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DEVELOPMENT AND VALIDATION OF GC-HS METHOD FOR DETERMINATION OF RESIDUAL SOLVENTS IN OLANZAPINE PAMOATE

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ABSTRACT

A simple GC-HS method for the determination of residual solvents in olanzapine pamoate using Helium as the carrier gas at 2.0 ml/min with HP-5 (30 meters × 0.53 × I.D, Film thickness-5.00µm) as a column using FID as a detector was developed. The developed method was validated and the parameters were to be found within the ICH limits. The retention time for residual solvents individually and spiked standard solution was determined. The %RSD for six injections should be NMT 15%. The percentage recovery ranges from 85-115%. The correlation coefficient (R^2) > 0.999. Selectivity, linearity, system suitability, limit of detection (LOD), limit of quantification (LOQ), precision, accuracy, robustness and ruggedness were found to be within the acceptance limit. Finally, the sample was tested for the presence of residual solvents mainly methanol, acetone, dichloromethane (DCM) and toluene, but which were found to be within ICH limits.

INTRODUCTION:

Residual solvents are the organic volatile chemicals that are used or produced in the manufacture of drug substances or excipients or in the preparation drug products. These solvents are not completely removed by practical manufacturing techniques [1]. Olanzapine is a thienobenzodiazepine derivative with chemical name 2-methyl-4-(4-methyl-1-piperazinyl)-10H-thieno [2,3-b] [1,5] benzodiazepine (Figure 1). It is a synthetic atypical antipsychotic agent. It is used in the treatment of various psychotic diseases. Olanzapine results from block the dopamine receptor, and used to treat the schizophrenia and maniac disease. Olanzapine has high affinity for serotonin, dopamine, muscarinic, adrenergic and histaminergic receptors [2,3].

Literature survey reveals that, several analytical methods were reported for the quantification of olanzapine pamoate by UV, RP-HPLC, HPTLC and LC-MS methods [4-7]. For the first time, in the present study an attempt is made to develop and validate a simple GC-HS method for the determination of residual solvents like methanol, acetone, dichloromethane (DCM) and toluene in olanzapine pamoate.

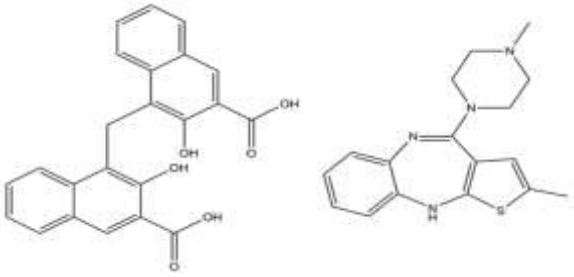

Figure 1: Chemical structure of olanzapine pamoate

MATERIALS AND METHODS

Chemicals and reagents used: Olanzapine pamoate API was procured as a gift sample from Neuland Pharmaceuticals Private Limited, Hyderabad, Telangana. Methanol, acetone, dichloromethane (DCM), toluene and di-methyl acetamide (DMA) were of GC grade (Merck). All the chemicals and reagents used were analytical grade.

Instrumentation: The analysis was performed using Shimadzu gas chromatography model no GC-2010, GC-2010 plus using HP-5 column and FID detector with helium as the carrier gas.

Solvents and diluents: Methanol, acetone, dichloromethane, toluene are used as solvents, and N-dimethyl acetamide used as a diluent.

Preparation of standard solution [8-10]

Standard preparation: Transfer 300 mg of methanol, 500 mg of acetone, 60 mg of DCM and 89 mg of toluene into 100 ml volumetric flask containing 10 ml of diluent and dilute up to the mark with diluents. Take 5 ml of above solution into a 50 ml of volumetric flask and dilute up to the mark with diluents.

Sample preparation: Weigh accurately 200 mg of sample (olanzapine pamoate) into HS vial and add the 2.0 ml of diluents (N-dimethyl acetamide) put septum, crimp the cap and seal it properly.

