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Identification of the Organic Volatile Impurities in Telmisartan Active Pharmaceutical Ingredient and Its Pharmaceutical dosage forms by using Head Space Gas Chromatography Technique

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ABSTRACT

Introduction: Residual Solvents or Organic Volatile Impurities are potential risk for quality and stability of drug products as well as human body if intake exceeds the permitted daily exposure. They do not provide any therapeutic benefit and must be removed to the maximum possible level

Objective: The work presented in this paper explains the simple and rapid Head Space Gas Chromatography (HS-GC) technique for the Quantitative estimation of Three Organic Volatile Impurities (OVIs) in Telmisartan Active Pharmaceutical Ingredient (API) and its Pharmaceutical dosage forms.

Methods: Organic solvents such as methanol, acetone, and n-butanol are frequently used in the manufacturing of Telmisartan. The process for quantification of OVIs in Telmisartan API has been done with Head Space Gas Chromatographic method with detector of Flame Ionization and utilizing the Shimadzu GC- 2010 with a capillary column of FID (DB-624, 30 m × 0.53 mm, 3 µ), with a carrier gas nitrogen at 4.0 mL/min flow rate. The experimental parameters like injection temperature, oven temperature, make-up flow, zero air, injection temperature; split ratio, headspace conditions, and the diluent selection have been considered and were optimized.

Results: Retention times are 2.23 min for methanol, 3.04 min for acetone, and 7.20 min for n-butanol respectively. The proposed technique has been statistically validated based on standard International Conference on Harmonization guidelines (ICH). The % Relative Standard Deviation (% RSD) for the system precision of six injections was should be not more than 10.0 %. The percentage recovery was found between 85-115 %. The correlation coefficient (R2) is not less than 0.99. Limit of Detection (LOD) was found as 19 ppm (methanol), 26 ppm (acetone), and 21 ppm (n-butanol). The Limit of Quantification (LOQ) was found as 58 ppm (methanol), 77 ppm (acetone), and 64 ppm for n-butanol. The intermediate precision and method precision were found to be within the limit of acceptance.

Conclusion: From the obtained validation results the proposed technique has been fruitfully applied for quantification of organic volatile impurities in Telmisartan Active Pharmaceutical Ingredient as well as its pharmaceutical dosage forms.

Key Words: Method development, Organic volatile impurities, Telmisartan API, Validation, Chromatography, Quantification

INTRODUCTION

Organic solvents are commonly used in the synthesis of various drugs, excipients and in the formulation of the drug. The presence of these solvents in the final product should not be present as they are highly harmful and they impact the drug substance stability and even impart taste and odour and which would be harmful. In the literature there are various procedures and technologies being reported to eliminate these organic solvents.[1] Some drugs contain even small amounts of these organic solvents after carrying out several operations to remove them and such minute concentrations of these solvents are regarded as residual chemical solvents. The major challenge faced by the pharma industries is to find various analytical activities to detect these residual solvents in the medicinally important compounds and drug products. The use of various active ingredients of medicinal importance and their formulations

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into pharmaceutical drug compounds under good conditions of industrial practice needs necessary quality control of these ingredients used in the synthesis. Hence, before the synthesis of medicinal compounds by any useful process these solvents need to be regulated and the compound purity has to be maintained.[2] The reports of the regulatory guidance shows the required amounts of various organic solvents.[3-5] Chemically the Telmisartan is 2-(4-{[4-methyl-6-(1- benzodiazol-1-yl] methyl} phenyl) benzoic acid. This is an Angiotensin Receptor Blocker and exhibits great affinity towards receptors of angiotensin II type 1, and its duration of action is long, and have higher long life than any other ARB.[6-8] The following scheme shows its synthetic route (Scheme-I).

In the preparation of the Telmisartan, the organic solvents like methanol, acetone, and n-butanol are used. These solvents are grouped with class-3 according to ICH Q3C (R6) guidance.[9] These organic solvents of this class have toxic effects on humans as a result we need to regulate the presence of these solvents in Telmisartan.

