Journal for Research in Applied Sciences and Biotechnology

www.jrasb.com

ISSN: 2583-4053

Volume-1 Issue-3 || August 2022 || PP. 186-194

https://doi.org/10.55544/jrasb.1.3.24

Method Development and Validation for Quantification of Residual Solvents in Atorvastatin Calcium Drug Substance by GC-HS Using Fid Detector

Dr. Rahul Kumar[1], Hari Darshan Singh[2], Harendra Singh[3], Rahul Dev[4] and Dr. Anil Tyagi[5]

[1]Mankind Research Centre, IMT Manesar, Gurugram (Haryana), INDIA.
[2]Mankind Research Centre, IMT Manesar, Gurugram (Haryana), INDIA.
[3]Mankind Research Centre, IMT Manesar, Gurugram (Haryana), INDIA.
[4]Mankind Research Centre, IMT Manesar, Gurugram (Haryana), INDIA.
[5]Mankind Research Centre, IMT Manesar, Gurugram (Haryana), INDIA.

[1,2]Corresponding Author: r.kumar31284@gmail.com and haridarshannara@gmail.com

www.jrasb.com || Vol. 1 No. 3 (2022): August Issue

Received: 14-07-2022	**Revised:** 04-08-2022	**Accepted:** 14-08-2022

ABSTRACT

A proficient GC-HS method was developed for quantification of THIRTEEN residual solvents in Atorvastatin Calcium drugs substance with flame ionization detector (FID) using column Rtx-624, (60m length X 0.25mm diameter) 1.4µm film thickness, Part No.: 10969, Make: Restek. Nitrogen is used as Carrier gas with Linear velocity of 27.7cm/se on Shimadzu /GC-2010 Plus/HS-20 instrument. The proposed method was validated for System suitability, Specificity, Linearity, LOD and LOQ determination, Recovery, Precision, Range and Robustness. All the parameters were found within the acceptable limits. Linearity of all thirteen residual solvents are in the range of LOQ to 150%. The established methodology was commercially useful, specific, accurate, precise and suitable for the analysis of Residual solvents in Atorvastatin Calcium drug substance.

Keywords- Gas Chromatography with Head space (GC-HS), Guideline for Residual Solvents Q3C(R8) and Method Validation, Atorvastatin Calcium drug substance.

I. INTRODUCTION

Atorvastatin is a lipid-lowering medication. It works by blocking an enzyme (HMG-CoA-reductase) that is required in the body to make cholesterol. It thus lowers "bad" cholesterol (LDL) and triglycerides, raising the level of "good" cholesterol (HDL). Atorvastatin is used along with a proper diet to help lower "bad" cholesterol and fats (such as LDL, triglycerides) and raise "good" cholesterol (HDL) in the blood. It belongs to a group of drugs known as "statins." It works by reducing the amount of cholesterol made by the liver. Lowering "bad" cholesterol and triglycerides and raising "good" cholesterol decreases the risk of heart disease and helps prevent strokes and heart attacks.

Methanol, Acetone, Ethyl acetate, Isopropanol, Methyl Acetate, Methyl tert butyl ether, Cyclohexane, tert-butanol, 2,2-Dimethoxy propane, Methylene dichloride, t-Butyl acetate, Ethanol, Tetrahydrofuran are organic solvents that may be used in the synthesis or purification of Atorvastatin key starting material, either of their intermediates or final API. Some of these solvents are falls under Class 2 and remaining are under Class 3 solvent list of Guideline for Residual Solvents Q3C(R8), so their limits are decided as per the ICH Guideline for Residual Solvents Q3C(R8). Further these organic solvents cannot be removed completely during the synthesis and even purification. Thus, monitoring of these residual organic solvent impurities in the drug substance is mandatory according to regulatory requirements to ensure human safety.

Generally, in the pharmacopoeias like USP, BP, EP, IP etc. monographs, specific methods for residual solvents have not reported for drug substance and drug

Journal for Research in Applied Sciences and Biotechnology

www.jrasb.com

ISSN: 2583-4053

Volume-1 Issue-3 || August 2022 || PP. 186-194

https://doi.org/10.55544/jrasb.1.3.24

products. To determine and quantitate at such lower level Residual solvents in Atorvastatin Calcium drug substance, highly sensitive, selective and accurate analytical methods is required. A rugged GC-HS method has been developed for Residual solvents in Atorvastatin Calcium drug substance. The objective of this work was to develop a simple and rapid GC-HS method which would be accurate and robust. The method was validated according to ICH guidelines.

