Asian Journal of Chemistry; Vol. 30, No. 8 (2018), 1791-1795

ASIAN JOURNAL OF CHEMISTRY

https://doi.org/10.14233/ajchem.2018.21311

GC-HS Method for Organic Volatile Impurities Determination and Quantification in Sertraline HCl API and Its Pharmaceutical Dosage Forms

MANNEM DURGA BABU* and KESANA SURENDRA BABU

Department of Chemistry, ANU Research Centre, Shree Velagapudi Ramakrishna Memorial P.G. College, Nagaram-522268, India

*Corresponding author: E-mail: m.durgababu1989@gmail.com

Received: 1 March 2018; *Accepted*: 3 May 2018; *Published online*: 30 June 2018; AJC-18976

In this work, a simple and sensitive GC-HS method for simultaneous determination of organic volatile impurities (methanol and ethyl acetate) in sertraline HCl API and its pharmaceutical dosage forms by GC-HS with FID. Based on good manufacturing practices, measuring organic volatile impurities are mandatory for the testing of all API's. In order to remove the potential toxic risk of residual solvents, an efficient and sensitive GC-HS method was successfully developed and validated. The method involved a thermal gradient elution of organic volatile impurities present in sertraline HCl API. DB-624, 30 m × 0.53 mm × 3.0 µm column using nitrogen as a carrier gas. The flow rate was 3 mL/min and FID was used. And the detector temperature is 250 ºC and injector temperature is 225 ºC. The total run time is 25 min. This method was validated for repeatability, method precession, linearity, limit of detection, limit of quantification, tablet analysis, solution stability and accuracy according to ICH guidelines.

Keywords: GC-HS method, Sertraline HCl, Methanol, Ethyl acetate.

INTRODUCTION

Sertraline HCl (Fig. 1) is a selective serotonin reuptake inhibitor for oral administration. The chemical name is (1S,4S)-4-(3,4-dichlorophenyl)-*N*-methyl-1,2,3,4-tetrahydronaphthalen-1-amine hydrochloride. Sertraline HCl is white crystalline powder and slightly soluble in water and isopropyl alcohol and sparingly soluble in ethanol [1].

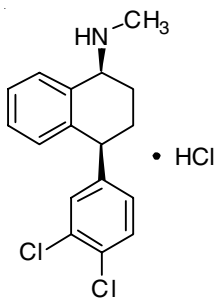

Fig. 1. Sertraline hydrochloride (m.f. $C_{17}H_{18}NCl_3$; m.w. 342.69)

The organic volatile impurities (OVI's) specifications were set in accordance with the toxicity of solvents vary from a low ppm to thousands of ppm. The static GC-HS deamination of OVI's is now a days mature technique well established in pharmaceutical analysis [2-4]. The OVI's are used in produced during the synthesis of drug substances and in excipients used in the production of drug formulations. Many of these OVI's generally cannot be completely removed by standard manufacturing processes preferably at low levels. These organic volatile impurities are encounter during manufacture and storage of active pharmaceutical ingredients.The OVI's in active pharmaceutical ingredients or from other drug manufacturing processes can be harmful for the human health [5-7].

This method for the simultaneously determination and quantification of two organic volatile impurities (ethyl acetate and methanol) in sertraline HCl by gas chromatography with headspace sampler fitted with flame ionization detector was proposed. This method is very simple, accurate and precise.

EXPERIMENTAL

Sertraline HCl was procured from local well-known laboratory in Hyderabad, India. HPLC grade acetonitrile (E. Merck, India), HPLC grade methanol (E. Merck. India). Milli-Q water, ethyl acetate and methanol manufactured by Merck were used.

The total analysis was performed on Shimadzu GC-2010 system with FID. Samples were injected through a Teledyne tekmar HT3TM Head space. The chromatographic data acquisition and integration was performed used by GC-solution software.

