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Original Research Paper

METHOD DEVELOPMENT AND VALIDATION OF OXCARBAZEPINE BY USING RP-HPLC METHOD

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ABSTRACT

A simple, specific, accurate and isocratic reversed phase HPLC method was developed and validated for the estimation of oxcarbazepine. Method was achieved with an Inertsil C-18 ODS-3V column, (25cm×4.6 mm, 5µm) with mobile phase (A)- 0.1 % NH_4OH in water with glacial acetic acid, (B)- acetonitrile water at the flow rate of 1.0 ml/min and at column temperature 35°C was developed. The detection was carried out using a detector set at a wavelength of 256 nm. The method was validated for accuracy, precision, linearity, specificity, stability of sample and robustness in accordance with ICH guidelines. Thus the above achieved method is suitable for estimation of oxcarbazepine.

Keywords: Oxcarbazepine, Reversed phase HPLC, Method validation.

INTRODUCTION

Oxcarbazepine (10, 11-dihydro-10-oxo-5H-dibenzazepine-5-carboxamide) is a 10-keto analogue of carbamazepine. It is an anticonvulsant and mood stabilizing drug, used primarily in the treatment of epilepsy. It is also used to treat anxiety and mood disorders (Mazza *et al.*, 2007). Oxcarbazepine is structurally a derivative of carbamazepine, adding an extra oxygen atom on the dibenzazepine ring. This difference helps reduce the impact on the liver of metabolizing the drug, and also prevents the serious forms of anaemia occasionally associated with carbamazepine. Aside from this reduction in side effects, it is assumed to have the same mechanism as carbamazepine - sodium channel inhibition, and is generally used to treat the same conditions (Rosa *et al.*, 2009). The pharmacological activity of Oxcarbazepine is primarily exerted through the 10-monohydroxy metabolite (MHD) of Oxcarbazepine. The precise mechanism by which Oxcarbazepine and MHD exert their Anti seizure effect is unknown; however in vitro electrophysiological studies indicate that they produce blockade of voltage-sensitive sodium channels, resulting in the stabilization of hyper excited neural membranes, inhibition of repetitive neuronal firing, and dimunition of propagation of synaptic impulses. These actions are thought to be important in the prevention of seizure spread in the intact brain. In addition, increased potassium conduction and modulation of high-voltage activated calcium channels may contribute to the anticonvulsive effects of the drug. No significant interactions of Oxcarbazepine or MHD with brain neurotransmitter or modulator receptor sites have been demonstrated.

Chromatography is an analytical method that finds wide application for the separation, identification and determination of chemical components in complex mixtures. This technique is based on the separation of components in a mixture (the solute) due to the difference in migration rates of the components through a stationary phase by a gaseous or liquid mobile phase. High-performance liquid chromatography

(HPLC) is a form of liquid chromatography to separate compounds that are dissolved in solution. It is now one of the most powerful tools in analytical chemistry, with the ability to separate, identify, and quantitate the ions or molecules that are present in sample and it can be dissolved in a liquid. Because of the relatively high pressure necessary to perform HPLC a more elaborate experimental setup is required and the ability to identify and quantitate the compounds that are present in any sample.

Analytical methods are required to evaluate the quality of drug substances, intermediates & drug product, and to monitor synthesis or manufacturing process drugs. Different method depending upon the physical, chemical & biological properties of drug need to be developed in order to evaluate their intended quality, performance. Best column, best mobile phase, best detection wavelength, efforts in their selection can make a world of difference while developing HPLC method for routine analysis, determining the ideal combination of these factors assures faster delivery of desired results. The USP and ICH prescribes the following parameters of validation for quantifying an analytical method:

- Accuracy
- Recovery
- Precision
- Specificity
- Linearity
- Stability
- Limit of Detection
- Limit of Quantification
- Ruggedness

MATERIALS AND METHOD

The literature survey displays that there was a lot of scope for method development by HPLC for Related Substances of OXCARBAZEPINE API. Thus, the work was planned as given below

- To check the identity of the drug sample.
- To check the authenticity of drug sample.
- Strategy for method development in HPLC.
- Column selection.
- Mobile phase selection.
- Sample will be chromatographic with HPLC condition, where all compound elute in a reasonable time.
- HPLC method will be optimizing with respect to analysis time.
- Resolution, selectivity and sensitivity.
- Oxcarbazepine preparation. standard and sample
- Preparation of diluent
- Optimization of chromatographic conditions viz selection of Wavelength, Chromatographic method and chromatographic conditions
- mobile phase, pH, stationary phase
- Compilation of all the results.

The method developed was also proposed to be validated using the various validation parameters such as

- Specificity
- Solution Stability
- Linearity and Range
- Precision
  - ➢ System precision
  - ➢ Repeatability
  - ➢ Intermediate precision
- Accuracy
- LOD and LOQ
- Robustness

Method Development

Method development and optimization of chromatographic parameters for determination of related substances of Oxcarbazepine API is mentioned here under

- Chemical structure
  Oxcarbazepine API chemical structure shows that it is a basic in nature. pKa value of Oxcarbazepine API is 10.7.
- Identification
  The IR spectrum of Oxcarbazepine API was recorded by scanning in the IR range of 450-4000 cm^{-1}.
- Column selection
  Nonpolar columns have been taken in order to decrease the run time and increase resolution.
- Detector selection

Since Oxcarbazepine API is a UV active compound. Therefore, UV detector has been chosen for detection.

- Selection of wavelength
  An UV spectrum of the Oxcarbazepine API at a concentration of 10µg/ml in Acetonitrile was recorded by scanning in the UV range of 200-400nm. From the scan 256nm was selected as wavelength for the detection and quantification.
- Mobile phase selection
  In mobile phase preparation following solvent and buffer has been taken:
  - Acetonitrile is used as it is having the UV-cut off 190nm and is commonly used solvent.
  - Different types of buffer solutions are used during method development to obtain an optimized method conditions.

