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Method Development and Validation of a Gc-Fid Assay for Determination of Residual Ethanol in Fluvastatin

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ABSTRACT
A simple, rapid, precise, sensitive and reproducible GC-FID method has been developed for the quantitative analysis of Fluvastatin in pharmaceutical dosage form. Chromatographic separation of Fluvastatin was achieved on Omega QC1 GC System by using DB-624 500 x 4.6mm, 5µ column. The flow rate was 5ml/min; detection was carried out by absorption at **210nm** using a photodiode array detector at ambient temperature. %Relative standard deviation of peak areas of all measurements always less than **2.0.** The proposed method was validated according to ICH guidelines. The method was found to be simple, economical, suitable, precise, accurate method for quantitative analysis of Fluvastatin.

Keywords: GC-FID, Fluvastatin, Chromatogrphic method

I INTRODUCTION

Chemically Fluvastatin (E,3R,5S)-7-[3-(4-fluorophenyl)-1-propan-2-ylindol-2-yl]-3,5-dihydroxyhept-6-enoic acid.Fluvastatin sodium is a competitive inhibitor of HMG-CoA reductase, the rate limiting enzyme that converts 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) to mevalonate, a precursor of sterols, including cholesterol. The inhibition of cholesterol biosynthesis reduces the cholesterol in hepatic cells, which stimulates the synthesis of LDL receptors and thereby increases the uptake of LDL particles. The end result of these biochemical processes is a reduction of the plasma cholesterol concentration.Fluvastatin is used together with a proper diet to lower high cholesterol and triglycerides (fats) in the blood. This medicine may help prevent medical problems, like atherosclerosis (hardening of the arteries), that are caused by fats clogging the blood vessels.Literature review reveals that for estimation of Fluvastarin individual dosage form and validated with parameters, various analytical methods such as HPLC and GC methods are available. Using eco friendly chemicals procedure was developed in the estimation of these compounds using GC methods and also the development and validation of a simple , precise, fast and specific method for the determination of Fluvastatin in pure form and its pharmaceutical dosage form was considered of interest (1-3).

II EXPERIMENTAL DETAILS

In this paper a successful attempt has been made to develop a simple, accurate for analysis of Fluvastatin by GC-FID.
Wavelength: 210 nm for Fluvastatin.
Column **:** DB-624 500x 4.6 mm x 5µ
Column temperature: Ambient temperature is always preferred as column temperature
Flow rate:5ml/min
Injection Volume:10 µl
Run time : 10 min
Retention time : 3.190 min Fluvastatin

2.1 Analytical method validation(4-10):

The following parameters were considered for the analytical method validation for assay of Fluvastatin in tablet dosage form.

1. System Suitability
2. Specificity / Selectivity,
3. Linearity and range
4. Robustness
5. Precision,

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System suitability: The standard and check standard solutions were prepared as per test method and injected into GC system. The system suitability parameters were evaluated as per the test method and found to be within the limits.

Specificity: Specificity is the ability to asses unequivocally the analytic in the presence of components which may be expected to be present. Typically these include impurities, degrades, matrix, etc.

Blank interference: Blank was prepared and injected as per test method .it was observed that no blank peak was eluting at the retention time of analytic peak.

Linearity: The linearity of an analytical procedure is its ability (within a given range) to obtain test results which are directly proportional to the concentration (amount) of analytic in the sample. A series of Fluvastatin standard solution were prepared in the range of 12.5-75µg/ml test concentration of 40mg tablet and injected into the GC system as per the test method.Linearity of detector response was established by plotting a graph of concentration Vs response of Fluvastatin peak. The detector response was found to be linear from about 12.5-75 µg/ml. The correlation coefficient, squared co- relation coefficient, slope, intercept and residual sum of squares were calculated and squared correlation coefficient was found to be within the acceptable limits.

Range: The range of an analytical procedure is the interval between the upper and lower concentration (amount) of analytic in the sample (including these concentrations) for which it has been demonstrated that the analytical procedure has a suitable level of precision, accuracy and linearity.Based on method precision, linearity and accuracy data it can be concluded that the assay method of Fluvastatin tablet is precise, linear and accurate in the range of 12.5-75 µg/ml of test concentration of 40mg tablet.

Precision: The precision of an analytical procedure express the closeness of agreement (degree of scatter) between a series of measurements obtained from multiple sampling of the same homogeneous sample under the prescribed conditions. Precision may be considered at three levels:

Repeatability
Reproducibility

The precision of an analytical procedure is usually expressed as the variance, standard deviation or co – efficient of variation of a series of measurements.

Method precision: To evaluate the method precision for assay method, six samples from 40 mg tablet were prepared and analyzed as per test method. % assay of each individual preparation, mean % assay and %RSD of six samples were calculated and found to be within the acceptance criteria.