Procedure: Prepared solutions are taken into 20 ml head space vial, sealed with aluminum septa. These standards are run under specified conditions and retention times are noted to calculate the % RSD. The concentration of residual solvents (ppm) in the drug samples can be determined using the below formula:

$$\text{Conc. of residual solvents (X)} = \frac{T \times S \times 5 \times 2}{A \times 100 \times 50 \times W} \times 10^6$$

Where; T = Area of individual solvent in test solution, S = Individual solvent wt. in standard solution (mg), A = Average area (six injections) of individual solvent in std. solution, and W = Sample wt. (mg)

Method validation [11-14] The method was validated in terms of the following parameters; specificity, system suitability, linearity, accuracy, precision, robustness, ruggedness, LOD and LOQ as per the ICH guidelines.

Specificity: Specificity is the ability to assess unequivocally the analyze in the presence of components which may be expected to be present. Typically, these might include impurities, degradants, matrix, etc. The chromatogram was taken by appropriate dilutions and the amount of each drug present in the sample mixture was determined and it was found that there is no interference with the analyte peak.

System suitability: The peak resolution, theoretical plates, tailing factor, peak symmetry were calculated for the standard solutions. The results obtained indicate the suitability of the system for the analysis of the drug and the system suitability parameters are within the range during method.

Linearity: The linearity of the method was determined by constructing calibration curves. Sample solutions of methanol, acetone, dichloromethane and toluene at different concentration levels (25%, 50%, 75%, 100%, 125%, and 150%) were used. Before injection of the solution, the column was equilibrated for at least 20 min with blank. The peak areas of the chromatograms were plotted against the concentrations of methanol, acetone, dichloromethane and toluene to obtain the calibration curves. Aliquots of standard methanol, acetone, dichloromethane and toluene stock solutions were taken in different 10 ml volumetric flasks and diluted up to the mark with diluents. such that the final concentrations of methanol, acetone, dichloromethane and toluene were in the range of 135.62 to 4520 ppm, 40.25 to 7542 ppm, 168.43 to 935 and 38.34 to 1369 ppm respectively.

Each of these drug solutions was injected Six times into the column, and the peak areas and retention times were recorded. Calibration graphs were obtained by plotting peak area versus concentration of methanol, acetone, dichloromethane and toluene.

Accuracy: Accuracy is the closeness in agreement between the accepted true value or a reference value and the actual results obtained. Accuracy studies are usually evaluated by determining the recovery of a spiked sample of the analyte into the mixture of the sample to be analyzed. A known amount of pure drug at three different levels i.e. LOQ, 100%, and 150% was added to preanalyzed sample solutions and total concentration was determined by the proposed GC-HS method.

Precision: Method precision was determined by injecting six replicates of the drug sample solution. The retention times and peak areas of six replicates are recorded. The precision expresses as the % RSD of peak areas and it should not be more than 15%. The low value (<1%) of RSD indicates the repeatability of the method. These data indicate a considerable degree of precision and reproducibility for the method both during one analytical run and between different runs.

Robustness: The robustness of an analytical procedure is a measure of its capacity to remain unaffected by small, but deliberate variation in method parameters and provides an indication of its reliability during normal usage. There was no change in system suitability parameters. The result of robustness studies along with its different parameters are tabulated in Table 8.

Ruggedness: Ruggedness is a measure of reproducibility of test results under normal, expected operational conditions from laboratory, and from analyst to analyst. There was no marked difference obtained in results. The results are tabulated in Table 8.

Limit of Detection and Quantification: Limit of Detection (LOD) of the method was determined as the lowest concentrations of active pharmaceutical ingredients producing a signal-to-noise (S/N) ratio of about 3. The Limit of Quantitation (LOQ) was determined as the lowest concentrations of active pharmaceutical ingredients capable of being quantified with acceptable accuracy and precision producing signal-to-noise (S/N) ratio of about 10.

RESULTS AND DISCUSSION

GC-HS method development and optimization: In response to lack of simple, reliable and easy-to-use method for the determination of Residual solvents in olanzapine pamoate. We examined several GC method variables with respect to their corresponding effects on the result of analysis. To optimize the chromatographic conditions, different columns, split ratios was promisingly preferred, because it resulted in greater resolution of residual solvents after several preliminary investigatory runs, compared with other columns and split ratios. The other parameters in this factorial design were temperature, flow rate, detection wavelength and volume of injection. Split ratios and oven programming temperature was changed and suitable split ratio and oven programming temperature was selected based on analyte boiling point and theoretical plates. Under these conditions, the analyte peaks were well defined and free from tailing. Considering the whole body of the data obtained from this extensive study, the set of conditions indicated earlier in this article was selected for further validation. Typical chromatogram of olanzapine pamoate (sample) has been shown in Figure 2.

