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Research Article

# DETERMINATION OF RESIDUAL SOLVENTS IN PAROXETINE BY HEADSPACE GAS CHROMATOGRAPHY

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**ABSTRACT**

**Objectives:** A simple and sensitive gas chromatographic method was developed and validated for simultaneous determination of acetone and isopropyl alcohol in paroxetine.

**Methods:** The separation was achieved on ZB-1, 30 m length × 0.53 mm ID, and film thickness 5 µm using a flame ionization detector (FID) with gradient column oven temperature program. The injection was carried out in split mode, with a split ratio of 10:1. Dimethylacetamide was selected as a diluent to obtain good sensitivity along with the recovery. 1-propanol was used as an internal standard which employed for area ratio method.

**Results:** The developed gas chromatographic method offers symmetric peak shape, good resolution of 2.3 min, and reasonable retention time for the solvents acetone 9.210 min and isopropyl alcohol 9.845 min. The limit of detection for acetone and isopropyl alcohol was 26.72 µg/ml and 82.96 µg/ml, respectively. Limit of quantitation for acetone and isopropyl alcohol was 80.96 µg/ml and 251.39 µg/ml, respectively. Precision was 0.83 and 0.63. Linearity was y = 0.0004x, $R^2$ = 0.9988 for acetone, and y = 0.0001x+0.0021, $R^2$ = 0.9987 for isopropyl alcohol, and accuracy along with robustness is performed and acceptable results were obtained.

**Conclusion:** The proposed, developed method was demonstrated to be simple, sensitive, linearity, accurate, and robust, hence can be used to determine the residual organic solvents in paroxetine drug substance and drug product.

**Keywords:** Paroxetine, Gas chromatography, Flame ionization detector.

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## INTRODUCTION

Paroxetine is an antidepressant in a group of drugs called selective serotonin reuptake inhibitors. Paroxetine affects chemicals in the brain that may become unbalanced. Paroxetine (Fig. 1) is used to treat depression, obsessive-compulsive disorder, anxiety disorders, post-traumatic stress disorder, and premenstrual dysphoric disorder. An impurity in a drug substance was defined by the International Conference on Harmonisation (ICH) guidelines that are any component of the drug substance that is not the chemical entity defined as the drug substance and affects the purity of active ingredient or drug substances [1]. Similarly, an impurity in a drug product is any component of the drug product that is not the chemical entity defined as the drug substance or an excipient in the drug product [2]. Therefore, any extraneous material present in the drug substance has to be considered an impurity even if it is inert or has superior pharmacological properties. The impurity profile of pharmaceuticals is of increasing importance as drug safety receives more and more attention from the public and the media. Several recent books and journal reviews address this topic and guidelines are available from the US and international authorities [3-10]. Most active pharmaceutical ingredients (APIs) are produced by organic chemical synthesis. Various components, including residual solvents, trace amounts of inorganic, and organic components, can be generated during such a process.

Analysis of a residual solvent in pharmaceuticals is an important issue due to the potential risk to human health from the toxicity of many of these solvents. The amount of such solvents is, therefore, limited by ICH guidelines [9]. The international conference on harmonization recommends and limits the amount of residual solvents considered safe in pharmaceutically finished goods and for human use. The ICH has published guidelines and daily exposure limit of many solvents. It has classified these solvents in three categories depending on their toxicity. Class I solvents are known human carcinogens and environmental hazards, the use of these solvents should be avoided if at all possible. Class II solvents are non-genotoxic animal carcinogens or possible causative agents of other irreversible toxicities such as neurotoxicity or teratogenicity. The use of these solvents should be limited. Class III solvents are the solvents with the low toxic potential to man; no health-based exposure limit is needed. In the pharmaceutical industries, all the pharmaceutical products must be analyzed for residual solvent content, regardless of the matrix.

