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Determination of 1,2-dibromoethane as a genotoxic impurity in escitalopram oxalate drug substance by gas chromatography

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ABSTRACT

A simple gas chromatographic method has been developed for the determination of 1,2-Dibromoethane in Escitalopram oxalate drug substance. The method was validated as per ICH guideline in terms of LOD, LOQ, Method precision, accuracy and specificity. The LOD and LOQ values were found to be 3 ppm (3 µg/g) and 10 ppm (10 µg/g) respectively.

KEYWORDS

Development;
Validation;
1,2-Dibromoethane;
Escitalopram oxalate;
Gas chromatography.

INTRODUCTION

Escitalopram, is an antidepressant of the selective serotonin reuptake inhibitor class. It is used for the treatment of adults and children over 12 years of age with major depressive disorder and generalized anxiety disorder. Escitalopram is the (S)-stereoisomer (Left-enantiomer) of the earlier Lundbeck drug citalopram, hence the name escitalopram. Escitalopram is effective in reducing the symptoms of premenstrual syndrome, whether taken in the luteal phase only or continuously. Escitalopram increases intrasynaptic levels of the neurotransmitter serotonin by blocking the reuptake of the neurotransmitter into the presynaptic neuron.

Various methods in the literatures involve determination of Escitalopram by different analytical technics in pharmaceutical drug substances or drug products(1-13). But in the present work we have developed a simple, precise and accurate method for the content of 1,2 dibromoethane in Escitalopram by Gas chromatography with flame ionisation detector (FID). In the present work we have developed a new, simple precise, accurate method for determination of 1,2-Dibromoethane in Escitalopram oxalate by gas chromatography in bulk drug. Structure of Escitalopram oxalate and 1,2-Dibromoethane are shown in Figure 1 and Figure 2.

EXPERIMENTAL

Chemicals

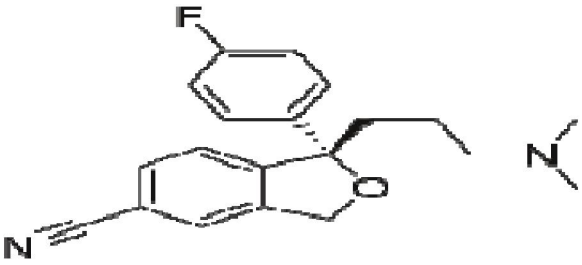

Figure 1

Figure 2

1,2-Dibromoethane was purchased from Aldrich chemicals; Merck grade n-Hexane was purchased from Merck ltd, Mumbai. Samples of Escitalopram oxalate are received from local market

Equipment

Analysis was carried on a GC system equipped with liquid auto sampler (Shimadzu2010 plus gas chromatograph with auto sampler AOC 20i + S) with Flame ionisation detector and Nitrogen as a carrier gas.

Chromatographic conditions

Analysis was done on DB-624 (6% cyanopropyl, 94% dimethylpolysiloxane stationary phase) column of 30 m length, 0.53 mm inner diameter and 3µm film thickness. Injector temperature and detector temperature were kept as 220°C and 260æ%C respectively. After optimisation the split ratio was decided as 1:5 for 5µL of injection volume. Flow of carrier gas (Nitrogen) is kept at 3.30 psi at constant pressure. The GC oven temperature is programmed as as 60°C for 5 minutes then raised to 240°C at a rate of 20°C/min and hold for 20 minutes.

TABLE 1 : Linearity

		1,2-Dibromoethane
LOQ	10.19	4660
50	36.39	18269
80	58.23	28931
100	72.79	37056
120	87.34	44855
150	109.18	55951
		0.9999

TABLE 2 : LOQ precision

	1,2-Dibromoethane
	3851
	3853
	3191
	3699
	3793
	3642
Mean	3672
SD	249.9726
RSD	6.81

Standard preparation

1,2-Dibromoethane solution was prepared by diluting 75 mg of 1,2-Dibromoethane to 100 mL with n-Hexane. Further 2 mL of this solution was diluted up to 100 mL with N-Hexane.

Sample preparation

Weighed about 1000 mg of Escitalopram oxalate sample into a 10 mL volumetric flask, added 5mL of diluent, shake well. Allow to settle down and inject the supernatant liquid.

RESULTS AND DISCUSSION

Method development and optimization

1,2-Dibromoethane, also known as ethylene dibromide (EDB), is the organobromine compound with the chemical formula (CH2Br)2. It is a colorless liquid with a sweet odor and sometimes-controversial fumigant.1,2-Dibromoethane is a liquid with a boiling point of 130°C.

