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Determination of Residual Solvents in Citalopram Hydrobromide by Gas Chromatography

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ABSTRACT

Residual solvents in intermediates and active pharmaceutical ingredient were monitored by using gas chromatography. It is mandatory to control adequately the quality of active pharmaceutical ingredient by checking the levels of residual solvents. A systematic approach for the identification and quantification of residual solvents in citalopram hydrobromide was described in proposed analytical method. The analysis was carried on DB624 (30 m x 0.32 mm id, 5 µm coating thickness) capillary column by gas chromatography with flame ionization detector. It was validated as per ICH guidelines[1]. The method was validated for system suitability, specificity, LOD, LOQ, linearity, accuracy, precision and robustness. The method described was simple, sensitive, reliable and reproducible for the quantization of residual solvents at levels as per ICH guideline.

Key words: Citalopram hydrobromide, Active pharmaceutical ingredient, Residual solvent, Gas chromatography

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INTRODUCTION

Organic solvents are widely used in the production of active pharmaceutical ingredient for synthesis and purification. They may not be completely removed by practical manufacturing techniques. The residual solvents are potentially undesirable substances, they change the proportion of active pharmaceutical ingredient compounds and also hazardous to the human beings. Organic solvents also affect physiochemical properties like crystallinity of the bulk drug. It gives change in the crystal structure. It leads to change in dissolution properties of finished solid dosage forms. Hence it is necessary to control the concentration of highly toxic solvents at low level concentration. It demands highly sensitive detection method. ICH has prescribed acceptable limits for such residual solvents in active pharmaceutical ingredient and excipients. Hence evaluation of residual solvents is considered as an important tool in the quality control of the pharmaceuticals. The solvents like isopropyl alcohol, acetone and tertiary butanol were used in manufacture of active pharmaceutical ingredient of citalopram hydrobromide The content of residual solvents like isopropyl alcohol, acetone and tertiary butanol in citalopram hydrobromide analyzed by gas chromatography using capillary column with flame ionization detector with extremely high separation efficiency. Accordingly the method has been developed and validated for detection and quantization of residual solvents like acetone, isopropyl alcohol and tertiary-butanol in citalopram hydrobromide.

MATERIALS AND METHODS

Materials:

Reference standards of acetone, isopropyl alcohol and tertiary -butanol were obtained of uvasolv grade from Merck Ltd. HPLC grade water was obtained using Millipore water system. Sample active pharmaceutical ingredient (citalopram hydrobromide) obtained from reputed pharmaceutical company with certificate of analysis.

Instrumentation

Gas chromatograph Clarus 500 was used equipped with standard oven for temperature gradient, injection port and flame ionization detector. DB 624 column (30 m x 0.32 mm id, 5 µm coating thickness, 6% cyanopropyl phenyl and 94% di-methyl polysiloxane stationary phase) was used with nitrogen as carrier gas with Turbomatrix 40HS Head Space. The chromatogram was recorded and peaks were quantified by means of PC based Total Chrome software.

Preparation of standard solution

About 200 mg of acetone, 200 mg of isopropyl alcohol and 200 mg of tertiary-butanol were

weighed accurately into 100 ml volumetric flask containing about 20 ml of water and volume was adjusted to 100 ml with distilled water. A 10 ml of this solution is further diluted to 100 ml with distilled water.

Preparation of vials

Blank vial

A exact 5.0 ml of HPLC grade water was taken into dry and clean vial. The vial was sealed.

System suitability vials

A 5.0 ml of standard solution was taken into six dry and clean vials. Vials were sealed immediately.

Sample vial

About 200 mg of the citalopram hydrobromide was weighed accurately and transferred into a dry and clean vial along with 5 ml of water. Vial was sealed immediately.

Chromatographic conditions

The chromatographic separation was performed on DB 624, column (30 x 0.32 mm id, 5 µm coating thickness). The 1 ml of system suitability solution and sample solution were injected separately. The temperature of injection port was maintained at 200°. Nitrogen gas is used as carrier gas. The pressure of 14 kpa with flow rate of 2.0 ml /min was maintained. The temperature of detector was set at 260°C. The column oven temperature gradient was intially set at 40°C for 2 min and then increased linearly at rate of 1°C/ min up to 50°C for 2 min then again increased at rate of 40°C/ min up to final column oven temperature 150°C and maintained for 2 min.

Method Development

Optimum conditions necessary for the quantitative determination of the acetone, isopropyl alcohol and t-butanol as residual solvent with maximum selectivity, were established by a number of preliminary experiments. Optimum conditions were fixed by varying one parameter at a time by keeping other parameters constant and observing its effect on the peak resolution. Different stationary phases such as DBFFAP (G25), DB5 (G27) were tried, the stationary phase DB 624 (G43) was found to be suitable for efficient separation of the components. The nitrogen gas was used as carrier gas. Flow rate of carrier gas as 2.0 ml / min was best suited for analysis. The oven temperature was varied from 35°C to 60°C and finally it was fixed at 40°C due to shorter time of analysis, sharp peak and ideal retention time. The injection and detector temperature were maintained at 200°C and 260°C for good chromatographic behavior respectively.