Gas chromatography is generally used to determine residual solvents due to its excellent separation abilities and low limit of detection. In gas chromatography, the sample is either dissolved in a suitable solvent than injected directly [11] or by headspace sampling [12]. Headspace sampling is preferred due to its ability to avoid direct liquid or solid probing. In the headspace sampling, complex sample matrix in a solid or liquid sample matrix in the liquid or solid sample can be simplified or even eliminated in its vapor phase [13].

The methods reported for quantitative determination of paroxetine in tablets and/or biological fluids include voltammeter [14,15], densitometry [16,17], high-performance liquid chromatography [18-23], gas chromatography[24-26], and capillary electrophoresis [27].

The objective of this work is to develop and validate a new gas chromatographic method for the simultaneous determination of acetone and isopropyl alcohol in paroxetine. These solvents should be estimated and checked so that they may not exceed the amount specified by the ICH guidelines.

## EXPERIMENTAL WORK

### Materials and reagents

Paroxetine raw material was procured from Spectrum Pharma Research Private Limited, Hyderabad. GC grade acetone, isopropyl alcohol, 1-propanol, (Table 1)and N, N-dimethylacetamide were purchased from Merck (India).

### General procedure

#### *Instrumentation*

A gas chromatograph (Agilent Technologies 7890A) equipped with flame ionization detector (FID) connected to Agilent G1888 Headspace sampler and a data processor Waters Empower three software was employed.

#### *Method optimization*

Various GC columns such as DB-1 and DB-5 were used of various dimensions, but the best separation was achieved on ZB-1, 30 m length x 0.53 mm ID, and film thickness 5 µm. Details of other optimized gas chromatographic and headspace parameters are given in Table 2 and Table 3, respectively. For suitability of a system, tailing factor kept was not more than 2.0, theoretical plate count not <5000, and %RSD, not more than 10.0%, was kept for peak area of each solvent for six standard solution replication injections.

#### *Internal standard solution*

Transfer 1.5 mL of 1-propanol into 25 mL volumetric flask containing about 10 mL of diluent and made up to mark with diluent. Further, dilute 5 mL of the above solution into 200 mL volumetric flask containing approximately 100 mL of diluent, mix and made to mark with diluent.

#### *Blank solution*

Transfer 5 mL of internal standard solution into Agilent Technologies manufactured 20 mL flat bottom headspace GC vials fitted with a septum and crimp cap, and seal. The chromatogram of blank solution showed in Fig. 2.

#### *Standard stock solution*

Accurately weighed 200 mg of acetone and 200 mg of isopropyl alcohol were added to a 20 mL volumetric flask containing about 10 mL of internal standard solution.

Pipette 2 mL of this solution into a 100 mL volumetric flask containing about 50 mL of internal standard solution. Makeup to the required volume with internal standard solution and mix.

Pipette 5 mL of this solution into 20 mL headspace GC vial and seal vial adequately fitted with a septum and crimp cap. This should be repeated 6 times.

This standard solution contains about 5000 ppm of acetone and 5000 ppm of isopropyl alcohol. The chromatogram of standard solution Showed in Fig. 3.

**Table 1: Residual solvent with their class and limits**

| Solvent | Class | Limit (ppm) |
|---|---|---|
| Acetone | 3 | 5000 |
| Isopropyl alcohol | 3 | 5000 |

**Table 2: Optimized gas chromatographic conditions**

| Parameter | Condition |
|---|---|
| Carrier gas | Helium |
| Flow mode | 2.0 mL/min |
| Injector temperature | 140°C |
| Carrier gas mode | Split |
| Split ratio | 1:10 |
| Split flow | 20 mL/min |
| Detector | FID |
| Detector temperature | 250°C |
| Hydrogen flow | 40 mL/min |
| Airflow | 400 mL/min |
| Makeup flow (helium) | 25 mL/min |
| Run time | 24 min |
| Oven temperature | $T_1$ 40°C; hold for 12 min<br>$T_2$ 220°C at the rate of 30°C/min; hold for 6 min |