Chromatographic conditions: The column is DB-624 (30 m × 0.53 mm × 3 µm) (6 % cyanopropylphenyl-94 % dimethyl

polysiloxane) and the carrier gas is nitrogen. The total flow rate is 3.0 mL/min and injector temperature is 225 ºC. The split ratio was 1:20. Oven program is initial temperature is 40 ºC hold for 5 min than increase 20 ºC/min up to 200 ºC than hold for 12 min. Detector temperature is 250 ºC, air flow is 400 mL/min and hydrogen flow is 40 mL/min. The total run time is 25 min.

Headspace sampler condition: Vial temperature: 80 ºC; needle temperature: 100 ºC; transfer line temperature: 110 ºC; vial conditioning time: 30 min; vial pressurize time: 3.0 min; inject time: 1.0 min; GC cycle time: 45 min.

Dimethyl sulfoxide used as diluent.

Blank preparation: Take 2 mL of dimethyl sulfoxide in a headspace vial and seal with aluminum septum and crimp the cap.

Standard solution preparation: Weighed and dissolved accurately 12.5 mg of methanol and 25 mg of ethyl acetate in 70 mL of diluent taken in a 100 mL volumetric flask. Finally make up to the mark with diluent (The final concentration of methanol is 500 ppm and ethyl acetate is 1000 ppm with respect to test solution).

Preparation of standard vial: Take 2 mL of standard stock solution in a headspace vial and seal seal with aluminum septum and crimp the cap.

Sample preparation: Accurately weighed and transferred about 500 mg of sertraline HCl API into a headspace vial. Then, added 2 mL of diluent and immediately sealed with aluminum septum and crimp the cap.

Tablet preparation: Twenty tablets were weighed and powdered. Accurately weighed and transferred an amount of powder equivalent to 500 mg of sertraline HCl to 2 mL head space vial then add 2 mL of diluent and immediately sealed with aluminum septum and crimp the cap. The mixture was sonicated for 5 min.

The organic volatile impurity content (ppm) was calculated by using the following formula:

$$\text{Calculation (ppm)} = \frac{\text{Impurity area in test solution}}{\text{Impurity area in standard solution}} \times \frac{\text{Standard concentration (mg)}}{\text{Sample concentration (mg)}} \times 10^6$$

RESULTS AND DISCUSSION

Method development: This method development was implemented following quality-by-design principles including diluent selection, column selection.

Diluent selection: Different diluents (DMF, NMP and DMSO) was experimentally tried for selection. Dimethyl sulfoxide was preferred over other diluents since, methanol, ethyl acetate and sertraline HCl are easily dissolved in DMSO.

Column selection: In this study, three columns are used namely, VF-1(30 m × 0.32 mm × 0.45 µm), DB-624 (30 m × 0.53 mm × 3.0 µm) and DB-624 (30 m × 0.25 mm × 0.25 µm) for evaluated for column screening. The GC-HS parameters were first optimized to achieve good retention time, acceptable resolution and better peak shapes for methanol and ethyl acetate in sertraline HCl and its formulations. The DB-624 eluted three sharp peaks with minimal peak tailing for methanol at retention time about 3.726 min and ethyl actate at about 8.33 min. It demonstrated that DB-624 column closely matched methanol and ethyl acetate. Hence, DB-624 column was selected for this study.

Method validation: The GC-HS method was validated as per ICH guidelines [8]. The validation parameters *viz.*, specificity, repeatability, method precision, limit of detection (LOD) and limit of quantitation (LOQ), linearity, accuracy, ruggedness and robustness were evaluated.

Specificity: This specificity was determined to confirm the analyte identity from other interferences. Specificity has been established by injections of methanol and ethyl acetate individually. The resolution obtained between the peaks was not less than 5.0. No peaks were observed in blank injection. A typical chromatograms and retention times are shown in Fig. 2 and Table-1, respectively.