System suitability: The system suitability tests were carried out on freshly prepared working stock solutions of olanzapine pamoate. Parameters that were studied to evaluate the suitability of the system were discussed and represented in Table 3 and 4.

Table 1: Chromatographic conditions

Column	HP-5 (5% Diphenyl and 95% dimethyl siloxane)
Carrier gas	Helium
Carrier gas flow	2.0 psi
Split ratio	10:1
Injector temperature	140^0 C
Detector	Flame ionization detector (FID)
Detector temperature	250^0 C
Oven temperature	40^0 C hold for 6 min and raise the 220^0 C at the rate 10^0C hold for 2 min
Run time	21.33 min
Diluent	N-Dimethyl acetamide (DMA)

Table 2: Head space conditions

Valve oven temperature	100 ^{0}C
Sample temperature	90 ^{0}C
Transfer line temperature	100 ^{0}C
Vial equilibration time	20.00 min
Mixing time	5.00 min
Mixer Stabilize time	0.50 min
Pressure time	2.0 min
Loop fill pressure	5PSIG
Loop fill time	2.00 min
Loop equilibration time	0.20 min
Injection time	1.0 min
GC cycle time	22.0 min

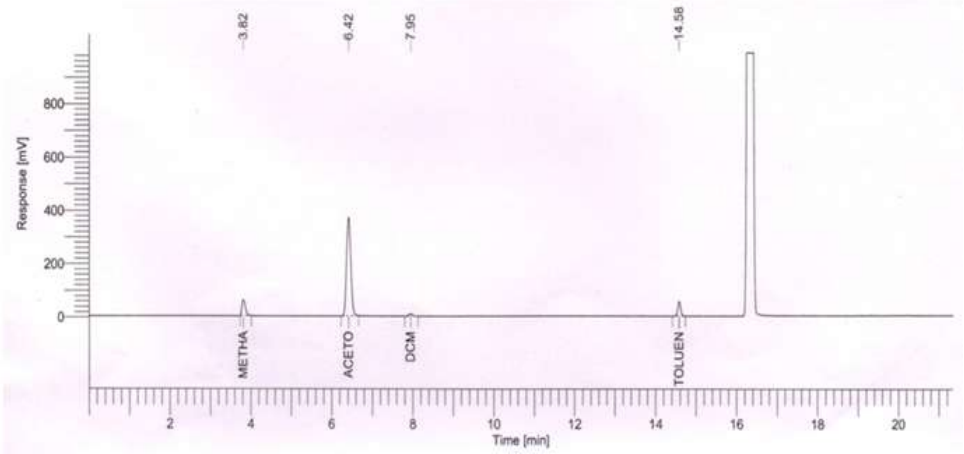

Figure 2: Olanzapine pamoate chromatogram (sample)

Table 3: System suitability

Residual solvents	Average of standards	Standard deviation	% RSD
Methanol	370003.88	2034.70	0.55
Acetone	2680378.91	13873.85	0.52
Dichloromethane	57454.87	381.87	0.66
Toluene	267926.14	1444.54	0.54

Table 4: System suitability parameters

Parameters	Methanol	Acetone	Dichloromethane	Toluene
Retention time	3.816	6.417	7.945	14.581
Resolution	ND	14.404	8.372	44.462
Tailing factor	1.482	1.079	1.049	1.007
Theoretical plates	8587.05	175054.63	35573.77	201291.46
Linearity range	135.6-4520 ppm	40.2-7547 ppm	168.4 -935.7 ppm	38.3-1396 ppm
Correlation coefficient	0.998	0.999	0.997	0.999
% RSD	0.55	0.52	0.66	0.54

Table 5: Linearity

Methanol		Acetone		Dichloromethane		Toluene	
Conc. (ppm)	Peak area	Conc. (ppm)	Peak area	Conc. (ppm)	Peak area	Conc. (ppm)	Peak area
135.62	17042	40.25	18854	168.43	14236	38.34	9521
753.43	108972.3	1257.8	715427	155.95	18130	228.20	65040
1506.85	216580	2515.7	1499540	311.905	36784	456.40	128233
226.28	318048	3773.5	2275961	467.85	55324	684.60	190278
3013.70	415604	5031.4	2978375	623.80	71783	912.80	247168
4520.55	537154	7547.1	3941679	779.75	93837	1141.00	31823s