The main objective of this work is to develop and validate a fast, simple, and reliable Quantitative identification of these OVIs (methanol, acetone, and n-butanol) in Telmisartan API and its Pharmaceutical dosage forms.[10] The various prominent aspects and novelty of the method described include short elution time, easy sample treatment at ambient temperature with sonication of little amount of powder, good precision, and more recovery rate (>100±15%). The applicability of the method designed and validated as per guidelines of ICH for determination of above said organic solvents in the bulk as well as in the tablet dosage form.

Methanol, acetone, and n-butanol are the generally used chemical solvents during the synthesis of many pharmaceutical drug compounds. These chemicals must be controlled in the finished product to minimum level and based on their toxic effects their limits are fixed according to ICH guidelines for residual solvents.

The level of these organic volatile impurities has to be determined and controlled. There is no literature available to simultaneously determination of methanol, acetone, and n-butanol in this Telmisartan. These structures are followed in (Figure 2**).**

MATERIALS AND METHODS

Chemicals and reagents

Telmisartan API was taken from local well-known laboratory. GC grade Methanol, Acetone, n-Butanol and Di methyl sulfoxide (DMSO) were obtained from Merck -Mumbai. The structures of the compounds are shown in figure 1.

Instrumentation

Chromatography was carried out on Shimadzu chromatography equipped with GC-2010 system with FID (Shimadzu). The samples have been injected by Teledyne tekmar HT3TM Headspace and acquisition and integration of data was done using GC-solution software.

Chromatographic condition

Column: DB-624 (30 m, 0.53 mm ID, 3 µm); Carrier gas: Nitrogen with a rate of flow of 3.6 mL/min; temperature of the Injector: 180 ºC; split ratio: 1:20; Oven program: initial 60 ºC hold for 5 min, increase @ 8 ºC/min up to 140 ºC, hold for 0.0 min, increase @ 30 ºC/min up to 200 ºC, hold for 13 min; temperature of the Detector (FID): 240 ºC; Flow of the air gas: 400 mL/min; flow of the hydrogen, 40 mL/min; overall run time: 30 min.

Condition of the Headspace sampler

Temperature of the Vial: 90 ºC; The needle temperature: 100 ºC; Temperature Transfer line: 115 ºC; Conditioning time of vial: 30 min; Pressurize time of Vial: 3.0 min; Volume of the Injection: 1.0 mL; Inject time: 1.0 min; Cycle time of GC: 45 min.

Preparations

Specifications for Organic volatile impurities

Methanol is 3000 ppm, Acetone is 5000 ppm and n-Butanol is 5000 ppm.

Standard Solution preparation

Weighed and transferred about each 750.35 mg of methanol, 1250.95 mg of acetone and 1250.85 mg of n-butanol along with 70 mL of diluents into 100 mL volumetric flask and it is diluted with the diluents. Further into 50 mL of volumetric flask 5 mL of the above solution is taken and diluted to a volume with the diluent.

Meanwhile with 2 mL of standard solution the standard Headspace vials have been prepared and sealed it aluminum closure. (The standard solution has been prepared as per the sample concentrations of Telmisartan).

Preparation of Telmisartan API sample solution (250 mg/mL)

About 500 mg of Telmisartan pure sample weighed accurately into a 10 mL of the vial and 2.0 mL of diluents is added and sealed it with aluminum closure immediately.

Preparation of Telmisartan Tablet solution

Twenty tablets of Telmisartan were weighed and they were powdered. An amount of powder equivalent to 500 mg Telmisartan was exactly weighed and transferred to a 10 mL of headspace vial, and add 2 mL of the diluent and sealed immediately with aluminum closure.