Method Development Trials

Following HPLC method trials have been run to resolve the above-mentioned impurities

Table 1: Methods trials

Trials	1	2
Mobile Phase Used	Comp. A - 0.1% H_3PO_4 Comp. B - ACN:MEOH (3:1) Gradient method	Phosphate buffer : ACN : IPA (50:32:18) Isocratic method
Column	Inertsil C-18 ODS-3V, (25cm×4.6 mm, 5µm)	Inertsil C-18 ODS-3V, (25cm×4.6 mm, 5µm)
Diluent	Water : ACN (1 : 1)	Water : ACN (1 : 1)
Temperature & Wavelength	35°C; 256 nm	25°C; 256 nm
Injection Volume	20µL	20µL
Flow	1.0 mL/min	1.0 mL/min
Run Time	30 min.	40 min.
Trials Observations	• Oxcarbazepine was not stable • Peaks were eluting late i.e. after 10 min.	• Peak purity was not passed. • Impurity D was eluting late • Resolution between peaks was not good.

Table 2: Methods trials

Trials	3	4
Mobile Phase Used	Comp. A - 0.1% NH_4OH in water Comp. B - ACN Gradient method	Comp. A-0.1% NH_4OH in water(pH-5.0 with GAA) Comp. B- ACN Gradient method
Column	Inertsil C-18 ODS-3V, (25cm×4.6 mm, 5µm)	Inertsil C-18 ODS-3V, (25cm×4.6 mm, 5µm)
Diluent	ACN : H_2O; (50 : 50)	CAN
Temperature & Wavelength	35°C; 256 nm	35°C; 256 nm
Injection Volume	20µL	20µL

Flow	1.0 mL/min	1.0 mL/min
Run Time	35 min.	35 min.
Trials Observations	• Solution was not stable in diluents	• Run time is very long

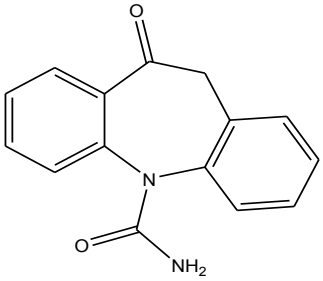

Figure 1: Structure of Oxcarbazepine

RESULT AND DISCUSSION

Identification

Fourier- Transform Infra Red Spectroscopy (FTIR)

The IR spectrum of Oxcarbazepine API presented characteristics signals. The FT-IR spectrum of Oxcarbazepine is represented in fig. 2.

