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DEVELOPMENT AND VALIDATION OF A HEADSPACE GAS CHROMATOGRAPHIC METHOD FOR DETERMINATION OF RESIDUAL SOLVENTS FOR FIVE ANTIDEPRESSANT DRUG SUBSTANCES

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ABSTRACT

A simple and sensitive method for the determination of 18 residual solvents for antidepressant drugs Bupropion, Fluoxetine, Milnacipran, Nortriptyline and Sertraline is developed using headspace technique with FID detector. These antidepressant drugs belong to different classes. The method was validated for repeatability, linearity, limit of detection, limit of quantification and recovery demonstrated as per the International Council for Harmonization (ICH) guidelines. Excellent results were obtained, within the globally accepted validation reference values, particularly taking into account the low concentration levels obtained.

KEYWORDS: Gas chromatography, HS-GC, Residual solvents (RS), FID, Method development, Validation.

1. INTRODUCTION

Residual solvents are the remaining solvents which are used in the production and purification steps in the manufacture of drug substances or products which are also Known as organic volatile impurities (OVI's).[1-5] Residual solvents are not desired product there for their limits and acceptance criteria are described in International conference of harmonization (ICH) guidelines. Residual solvents are classified according to their hazards and potential risk to the health during their therapeutic use.[6] Residual Solvents are categorized according to

their toxicity and health hazards namely class 1 solvents (to be avoided), class 2 solvents (to be limited) and class 3 solvents (low toxic potential).[1]

The goal of this chapter is to provide common method for the some selected antidepressant drugs. Antidepressants are a category of drugs used to treat the symptoms of depressive disorders by correcting chemical imbalances of neurotransmitters within the brain. The selected Antidepressants are of different classes that are Bupropion (Norepinephrine-dopamine reuptake inhibitor), Fluoxetine (selective serotonin reuptake inhibitors), Milnacipran (Serotonin-norepinephrine reuptake inhibitors), Nortriptyline (Tricyclic) and Sertraline (Selective serotonin reuptake inhibitors).

The objective of this study is to provide acceptable amounts of residual solvents in drug product. This study provides common method for calculate the residual solvents in API or drug product. The residual solvents taken in this method are the only which are used in the production and purification processes are known to result.

2. EXPERIMENTAL

2.1. Chemicals

Carbon tetrachloride, Nitromethane, tetrahydrofuran, dioxin, pyridine, N,N-dimethyl formamide, n-hexane, Cyclohexane, Acetone, Dimethyl sulphoxide, diethyl ether, ethyl acetate, n-butanol, ethanol are taken from Spectrochem. Benzene, methanol, Acetonitrile, dichloromethane, toluene and n-propanol are taken from Merck.

2.2. Instrumentation

The experiments were performed on PERKIN ELMER Clarus 500 GC Equipped with Flame Ionization Detector (FID) using Head Space Turbometrix 40 sampling technique. The processing system for GC-FID is Total chrom Navigator (version 6.3.1) and for HS-GC is Turbomatrix.

2.3. Chromatographic condition

The separation was performed on column ZB-624 (lenth-30m, ID-0.32 mm, film thickness-1.80 µm, column composition- cyanopropylphenyl dimethyl polysiloxane and the remaining parameters described in Table 1.

Table 1: Summary of method parameters.

GC-FID Parameters			
Gases		**Heated Zones**	
Injection Mode	Split	Column Oven Temperature:	
Split Ratio	20:1	Initial	35 ^{0}C
Carrier Gas	N_2	Hold	2 min
Control	Velocity	Ramp1	10 ^{0}Cmin^{-1} to 210 ^{0}C
Flow	25 cm/s	Hold	5 min
Sampling Rate	12.5	Total run time	24.50 min
Column	ZB-624 (length-30m, ID-0.32 mm, film thickness-1.80 µm, column composition-phenylmethyl polysiloxane	**Injector Temperature:**	
		Initial	200 ^{0}C Hold 999.9 min
		Detector Temperature	250 ^{0}C

HS Parameters			
Heated zones Temperature		**Time**	
Vial oven	100^{0}C	Thermostat	30 min
Needle	105^{0}C	Injection	0.5 ml
Transfer line	110^{0}C	Pressurize	0.5 min
Injection mode	Volume	Withdrawal	0.2 min
		Injection Pressure	15 psi

2.4. Sample preparation

2.4.1. Diluents

Water, dimethyl sulphoxide and dimethyl formamide are used as diluents.