TABLE-1
SPECIFICITY DATA FOR METHANOL AND ETHYL ACETATE

Name	Retention time	Area	USP resolution	USP plate count	USP tailing
Methanol	3.726	161010	0.00	30225	1.49
Ethyl acetate	8.330	1013141	46.04	84248	1.11

System and method precision: The system precision of proposed method was expressed in the terms of % RSD of data. System precision has been demonstrated by six replicates injection of standard solutions. The RSD was found out to be less than 10 % (Table- 2). While the method precision has been demonstrated by separately analyzing of sample six preparations. RSD was found to be less than 10 % (Table-3).

TABLE-2
SYSTEM PRECISION DATA FOR METHANOL AND ETHYL ACETATE

SST parameters	Methanol		Ethyl acetate	
	RT (n = 6)	Area (n = 6)	RT (n = 6)	Area (n = 6)
Mean	3.70	142539	8.30	960498
STDV	0.00	4128	0.001	22666
RSD (%)	0.01	2.90	0.01	2.36

TABLE-3
METHOD PRECISION DATA FOR METHANOL AND ETHYL ACETATE

SST parameters	Methanol		Ethyl acetate	
	RT (n = 6)	Area (n = 6)	RT (n = 6)	Area (n = 6)
Mean	3.71	105402	8.31	892873
STDV	0.00	3600	0.001	30835
RSD (%)	0.01	3.42	0.01	3.45

Linearity (low level) for LOD and LOQ: This method was determined over the concentration range of 25-125 ppm for methanol and 50-250 ppm for ethyl acetate. Two replicates were performed at each level. Correlation coefficient (R^2), steyx, slope, LOD and LOQ were calculated from these linearity data and are shown in Table-4.

Linearity: The linearity solutions were prepared for each organic volatile impurity over the range of LOQ to 750 ppm for methanol, LOQ to 1500 ppm for ethyl acetate. For each level