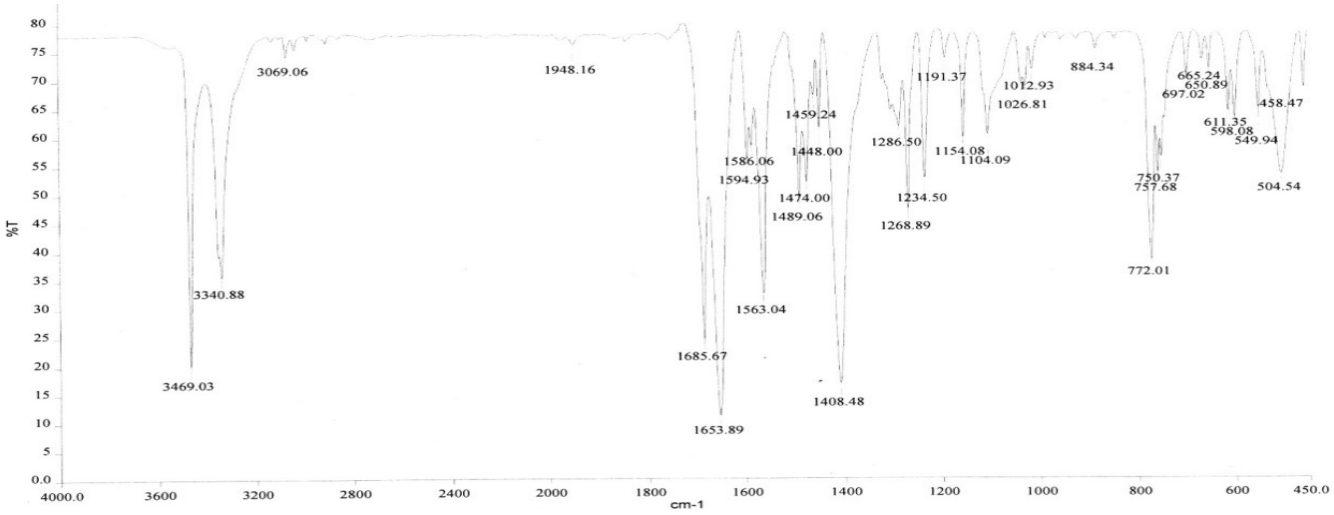

Figure 2: FT-IR spectrum of Oxcarbazepine sample

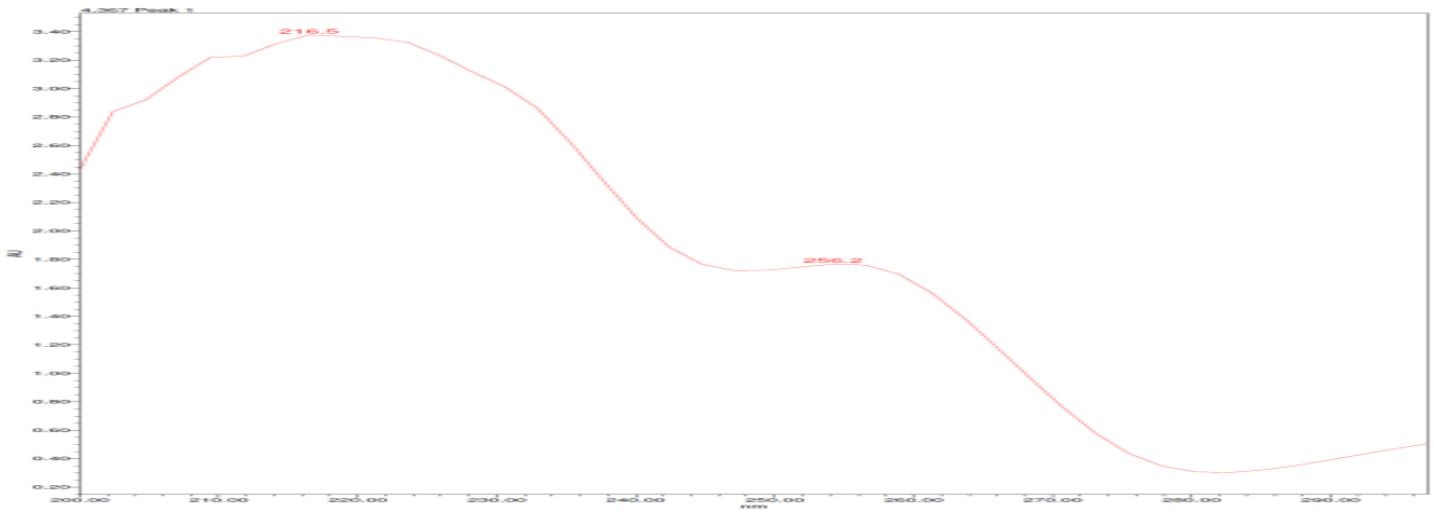

Figure 3: UV Scan of Oxcarbazepine sample

Analytical Method Validation

System suitability

Data from six injections of system suitability solution were utilized for calculating parameters for system suitability. The resolution between Oxcarbazepine and impurity A was more than 3, USP tailing factor was 1.2 i.e. less than 1.5, theoretical plates were 6118 i.e. more than 4000 and the %RSD of the area of Oxcarbazepine was less than 5. It showed that the proposed method is precise. Hence, it can be concluded that the system suitability parameter meets the requirement of method validation.

System suitability parameter	Observation(n=6)	Acceptance criteria
Tailing factor	1.06	NMT 1.5
Resolution between Oxcarbazepine and impurity A	3.96	NLT 3.0
Theoretical plates	6154	NLT 4000
% RSD of 6 injections	0.09	NMT 5.0

Table 3 System suitability showing resolution & area

Conclusion

- The resolution between the Oxcarbazepine and impurity A was observed more than 3.
- The % RSD of area of Oxcarbazepine was within the limit (less than 5) as shown in the table 7.1.
- The USP theoretical plate was observed more than 4000.
- The USP tailing was found within the acceptance limit i.e. less than 1.5

Specificity

Specificity of the method is its ability to measure accurately and specifically the analyte in the presence of impurity, degradation product and related impurity or formulation excipients and ability to separate the analyte in the presence of all the impurity and other expected compound. It is a measure of the degree of interference from such things as other active ingredients, excipients, impurities, and degradation products, ensuring that a peak response is due to a single component only i.e. no co- elutions exist

Interference study

Table 4: Peak purity data

Sample	Purity angle	Purity threshold
Oxcarbazepine(Unspiked sample)	1.153	29.160
Oxcarbazepine(Spiked sample)	1.720	12.127
Impurity A	0.819	0.942
Impurity B	0.930	1.118
Impurity C	0.638	0.932
Impurity D	0.501	0.725

Table 5: RRT & RT of Oxcarbazepine and its impurities

Name	RRT	RT in spiked solution	RT in individual solution
Oxcarbazepine(Spiked sample)	1.000	4.353	4.36
Impurity A	1.198	5.22	5.24
Impurity B	1.355	5.90	5.91
Impurity C	1.919	8.35	8.36
Impurity D	2.914	12.69	12.69

