

Quantitative determination of residual 2-(2-chloroethoxy) ethanol (CEE) in quetiapine fumarate by gas chromatography

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ABSTRACT

A simple and specific gas chromatographic method developed and validated for the determination of 2-(2-chloroethoxy) ethanol in Quetiapine Fumarate. The method is carried out with a flame ionization detector and DB-FFAP capillary column. The linearity was established over a range of 40-150 $\mu\text{g ml}^{-1}$ and correlation coefficient is more than 0.999.

Keywords: GC; 2-(2-Chloroethoxy) Ethanol

1. INTRODUCTION

Quetiapine is an antipsychotic drug belonging to the group of the dibenzothiazepines and used for the treatment of schizophrenia and other psychotic syndromes [1,2]. Quetiapine is used in a form of tablets containing 50, 100, 200 and 300 mg of the active substance. The starting material which is used in the synthesis of Quetiapine fumarate is 2-(2-chloroethoxy) ethanol. 2-(2-chloroethoxy)-ethanol: CEE, structural formula $\text{C}_4\text{H}_9\text{ClO}_2$; CAS number 628-89-7, boiling point 200°C at 101.3 kPa. The starting material are often not totally removed by practical manufacturing techniques, and consequently low levels are present in most pharmaceuticals. An acceptable level of CEE is unclassified but it is known impurity so was specified with acceptance criterion of 0.01% [3]. {Based on NOEL and PDE Value of CEE and Quetiapine} The European Pharmacopoeia (Eur. Ph.) included this guideline in the chapter Residual Solvents [4,5] and described a general procedure for identification and control of residual solvents in drug substances. Some problems have been overcome, for instance quantitative determination of non-volatile solvents such as 2-(2-chloroethoxy)-ethanol (CEE). In the literature there is no information about the methods for determination of CEE in the Quetiapine. In the present study, a gas chromatographic method with direct injection for the determination of CEE in the active substance

has been developed.

The separation was obtained on a DB-FFAP column (30 m \times 0.32 mm i.d. \times 1.0 μm coating thickness).

2. EXPERIMENTAL

The active substance was synthesized by Precise pharmaceutical Ltd (Pharmaceutical Research Centre, Mumbai, India). Acetonitrile was purchased by J.T baker (USA), Hydrochloride was purchased by S.D. Fine chem. (India), Water was purchased by Lab chem. (India), and 2-(2-chloroethoxy) ethanol was purchased by Sigma Aldrich, (Germany).

2.1. Preparation of Solution

Quantitative standard solution of CEE Standard solutions were prepared from standard stock solutions. Standard stock solutions were prepared in Diluent {0.2N Hydrochloride in Acetonitrile: Water (70:30 v/v)}. Standard stock solution A: containing 1mg ml^{-1} of CEE; Standard solution: containing 0.01mg ml^{-1} of CEE which corresponds to 0.1mg ml^{-1} of CEE in the tested substance. Qualitative standard solution of CEE for system suitability: Selectivity solution was prepared to check Eur. Ph. system suitability requirements. A total of 7 solvents were included in this standard solution. Selectivity solution contained 300 ppm of methanol, 500ppm of Ethanol, 500ppm of Acetone, 500 ppm of Isopropyl alcohol, 89 ppm of Toluene, 88 ppm of N, N-dimethyl formamide, 60 ppm of Dichloromethane and 10 ppm of CEE [6]. Test solution was prepared solution 1 containing 100mg ml^{-1} . A blank was prepared using the diluent, but without sample or standard solution.

2.2. Instrumentation and Operating Condition

The experiments were performed on an Agilent 7890A gas chromatograph (GC) equipped with a CTC combipal autosampler and a flame ionization detector. A DB-FFAP column (phase composition: Nitroterephthalic acid modi-

fied polyethylene Glycol) film thickness 1.0 μm , 30 m long, 0.32 mm ID was used. GC conditions: Inlet heater 200°C, detector 280°C, Oven initial temperature 100°C for 5 minutes, then raised at a rate of 15°C/min to 180°C and hold for 2 minutes, then raised at a rate of 35°C/min to 230°C and hold for 2 minutes. Helium gas was used as a carrier gas at 3.0 ml min⁻¹ and a split flow of 1:1. FID air flow was 400 ml min⁻¹ and FID hydrogen flow was 40 ml min⁻¹. 1 μl was injected.