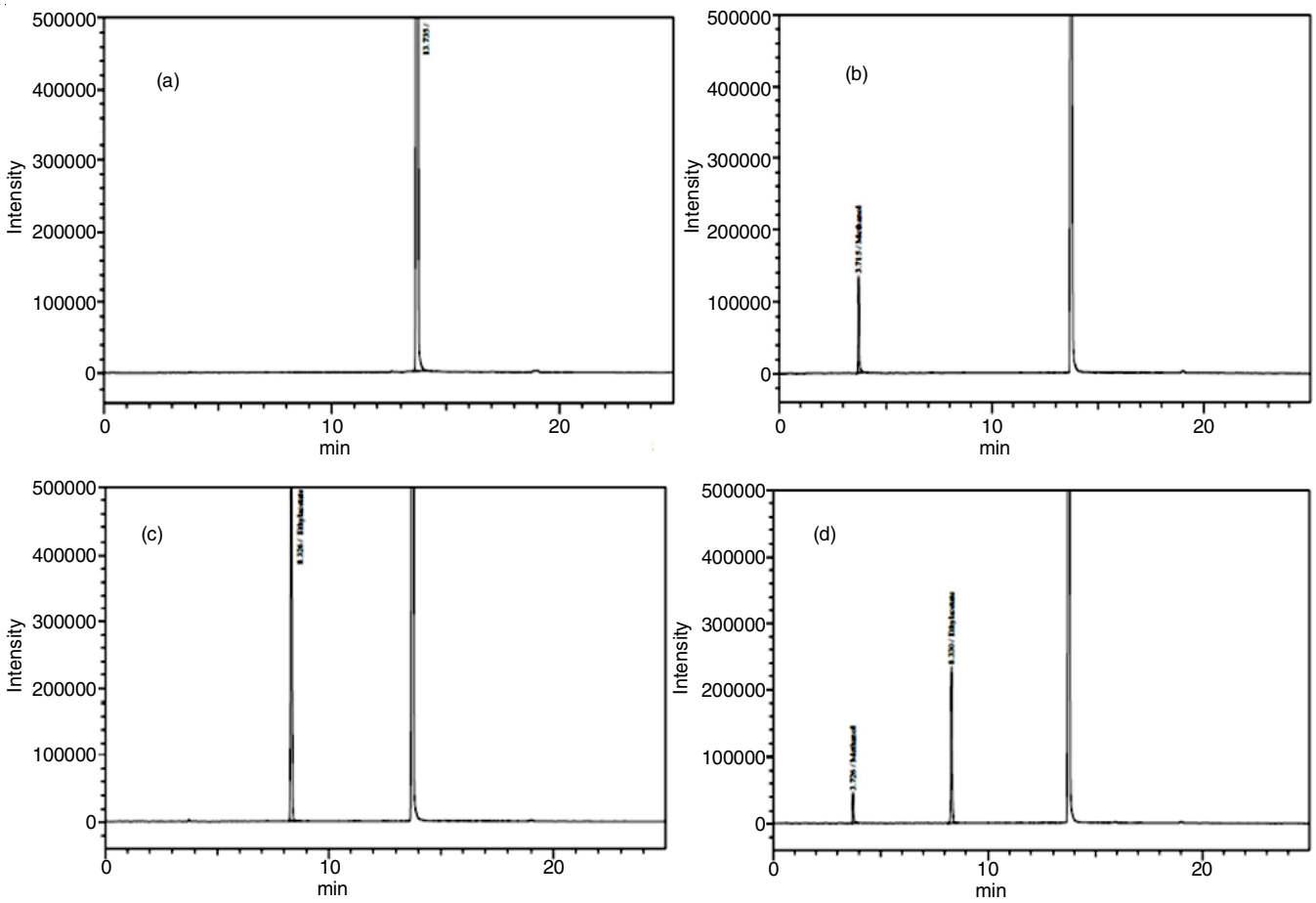

Fig. 2. Specificity for (a) blank (b) methanol (c) ethyl acetate and (d) spiked

TABLE-4
LINEARITY (LOW LEVEL) DATA FOR METHANOL AND ETHYL ACETATE

Methanol		Ethyl acetate	
r^2	0.997	r^2	0.9996
STEYX	1085	STEYX	2332
Slope	308	Slope	870
LOD (ppm)	12	LOD (ppm)	9
LOQ (ppm)	35	LOQ (ppm)	27

two replicates were performed. To draw the linearity graph between concentration and area of two replicates of organic volatile impurities. Finally the obtained correlation coefficient (r^2) was not less than 0.999 for two organic volatile impurities. The linearity data is presented in Table-5.

Limit of detection (LOD) and limit of quantitation (LOQ): The LOQ and LOD of organic volatile impurities in sertraline HCl were determined through slope method. The data and chromatograms of LOD and LOQ are presented in Table-6 and Fig. 3, respectively.

TABLE-5
LINEARITY DATA FOR METHANOL AND ETHYL ACETATE

Methanol		Ethyl acetate	
Conc. (ppm)	Average area	Conc. (ppm)	Average area
35 (LOQ)	9627	27 (LOQ)	16096
250	59150	500	457073
375	87243	750	670066
500	115520	1000	878032
625	150270	1250	1136705
750	176101	1500	1302636
r^2	1.000	r^2	0.999

TABLE-6
LOD AND LOQ DATA FOR METHANOL AND ETHYL ACETATE

Name	LOQ (ppm)	LOD (ppm)	Area of LOD	Area of LOQ
Methanol	35	12	5652	9627
Ethyl acetate	27	9	3966	16096

Accuracy: A known amount of methanol and ethyl acetate standard solutions were spiked to sertraline HCl sample at three different concentrations (50,100,150 and LOQ) and injected in triplicate. The percentage recovery of organic volatile impurities were obtained 90 to 110 % and % RSD is less than 10 (Table-7).

System precision at LOQ: The system precision of this GC-HS method is expressed in term of % RSD of data. System precision at LOQ concentration has been demonstrated by inject the six replicates of standard solutions. The obtained % RSD was less than 10 % (Table-8).