Residual solvents name, limits and their Class are mentioned below:

Sr. No.	Name of standard	Limit (ppm)	Class
1	Methanol	NMT 3000	Class 2
2	Acetone	NMT 5000	Class 3
3	Ethyl acetate	NMT 5000	Class 3
4	Isopropanol	NMT 5000	Class 3
5	Methyl Acetate	NMT 5000	Class 3
6	Methyl tert butyl ether	NMT 5000	NA
7	Cyclohexane	NMT 3880	Class 2
8	tert-butanol	NMT 1000	Class 3
9	2,2-Dimethoxy propane	NMT 1000	NA
10	Methylene dichloride	NMT 600	Class 2
11	t-Butyl acetate	NMT 100	Class 3
12	Ethanol	NMT 5000	Class 3
13	Tetrahydrofuran	NMT 720	Class 2

II. METHODOLOGY DEVELELOPED AND MATERIALS USED

Chemicals and Reagents

Name of Material	Batch No.	Potency/Purity
Methanol	WSS19002	99.90%
Acetone	WSS18051	99.96%
Ethyl acetate	WSS19017	99.93%
Isopropanol	WSS18049	99.96%
Methyl acetate	WSS19016	99.80%
Methyl tert butyl ether	WSS18042	99.93%
Cyclohexane	WSS19013	99.92%
Tert-Butanol	WSS18034	99.90%
2,2-Dimethoxypropane	WSS19012	97.80%
Methylene dichloride	WSS18009	100.00%
Tert- butyl acetate	WSS19014	99.50%
Ethanol	WSS19003	99.90%
Tetrahydrofuran	WSS18024	99.90%

III. INSTRUMENTATION

Gas chromatography, model no:2010 with head space, Model no.: HS-20 Make: Shimadzu was utilized for this work.

Chromatographic conditions:

The column Rtx-624, (60m length X 0.25mm diameter) 1.4µm film thickness, Part No.: 10969, Make: Restek, Column oven temperature; Initial temperature (40 ºC) for 5 min; hold for 10.0 minutes increased to 70 ºC @ 3 ºC/min, hold for 0 min; then increased to 220 ºC @ 25 ºC/min, hold for 9 min; detector temperature: 300 ºC; Carrier gas: Nitrogen employed as a carrier gas with linear velocity 27.7cm/sec. Make-up gas for FID: nitrogen gas with 40 mL/min flow rate was used; Fuel gases: Used hydrogen gas and zero air with flow rate of 40 and 400 mL/min. correspondingly. Split ratio: 1:10. Total run time of chromatography: 35 min.

Head space conditions:

Oven temperature: 80 ºC; Transfer line temperature: 100 ºC; Loop temperature: 90 ºC; Vial equilibration duration: 30 min; Vial pressurization duration: 2.0 min; Loop equilibration time: 0.05 duration; Loop fill time: 0.5 min; Inject duration: 0.5 min; Vial pressure: 20 psi.

Preparation of blank, standard and sample solution:

The diluent used was N, N- Dimethylacetamide same was used as Blank solution. Residual solvents standard solution was prepared by using Residual solvents reference standards to attain respective concentration of Methanol is 3000ppm, Ethanol is 5000 ppm, Acetone is 5000ppm, Isopropanol is 5000ppm, Methyl acetate is 5000ppm, Methylene dichloride is 600ppm, tert-butanol is 1000ppm, Methyl tert butyl ether is 5000ppm, Ethyl acetate is 5000ppm, Tetrahydrofuran is 720ppm, Cyclohexane is 3880ppm, 2,2-Dimethoxy propane is 1000ppm and t-butyl acetate is 100 ppm, for a sample concentration of 50mg per mL. Transfer 2.0 mL of standard solution into 20 mL headspace vial. Close the vial with a rubber septum and seal with an aluminium crimp cap. For sample preparation, weigh accurately about 100.0mg of sample and transfer into 20 mL headspace vial. Add 2.0 mL of diluent. Close the vials with rubber septum and seal with an aluminium crimp cap. The concentration of this solution is 50 mg per mL

Acceptance criteria for System suitability:

%RSD: The % relative standard deviation of six replicate injections of standard solution for each solvent should not be more than 10%.