2.3. Procedure

Separately inject 1 μl of standard solution and test solution into gas chromatograph. Record chromatograms and

compare peak areas of analytes from the test and standard solution. Under described conditions the retention time of CEE is 10.7 minutes. The area of the peak of CEE in the chromatogram from the test solution must not be greater than the mean area of the peak from the standard solution (0.1 mg ml⁻¹ corresponds to the substance).

3. RESULTS

3.1. System Suitability Test (SST)

The selectivity of the method was evaluated by injecting the selectivity solution to ensure the separation of all

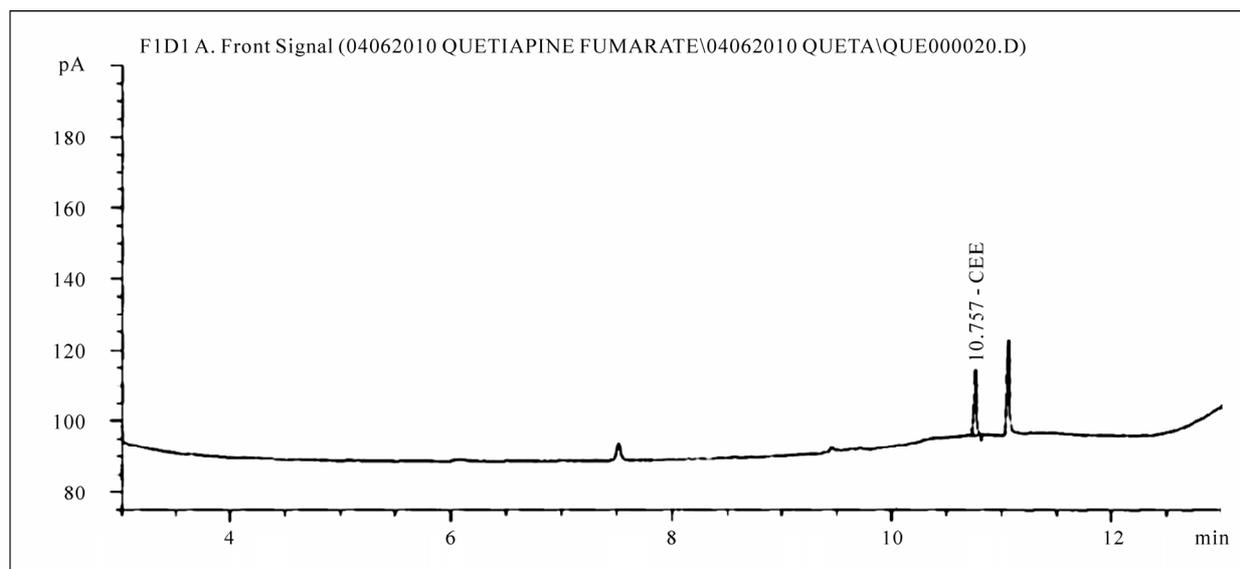


Figure 1. Standard chromatogram of CEE.