Robustness: To determine the robustness of present GC-HS method, % RSD was checked for, to change the any two method parameters from the initial conditions. That parameters are column flow ± 0.2 mL/min and vial condition temperature ± 5 ºC. Finally in two changed method parameters, the %RSD

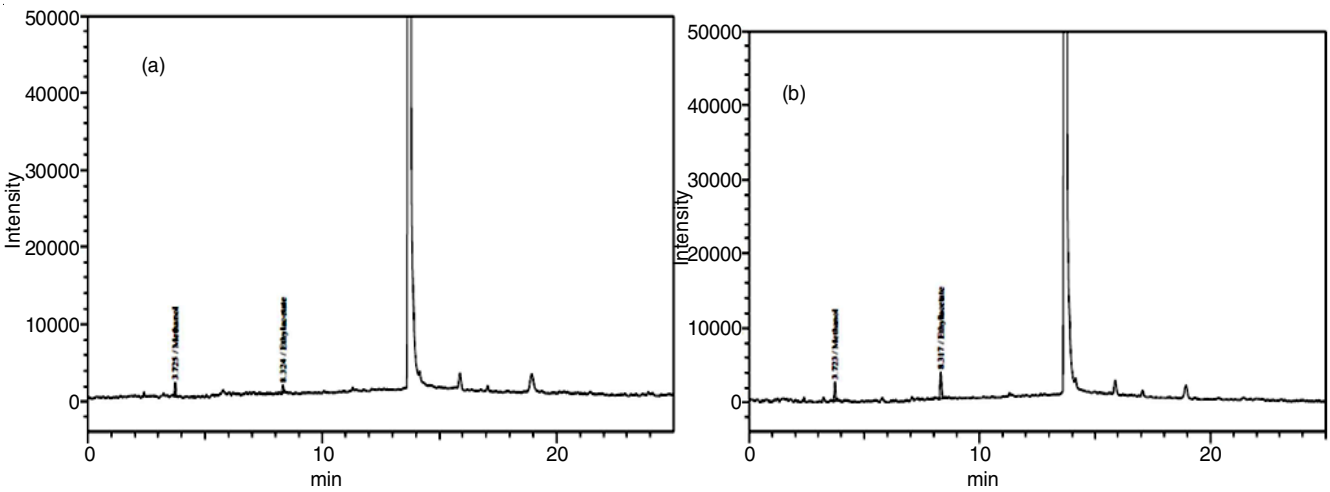

Fig. 3. LOD and LOQ graph for (a) methanol and (b) ethyl acetate

TABLE-7
ACCURACY DATA FOR METHANOL AND ETHYL ACETATE

No. of injections	Methanol					Ethyl acetate				
	Sample (n = 3)	50 % (n = 3)	100 % (n = 3)	150 % (n = 3)	% LOQ (n = 3)	Sample (n = 3)	50 % (n = 3)	100 % (n = 3)	150 % (n = 3)	% LOQ (n = 3)
Inj-1	Not detected	55973	109895	180177	9337	52079	442967	891608	1414912	67565
Inj-2	Not detected	62326	107382	172024	9459	51642	471179	885993	1365105	67456
Inj-3	Not detected	65508	118351	178764	9463	51979	471929	931372	1381722	67586
Average	Not detected	61269	111876	176988	9420	51900	462025	902991	1387246	67536
STD 100 % methanol average area		116350	–	–	9627		–	–	–	–
Recovery (%)		105.32	96.15	101.41	97.85		–	–	–	–
STD 100 % ethyl acetate average area		–	–	–	–		818620	–	–	16096
Recovery (%)		–	–	–	–		100.20	103.97	108.75	97.14

TABLE-8
SYSTEM PRECISION DATA AT LOQ FOR METHANOL AND ETHYL ACETATE

No. of injections	Methanol		Ethyl acetate	
	RT	Area	RT	Area
1	3.722	9551	8.320	15931
2	3.723	9644	8.316	16015
3	3.724	9687	8.318	16103
4	3.723	9557	8.317	16091
5	3.723	9645	8.317	16362
6	3.722	9677	8.316	16073
Mean	3.72	9627	8.32	16096
STDV	0.00	59	0.002	145
RSD (%)	0.02	0.61	0.02	0.90

was less than 10 % for each organic volatile impurity (Tables 9 and 10).