Calculate the residual solvents in the sample solution using the following equation:

$$\text{Conc. in ppm} = \frac{(AT-AB)}{(AS-AB)} \times \frac{WS}{DS} \times \frac{DT}{WT} \times P \times 10000$$

Where,

ISSN: 2583-4053

Volume-1 Issue-3 || August 2022 || PP. 186-194

https://doi.org/10.55544/jrasb.1.3.24

AB = Average peak area of Respective Analyte in the chromatogram of blank.
AT = Peak area of Respective Analyte in the chromatogram of the sample solution.
AS = Average peak area of Respective Analyte standard in the chromatogram of standard solution.
WS = Weight of Respective Analyte in standard.
WT = Weight of sample solution.
DS = Dilution factor of standard solution.
DT = Dilution factor of sample solution.
P = Purity of Respective working standard.

Similarly calculate the content of the other residual solvent.

Report the average result of two sample preparations.

IV. VALIDATION RESULTS AND DISCUSSION

Specificity:

The specificity is defined as the ability to assess unequivocally the analyte in the presence of components that may be expected to be present such as residual, degradation product and matrix components. In HPLC method, it is assured/proved by complete separation of peak of analyte from other peaks that are of other impurities that might be present in sample or blank.

Inject the Blank (as Diluent) and spiked solution. Check the interference at the retention time of analyte. There should not be any interference in blank (as Diluent) and spiked sample at the retention time of analyte. If any peak is present at the retention time of analyte its response should not be more than 20% of the response at the quantification limit (LOQ).

There is no interference observed between the responses of blank (as diluent) and spiked solution at RT of Residual solvents. Hence, the method is very selective and specific for the estimation Residual solvents residues in Atorvastatin Calcium.

GC-HS Chromatograms of study

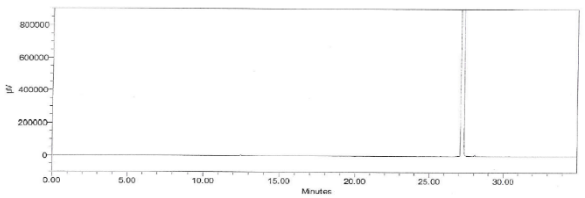

Fig No. 1: Blank Chromatogram

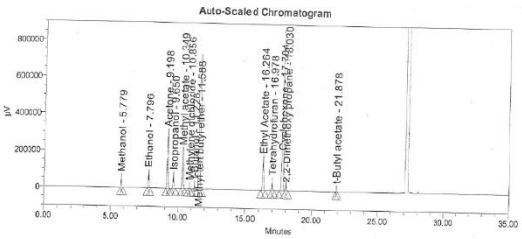

Fig No 2.: Spiked sample Chromatogram

Table 1: Specificity Verification: Interference study

Name of Solvent	Blank	Spiked Solution
Methanol	ND	5.8
Acetone	ND	9.2
Ethyl acetate	ND	16.3
Isopropanol	ND	9.7
Methyl acetate	ND	10.4
Methyl tert butyl ether	ND	11.6
Cyclohexane	ND	17.7
Tert-Butanol	ND	11.2
2,2-Dimethoxypropane	ND	18
Methylene dichloride	ND	10.9
Tert- butyl acetate	ND	21.9
Ethanol	ND	7.8
Tetrahydrofuran	ND	17

Linearity:

A linear relationship should be evaluated across the range of the analytical procedure. It may be demonstrated directly on the analyte by dilution of a standard stock solution using the proposed procedure. Linearity should be evaluated by visual inspection of a plot of signals as a function of analyte concentration or content. If there is a linear relationship, test results should be evaluated by appropriate statistical methods by calculation of a regression line. The correlation coefficient, y-intercept, slope of the regression line should be calculated.

The test method linearity was established from, six levels of concentration over the range LOQ to 150% of, ICH limit for each residual solvent impurity. A linear correlation, and regression were determined among the concentrations, and peak area responses of each residual solvent. The correlation coefficient (r) and regression coefficient (R2) values, for both residual solvent impurities found to be higher than, 0.990. The statistical characteristics like slope, y-intercept and, % y-intercept were interpreted and found within the acceptable, limit for both solvent impurities. The results are tabulated in Table-2 to 6.