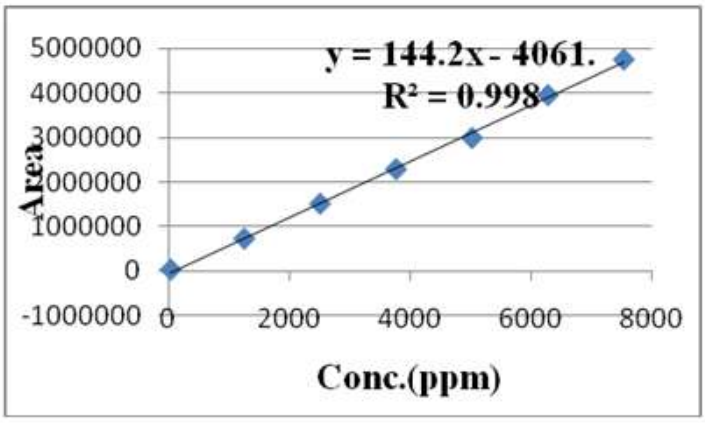

Figure 3: Methanol linearity

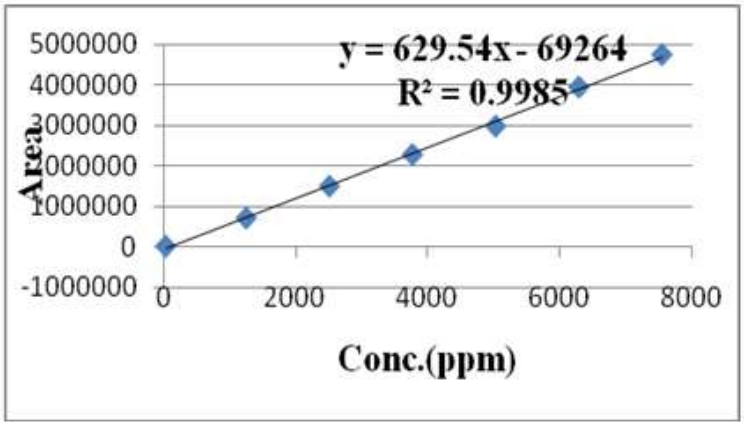

Figure 4: Acetone linearity

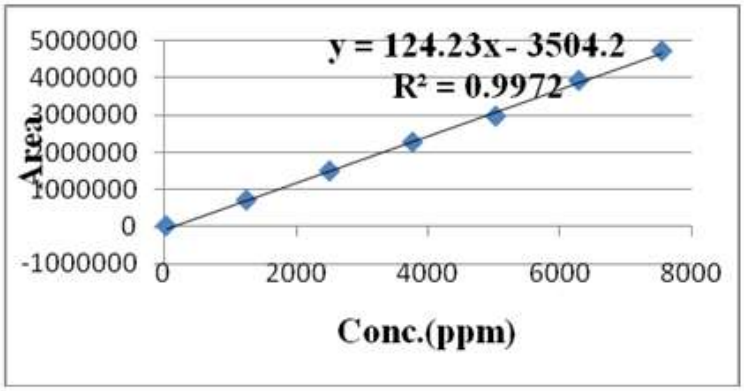

Figure 5: Dichloromethane linearity

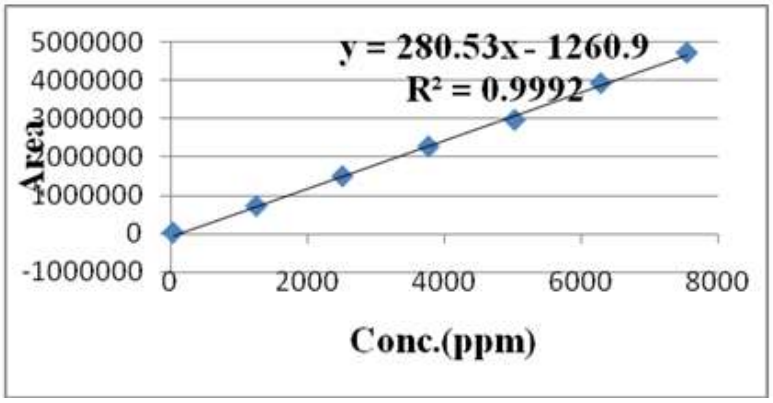

Figure 6: Toluene linearity

Table 6: Accuracy

Levels of recovery	% Recovery			
	Methanol	Acetone	Dichloromethane	Toluene
LOQ level	104.34	103.50	100.34	99.16
100% level	104.24	101.88	106.38	103.96
150%level	104.75	104.31	107.57	105.12