Ruggedness: Ruggedness has been established by separate six analyses of single batch of sample prepared by two different analysts on different days. Overall RSD of residual solvents were found out to be less than 10 % (Table-11).

Tablet analysis: The prepared tablet solution (250 mg/mL) was injected and run into GC-HS. The methanol and ethyl acetate contents in sertraline HCl tablets were found within the limits. Results are summarized in Table-12. Typical chromatogram of sertraline HCl tablet is shown in Fig. 4.

Conclusion

The developed GC-HS method is simple, sensitive, accurate and highly precise for the determination and quantification of methanol and ethyl acetate in sertraline HCl and its pharmaceutical dosage forms. This GC-HS method was proposed for the quality control sertraline HCl in relation to the organic volatile

TABLE-9
ROBUSTNESS DATA FOR METHANOL

No. of injections	Flow 2.8 mL/min		Flow 3.2 mL/min		Vial condition 75 °C		Vial condition 85 °C	
	RT	Area	RT	Area	RT	Area	RT	Area
1	3.909	100567	3.533	104371	3.705	106534	3.707	149008
2	3.914	102727	3.532	106105	3.708	108216	3.707	151540
3	3.911	107945	3.531	107760	3.708	102059	3.707	151644
4	3.916	102243	3.532	110753	3.708	107026	3.711	153567
5	3.909	103482	3.533	105958	3.709	106931	3.717	140877
6	3.911	102130	3.523	106498	3.711	105983	3.715	142112
Mean	3.912	103182	3.531	106908	3.708	106125	3.711	148125
STDV	0.003	2522	0.004	2175	0.002	2124	0.004	5350
%RSD	0.07	2.44	0.11	2.03	0.05	2.00	0.12	3.61

TABLE-10
ROBUSTNESS DATA FOR ETHYL ACETATE

No. of injections	Flow 2.8 mL/min		Flow 3.2 mL/min		Vial condition 75 °C		Vial condition 85 °C	
	RT	Area	RT	Area	RT	Area	RT	Area
1	8.523	819258	8.107	858241	8.296	815901	8.304	1106807
2	8.530	916458	8.107	938295	8.300	801840	8.304	1168373
3	8.526	841955	8.106	993931	8.302	806949	8.305	1174338
4	8.529	843132	8.107	928268	8.300	832997	8.311	1178120
5	8.526	876036	8.106	922987	8.303	832113	8.314	1063748
6	8.529	851868	8.101	931002	8.304	748047	8.314	1098480
Mean	8.527	858118	8.106	928787	8.301	806308	8.309	1131644
STDV	0.003	33940	0.002	43243	0.003	31257	0.005	48287
RSD (%)	0.03	3.96	0.03	4.66	0.03	3.88	0.06	4.27