System precision: To evaluate the system precision for assay method, 50ppm of standard solution prepared and injected 6 times and analyzed as per test method. % assay of each individual preparation, mean % assay and %RSD of six standards were calculated and found to be within the acceptance criteria.

Intermediate precision: To evaluate the Intermediate precision for assay method, six samples from 40 mg tablet were prepared and analyzed as per test method. % assay of each individual preparation, mean % assay and %RSD of six samples were calculated and found to be within the acceptance criteria.

Robustness: As part of the Robustness, deliberate change in the Carrier gas, Variation was made to evaluate the impact on the method.On evaluation of the above results, it can be concluded that the variation in Carrier gas affected the method significantly. Hence it indicates that the method is robust even by change the carrier gas.

III RESULTS AND DISCUSSIONS

ANALYTICAL METHOD VALIDATION OF FLUVASTATIN:-

System suitability:

Results for system suitability of Fluvastatin**:**

Table No 1: Results for System Suitability of Fluvastatin

Injection	Peak area		
	1.278	2.226	Ethanol
1	861954	587514	1290154

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2	862103	586369	1277640
3	864278	583477	1259267
4	865314	586091	1271633
5	862695	585832	1268494
6	863374	584130	1262321
Mean	863286	585569	1271585
SD	1313.589	1497.455	11212.334
%RSD	0.15	0.26	0.88

Linearity:

Linearity of detector response for Fluvastatin:

Table No 2: Linearity of Detector Response for Fluvastatin

S.No	Linearity	1.275	2.221	Ethanol
1	**25%**	230311	145134	358861
2	**50%**	439623	290268	679723
3	**75%**	645935	435402	979584
4	**100%**	861247	589536	1295446
5	**125%**	1176558	725670	1629307
6	**150%**	1291870	870804	1893169

Table No 3: Linearity results for Fluvastatin

S.No	Linearity Parameters	Fluvastatin
1.	Linearity range	12.5-75µg/ml
2.	Correlation coefficient	0.99950
3.	Y intercept	25246.06x + 29856.93

Acceptance criteria:

For linearity of test method, the squared co relation coefficient derived from least square fit of the data should not be less than 0.999.

Assay:

Table No 4: - Assay data of Fluvastatin

Assay of Fluvastatin	Peak area		
	1.280	2.256	Ethanol
Assay-1	1728569	5860412	2579412
Assay-2	1733041	5855437	2571580

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Precision:
Method precision data

Table No 5: - Method precision data for Fluvastatin

Injection	Peak area		
	1.263	2.212	Ethanol
1	862154	586594	1288475
2	861420	584822	1265291
3	863695	585479	1252880
4	864027	582961	1270339
5	863232	583865	1283122
6	862964	585181	1258614
Mean	862915	584817	1269787
SD	975.908	1271.183	13843.879
%RSD	0.11	0.22	1.09

Acceptance criteria:
The % assay for each individual preparation should be 98 to 102% of labeled amount of Fluvastatin.
The %RSD for assay of six replicate preparations should not more than 2.0 for Fluvastatin.

Intermediate precision data

Table No 6: - Intermediate precision data for Fluvastatin

Injection	Peak area		
	1.293	**2.266**	**Ethanol**
1	862017	584679	1264210
2	862965	585520	1257874
3	863814	585819	1255203
4	864290	586111	1267891
5	863201	584372	1260227
6	893955	584237	1252368
Mean	868374	585123	1259629
SD	12556.185	795.525	5744.483
%RSD	1.45	0.14	0.46

Acceptance criteria:
The % assay for each individual preparation should be 98 to 102% of labeled amount of Fluvastatin.
The %RSD for assay of six replicate preparations should not more than 2.0 for Fluvastatin.

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Robustness:

Table No 7: - Robustness data of STD

Injection	Peak area		
	1.295	**2.262**	**Ethanol**
1	861651	586165	1270354
2	862422	584242	1251220
3	863305	585411	1257846
Mean	862459	585273	1259807
STD Dev.	827.63	968.93	9716.51
% RSD	0.10	0.17	0.77

Table No 8: - Robustness data of Sample

Sample	Peak area		
	1.276	**2.248**	**Ethanol**
1	861246	583965	1248671
2	862177	584677	1260302
3	863085	585832	1255796
Mean	862169	584825	1254923
STD Dev.	919.52	942.22	5864.44
% RSD	0.11	0.16	0.47

IV CONCLUSION

Development and validation of GC-FID method for the estimation of Residual ethanol in fluvastatin bulk and pharmaceutical dosage forms" with the facilities and the results are incorporated in this paper. In conclusion a validated GC-FID method has been developed for determination of Fluvastatin the bulk and tablet dosage form. The results show that the method was found to be specific, simple, accurate, precise and sensitive. The method was successfully applied for the determination of Ethanol.

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CONFLICT OF INTEREST

The authors declare that no conflict of interest for this research.

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