Solvents used for development were Methanol, Acetonitrile and N-Hexane. N-Hexane is finalised as the diluent as 1,2-Dibromoethane shows good response compared to Methanol and Acetonitrile. The experiment was carried out on a DB-624 column for sharper peak and retention time. The effect of injection volume and split was observed and optimised up to 5 µL with a split ratio of 1:5 for

TABLE 3 : Accuracy at LOQ, 50%, 100% and 150%

	1,2-Dibromoethane
	100.1
LOQ	101.5
	100.0
	103.1
50	100.4
	99.4
	100.3
100	101.5
	100.5
	98.6
150	100.6
	99.8

Full Paper

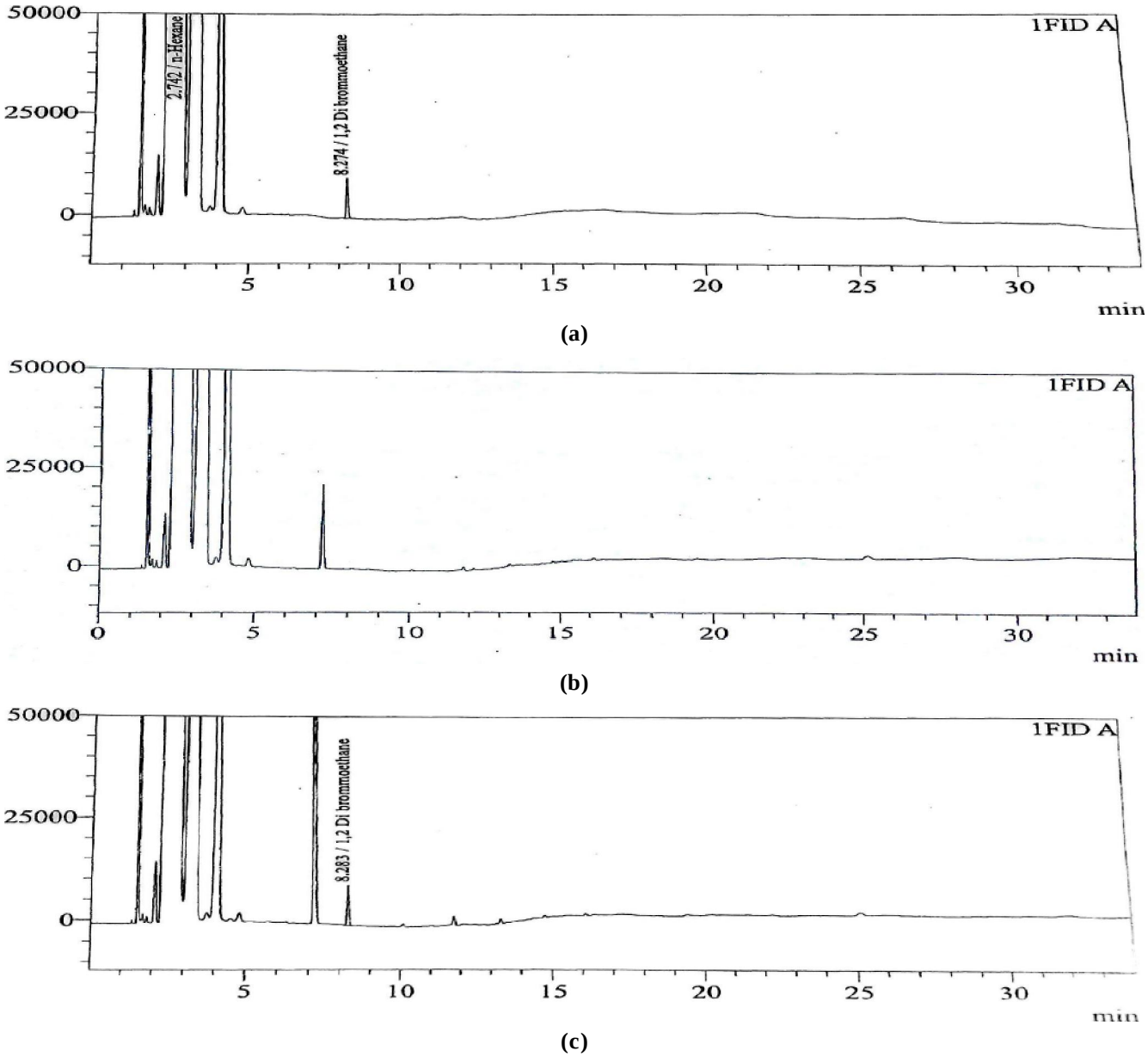

Figure 3 : Typical chromatograms of (a) Standard (b) Sample (c) spiked sample

sample concentration of 200 mg/mL

Method validation

The method validation work was conducted according to the ICH guidelines. The Validated method parameters include specificity, accuracy, Sensitivity, Precision, linearity, robustness, ruggedness and solution stability. LOD, LOQ values were obtained by preparing a series of known concentration solutions of increasing concentration and plotted a graph of concentration against area of analyte. LOD and LOQ values were found to be 3 ppm and 10 ppm respectively. Linearity of the method was determined by preparing and analyzing a series of 7 standard solutions to cover the concentration range of LOQ to 75 ppm for 1,2-Dibromoethane. The linearity correlation coefficient was found to be 0.9993.

The method is precise which is indicated by the low % relative standard deviation of six replicate standards, which was 1.95. The accuracy of method was determined by spiking the samples at 50 %, 100 % and 150 % level.

CONCLUSIONS

A simple and sensitive GC method has been

developed and validated for the trace analysis of 1,2-Dibromoethane in pharmaceuticals. The validation has been conducted according to ICH guidelines. This method is sensitive enough to detect 3 ppm and quantify 10 ppm level of 1,2-Dibromoethane in pharmaceutical drug substances.

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