FID: Flame ionization detector

**Table 3: Optimized headspace conditions**

| System parameter | Optimum conditions |
|---|---|
| Oven temperature | 90°C |
| Loop temperature | 100°C |
| Transfer line temperature | 120°C |
| GC cycle time | 35 min |
| Vial equilibration time | 20 min |
| Vial pressurization time | 0.5 min |
| Loop fill time | 0.5 min |
| Loop equilibration time | 0.05 min |
| Injection time | 1.0 min |
| Vial agitation | Low |

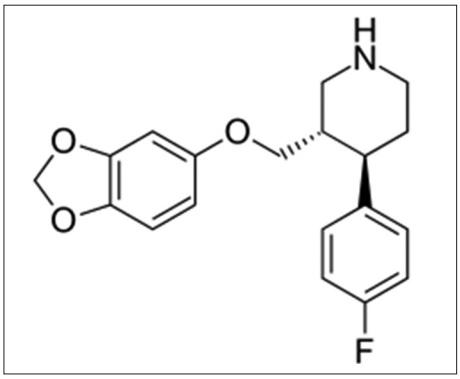


**Fig. 1: Structure of paroxetine**

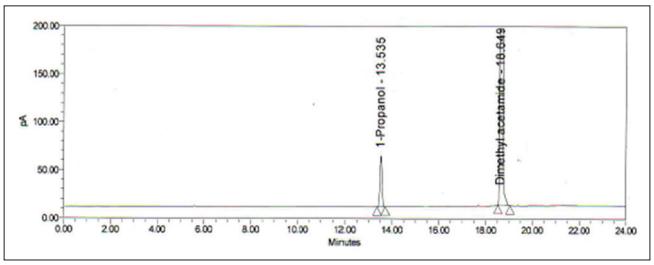


**Fig. 2: Typical blank chromatogram**

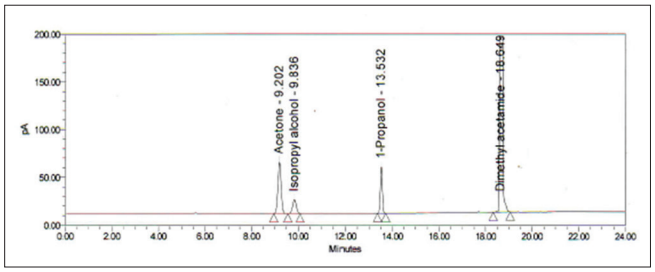


**Fig. 3: Typical chromatogram of standard solution**

**Sample preparation**

Weigh accurately 200 mg of tablets crushed powder into 20 mL flat bottom headspace GC vials; add 5 mL of internal standard solution fitted with a septum and crimp cap and seal.

**METHOD DEVELOPMENT AND VALIDATION**

**System suitability**

System performance parameters of the optimized GC method were determined by analyzing standard solution. Chromatographic parameters such as plate count, asymmetry, and resolution were determined. The results are within the specifications, indicating the excellent performance of the system. System repeatability was established by six replicate injections of the standard solution, and the relative standard deviations (RSD) for the peak area ratio of the solvents were calculated to evaluate the repeatability. The obtained results were within the ICH permissible limits mentioned in Table 4. The blank chromatogram is shown in Fig. 2, and the typical chromatogram shows that all the solvents are shown in Fig. 3.

**Linearity**

The linearity of the relationship between the peak area ratio and the concentration in ppm evaluated for all the residual solvents mentioned in the present study was investigated by linear regression analysis. Six linearity solutions were prepared to range from limit of quantitation (LOQ) to 150% of the limit level concentration of each solvent. The linear range investigated for each solvent is mentioned in Table 5. Linearity curves were drawn by plotting the graph of the average peak area ratio of solvent against its concentration in ppm for linearity solutions, Figs. 4 and 5.