ISSN: 2583-4053
Volume-1 Issue-3 || August 2022 || PP. 186-194
https://doi.org/10.55544/jrasb.1.3.24

Table 2: Linearity of methanol, Acetone & Ethyl acetate

Linearity Conc. level	Methanol		Acetone		Ethyl acetate	
	Conc. (ppm)	Mean area	Conc. (ppm)	Mean area	Conc. (ppm)	Mean area
LOQ level	22.6	27788	3.8	17946	15	41418
50% level	75.6	94086	127.1	706626	127.1	394403
75% level	113.4	144213	190.6	1090933	190.6	611499
100% level	151.2	197271	254.1	1481919	254.2	837450
125% level	188.9	249396	317.6	1871741	317.7	1061248
150% level	226.7	304370	381.2	2275422	381.2	1293739
Correlation coefficient		1	1		1	
Squared Correlation coefficient		0.999	0.999		0.999	
Slope		1357.535	5995.544		3430.249	
Y-Intercept		-6577.663	-32585.907		-28497.969	
Residual sum of square		39493734	2246813605		941308490	

Table 3: Linearity of isopropanol, methyl acetate & methyl tert butyl ether

Linearity Conc. level	Isopropanol		Methyl acetate		Methyl tert butyl ether	
	Conc. (ppm)	Mean area	Conc. (ppm)	Mean area	Conc. (ppm)	Mean area
LOQ level	15	17986	7.5	24936	3.7	50739
50% level	126.4	163258	128	490503	125.6	2148164
75% level	189.7	251047	192	760502	188.4	3294423
100% level	252.9	345381	256	1036104	251.2	4408459
125% level	316.1	437932	320	1312298	314	5545877
150% level	379.3	533767	384	1600441	376.8	6744676
Correlation coefficient		0.999	1.000		1.000	
Squared Correlation coefficient		0.999	0.999		1.000	
Slope		1420.227	4193.344		17920.785	
Y-Intercept		-11303.67	-29143.313		-63970.252	
Residual sum of square		184181736	1483498942		8437565701	

Table 4: Linearity of cyclohexane, Tert-butanol & 2,2-Dimethoxypropane

Linearity Conc. level	Cyclohexane		Tert-Butanol		2,2-Dimethoxypropane	
	Conc. (ppm)	Mean area	Conc. (ppm)	Mean area	Conc. (ppm)	Mean area
LOQ level	3	62603	15	26141	7.3	29092
50% level	97.3	2520864	25.9	44290	24.9	102551
75% level	145.9	3850927	38.8	67139	37.3	156729
100% level	194.5	5145973	51.7	91450	49.7	213620
125% level	243.1	6467866	64.6	115076	62.1	270522
150% level	291.8	7867161	77.6	139821	74.6	330302
Correlation coefficient		1.000	1.000		1.000	
Squared Correlation coefficient		1.000	1.000		0.999	
Slope		26973.853	1822.511		4479.06	
Y-Intercept		-66525.575	-2452.239		-7166.87	
Residual sum of square		9782802116	3777878		41953027	

ISSN: 2583-4053
Volume-1 Issue-3 || August 2022 || PP. 186-194
https://doi.org/10.55544/jrasb.1.3.24

Table 5: Linearity of methylene dichloride, tert- butyl acetate & Ethanol

Linearity Conc. level	Methylene dichloride		Tert- butyl acetate		Ethanol	
	Conc. (ppm)	Mean area	Conc. (ppm)	Mean area	Conc. (ppm)	Mean area
LOQ level	12.7	10805	2	5504	37.2	46367
50% level	16.9	14371	2.5	6612	126.1	165414
75% level	25.3	21503	3.7	9874	189.1	254751
100% level	33.8	29122	5	13350	252.2	350207
125% level	42.2	36410	6.2	16772	315.2	443808
150% level	50.7	44300	7.5	20128	378.3	541288
Correlation coefficient		1		1		1
Squared Correlation coefficient		1		1		0.999
Slope		879.127		2696.654		1455.417
Y-Intercept		-531.058		-39.922		-14603.194
Residual sum of square		214905		55270		127144834

Table 6: Linearity of tetrahydrofuran

Linearity Conc. level	Tetrahydrofuran	
	Conc. (ppm)	Mean area
LOQ level	5.4	29961
50% level	18.2	103571
75% level	27.4	158447
100% level	36.5	215340
125% level	45.6	272734
150% level	54.7	332893
Correlation coefficient		1
Squared Correlation coefficient		0.999
Slope		6146.495
Y-Intercept		-6897.424
Residual sum of square		40175499

Limit of detection (LOD):

It is the smallest amount or concentration of an analyte that can be estimated with acceptable reliability. The detection limit is determined by the analysis of standard with known concentrations of analyte and by establishing the minimum level at which the analyte can be reliably detected.