RESULTS AND DISCUSSION

Method Validation

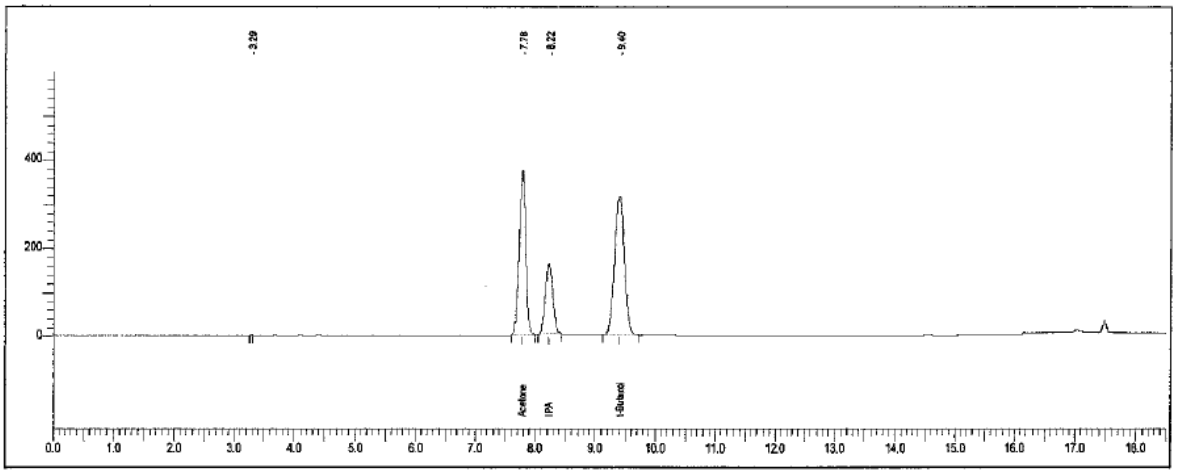
The analytical method validation was carried out as per ICH guideline [ICH Q2 (R1)]. The validation parameters such as specificity, limit of detection, limit of quantization, linearity, accuracy, precision, system suitability and robustness were studied. Standard calibration curves were constructed for acetone, isopropyl alcohol and tertiary-butanol in the range of 10 µg/ ml to 300 µg/ ml for all the three solvents.

System suitability

System performance parameters of developed GC method were determined by injecting system suitability solution in six replicates. Parameters such as number of theoretical plates, tailing factor, resolution and relative standard deviation were determined. The results are shown in Table 1. It indicates good performance of the system.

Table 1: System performance parameter for each solvent (n= 6)

Name of the solvent	Retention Time	Tailing Factor	No. of theoretical plates	% RSD	Resolution
Acetone	7.77	1.05	22872	0.7	0.00
Isopropyl alcohol	8.22	1.05	20157	0.8	2.06
Tertiary-butanol	9.38	1.02	15048	1.1	4.38



Peak #	Ret [min]	Component Name	Area	Area%	Tailing	Tan Plates	Resl'n
1	3.29		1866	0.000	0.000	0.00	0.00
2	7.78	Acetone	2818771	0.362	1.024	22396.10	0.00
3	8.22	IPA	1381477	0.178	1.056	21400.90	2.06
4	9.40	t-Butanol	3576557	0.460	1.012	14618.62	4.38
Sum			7778671				

Figure 1: Typical chromatogram of mixture of acetone, isopropyl alcohol and t-butanol

Limit of detection (LOD) and Limit of quantization (LOQ):

Specificity

The specificity of the analytical method was determined by injecting blank solution as distilled water, individual solvents, all solvents doped with sample solution and sample solution under the same experimental conditions. No peak was obtained for the blank solution. The retention times of individual solvents were identified in sample solution which is well separated from each other as shown in Figure 1.

The LOD and LOQ were calculated by statistical methods. For statistical method LOD and LOQ determined by statistical formula,

$$LOD = 3.3\ \sigma / S$$

$$LOQ = 10\ \sigma / S$$

Where, σ is the standard deviation of the response.

S is the slope of the calibration curve.

The values for the LOD and LOQ for acetone, isopropyl alcohol and t-butanol are mentioned in Table 2

Table 2: LOD and LOQ of each solvent

Name of solvent	LOD (in µg/ml)	LOQ (in µg/ml)
Acetone	11.90	36.06
Isopropyl alcohol	11.62	35.22
Tertiary-butanol	13.73	41.62

Linearity

Under the experimental conditions described above, linear calibration curves for the three solvents were obtained throughout the concentration ranges studied. Regression analysis was done on the peak areas of the three solvents i.e. (Y) v/s concentrations (x). The regression analysis data is represented in Table 3. The linear range of concentration was 10 µg/ ml to 300 µg/ ml for each solvent.

Table 3: Linearity –regression analysis data

Parameter	Acetone	Isopropyl alcohol	Tertiary-butanol
Correlation Coefficient	0.9987	0.9986	0.9984
Intercept (y)	79880.34	35408.44	12715.60
Slope (m)	9670.21	4770.89	12010.42

Accuracy:

Accuracy of the method was determined by applying the above method to sample. The sample solution contained 50 %, 100 % and 150 % of the acetone, isopropyl alcohol and tertiary-butanol. The accuracy was then calculated in terms of percentage of solvent recovered. The results of analysis were given in Table: 4.