2.4.2. Preparation of blank

For water soluble solvents Water was used as a diluent. For water insoluble solvents Water and dimethyl sulphoxide (50:50) mixture and the other diluent system was Water and dimethyl formamide (50:50).

2.4.3. Preparation of Stock solution

Class 1 Water Insoluble

Take water and dimethyl sulphoxide mixture (50:50) Add 10 and 50 µl of Benzene and CCl4 respectively, make upto 10 ml.

Class 2 Water soluble

Take Milli-Q water, Add 20, 150, 150, 150, 250 and 300 µl of Tetrahydrofuran, Acetonitrile, 1, 4-Dioxane, Pyridine, Nitromethane and Methanol respectively, make up to 10 ml with Milli-Q water.

Class 2 Water Insoluble

Take water and dimethyl sulphoxide mixture (50:50), Add 5, 8, 10 and 100 µl of Cyclohexane, n-Hexane, Toluene and Dichloromethane respectively, make up to 10 ml.

Class 3 Water soluble

Take Milli-Q water, Add 50, 200 and 250 µl of Acetone, n-Propanol and Ethanol respectively, make up to 10 ml.

Class 3 Water Insoluble

Take mixture of Milli-Q water and DMF (50:50), Add 10, 20 and 100 µl of Diethyl Ether, Ethyl Acetate and n-Butanol respectively, make up to 10 ml.

2.4.4. Preparation of Standard solution

Class 1 water Insoluble

Take 1 ml stock solution in 20 ml HS-GC vial and make up to 5 ml with Milli-Q water and DMSO (50:50). From this vial inject 0.5 ml (120 ppm) of generated vapor in HS-GC/FID system.

Class 2 Water soluble

Take 1 ml stock solution in 20 ml HS-GC vial make up to 5 ml with Milli-Q water. From this vial inject 0.5 ml (2000 ppm) of generated vapor in HS-GC/FID system.

Class 2 Water Insoluble

Take 1 ml stock solution in 20 ml HS-GC vial and make up to 5 ml with Milli-Q water and DMSO (50:50). From this vial inject 0.5 ml (246 ppm) of generated vapour in HS-GC/FID system.

Class 3 Water soluble

Take 1 ml stock solution in 20 ml HS-GC vial and make up to 5 ml with Milli-Q water. From this vial inject 0.5 ml (1000 ppm) of generated vapor in HS-GC/FID system.

Class 3 Water Insoluble

Take 1 ml stock solution in 20 ml HS-GC vial and make up to 5 ml with Milli-Q water and DMF. From this vial inject 0.5 ml (260 ppm) of generated vapor in HS-GC/FID system.

3. RESULT AND DISCUSSION

3.1. Analytical method development, Validation and Optimization

Critical elements of a new head space gas chromatography method development are identifying an appropriate diluent which would completely dissolve the residual solvents, determining suitable headspace parameters (i.e. Headspace temperature, vial equilibration time, vial pressurization), GC parameters (i.e., inlet split ratio, inlet temperature) and GC temperature programming to improve the sensitivity of the method.[5]

3.1.1. Selection of solvent for sample preparation

Solution preparation was carried out using different compositions of diluents (1) for both water soluble and insoluble, DMSO and Water (50:50), (2) For water soluble, DMF and Water (50:50) and for water insoluble only DMSO, (3) For water soluble, only water and for water insoluble only DMF Different concentration of residual solvents were prepared (variation was in the form of addition of different micro litters for each class solvents to get proper response).

3.1.2. Selection of headspace oven temperature and other GC parameters

The sensitivity of method depends on headspace sample oven temperature and injector temperature because temperature has direct impact on the equilibrium concentration of residual solvent in the head space of the sample vial.