Calculation:

Organic volatile impurity content was calculated from,

$$PPM(OVI's) = \frac{\text{Impurity area in API}}{\text{Impurity area in Standard solution}} \times \frac{\text{Standard Solution Concentration}}{\text{Sample Solution Concentration}} \times 10^6$$

RESULTS AND DISCUSSION

Development of the Method

The development of the method was done by following the principles of Quality-by-Design along with column selection and diluents. During the development of HS-GC method, we have selected the appropriate system parameters in order to obtain the best separation, time efficiency and sensitivity the three organic volatile impurities mixtures were injected under various types of conditions. Example, at different GC Columns (DB-5, VF-1, DB-624), HS Vial temperature (70-90 ºC), HS Needle temperature (80-110 ºC), HS Transfer line temperature(90-130 ºC), GC-FID temperatures (200-300 ºC), GC Injector temperatures (100-220 ºC), GC gradients (40-200 ºC, at the rate of 5–40 ºC /min), carrier gas flow rates (2.0-5.0 mL/min), different diluents (NMP, DMSO and DMF) etc. The final HS-GC conditions were used for the validation of the method was obtained on the basis of GC parameters. These solvents were individually injected once separately in order to find the specificity of the method and sensitivity of the signal response.

Method validation

The validation of the method was studied by evaluating repeatability, specificity method, limit of quantification (LOQ), method precision, limit of detection (LOD), and accuracy, linearity, ruggedness, and stability if the solution Organic volatile impurities according to the guidelines given by ICH.[11]

Specificity

Table 1 shows the specificity data for three organic volatile impurities Specificity was studied by injecting blank, sample preparation, and Standard solution and showing resolution between all peaks are in both sample solution and Standard Solution and there was no interference from the blank at the retention times of analyte peaks those were obtained from standard solution and resolution of more than 2.0 was obtained between two closely eluting peaks which meet the acceptance criteria. Typical Chromatograms for Specificity is shown in figure 2.

System precision

The system precision has been determined by injecting the six replicate injections of the standard solution respectively and analyzed as per ICH guidelines. The precision of the system is expressed in terms of % RSD. The RSD was found out to be less than 10 %. A typical overlay chromatogram for System precision is shown in figure 3.

Precision Method

Table 2 shows method precision data for three OVI'S**.** The method precision is shown in terms of % RSD. The precision method was demonstrated by separately analyzing of sample six preparations as per the method. RSD was found to be less than 10. Typical overlay chromatogram for Method precision is shown in figure 4.

Linearity (Low level) for LOD and LOQ

Linearity of the technique which was proposed is found out over 1-10 % concentration range for three organic volatile impurities. At each level two replicates have been conducted. The correlation coefficient (R^2), LOD, SLOPE, LOQ, and STEYX have been measured by this data and the results are have been recorded. Tables 3 contain the linearity data for three organic volatile impurities. Correlation graph for three OVI'S is shown in figure 5.

Linearity with LOQ

Linearity has been measured by injection of each organic volatile impurity over 50-150 % range and LOQ level. Two replicates were varied out at every level. By averaging the peak area ratio of these two replicates we obtain calibration curves. The correlation coefficient values (r2) of all organic volatile impurities were observed to be greater than 0.99 and found that in this range the calibration curves are linear.

LOD and LOQ

Table 4 shows the LOD and LOQ data of OVI'S. The **Limit of Detection** and the **Limit of Quantification** for the method proposed have been measured by using calibration standards and calculations were done using respectively by 3.3 σ /s and 10 σ/s formulae, in which 's' indicates slope of the calibration curve and 'σ' indicates the standard deviation of y-intercept. Typical LOD and LOQ Chromatograms for three OVI'S is shown in figure 6.

The System precision at LOQ

This method's system precision has been shown in terms of % RSD. At the LOQ concentration, the system precision at LOQ concentration was denoted with six replicate injections of the standard solution. The percentage RSD (% RSD) is found out to be less than 10 %. A typical overlay chromatogram for LOQ precision is shown in figure 7**.**

Accuracy

With the application of the standard addition technique, the method accuracy has been assured . The % recovery has been measured. Mean percentage recovery of each solvent at 50

%, 100 %, 150 % and LOQ levels must not be less than 85.0 and not more than 115.0. The obtained results in this method were lie within the given limits indicate that this process is accurate. Table 5 shows accuracy data for three OVI'S.