Table 4 : Accuracy - % recovery of each solvent

Drug	Level	Amount of drug taken (in mg)	Amount of solvent added (µg/ml)	Total amount of solvent found (mg)	Percentage Error (%)	% Recovery	RSD (%) N = 6
Acetone	LOQ	72.5	49.55	52.99	6.9	106.9	2.1
	80 %	4008.2	3990.27	4053.42	1.58	101.6	2.1
	100 %	4008.2	4982.45	4953.18	0.59	99.4	1.7
	120 %	4008.2	5977.96	6081.94	1.74	101.7	2.2
Isopropyl alcohol	LOQ	78.3	39.15	40.90	4.47	104.5	2.9
	80 %	4016.0	3998.03	3895.21	2.57	97.4	1.5
	100 %	4016.0	4980.16	4863.65	2.34	97.7	2.2
	120 %	4016.0	6008.98	6122.47	1.89	101.9	2.3
Ter-Butanol	LOQ	83.2	50.75	54.07	6.54	106.5	3.2
	80 %	4010.3	3992.36	3987.06	0.13	99.9	2.0
	100 %	4010.3	4985.06	4943.63	0.83	99.2	1.9
	120 %	4010.3	5981.10	6087.63	1.78	101.8	2.6

Precision

The method precision was established by carrying out the analysis of citalopram hydrobromide sample containing three solvents. The estimation was carried out for the solvents using proposed analytical method is six replicates. The value of relative standard and deviation were well within limits 1.82 %, 1.99% and 1.63 % for acetone, isopropyl alcohol and tertiary-butanol respectively indicating the sample repeatability of the method. The results obtained are tabulated in Table: 5.

Table 5: Precision – Method Precision

Experiment No.	Sample weight taken (in mg)	Content in µg/ml		
		Acetone	Isopropyl alcohol	t-Butanol
1	201.9	5144.42	5120.92	5117.67
2	201.5	5141.66	5130.41	5145.12
3	202.4	4932.55	4908.13	4964.38
4	201.3	5148.66	5106.47	5142.00
5	200.9	5115.68	5169.86	5089.07
6	200.8	4995.66	4986.02	4972.38
	% RSD	1.82%	1.99 %	1.63 %

Robustness

The robustness of the method is determined by small variations in method parameters. The different variations are as given below: Variation in flow rate of carrier gas by ± 0.2 ml/ min. Variation in initial column oven temperature by ± 5.0°CVariation in vial conditioning time by ± 2.0 minutes. The results of the analysis of the samples under the condition of the above variation indicated the nature of robustness of the method.

Method application

The validated gas chromatographic method was applied to simultaneous determination of acetone, isopropyl alcohol and tertiary-butanol as residual solvent in citalopram hydrobromide. About 200 mg of each of acetone, isopropyl alcohol and tertiary-butanol diluted in 100 ml water. 10 ml of this solution was diluted to 100 ml with distilled water and injected. About 200 mg of citalopram hydrobromide weighed accurately and dissolved in 5 ml of water. From this solution 1 ml was injected into chromatograph under specified conditions. The analyte peaks were identified by comparison with those respective standards.

CONCLUSION

The reproducibility, repeatability and accuracy of the proposed method were found to be satisfactory which evidence is low value of standard deviations and percentage relative standard deviation. The accuracy and reproducibility of the proposed method was confirmed by recovery experiments performed by adding known amount of the solvents to the pre-analyzed sample and reanalyzed the mixture by proposed method. The percent recovery indicated non-interference from the other solvents.

The proposed GC method is novel method for the simultaneous estimation of acetone, isopropyl alcohol and tertiary-butanol as residual solvent in citalopram hydrobromide. It is precise, accurate, linear, robust, simple and rapid. Hence the proposed GC method is simply recommended for the quality control of the raw material.

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REFERENCES:

1. ICH Guidelines, Q2 (R1), Validation of Analytical Procedure: Text methodology.
2. ICH Guidelines, Q3C (R3), Impurities: Guidelines for Residual solvents.
3. The United States Pharmacopeia, United States Pharmacopoeia conversion, Inc, Rock Ville. 2009, USP 32 NF 26, Vol I, General Chapter <467> “Residual solvent”.
4. Puranik SB, Pai PNS, Rao GK. Organic Volatile Impurities in Pharma. Indian J Pharma Sci 2007; 69: 352-359.
5. Puranik SB, Varun R, Pawar N, Lalitha PN. Sanjay Pai, G. K. Rao, Gas Chromatographic Determination of Residual solvents in Pharmaceutical Excipients. The Pharma Review 2008:147-149.

6. Puranik SB, Varun R, Pawar VR, Lalitha N, Pai PNS, Rao GK. Determination of Residual solvents in intermediates and active Pharmaceutical Ingredients in Gas chromatography. Indian Drugs 2008; 45 (5).