For the experiment the transfer line was kept 5-20 º C higher than the vial temperature, vial temperature 5-10 º C higher than the vial oven temperature and vial oven temperature 5-10 ºC higher needle temperature. Vial oven temperature was varying from 80 ºC to 120 ºC and according to that temperature needle and transfer line temperature was changed accordingly. The GC inlet temperature was kept constant at 180 ºC and split ratio at 40:1. By using this conditions all the residual solvents were detected but the peak shape and the peak height were not showing the acceptance criteria.

To overcome this problem injector temperature and split ratio were changed from 180 to 190 to 200 and 220 º C and 40:1, 30:1, 20:1, 10:1 respectively, To improve peak shape and peak response. On decreasing the inlet split ratio would naturally leads to increase in sensitivity because of higher amount of samples inject to the column.

On decreasing inlet split ratio all the RS were showing proper sensitivity. For this method 20:1 inlet split ratio was found optimum.

3.1.3. Evaluation of different GC temperature programing

DMF and DMSO are high boiling point solvents comparing to residual solvents 153 ºC and 189 ºC respectively. During the preliminary evaluations the highest temperature used in the GC program was only 150 ºC. By using this temperature programming DMF and DMSO did not elute from the column within the run time of the method. Therefore they were carried over to the subsequent run. This carryover peak interfered with the identification and quantitation of the other residual solvents. So to ensure that peaks from DMSO and DMF are completely eluted from the column. The column oven temperature is taken to the higher temperature up to 200ºC.By using the fast GC ramp of 25 ºC /min , Some residual solvent of different class were retained at same time .due to the fast ramp a very noisy baseline and merged peaks were obtained. To overcome these problems, the final ramp, hold time and the column/oven temperature were varied in the GC temperature programming.

3.1.4. Evaluation of signal to noise ratio

The limit of detection (LOD) and limit of quantification (LOQ) for each class of solvent were determined by calculating the signal to noise ratio of the LOD preparation and LOQ preparation. The guideline suggest minimum signal to noise ratio should be more than 3:1 for LOD and more than 10:1 for LOQ.

Table 2: LOD and LOQ level obtained for this method for each class of solvent.

Class	LOD (ppm)	LOQ (ppm)
Class1 Insoluble	1.30	4
Class 2 Insoluble	7	21
Class 2 Soluble	40	120
Class 3 Insoluble	2.60	7.80
Class 3 Soluble	12.70	40

3.2. Analytical method validation

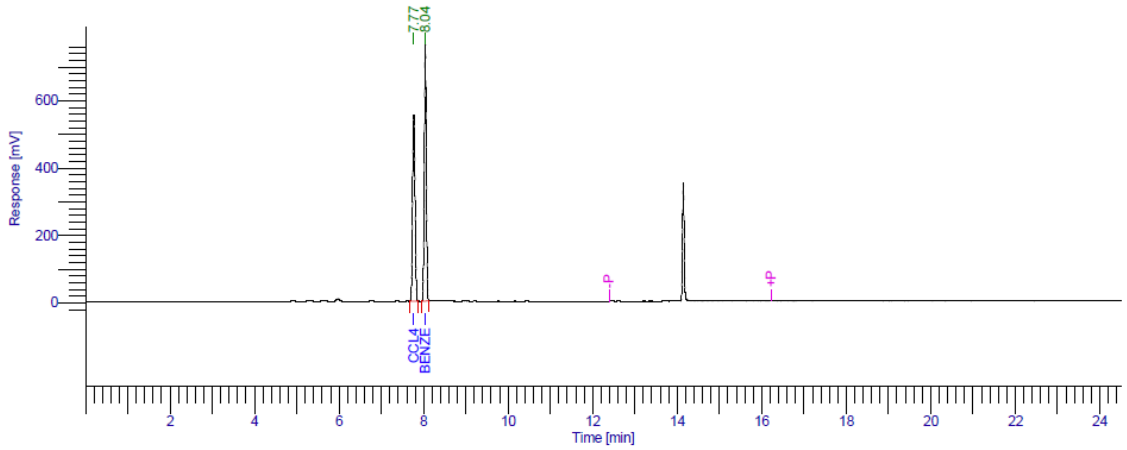
Validation of method was performed with respect to parameters such as linearity, accuracy, QL and DL, ruggedness and precision, Specificity, robustness, sample stability. Method validation was performed according to ICH guidelines.

