sample no.	Methanol	Ethanol	Toluene
1	0.0049	0.0052	0.0064
2	0.0056	0.0056	0.0057
3	0.0054	0.0054	0.0057
4	0.0052	0.0055	0.0059
5	0.0054	0.0060	0.0064
6	0.0050	0.0054	0.0060
7	0.0055	0.0053	0.0058
8	0.0051	0.0054	0.0058
9	0.0047	0.0054	0.0057
10	0.0053	0.0053	0.0057
Average	0.0052	0.0055	0.0059
RSD (%)	5.46	4.08	4.68
Theoretical (%)	0.0049	0.0049	0.0054
Accuracy (%)	6.12	12.24	9.26

Table 4
Conditions of the method altered for the determination of ruggedness and the system suitability results

Conditions of method		Altered conditions	Pass system suitability*	Sample assay	
				% Ethanol	% Toluene
Initial column temperature	55°C	None	Yes	0.09	0.01
		50°C	Yes	0.09	0.01
		60°C	Yes	0.09	0.01
Injector temperature	120°C	110°C	Yes	0.09	0.01
		130°C	Yes	0.09	0.01
Column from alternate supplier	J & W Scientific	Restek (Stabilwax-DB)	Yes	0.09	0.01
		Supelco (Supelcowax 10)	Yes	0.09	0.01
Different column same supplier	J & W Scientific, Serial No. 23102075	J & W Scientific, Serial No. 2312076	Yes	0.09	0.01

*System suitability criteria are defined as having a resolution of at least 1.5 between methanol and ethanol, the diluted standard (50.0%) assayed is from 47–53%, and the diluted standards (0.05% level) are detected and integrated by the computer system.

Table 5
Results of the method when used by two different analysts on two different instruments

Analyst	Instrument	Methanol precision RSD (%)	Ethanol precision RSD (%)	Toluene precision RSD (%)	Resolution*	Sample assay		
						Methanol (%)	Ethanol (%)	Toluene (%)
1	1	1.09	0.61	0.81	5.21	0.00	0.09	0.01
2	2	0.46	0.32	0.33	3.0	0.00	0.09	0.01

The sample lot was run in duplicate by each analyst.
* Resolution was determined between methanol and ethanol.

Table 6
Sample solution stability

Sample	Initial	Weight (%) Day 2		Day 3		Day 7	
		RT	4°C	RT	4°C	RT	4°C
Methanol	0.09	0.09	0.10	0.09	0.10	0.09	0.09
Ethanol	0.11	0.11	0.11	0.11	0.11	0.11	0.11
Toluene	0.01	0.01	0.01	0.01	0.01	0.01	0.01

Sample used a lot of topiramate drug substance spiked with methanol assayed to be 0.09%.