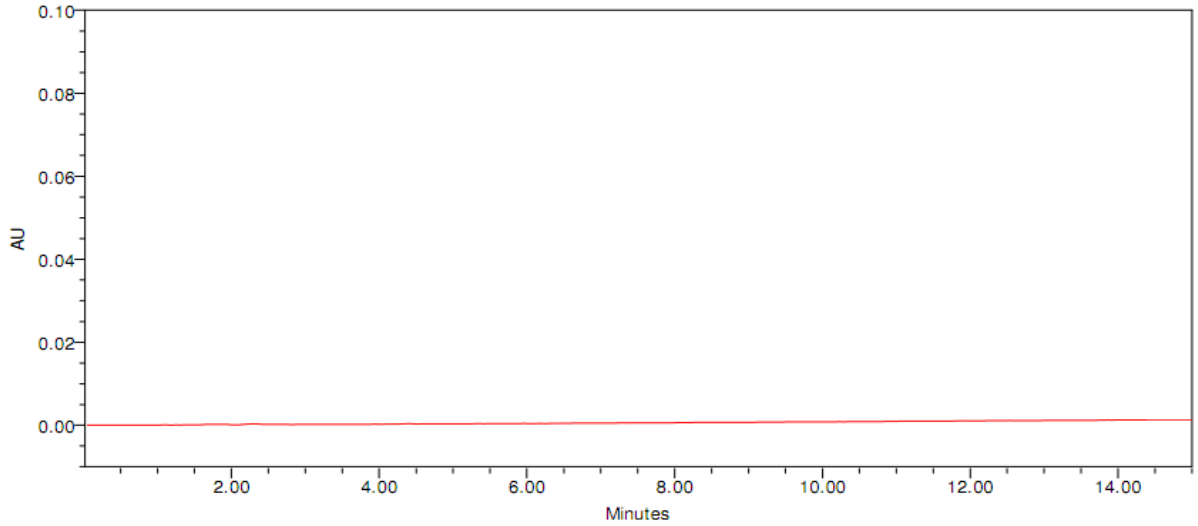

Figure 4: The chromatogram for specificity showing Blank

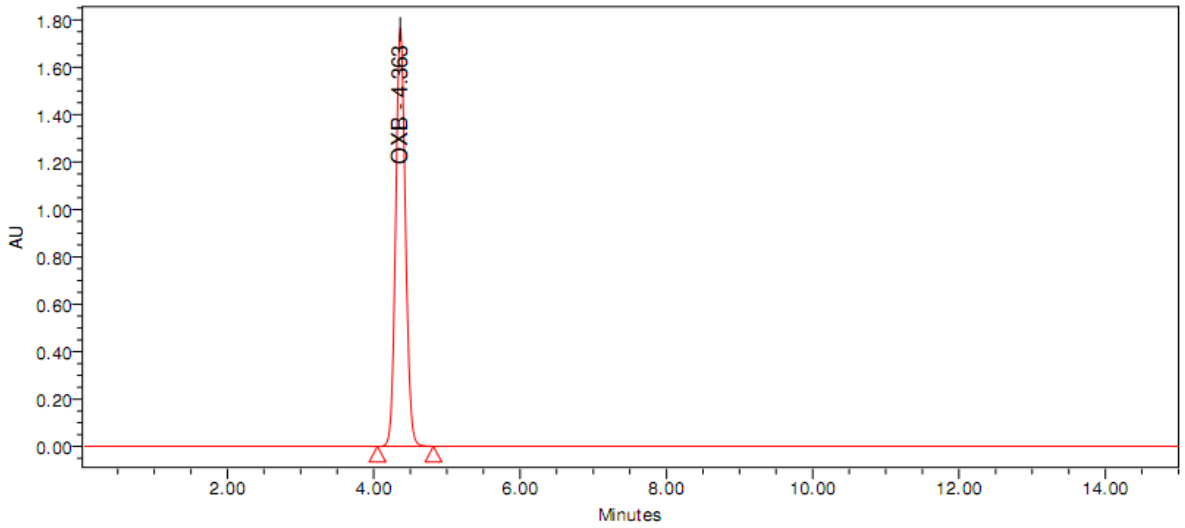

Figure 5: Chromatogram for RT check of Oxcarbazepine

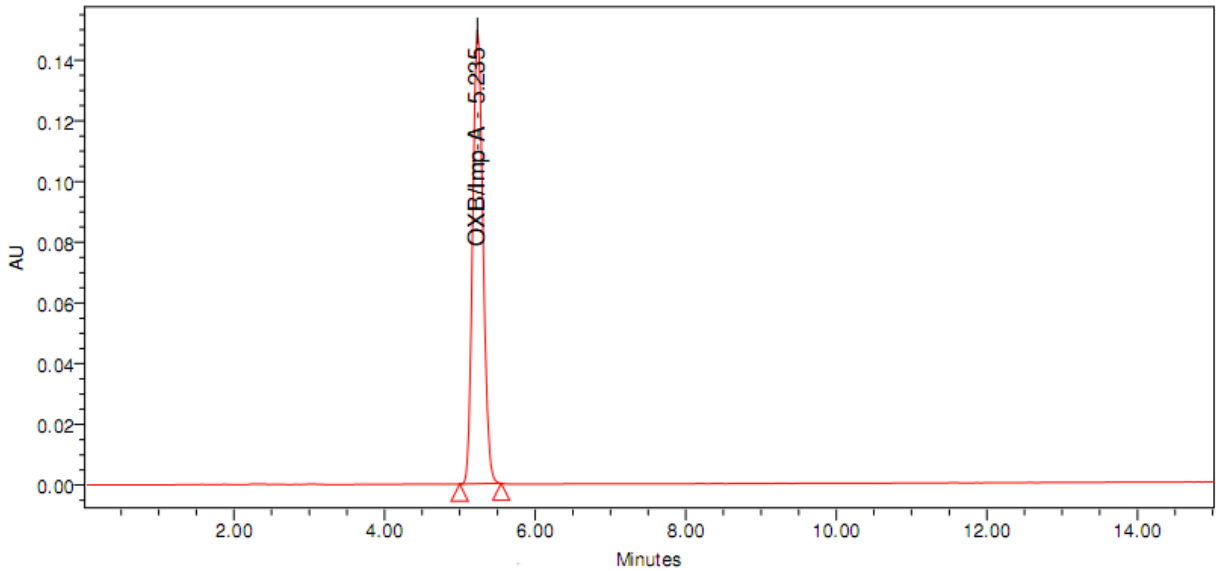

Figure 6: Chromatogram for RT check of impurity A

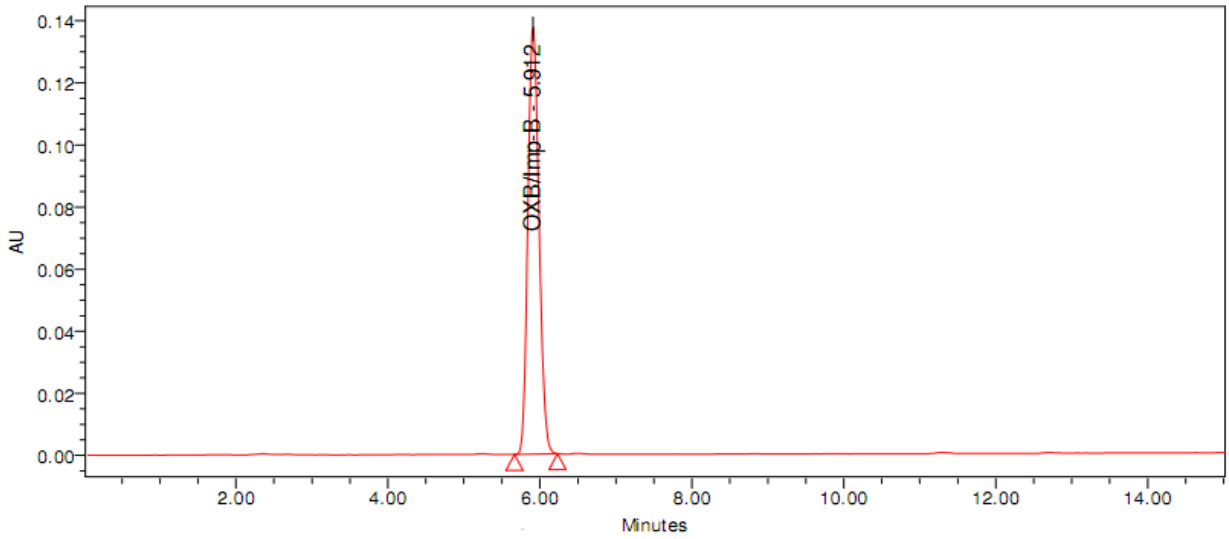

Figure 7: Chromatogram for RT check of impurity B

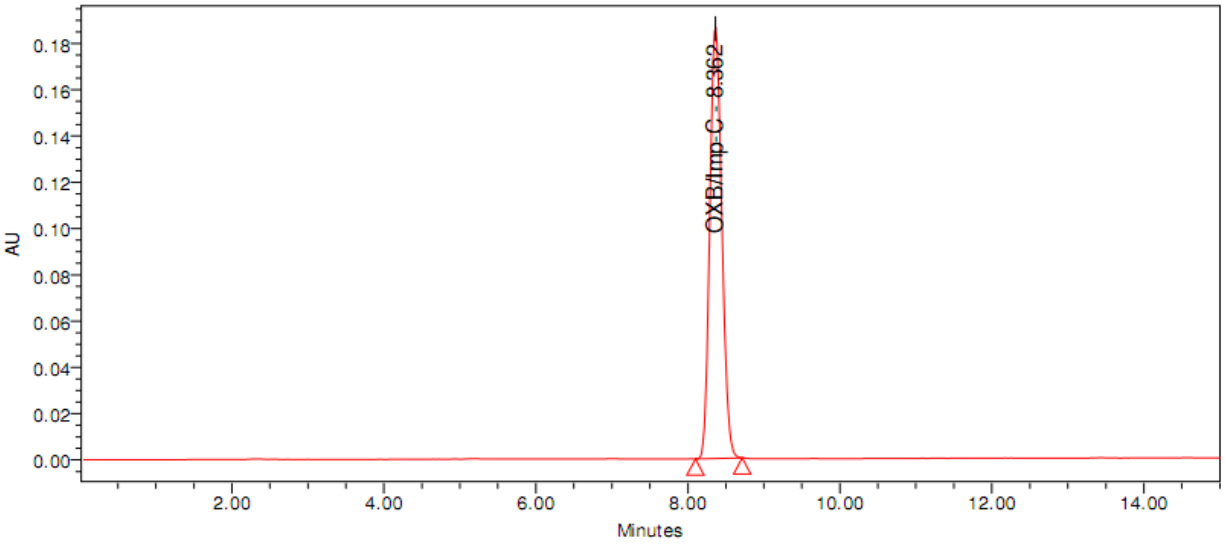

Figure 8: Chromatogram for RT check of impurity C

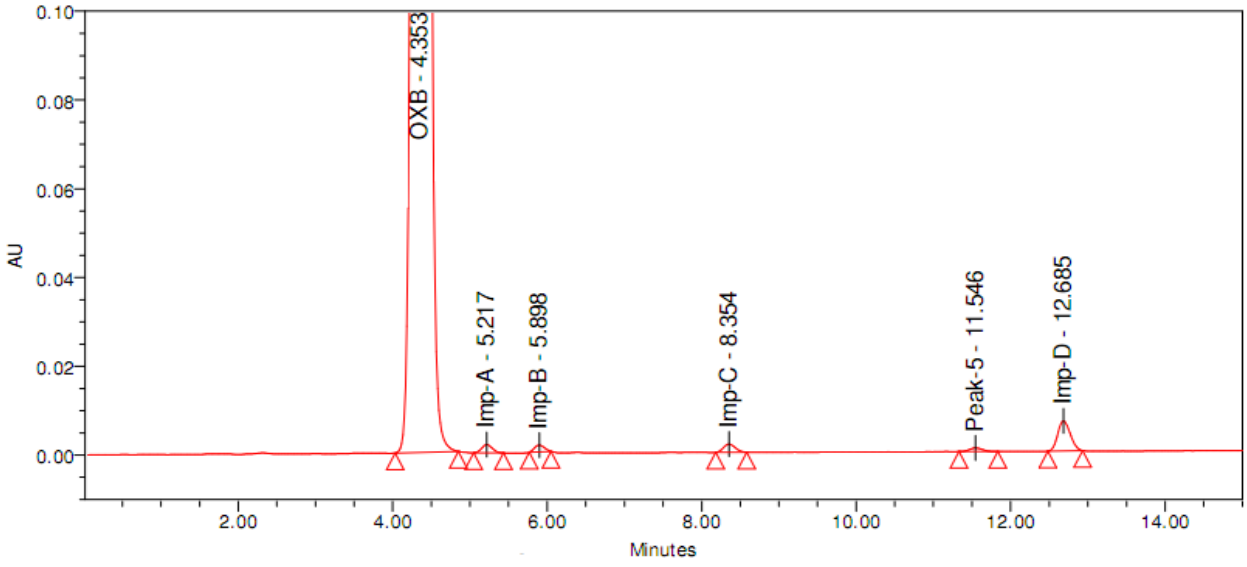

Figure 9: Chromatogram for RT check of impurity D

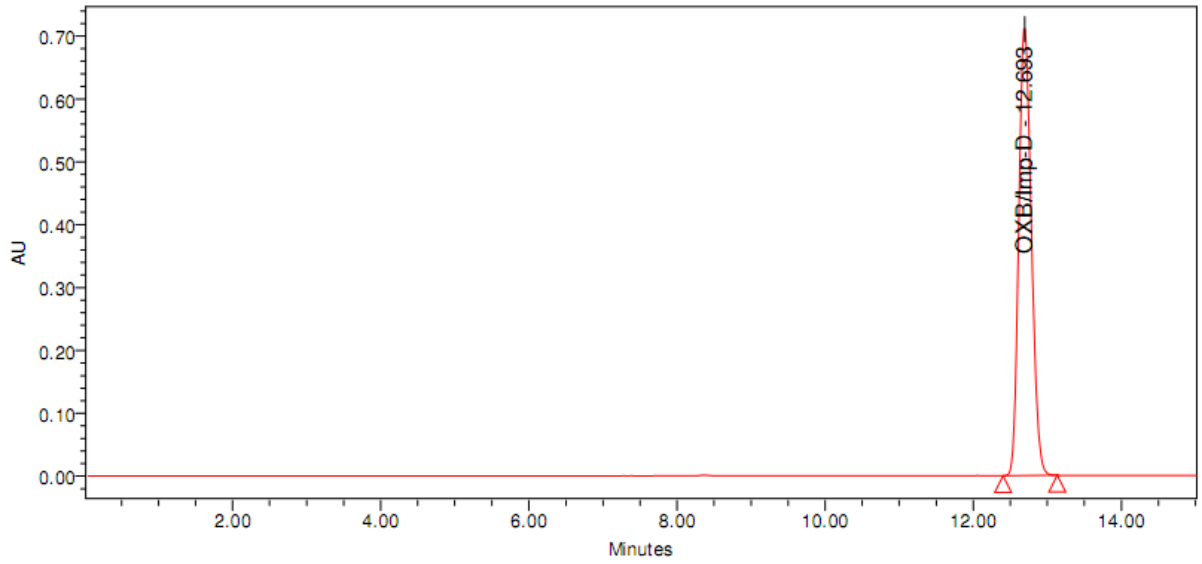

Figure 10: Chromatogram for spiked sample solution

CONCLUSION

No peak was observed in blank chromatogram at the retention time of Oxcarbazepine peak and all known impurities as shown in figure 4.