3.2.1. Linearity and Accuracy

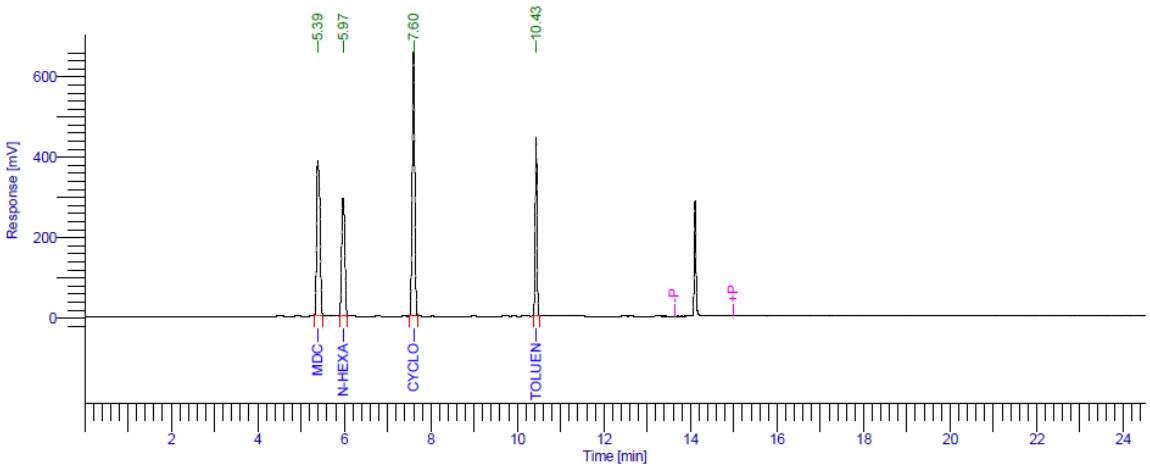
The linearity was prepared with five concentration levels by injecting 0.1, 0.3, 0.5, 0.7 and 0.9 ml of stock solution for each class. The injected concentration will be the response of the each solvent for each class was found to be linear in the investigation concentration range.

The slope, y-intercept, and coefficient of determination (r2) for linearity study were obtained from linear regression curve. The peak areas (corrected peak areas in spiked API) of each individual RS were plotted against corresponding theoretical concentrations (g/mL) obtained from each linearity solution.

Linear regression analysis showed that a coefficient of determination (r^2) values is between 0.98 - 0.99 for all the RS method has been demonstrated to be linear and accurate for routine analysis.



(A)



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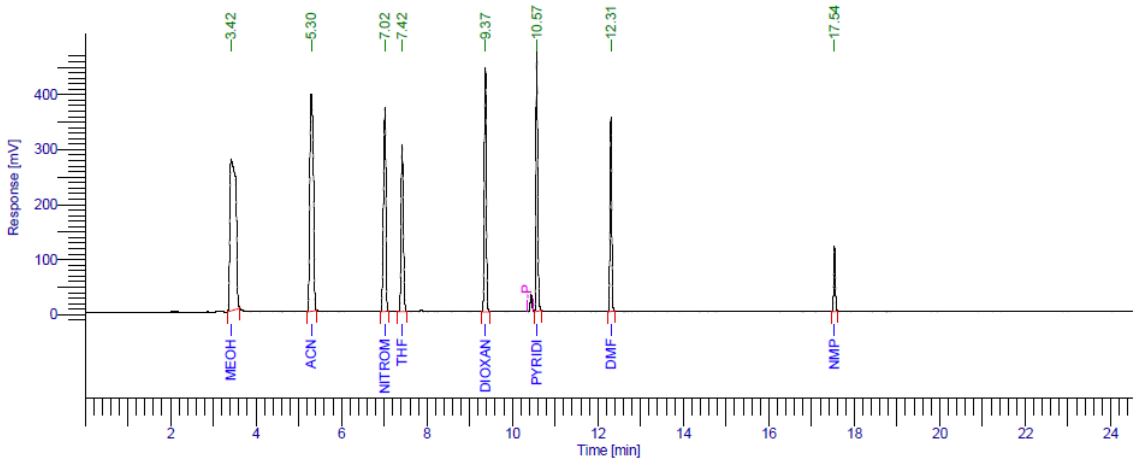