Robustness

The study of robustness was carried by making variations which are small in parameters of this method. Changes in flow of the column (±0.4 mL/min) and the temperature of vial condition (±5°C) have been carried out. The results obtained lie within the criteria of acceptance that indicates this process is robust in the specified range. The values of % RSD are less than 10.

Ruggedness

The evaluation of the method's ruggedness was carried out by doing analysis of the sample in six replicates by various analysts on various days. The obtained results lie within the limit of criteria of acceptance which indicates that the process is rugged in the given range. The values of % RSD are less than 10.0. Table 6 shows the ruggedness data for three OVI'S.

Application of the proposed method (Analysis of Telmisartan tablet)

The method proposed has been evaluated by commercially available Telmisartan tablet for quantification of organic volatile impurities present in this. Results obtained for organic volatile impurities have been compared with specified limits of given guidelines and are recorded. It shows the concentrations of organic volatile impurities in Telmisartan tablet in ppm which was less than the limit specified.

Solution stability

The six organic volatile impurities standard and Telmisartan API sample solutions were prepared in Dimethyl sulfoxide as a diluent. So we have to check whether these standard and sample solutions are stable or not. To prepare the standard and sample solutions for Three-time intervals (Initial hours, after 12 h and after 24 h) on the first day and kept at room temperature. These solutions are injected at Initial hours, after 12 hours and after 24 h. Then, we calculated the percentage of solution stability for the area at each time interval. We got a % of solution stability is 100±5%. Based on these data, six organic volatile impurities standard and Telmisartan API solutions were stable up to 24 h. Table 7 shows the solution stability data for three OVI'S.

CONCLUSION

The HS-GC method which is single, rapid and highly selective one has been developed and validation was carried out for the quantification of three organic volatile impurities present in Telmisartan API with the knowledge of the synthetic process, solvents nature, and kind of column stationary phase. The process that has been developed has to evaluate the reliability and the economical result in the determination of Methanol, Acetone and n-Butanol as organic volatile impurities present in Telmisartan. The results obtained in different validation parameters shows that this process is Specific, Limit of Detection, System Suitability, Limit of Quantification, and Accurate (% of recovery studies) as per the guidelines of ICH. The process was found to be applicable for the routine analysis of the Telmisartan API and its pharmaceutical dosage forms in pharmaceutical industry.

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Conflict of Interest

The authors declare that there is no conflict of interests regarding the publication of this article.

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Author's Contribution: First author has developed methods and validated the proposed methods. Second author guided in entire work.

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Table 1: Specificity data for three organic volatile impurities

S. No.	Name of OVI'S	RT	Theoretical Plates	Tailing Factor	USP Resolution
1	Methanol	2.23	21470	1.26	0.0
2	Acetone	3.04	16795	1.07	10.60
3	n-Butanol	7.20	26764	1.07	30.91

Table 2: Method precision data for Three OVI'S

No. of Preparations	Methanol	Acetone	n-Butanol
1	134806	1019173	152803
2	136633	1017319	154447
3	135757	1017366	158625
4	139067	1018571	158845
5	136855	1018347	155571
6	138632	1016513	158786
ACVG	136958	1017882	156513
STDV	1640	981	2607
% RSD	1.20	0.10	1.67

Table 3: Linearity data for three organic volatile impurities

Con.(%)	Methanol	Acetone	n-Butanol
LOQ	4333	18666	2238
50	88857	532527	76031
75	117446	804395	118465
100	157039	1093739	159495
125	194632	1351038	197873
150	235033	1657340	245581
r2	0.999	1.000	0.999