Limit of detection (LOD) determination was carried out by visual detection of response at 0.5%,5.0%,10.0%,15.0% and 25.0% concentration of Methanol, Acetone, Ethyl acetate, Isopropanol, Methyl acetate, Methyl tert butyl ether, Cyclohexane, Tert-Butanol, 2,2-Dimethoxypropane, Methylene dichloride, Tert- butyl acetate, Ethanol and Tetrahydrofuran is reliably detected visually was considered as LOD.

The detection limit for Residual solvents in Atorvastatin Calcium is captured In Table 7.

Table 7: LOD

Solvent	LOD Level (ppm)	
	Standard Conc.	w.r.t test
Methanol	7.5	151
Acetone	1.3	25
Ethyl acetate	5	101
Isopropanol	5	101
Methyl acetate	2.5	51

ISSN: 2583-4053
Volume-1 Issue-3 || August 2022 || PP. 186-194
https://doi.org/10.55544/jrasb.1.3.24

Methyl tert butyl ether	1.3	25
Cyclohexane	1	20
Tert-Butanol	5	101
2,2-Dimethoxypropane	2.5	51
Methylene dichloride	4.3	87
Tert- butyl acetate	0.7	13
Ethanol	12.5	249
Tetrahydrofuran	1.9	37

Limit of quantitation (LOQ):

The Quantitation limit is generally determined by the analysis of samples with known concentrations of analyte and by establishing the minimum level at which the analyte can be quantified with acceptable accuracy and precision.

The limit of quantification is determined by establishing the signal to noise ratio. Inject the blank sample and the spiked sample at LOQ level in six replicates and calculate signal to noise ratio and the % RSD at LOQ level.

A signal-to-noise ratio between 10:1 estimating the quantification limit.

The quantification limit for Residual solvents in Atorvastatin Calcium is captured in Table 8.

Table 8: LOQ Precision and s/n Ratio

Solvent	**LOQ Level (ppm)**	
	Standard Conc.	**w.r.t test**
Methanol	22.6	452
Acetone	3.8	76
Ethyl acetate	15.1	302
Isopropanol	15.1	301
Methyl acetate	7.6	152
Methyl tert butyl ether	3.8	75
Cyclohexane	2.9	59
Tert-Butanol	15.1	302
2,2-Dimethoxypropane	7.6	152
Methylene dichloride	13	261
Tert- butyl acetate	2	40
Ethanol	37.4	748
Tetrahydrofuran	5.6	112

Recovery:

Recovery means the percentage of the true concentration of a substance recovered during the analytical procedure.

Recovery assessed using a minimum of 6 determinations over a minimum of 3 concentration levels.

Acceptable limits for a recovery result during validation should be between 50.0 to 150.0 % for LOQ Level and should be between 80.0 to 120.0% for 50%, 100.0% and 150.0% Level.

The percentage of average recovery for Residual solvents in Atorvastatin Calcium captured in Table 9.

Table 9: Recovery results

Solvent	**Result (% Recovery)**			
	LOQ Level	**50% level**	**100% level**	**150% level**
Methanol	100.1	99.2	101.5	101.7
Acetone	93.3	99.1	102.1	102.3

ISSN: 2583-4053
Volume-1 Issue-3 || August 2022 || PP. 186-194
https://doi.org/10.55544/jrasb.1.3.24

Ethyl acetate	104.2	102.6	104.8	104.7
Isopropanol	98.6	100.8	103	103.3
Methyl acetate	95.2	99.6	102.6	102.9
Methyl tert butyl ether	99.3	101.7	103.7	103.3
Cyclohexane	101.1	103.1	104.3	103.7
Tert-Butanol	106.3	103.1	103.9	103.3
2,2-Dimethoxypropane	103	102.3	103.3	102.9
Methylene dichloride	104.7	103.7	103.7	102.7
Tert- butyl acetate	112.5	103.6	103.8	102.4
Ethanol	97.8	99.4	102.1	102.6
Tetrahydrofuran	101.2	100.1	101.3	101

Precision: (Method Precision)

The precision determined under equal conditions with same homogeneous spiked sample (six different sample preparation) as per recommended test method and % RSD of the results obtained shall be calculated.