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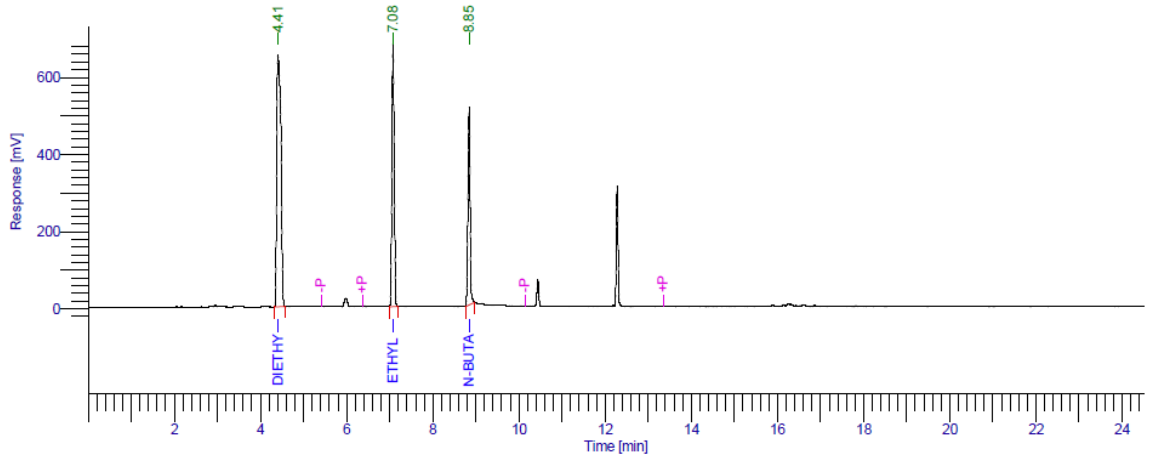

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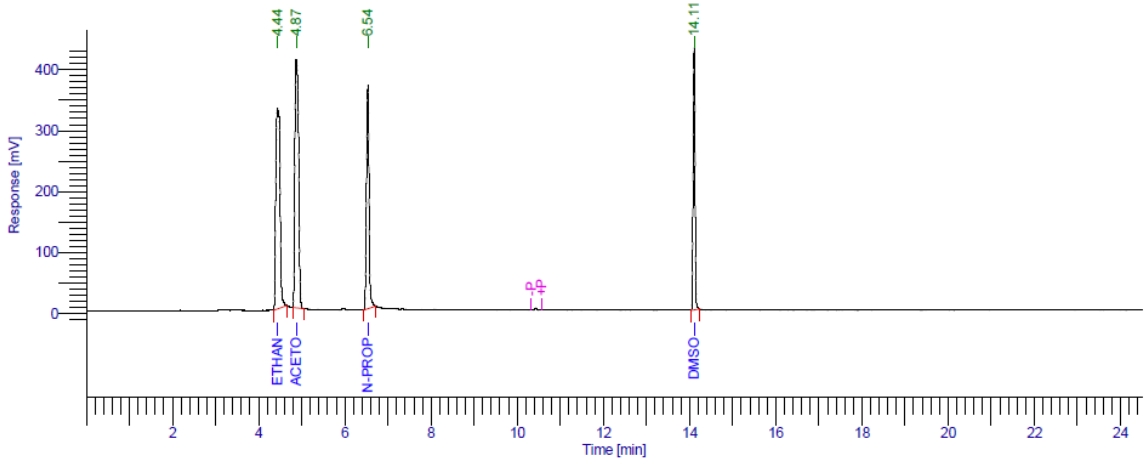

(E)

Fig.1. Chromatograms RSs standard mixture (A) Class 1 water insoluble, (B) Class 2 water insoluble, (C) Class 2 water soluble, (D) Class 3 water insoluble, (E) Class 3 Water soluble.