**Accuracy and precision**

Both the terms accuracy and precision are mutually correlated, where accuracy is the difference between the true value and the observed value. With the precision, it has a limited significance. Accuracy and precision were determined by applying the optimized method in which known amount of each solvent corresponding to LOQ, 50%, 100%, and 150% of target concentration. Each level was prepared in triplicate. The accuracy was then calculated as the percentage of analyte recovered. From the results, it is evident that the recovery of each in spiked samples ranged from 97.0% to 115.0%. Mean recoveries for paroxetine are shown in Table 6. The precision of an analytical procedure expresses the closeness of agreement (degree of scattering) between a series of measurements obtained from multiple sampling of the same homogeneous sample under the prescribed conditions Table 7. Precisions may be considered at three levels: repeatability, intermediate precision, and reproducibility. The precision of an analytical procedure is usually expressed as the variance, standard deviation, or coefficient of variation of a series of measurements. Method precision shall be established by determining the assay in six different preparations of a standard solution. Intermediate precision shall be determined by studying the variation in assay of a homogeneous sample analyzed by two different equipment, analyst, and days. The average, standard deviation, and relative standard deviation shall be calculated. The results for the method and intermediate precision are found to be under the acceptable limit for each residual solvent as revealed by relative standard deviation data (RSD <5.0% for the solvents). The precision results are shown in Table 8.

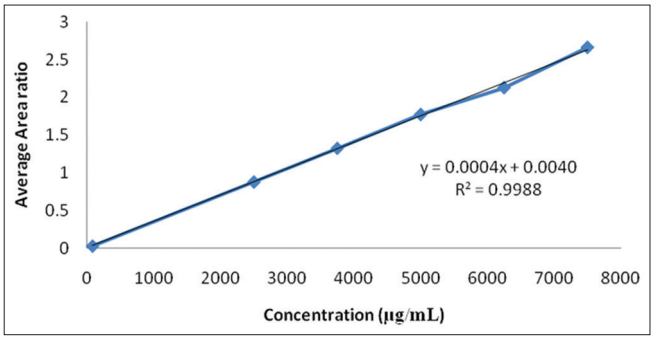


**Fig. 4: Linearity graph of acetone**

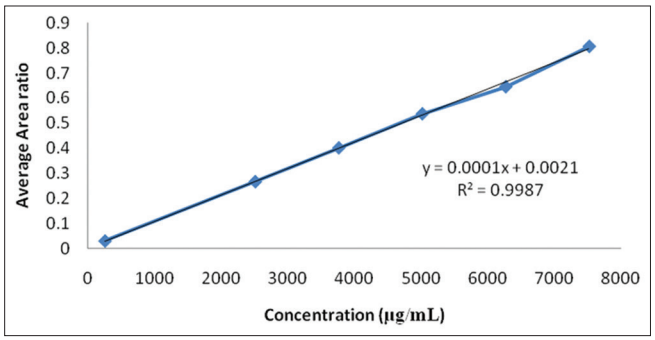


**Fig. 5: Linearity graph of isopropyl alcohol**

**Table 4: Results of system suitability study**

| System suitability parameters | Observed value | | Acceptance criteria |
|---|---|---|---|
| | Acetone | Isopropyl alcohol | |
| Retention time | 9.210 | 9.845 | For information |
| Percentage RSD for area count of six replicate injection of standard | 2.5 | 0.5 | NMT 10.0 |
| Tailing factor | 1.1 | 1.1 | NMT 2.0 |
| Theoretical plates | 58421 | 24813 | NLT 2000 |
| Resolution | 2.3 | | NLT 1.5 |

RSD: Relative standard deviations, NLT: Not less than, NMT: Not more than

**Table 5: Linearity and range of solvents**

| S.No | Percentage level | Acetone | | Isopropyl alcohol | |
|---|---|---|---|---|---|
| | | Concentration (µg/mL) | Mean peak area ratio | Concentration (µg/mL) | Mean peak area ratio |
| 1 | LOQ | 80.96 | 0.031 | 251.39 | 0.029 |
| 2 | 50 | 2500.75 | 0.881 | 2507.62 | 0.266 |
| 3 | 75 | 3751.12 | 1.328 | 3761.43 | 0.401 |
| 4 | 100 | 5001.5 | 1.777 | 5015.24 | 0.537 |
| 5 | 125 | 6251.87 | 2.133 | 6269.06 | 0.645 |
| 6 | 150 | 7502.25 | 2.667 | 7522.87 | 0.806 |