The repeatability is established by estimating the six replicates of spiked sample and calculates the % RSD of the results obtained.

The %RSD of results for the analysis of spiked sample should not be more than 20%.

The % RSD of all residual solvents of six different sample preparation found <2.0% refer Table-10.

Table 10: Method Precision results

Solvent	**Sample Result (in ppm)**								
	1	**2**	**3**	**4**	**5**	**6**	**Mean**	**SD**	**%RSD**
Methanol	3040	3065	3113	2965	3033	2989	3034	52.9	1.7
Acetone	5185	5240	5324	5070	5188	5106	5186	91.35	1.8
Ethyl acetate	6047	6079	6190	5890	6033	5925	6027	108.4	1.8
Isopropanol	5242	5267	5359	5099	5211	5136	5219	93.73	1.8
Methyl acetate	5161	5212	5298	5042	5161	5079	5159	91.89	1.8
Methyl tert butyl ether	5229	5284	5376	5118	5238	5151	5233	92.79	1.8
Cyclohexane	4190	4232	4306	4103	4198	4128	4193	73.05	1.7
Tert-Butanol	1077	1080	1101	1048	1071	1056	1072	18.5	1.7
2,2-Dimethoxy propane	1052	1058	1079	1024	1049	1029	1048	19.9	1.9
Methylene dichloride	673	677	689	656	669	660	671	11.97	1.8
Tert- butyl acetate	109	109	112	106	109	107	109	1.88	1.7
Ethanol	5152	5184	5267	5012	5127	5051	5132	92.11	1.8
Tetra-hydrofuran	741	747	761	723	741	728	740	13.39	1.8

Precision: (Intermediate Precision)

Intermediate Precision means the susceptibility of an analytical method to changes in experimental conditions which can be expressed as different columns, different analyst and different days.

Intermediate Precision of the method is established by estimating the six replicates of spiked sample by different analysts, on different days and on different columns. Calculate the % RSD of the results obtained.

The %RSD of results for the analysis of spiked sample should not be more than 20%.

The % RSD of six different sample preparation found below 2.0% refer table-11.

ISSN: 2583-4053
Volume-1 Issue-3 || August 2022 || PP. 186-194
https://doi.org/10.55544/jrasb.1.3.24

Table 11: Intermediate Precision results

Solvent	Sample Result (in ppm)								
	1	2	3	4	5	6	Mean	SD	%RSD
Methanol	3050	3128	3045	3063	3020	2964	3045	53.71	1.8
Acetone	5067	5195	5041	5078	5006	4905	5049	94.95	1.9
Ethyl acetate	5909	6060	5883	5928	5842	5727	5892	109.04	1.9
Isopropanol	5101	5230	5102	5134	5060	4950	5096	91.69	1.8
Methyl acetate	5093	5223	5064	5105	5032	4930	5074	96.07	1.9
Methyl tert butyl ether	5104	5231	5056	5102	5037	4931	5077	98.31	1.9
Cyclohexane	4132	4234	4093	4128	4080	3992	4110	79.06	1.9
Tert-Butanol	1005	1030	1005	1014	999	979	1005	17.08	1.7
2,2-Dimethoxy propane	999	1024	994	1000	987	969	995	18.03	1.8
Methylene dichloride	647	661	641	648	637	627	644	11.6	1.8
Tert- butyl acetate	102	106	102	103	102	99	102	2.05	2
Ethanol	5051	5184	5054	5087	5009	4909	5049	90.41	1.8
Tetra-hydrofuran	754	773	750	756	746	731	752	13.9	1.8

Robustness:

The robustness of an analytical procedure is measure of its capacity to remain unaffected by small, but deliberate variations in method parameters and provides an indication of its reliability during normal usage.

The robustness of the GC-HS method is established by estimating minimum six replicates of standard solution. Calculate the accuracy and % RSD of the results.