The peak purity (purity angle should be less than purity threshold) of Oxcarbazepine peak and all known impurities peaks passes as per acceptance limit which indicates that the peaks are homogeneous and there is no interference of all known impurities with Oxcarbazepine peak and with each other.

It was observed from the data tabulated above all known impurities are well separated from the Oxcarbazepine peak and with each other.

Linearity and Range

The linearity of an analytical method is its ability to obtain test results which has a definite mathematical relation to the concentration of analyte. Linearity of the proposed method was carried out over the range of LOQ to 150% of considered target limit for all known impurities. A stock solution containing 2.5 µg/mL of all known impurities was used to prepare the linearity solutions of desired concentration of LOQ, 0.25, 0.375, 0.5, 0.625, 0.75 µg/mL for all known impurities and for Oxcarbazepine stock solution containing 25 µg/mL was used to prepare the linearity solutions of desired concentration of 2.5, 3.75, 5, 6.25, 7.5 µg/ml.

Table 6-10 shows the result for the linearity of the plot of concentration against the peak area. The correlation coefficient "r^2" was found to be "0.999" for all known impurities. The results indicated that the method is linear in the concentration range of LOQ to 0.75 µg/mL for all known impurities i.e. impurity A, impurity B, impurity C, and impurity D.

Table 6: Linearity of Oxcarbazepine

Conc.(µg/ml)	Mean area (n=3)
2.501	91224
3.752	133750
5.003	183945
6.254	224021
7.504	271175
Slope	**179906**
Intercept	**821**
Correlation coefficient	**0.9996**
Response factor	**1.00**