Table 7: Precision

Methanol			Acetone		Dichloromethane		Toluene	
S. No.	RT	Peak area	RT	Peak area	RT	Peak area	RT	Peak area
1	3.816	391677	6.421	2723612.2	7.956	9803.90	14.585	276083
2	3.820	394955	6.418	2723967.6	7.951	61624.8	14.582	276083.1
3	3.812	394144	6.416	2722714.3	7.950	61572.8	14.580	278188.4
4	3.819	395492	6.420	2722485.0	7.949	61572.8	14.584	277018.5
5	3.817	395182	6.414	2720248.7	7.954	61488.2	14.579	277275.4
6	3.813	396399	6.417	2713748.5	7.953	61407.8	14.583	277455.8
Average	3.816	394641	6.417	2721129.3	7.952	61508.1	14.582	278241.2
% RSD	0.49	0.53	0.31	0.38	0.36	0.40	0.43	0.50

Table 8: Ruggedness

Systems	Methanol	Acetone	Dichloromethane	Toluene
System 1	736164	4128944	94706	498010
System 2	742943	4096705	95641	495709

Linearity: The plot of peak areas of each sample against respective concentration of methanol, acetone, dichloromethane and toluene were found to be linear in the range of 135.62 to 4520 ppm, 40.25 to 7547 ppm, 168.43 to 935 and 38.34 to 1369 ppm with correlation coefficient of 0.998, 0.999, 0.997 and 0.999. The regression characteristics, such as slope, intercept, and % RSD were calculated for this method. The results obtained were presented in Table 5. And showing the linearity graphs of methanol, acetone, dichloromethane and toluene Figure 3, 4, 5 and 6.

Accuracy: Recovery of the individual substances LOQ level, 100% level and 150% level of specified concentrations were between 104.34%-104.75% for methanol, 103.50%-104.31% for acetone, 100.34%-107.57% for dichloromethane and 99.16%-105.12% for toluene. which proves the accuracy of the method. Results of the recovery studies are tabulated in Table 6. From the data obtained, it is obvious that the method is remarkably accurate, which ensures that this method produces reliable results.

Precision: Method precision was determined by injecting six replicates of the drug sample solution. The retention times and peak areas of six replicates are recorded. The precision expresses as the % RSD of peak areas and it should not be more than 15%. The low value (<1%) of RSD indicates the repeatability of the method. These data indicate a considerable degree of precision and reproducibility for the method both during one analytical run and between different runs (Table 7).

LOD and LOQ: The Limit of Detection (LOD) was found to be methanol 41.04 ppm, acetone 12.20 ppm, dichloromethane 50.79 ppm and toluene 9.97 ppm. The Limit of Quantification (LOQ) analyzed was 135.45, 40.27, 167.62 and 32.90 ppm for methanol, acetone, dichloromethane and toluene respectively. These values reflect the sensitivity of the method, which is of great importance in most studies and also indicating the method can be used for detection and quantification of analytes in a very wide concentration range.

CONCLUSION

The objective of the present research work is to develop GC-HS method for the determination of residual solvents in olanzapine pamoate. A simple, rapid and highly selective GC-HS method was developed and validated for the quantification of residual solvents present in olanzapine pamoate in bulk drug through an understanding of the synthetic process, nature of solvents and nature of stationary phases of columns. The residual solvents methanol, acetone, dichloromethane and toluene were determined. The method was shown to be specific for olanzapine pamoate and was applied successfully to monitor and control these solvents on a manufacturing level. The method was found to be applicable for the routine analysis of the olanzapine pamoate in pharmaceutical industry.

Consent: It is not applicable

Ethical approval: It is not applicable

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