**Table 6: Results of recovery study for acetone**

| S.No | Recovery level (%) | Amount added (µg/ml) | Amount recovered (µg/ml) | Recovery (%) |
|---|---|---|---|---|
| 1 | LOQ | 80.96 | 87.48 | 108.05 |
| | | | 84.66 | 104.57 |
| | | | 93.13 | 115.03 |
| 2 | 50 | 2500.75 | 2449.55 | 97.95 |
| | | | 2460.84 | 98.40 |
| | | | 2548.32 | 101.90 |
| 3 | 100 | 5001.5 | 4901.92 | 98.01 |
| | | | 4924.5 | 98.46 |
| | | | 5099.46 | 101.96 |
| 4 | 150 | 7502.25 | 7351.47 | 97.99 |
| | | | 7388.16 | 98.48 |
| | | | 7647.79 | 101.94 |

LOQ: Limit of quantitation

**Table 7: Results of recovery study for isopropyl alcohol**

| S.No | Recovery level (%) | Amount added (µg/ml) | Amount recovered (µg/ml) | Recovery (%) |
|---|---|---|---|---|
| 1 | LOQ | 251.39 | 269.34 | 107.14 |
| | | | 278.62 | 110.83 |
| | | | 287.91 | 114.53 |
| 2 | 50 | 2507.62 | 2498.33 | 99.63 |
| | | | 2498.33 | 99.63 |
| | | | 2507.62 | 100.0 |
| 3 | 100 | 5015.24 | 4996.67 | 99.63 |
| | | | 4996.67 | 99.63 |
| | | | 5005.96 | 99.81 |
| 4 | 150 | 7522.87 | 7495.0 | 99.63 |
| | | | 7495.0 | 99.63 |
| | | | 7513.58 | 99.88 |

LOQ: Limit of quantitation

**Table 8: Results of precision study for acetone and isopropyl alcohol**

| Parameter | Percentage RSD | |
|---|---|---|
| | Acetone | Isopropyl alcohol |
| System precision (standard solution) (peak area ratio) | 2.53 | 0.54 |
| Precision at LOQ (peak area ratio) | 3.22 | 2.46 |
| Repeatability (intraday) (content ppm) | 0.93 | 0.73 |
| Intermediate precision (interday) (content ppm) | 0.69 | 0.65 |
| Cumulative (intraday and interday) (content ppm) | 0.83 | 0.67 |

RSD: Relative standard deviations, LOQ: Limit of quantitation

**Table 9: Limit of detection and limit of quantitation of each solvent**

| S.No | Solvent name | LOD (µg/mL) | S/N | LOQ (µg/mL) | S/N |
|---|---|---|---|---|---|
| 1 | Acetone | 26.72 | 3.9 | 80.96 | 10.2 |
| 2 | Isopropyl alcohol | 82.96 | 4.3 | 251.39 | 11.2 |

LOD: Limit of detection, LOQ: Limit of quantitation, S/N: Signal-to-noise ratio

**Limit of detection (LOD) and limit of quantitation (LOQ)**

The limit of detection of an individual analytical procedure is the lowest amount of analyte in a sample, which can be detected but not necessarily quantitated as an exact amount. While the limit of quantitation was the minimum level of concentration of analyte at which it can be quantitated with acceptable precision and accuracy. LOD and LOQ were calculated using the signal-to-noise ratio (S/N) method using the Empower software. Six replicate solutions were injected into the chromatograph and recorded. Obtained LOD and LOQ of each solvent are mentioned in Table 9.

**Robustness**

For robustness, three deliberate changes were done concerning carrier gas flow rate, column oven temperature, and vial oven temperature. Each change consists of one upper set and one lower set. For each set, six replicate determinations were analyzed. The results were found to be satisfactory and within the acceptable limits. The obtained results are mentioned in Tables 10 and 11.