Table 7
Recovery of residual solvents

Sample no.	Methanol			Ethanol			Toluene		
	Theor. (%)	Assay (%)	Recov. (%)	Theor. (%)	Assay (%)	Recov. (%)	Theor. (%)	Assay (%)	Recov. (%)
1	—	—	—	0.0049	0.0050	102.0	—	—	—
2	—	—	—	0.0049	0.0045	91.8	—	—	—
3	0.0049	0.0046	93.9	0.0123	0.0129	104.9	0.0054	0.0054	100.0
4	0.0049	0.0045	91.8	0.0123	0.0121	98.4	0.0054	0.0057	105.6
5	0.0098	0.0096	98.0	0.0246	0.0245	99.6	0.0180	0.0107	99.1
6	0.0098	0.0095	96.9	0.0246	0.0251	102.0	0.0108	0.0110	101.9
7	0.0246	0.0243	96.8	0.0615	0.0627	102.0	0.0271	0.0276	101.8
8	0.0246	0.0242	98.4	0.0615	0.0631	102.6	0.0271	0.0277	102.2
9	0.0492	0.0497	101.0	0.1230	0.1256	102.1	0.0541	0.0544	100.6
10	0.0492	0.0495	100.6	0.1230	0.1223	99.4	0.0541	0.0544	100.6
11	0.0737	0.0757	102.7	0.1845	0.1863	101.0	0.0812	0.0815	100.4
12	0.0737	0.0779	105.7	0.1845	0.1857	100.7	0.0812	0.0798	98.3
13	0.0983	0.0950	96.6	0.2459	0.2391	97.2	0.1083	0.1060	97.9
14	0.0983	0.0977	99.4	0.2459	0.2460	100.0	0.1083	0.1083	100.0
15	0.1229	0.1212	98.6	0.3074	0.2983	97.0	0.1353	0.1333	98.5
16	0.1229	0.1230	100.1	0.3074	0.3037	98.8	0.1353	0.1340	99.0
17	0.1475	0.1404	95.2	0.3689	0.3638	98.6	0.1624	0.1599	98.5
18	0.1475	0.1404	95.2	0.3689	0.3625	98.3	0.1624	0.1614	99.4
19	0.1721	0.1657	96.3	0.4304	0.4213	97.9	0.1895	0.1862	98.3
20	0.1721	0.1731	100.6	0.4304	0.4230	98.3	0.1895	0.1861	98.2
21	0.1967	0.1882	95.7	0.4919	0.4901	99.6	0.2165	0.2153	99.4
22	0.1967	0.1883	95.7	0.4919	0.4879	99.2	0.2165	0.2145	99.1
23	—	—	—	0.5621	0.5570	99.1	—	—	—
24	—	—	—	0.5621	0.5500	97.8	—	—	—
25	—	—	—	0.7377	0.7529	102.1	—	—	—
26	—	—	—	0.7377	0.7596	103.0	—	—	—
27	—	—	—	0.9836	0.9797	99.6	—	—	—
28	—	—	—	0.9836	0.9851	100.2	—	—	—
Average			98.1			99.8			99.9
RSD (%)			3.2			2.5			1.9

Recovery was conducted on samples from the limit of quantitation, 0.005–0.2% for methanol and toluene, and 1.0% for ethanol.

baseline noise was taken by measuring the average peak to valley fluctuation over a period of time of a chromatogram of a 0.002% standard (w/w)] for all the solvents of interest (methanol, ethanol and toluene). The experimentally verified limit of quantitation (arbitrarily defined as having an accuracy of better than 15% with a precision of at least 6% or better for 10 replicate injections) was 0.005% for methanol, toluene and ethanol (w/w) with an experimentally determined precision of better than 5.46% (RSD) and an accuracy of 12.24% or better (for 10 replicate injections, Table 3).

Ruggedness

Table 4 shows the method parameters that were modified to study ruggedness, the variations used and the system suitability results obtained. All of the modified conditions (column temperature, injector temperature and column supplier) resulted in satisfactory chromatography for the determination of the levels of methanol, ethanol and toluene in topiramate and system suitability requirements (resolution, precision and linearity) were met. Results obtained from two different analysts using different instruments are given in Table 5.

Solution stability

In order to demonstrate that the samples are stable during the normal chromatographic analysis time, the stability of the sample solutions was determined. The solutions (stored in 1/2 oz bottles) were determined to be stable for 7 days when kept at room temperature on an open bench (approximately 26°C). Results are given in Table 6.

Recovery

The recovery was determined by analysing topiramate samples (known to contain 0.02% ethanol from previous analysis) spiked with methanol, ethanol and toluene at varying levels. The experimental recovery of more than 10 samples for methanol, ethanol and toluene was 98.6, 99.2 and 100.0%, respectively (Table 7) and the % RSD were 3.1, 2.6 and 1.8, respectively. These data are the mean of many spiking experiments performed at many levels. The range of levels studied was 0.005–0.2% for methanol and toluene and 0.005–1.0% for ethanol.

It is recommended to change the GC injection liner after each sequence of injections to avoid carry over of degraded topiramate. This will also prolong column life. After completing the analysis of all samples, it is strongly recommended to bake the column at 200°C for 24 h. This will help to clean the column of any impurities and maintain column efficiency.

Conclusion

The results of these studies demonstrate that this method is specific, linear, precise, sensitive, and rugged. This method is suitable for the analysis of residual methanol, ethanol and toluene in topiramate drug substance. The DMF must be pretreated with molecular sieves to remove trace amount of alcohols that may interfere with the assay.

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