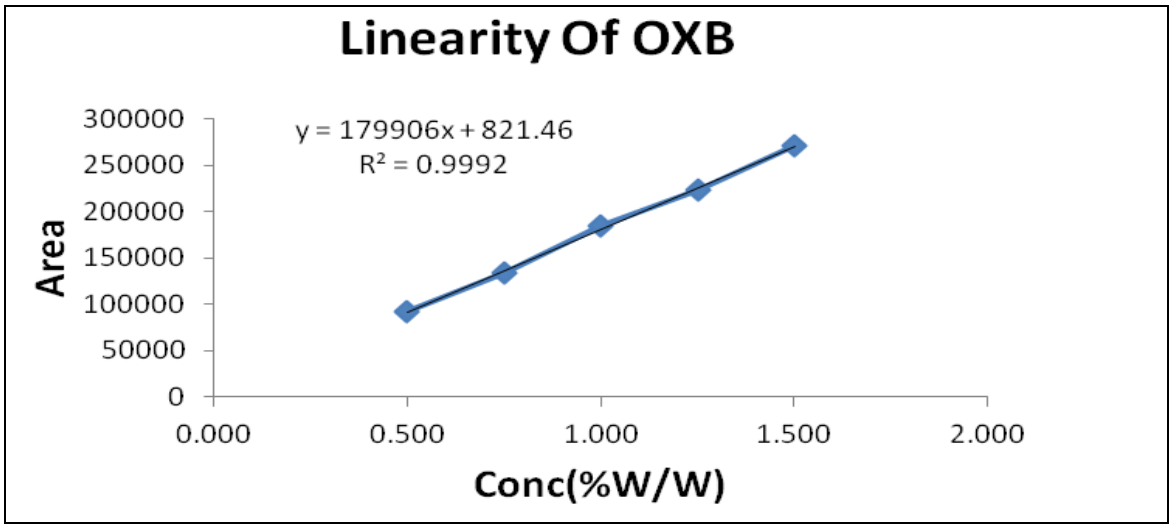

Figure 11: Linearity for Oxcarbazepine

Table 7: Linearity of impurity A

Conc. level	Conc. (µg/ml)	Mean area (n=3)
QL	0.018	554
50%	0.269	8373
75%	0.403	12517
100%	0.538	17401
125%	0.672	21154
150%	0.806	25800
Slope		**160855**
Intercept		**-231**
Correlation coefficient		**0.9997**

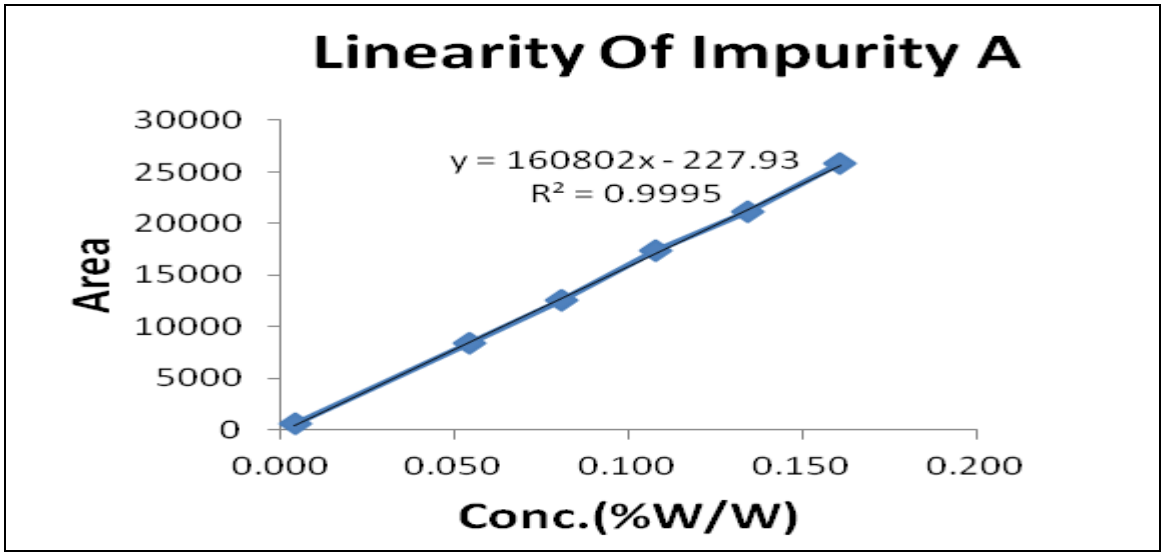

Figure 12: Linearity for impurity A

Table 8: Linearity of impurity B

Conc. level	Conc. (µg/ml)	Mean area (n=3)
QL	0.022	599
50%	0.260	7612
75%	0.391	11371
100%	0.521	15816
125%	0.651	19309
150%	0.781	23501
Slope		**150807**
Intercept		**-136**
Correlation coefficient		**0.9997**