TABLE-11
RUGGEDNESS DATA FOR METHANOL AND ETHYL ACETATE

Days and analysts	Methanol				Ethyl acetate			
	Mean ± SD (n = 6)		% RSD (n = 6)		Mean ± SD (n = 6)		% RSD (n = 6)	
	RT	Area	RT	Area	RT	Area	RT	Area
Day-1 (Analyst-1)	3.732±0.001	113814±2405	0.03	2.11	8.331±0.002	810161±10401	0.03	1.28
Day-1 (Analyst-2)	3.725±0.003	114885±2889	0.07	2.52	8.324±0.005	854453±18051	0.06	2.11
Day-2 (Analyst-1)	3.721±0.003	116405±2256	0.09	1.94	8.317±0.006	809570±4535	0.06	0.56
Day-2 (Analyst-2)	3.731±0.001	114109±3125	0.02	2.74	8.320±0.001	818964±16448	0.01	2.01
	Mean ± SD (n = 12)		% RSD (n = 12)		Mean ± SD (n = 12)		% RSD (n = 12)	
	RT	Area	RT	Area	RT	Area	RT	Area
Day-1 (Analyst-1&2)	3.729±0.004	114350±2596	0.11	2.27	8.327±0.005	832307±27061	0.06	3.25
Day-2 (Analyst-1&2)	3.721±0.002	115257±2862	0.06	2.48	8.318±0.004	814267±12505	0.05	1.54
Analyst-1 (Day1&2)	3.726±0.006	115110±2603	0.17	2.26	8.324±0.008	809865±7656	0.10	0.95
Analyst-2 (Day1&2)	3.723±0.003	114597±2898	0.07	2.53	8.322±0.004	836709±24790	0.02	2.96

TABLE-12
METHANOL AND ETHYL ACETATE
CONTENT IN TABLET ANALYSIS

Name of drug	Label claim (mg)	Methanol (ppm)	Ethyl acetate (ppm)
Sertraline HCl	500	Not detected	75

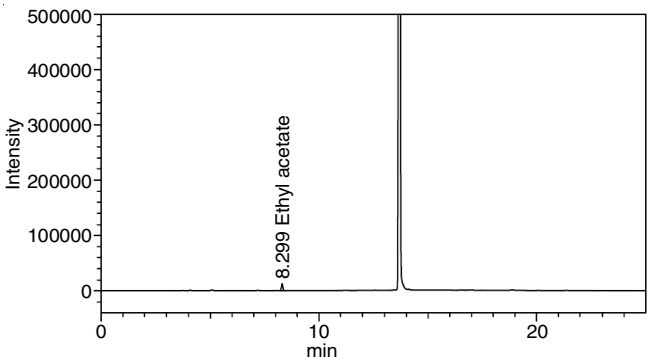

Fig. 4. Chromatogram for sertraline HCl tablet

methanol and ethyl acetate contents and meets the validation requirements. The good results were found within the range as per ICH guidelines. Three randomly selected batches of each drug substance were analyzed under validated method conditions and the concentrations of residual methanol and ethyl acetate were much lower than their maximum limits.

REFERENCES

1. M.M. Khater, Y.M. Issa, H.B. Hassib and S.H. Mohammed, *J. Adv. Res.*, **6**, 459 (2015); https://doi.org/10.1016/j.jare.2014.11.005.
2. F. Bonadio, P. Margot, O. Delémont and P. Esseiva, *Forensic Sci. Int.*, **187**, 73 (2009); https://doi.org/10.1016/j.forsciint.2009.03.004.
3. J. Li, S. Shao, M. Solorzano, G.J. Allmaier and P.T. Kurtulik, *J. Chromatogr. A*, **1216**, 3328 (2009); https://doi.org/10.1016/j.chroma.2009.02.029.
4. R. Barro, J. Regueiro, M. Llompart and C. Garcia-Jares, *J. Chromatogr. A*, **1216**, 540 (2009); https://doi.org/10.1016/j.chroma.2008.10.117.
5. V. Pinnel, P. Rosseels and J. Vandegans, *J. High Resolut. Chromatogr.*, **18**, 776 (1995); https://doi.org/10.1002/jhrc.1240181212.
6. ICH Harmonized Tripartite Guidelines for Residual Solvents. Step 4, 17 July (1997).
7. K. Fliszar, J.M. Wiggins, C.M. Pignoli, G.P. Martin and Z. Li, *J. Chromatogr. A*, **1027**, 83 (2004); https://doi.org/10.1016/j.chroma.2003.08.086.
8. ICH, Guidelines Q2B Validation of Analytical Procedures Methodology, In: Proceedings of I.C.H. Public Meeting, Rockville, USA, pp. 1-10 (1996).