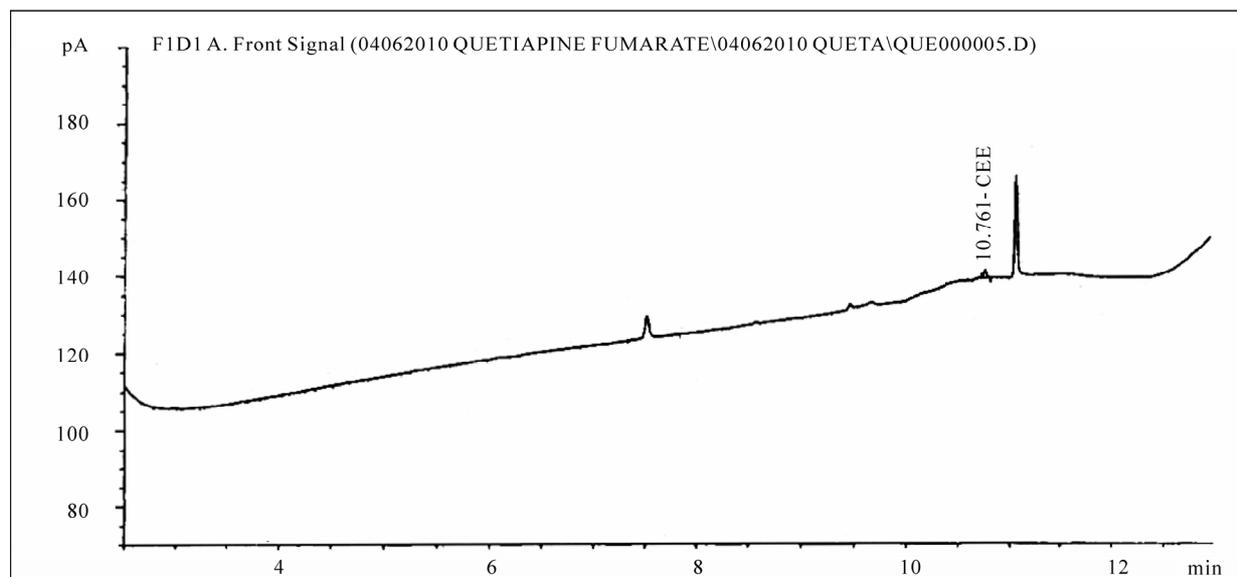


Figure 2. Limit of Detection of CEE.

analytes. The selectivity solution contained: Methanol, Ethanol, Acetone, Dichloromethane, toluene, Isopropyl alcohol, N, N-Dimethyl formamide, CEE. Resolution was calculated directly by the software: Chemstation solution ver. Rev.13.03.02 [341]. Chromatogram of selectivity solution is shown in **Figure 1**; the results are presented in **Figure 1** (inset). Good separation was obtained between CEE and other solvents used in the synthetic route of the active substance. For the drug substance excellent recoveries of 92-95% were obtained at

0.1 mg ml⁻¹ corresponds to the substance.

3.2. Validation of Method for CEE in API

Full validation data was required for API as it was in last stage development.

3.3. Limit of detection and limit of Quantification for CEE

The LOD and LOQ were calculated from S/N data generated from six injection of CEE (with API) containing

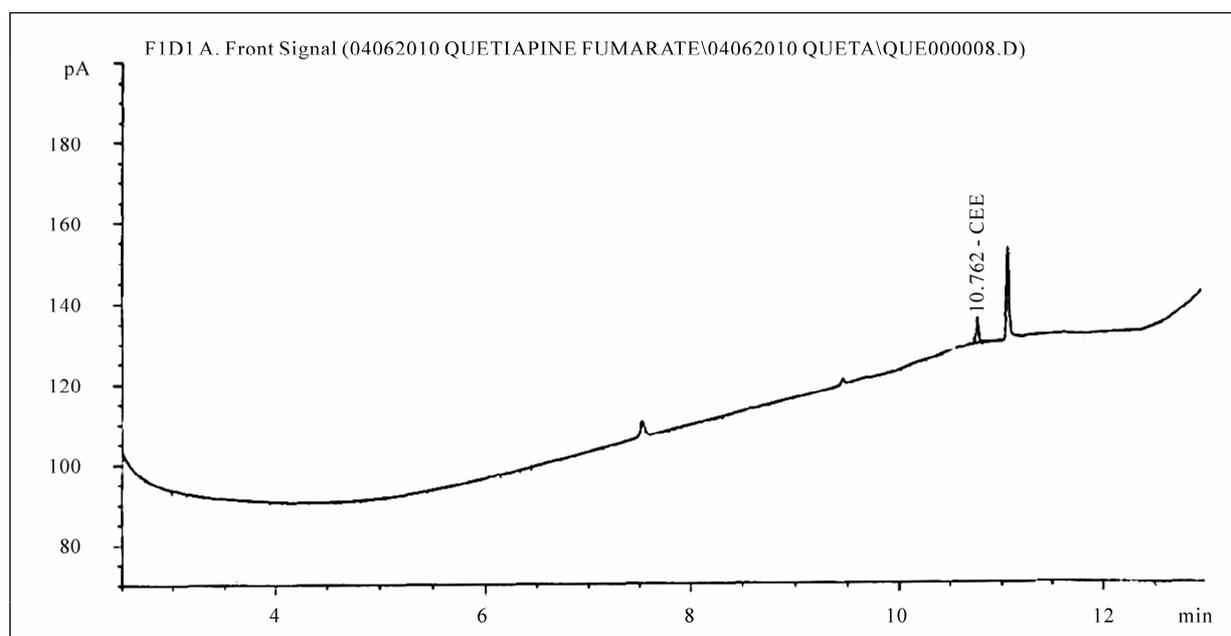


Figure 3. Limit of Quantification of CEE.