## RESULTS AND DISCUSSION

The retention time of the solvent peak of standard solution matches with that of the spiked test sample solution. No interference was observed at a retention time of the solvent peak from blank and test sample. The percentage recovery obtained for each solvent was in the range of 80%–120%, which is within ICH acceptance. Precision parameter shows that the RSD was <5.0% for all the solvents in system precision, repeatability, and intermediate precision at 100% concentration. Linearity was observed in the concentration range of LOQ to 150% with $r^2$ values >0.999 and y-intercept <5.0% showing a good correlation between the response and solvent concentration. The calculated limit of detection and limit of quantitation for each solvent found to be

**Table 10: Robustness study results of acetone**

| S.No | Parameter | System conditions | Percentage RSD for peak area (n=6) | Retention time | Plate count | Tailing factor |
|---|---|---|---|---|---|---|
| 1 | Flow rate (±0.2 mL/min) | 1.8 | 2.8 | 10.369 | 354,692 | 1.0 |
| | | 2.0 | 2.5 | 9.185 | 365,249 | 1.2 |
| | | 2.2 | 1.8 | 8.331 | 375,912 | 1.1 |
| 2 | Column oven temperature (±5°C) | 35°C | 2.0 | 10.216 | 395,462 | 1.1 |
| | | 40°C | 2.5 | 9.185 | 406,205 | 1.2 |
| | | 45°C | 1.5 | 8.380 | 410,506 | 1.2 |
| 3 | Vial oven temperature (±5°C) | 85°C | 2.4 | 9.175 | 351,212 | 1.3 |
| | | 90°C | 2.5 | 9.185 | 356,981 | 1.2 |
| | | 95°C | 1.7 | 9.172 | 322,978 | 1.2 |

RSD: Relative standard deviation

**Table 11: Robustness study results of isopropyl alcohol**

| S.No | Parameter | System conditions | Percentage RSD for peak area (n=6) | Retention time | Resolution | Plate count | Tailing factor |
|---|---|---|---|---|---|---|---|
| 1 | Flow rate (±0.2 mL/min) | 1.8 | 1.2 | 11.087 | 2.3 | 562,920 | 1.2 |
| | | 2.0 | 0.5 | 9.821 | 2.3 | 659,621 | 1.3 |
| | | 2.2 | 0.9 | 8.907 | 2.2 | 654,810 | 1.0 |
| 2 | Column oven temperature (±5°C) | 35°C | 1.5 | 11.043 | 2.6 | 687,502 | 1.0 |
| | | 40°C | 0.5 | 9.821 | 2.3 | 687,101 | 1.3 |
| | | 45°C | 0.7 | 8.876 | 1.9 | 689,481 | 1.2 |
| 3 | Vial oven temperature (±5°C) | 85°C | 1.2 | 9.842 | 2.3 | 462,952 | 1.5 |
| | | 90°C | 0.5 | 9.821 | 2.3 | 479,202 | 1.3 |
| | | 95°C | 1.0 | 9.834 | 2.2 | 498,822 | 1.2 |

RSD: Relative standard deviation

satisfactory. The method is robust as in robustness parameter with deliberate changes made for which individual and cumulative RSD values for each set were <5.0%.

## CONCLUSION

The developed GC method with FID detector offers simplicity, selectivity, precision, and accuracy. It produces symmetric peak shape and reasonable retention time for various solvents. It can be seen from the chromatogram that all the solvents were eluted before 20 min of injection of sample. It can be used for the determination of residual solvents in paroxetine API and also in the finished dosage forms where the particular solvents used for the coating purpose in the pharmaceutical companies and research laboratories.

## AUTHORS' CONTRIBUTIONS

All authors contribute equally in data collection, experimental design, interpretation, statistical analysis, literature review, manuscript preparation, and review.

## COMPETING INTERESTS

Nil.

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