Table 4: LOD and LOQ data of OVI'S

OVI'S	LOD Con.(ppm)	LOQ Con.(ppm)	LOD Area(n=3)	LOQ Area(n=6)
Methanol	19	58	1691	4333
Acetone	26	77	7235	18666
n-Butanol	21	64	741	2238

Table 5: Accuracy data for Three OVI'S

No of OVI'S	Recovery at 50%	Recovery at 100%	Recovery at 150%	Recovery at LOQ%
Methanol	110.06	97.40	97.71	100.64
Acetone	92.2	96.92	99.09	94.41
n-Butanol	90.27	92.46	94.79	100.51

Table 6: Ruggedness data for Three OVI'S

Different Days and Analysts		%RSD for ethanol	%RSD for Acetone	%RSD for n-Butanol
Day-1	Analyst-1	1.15	0.6	1.69
	Analyst-2	1.26	0.03	1.28
	Analyst-1 & 2	1.21	0.6	1.47
Day-2	Analyst-1	2.22	0.07	3.33
	Analyst-2	1.31	2.12	2.57
	Analyst-1 & 2	2.89	1.48	3.44
Analyst-1	Day-1&2	1.95	0.64	1.47
Analyst-2	Day-1&2	3.87	1.47	3.44

Table 7: Solution stability data for Three OVI'S

Methanol	% Solution stability for Standard	% Solution stability for API
Initial hours	Not applicable	Not applicable
After 12 h	98.91	Not detected
After 24 h	97.92	Not detected
Acetone	% Solution stability for Standard	% Solution stability for API
Initial hours	Not applicable	Not applicable
After 12 h	100.02	97.18
After 24 h	98.43	96.55
n-Butanol	% Solution stability for Standard	% Solution stability for API
Initial hours	Not applicable	Not applicable
After 12 h	98.17	Not detected
After 24 h	97.25	Not detected

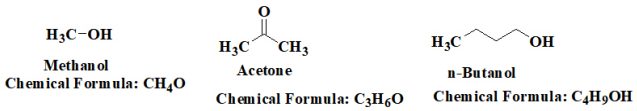

Figure 1: Chemical structure of Organic volatile impurities.

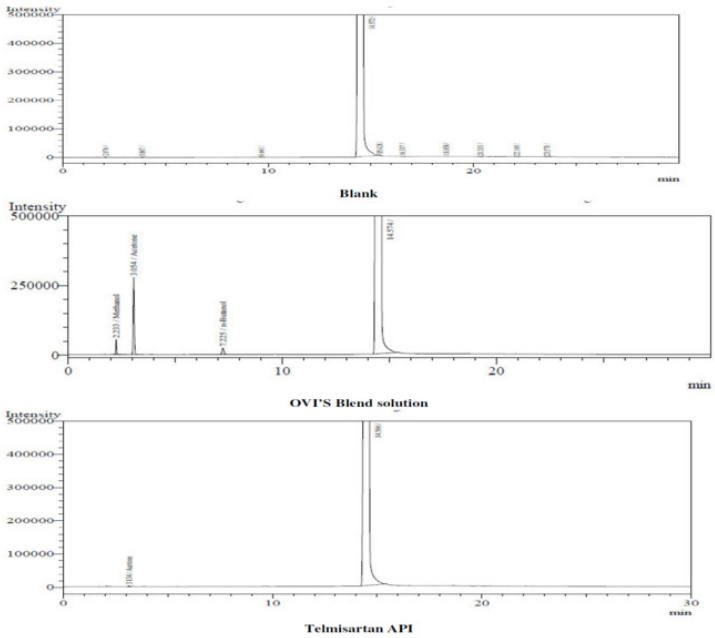

Figure 2: Typical Chromatograms for Specificity.