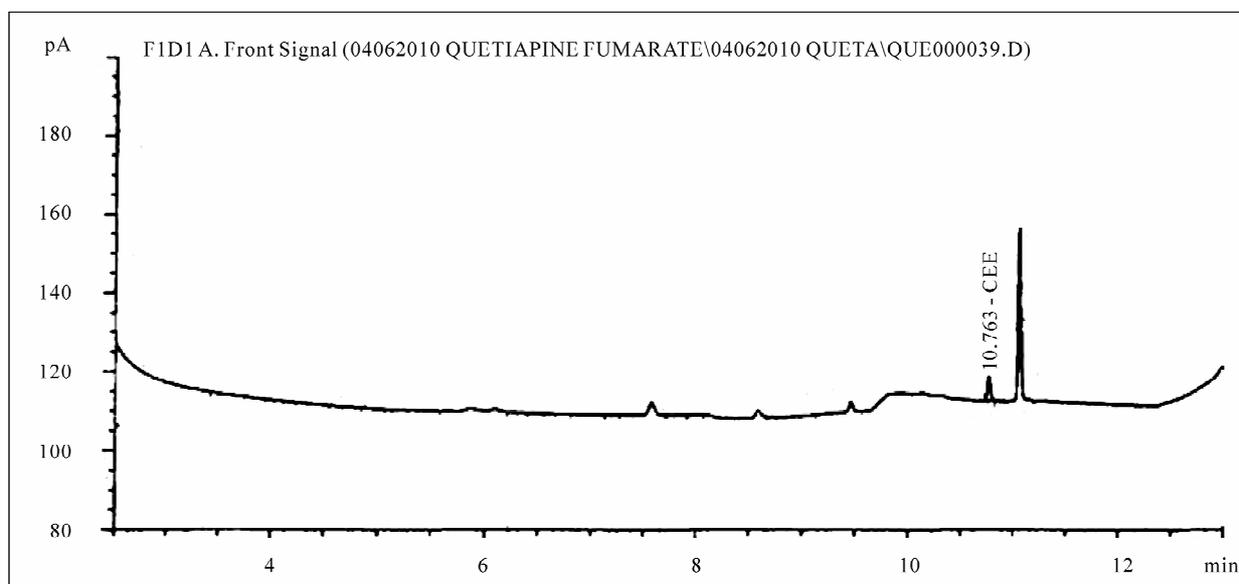


Figure 4. Accuracy at Limit of quantification level.

0.1 mg ml⁻¹ with respect to an API sample concentration 100mg ml⁻¹. A LOQ of 0.04mg ml⁻¹ is typical for the CEE with a LOD approximately three times less than LOQ. LOD and LOQ chromatograms are shown in the **Figures 2 & 3**.

3.4. Recovery of CEE in API

The accuracy of the method was evaluated in triplicate at LOQ level in bulk drug sample. The percentage recoveries were calculated. A satisfactory recovery value of CEE (90-92%) was obtained. At such low levels these recoveries and %RSD were satisfactory. Accuracy at LOQ and STD chromatogram was shown in **Figures 4 &**

5.

3.5. Linearity of the CEE on Gas Chromatography

The linearity of CEE was satisfactorily demonstrated with six point calibration graph between LOQ to 150% of analyte concentrations (LOQ, 50, 75,100,125 & 150). The peak area *versus* concentration data was performed by least-squares linear regression analysis. The calibration curve was produced by plotting the average of triplicate CEE injections against the concentration expressed in percentage. Correlation coefficient for CEE was 0.99. Linearity of the CEE chromatogram was shown in the