The Relative Standard Deviation (%RSD) of peak areas of six replicate injections of standard solution for each solvent peak should not be more than 20.0.

The Relative Standard Deviation (%RSD) of peak areas of six replicate injections of standard solution for Residual solvents peak was found below 10.0 with all the robust conditions refer Table – 12.

Table 12: Conditions for Robustness and their observations

Name of Material	Acceptance criteria	Column oven temp. Low (-2°C)	Column oven temp. High (+2°C)	Linear velocity Low (-10%)	Linear velocity Low (+10%)
Methanol	Should not be more than 10.0%.	0.9	0.6	0.9	0.7
Acetone		0.6	0.6	0.8	0.9
Ethyl acetate		0.7	0.6	0.8	0.7
Isopropanol		1.1	0.6	0.9	0.9
Methyl acetate		0.5	0.6	0.8	0.7
Methyl tert butyl ether		0.5	0.5	1.1	0.6
Cyclohexane		0.5	0.5	1	0.9
Tert-Butanol		1.1	0.6	0.8	0.7
2,2-Dimethoxypropane		0.6	0.7	0.9	0.7
Methylene dichloride		0.8	0.9	0.8	0.7
Tert- butyl acetate		0.9	0.6	0.8	0.7
Ethanol		1	0.6	0.9	0.6
Tetrahydrofuran		0.7	0.7	1.1	0.7

ISSN: 2583-4053

Volume-1 Issue-3 || August 2022 || PP. 186-194

https://doi.org/10.55544/jrasb.1.3.24

V. DISCUSSION

The different validation parameters are performed for developed method. Performed for linearity, precision, Accuracy, specificity, LOD LOQ determination and Robustness and results for all these parameters are well within the range.

VI. CONCLUSION

A simple and sensitive method for the quantification of Residual solvents in Atorvastatin Calcium drug substance by using GC-HS with FID detector was developed, validated in accordance to ICH validation guidelines and applied for the analysis of Atorvastatin Calcium samples. The method was validated to ensure the feasibility of the method for its application in routine analysis. The LOQs achieved through this method were very low. The methodology established was specific, robust, accurate, sensitive and linear in the range LOQ to 150% specification limit as per ICH.

REFERENCES

[1] Parris P, Duncan JN, Fleetwood A, Beierschmitt WP. Calculation of a permitted daily exposure value for the solvent 2-methyltetrahydrofuran. Regul Toxicol Pharmacol 2017;87:54-63.

[2] Inoue K, Suzuki H, Yamada T. Comprehensive toxicity evaluation of cyclopentyl methyl ether (CPME) for establishing a permitted daily exposure level. Fundam. Toxicol. Sci. 2019;6:145-65.

[3] European Chemicals Agency (ECHA), 2020. Cyclopentyl methyl ether. CASRN 5614-37-9. URL: https://echa.europa.eu/registration-dossier/-/registered-dossier/26626/7/6/2. (last accessed on 15 November 2020)

[4] ECHA 2020. Tetrahydro-2-methylfuran. URL: https://www.echa.europa.eu/de/web/guest/registration-dossier/-/registered-dossier/13699/7/9/1. (last accessed 5 November 2020)

[5] United States National Toxicology Program (NTP), Toxicology and carcinogenesis studies tert-butyl alcohol (CAS No. 75-65-0), 1995; Number 436; NIH Publication No. 95-3167. URL: https://ntp.niehs.nih.gov/ntp/htdocs/lt_rpts/tr436.pdf. (last accessed 22 December 2020)

[6] European Chemicals Agency (ECHA), 2019. 2-Methylpropan-2-ol. CASRN 75-65-0. URL: https://echa.europa.eu/registration-dossier/-/registered-dossier/14112/1. (Last accessed 22 December 2020)

[7] ICH Q2 (R1) Validation of Analytical Procedures: Definitions and Methodology, Geneva, 2005, in 2005 incorporated in Q2 (R1).

[8] ICH Q3 (R8) Guideline for residual solvents (6 July 2020).

[9] ICH M7 Assessment and Control of DNA Reactive (Mutagenic) Impurities in Pharmaceuticals to limit potential Carcinogenic Risk, Business plan 2010. Position paper 2010.

[10] National Library of Medicine, National Center for Biotechnology information Bookshelf ID: NBK526037PMID: 30252293