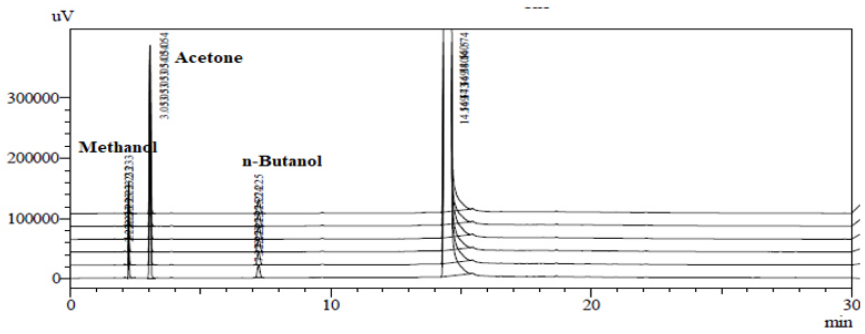

Figure 3: Typical overlay chromatogram for System precision.

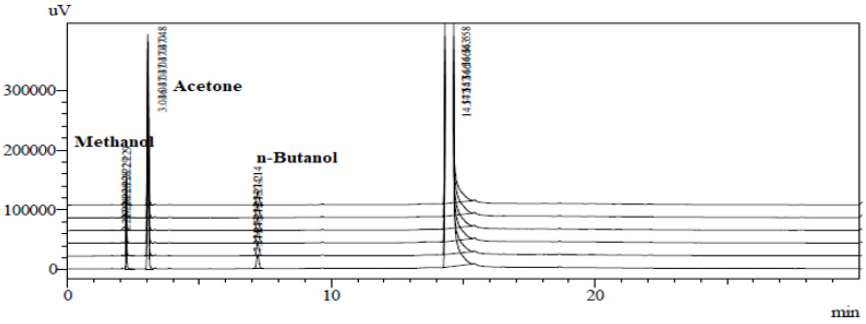

Figure 4: Typical overlay chromatogram for Method precision.

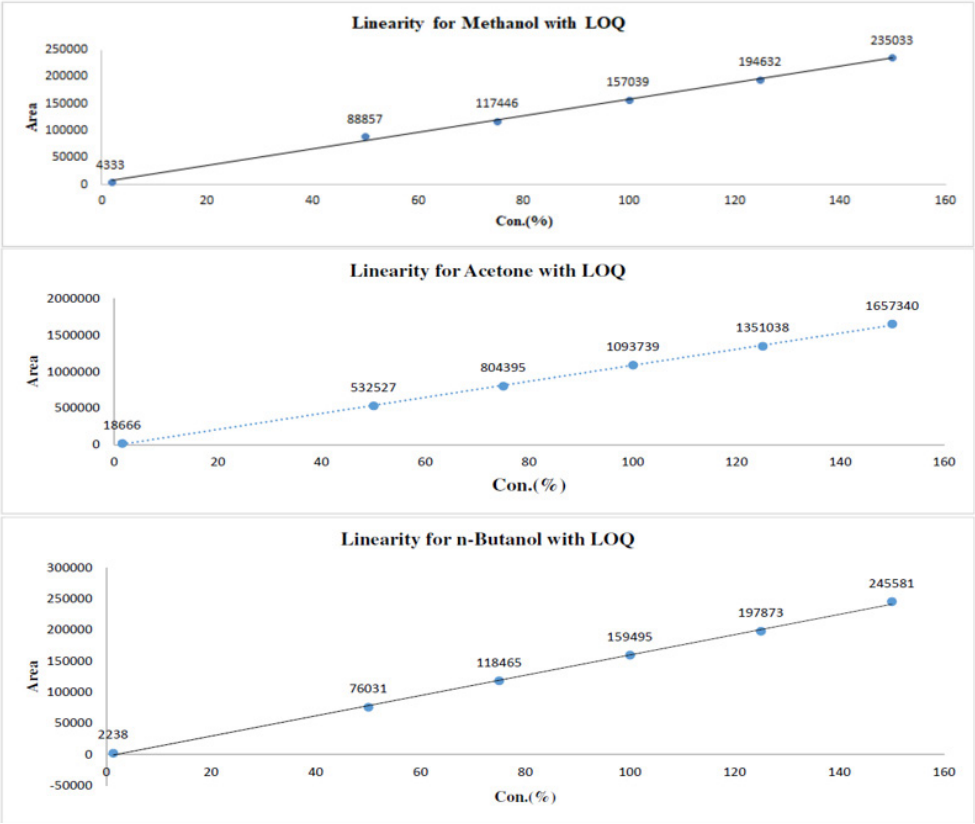

Figure 5: Correlation graph for three OVI'S.