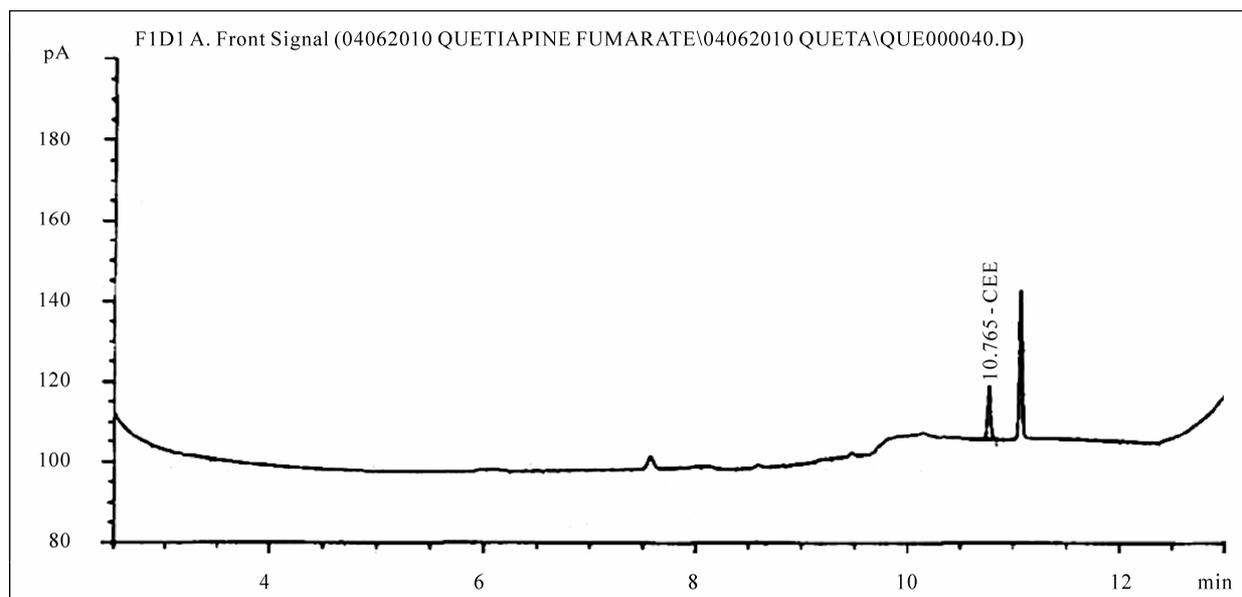


Figure 5. Accuracy at Standard level.

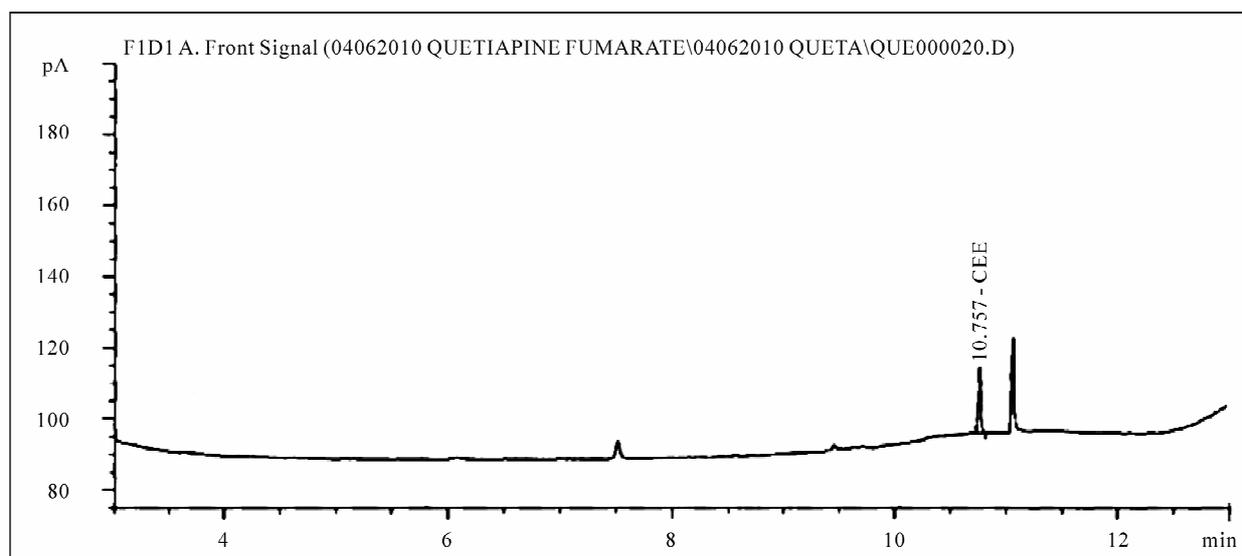


Figure 6. Linearity at standard level CEE.

Figure 6.**4. DISCUSSION AND CONCLUSION**

In this study, a GC analytical method was developed for control of residual 2-(2-chloroethoxy)ethanol (CEE) in the active substance. Sample solvent diluent was selected to obtain good selectivity and sensitivity for CEE. The sample dilution factor was adapted to detect unclassified solvent CEE at known impurity levels (100 ppm) by FID. This GC method is suitable for its intended purpose.

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