3.2.2. Precision

A precision study was established by evaluating method precision, intraday and interday precision study. The precision of the method was evaluated by carrying out six replicates of 100% test solution on the same day (intraday) and performing the same procedures on a different day (inter day) for each class of residual solvents.

Table 3: Result summary of linearity, accuracy and precision study for each class of residual solvents.

Class	Solvents	Linearity	Accuracy		Precision		
		R^2	Concentration Level	% RSD	Concentration Level	%RSD	
						Inter-Day	Intra-Day
Class 1 Water Insoluble	Benzene	0.9939	20%	2.02	100%	1.59	1.82
			100%	1.88			
			180%	2.04			
	Carbon Tetra chloride	0.9800	20%	2.07		2.06	2.03
			100%	1.89			
			180%	1.99			
Class 2 Water Soluble	Methanol	0.9856	20%	2.00	100%	1.79	0.82
			100%	0.19			
			180%	2.09			
	Aceto-nitrile	0.9864	20%	1.80		2.05	1.42
			100%	1.92			
			180%	1.97			
	Nitro methane	0.9932	20%	2.05		1.98	1.85
			100%	1.97			
			180%	2.08			
	Tetra Hydro furan	0.9948	20%	0.89		1.97	2.07
			100%	1.62			
			180%	2.07			
	1,4-Dioxane	0.9884	20%	2.00		1.57	2.04
			100%	1.16			
			180%	2.06			
	Pyridine	0.9877	20%	2.07		2.08	1.33
			100%	1.94			
			180%	1.57			
Class 2 Water Insoluble	Dichloro-methane	0.9931	20%	2.02	100%	1.93	2.08
			100%	0.15			
			180%	1.90			
	n-Hexane	0.9806	20%	2.03		2.08	2.05
			100%	1.94			
			180%	2.05			
	Cyclo-hexane	0.9790	20%	1.94		1.96	2.07
			100%	1.88			
			180%	2.05			

	Toluene	0.9883	20%	2.01		1.81	1.9
			100%	1.93			
			180%	1.92			
Class 3 Water Soluble	Ethanol	0.9885	20%	2.07	100%	0.69	1.34
			100%	2.02			
			180%	0.69			
	Acetone	0.9910	20%	1.99		2.05	0.93
			100%	0.31			
			180%	0.50			
	n-Propanol	0.9878	20%	0.34		1.05	1.79
			100%	2.01			
			180%	2.05			
Class 3 Water insoluble	Diethyl Ether	0.9808	20%	1.12	100%	1.99	2.03
			100%	2.10			
			180%	2.02			
	Ethyl Acetate	0.9844	20%	0.23		2.02	1.44
			100%	2.09			
			180%	2.05			
	n-Butanol	0.9887	20%	1.99		1.64	2.01
			100%	2.04			
			180%	1.97			

3.2.3. Specificity of method

The specificity of the method was determined by checking the interference of diluents (Water, DMF, and DMSO) which were used for sample preparation to determine residual solvents. There was no any peak of diluents affecting or interfering with the analytes peaks.

3.2.4. Method robustness

The system suitability criteria were met for all the variations. The S/N ratios of QL were all above 10. The retention times of the RS obtained from parameter variations were within ±1min of the retention time obtained from the procedural conditions. This study demonstrated that the proposed method is robust for quantitation analysis.

CONCLUSION

In this work, the convenient HS-GC–FID method was optimized for profiling of RSs in Antidepressant drugs. The method was applied in the analysis of different Antidepressant Drugs and showed good overall performance. It was also found that regardless of the sample solubility in the dilution media, the use of water in the sample preparation was crucial for better sensitivity. Validation data showed satisfactory linearity, sensitivity, accuracy and precision of the method for the tested RSs. The data obtained proved that the proposed

method was suited for the intended purpose and can be used for profiling of RSs in different classes of antidepressant drugs. This is the first reported method for 18 residual solvents with high sensitivity since have low LOD and LOQ values. This method has also been demonstrated to be accurate, linear, precise, reproducible, repeatable, specific, and robust thought out analysis.

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