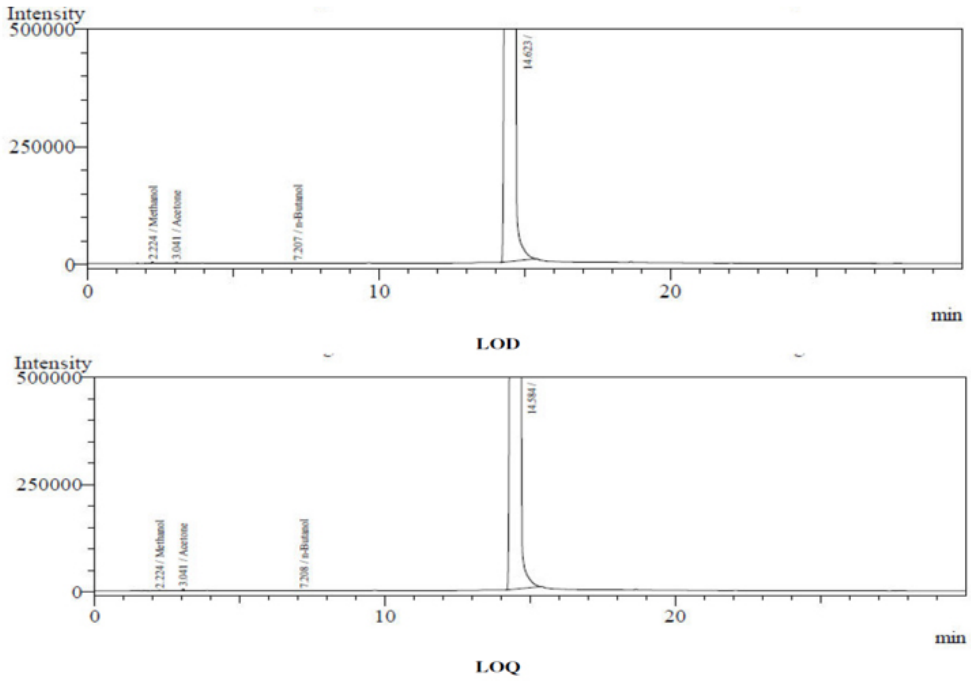

Figure 6: Typical LOD and LOQ Chromatograms for three OVI'S.

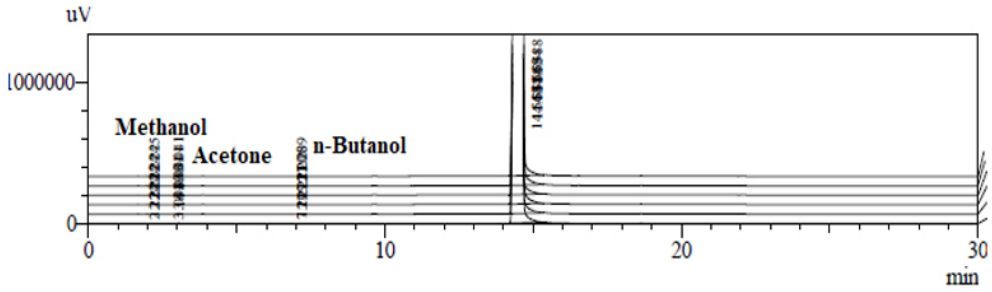

Figure 7: Typical overlay chromatogram for LOQ precision.