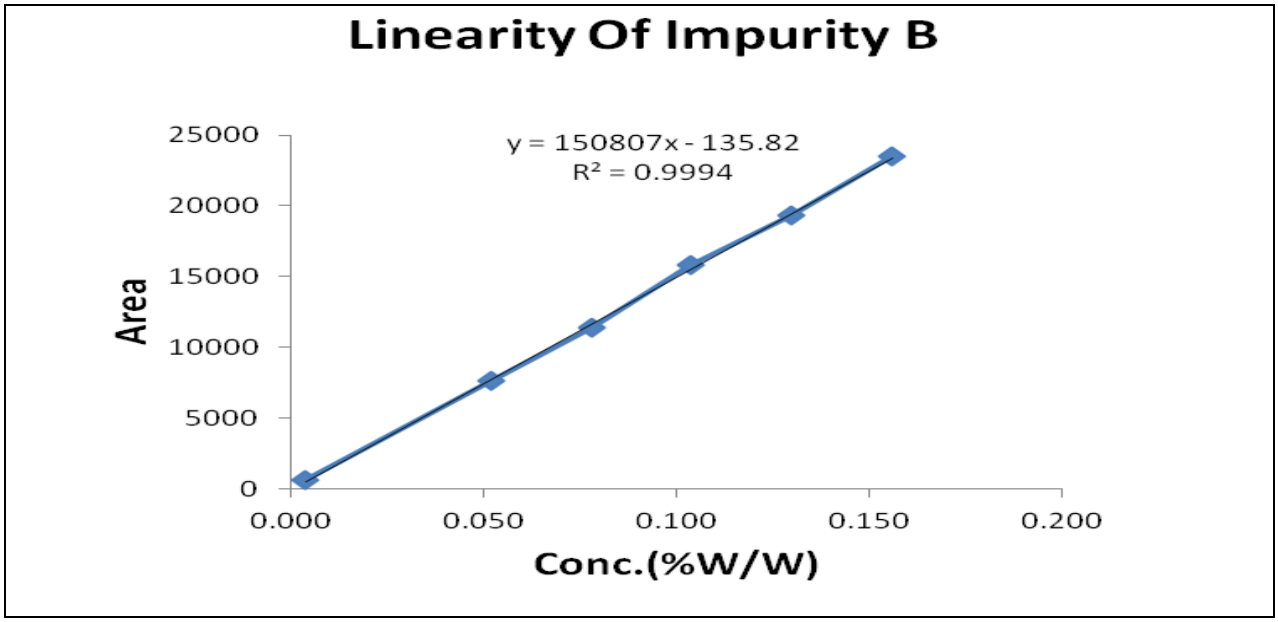

Figure 13: Linearity for impurity B

Table 9: Linearity of impurity C

Conc. level	Conc. (µg/ml)	Mean area (n=3)
QL	0.013	624
50%	0.251	13432
75%	0.377	19819
100%	0.503	27223
125%	0.628	32964
150%	0.754	39896
Slope		**264307**
Intercept		**36**
Correlation coefficient		**0.9998**
Response factor		**0.68**

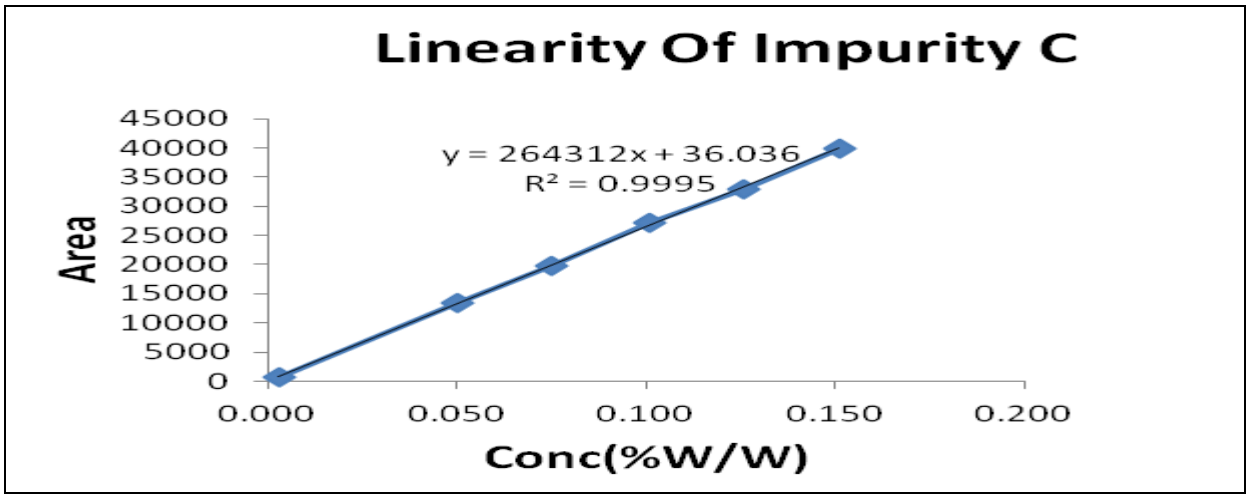

Figure 14: Linearity for impurity C

Table 10: Linearity of impurity D

Conc. Level	Conc. (µg/ml)	Mean area (n=3)
QL	0.003	613
50%	0.247	43629
75%	0.371	64467
100%	0.495	88968
125%	0.619	10837
150%	0.742	131446
Slope		**886290**
Intercept		**-203**
Correlation coefficient		**0.9998**
Response factor		**0.20**

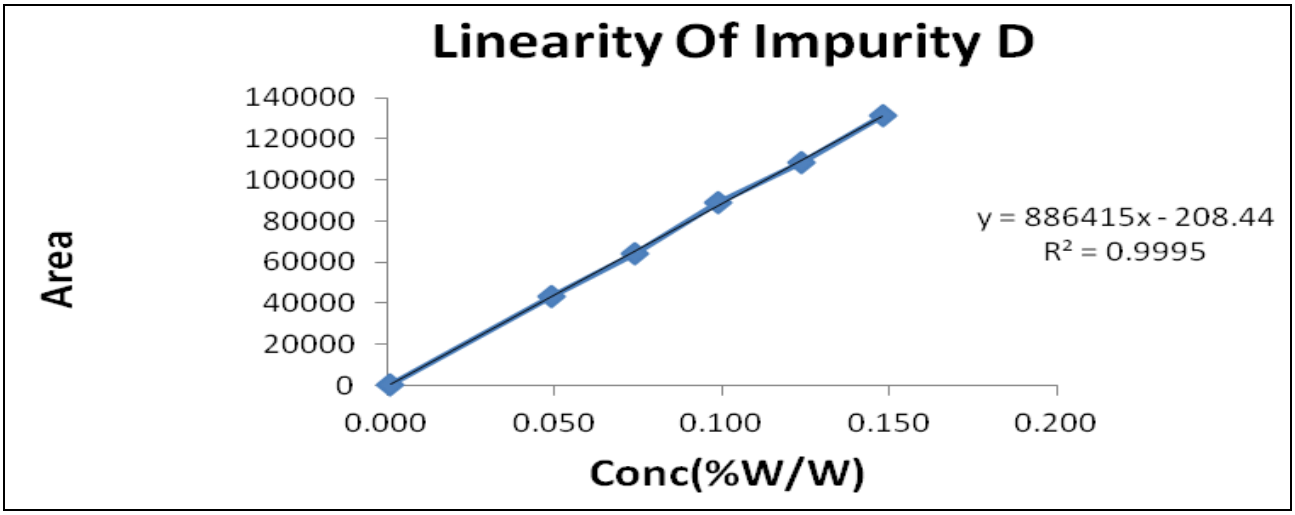

Figure 15: Linearity for impurity D

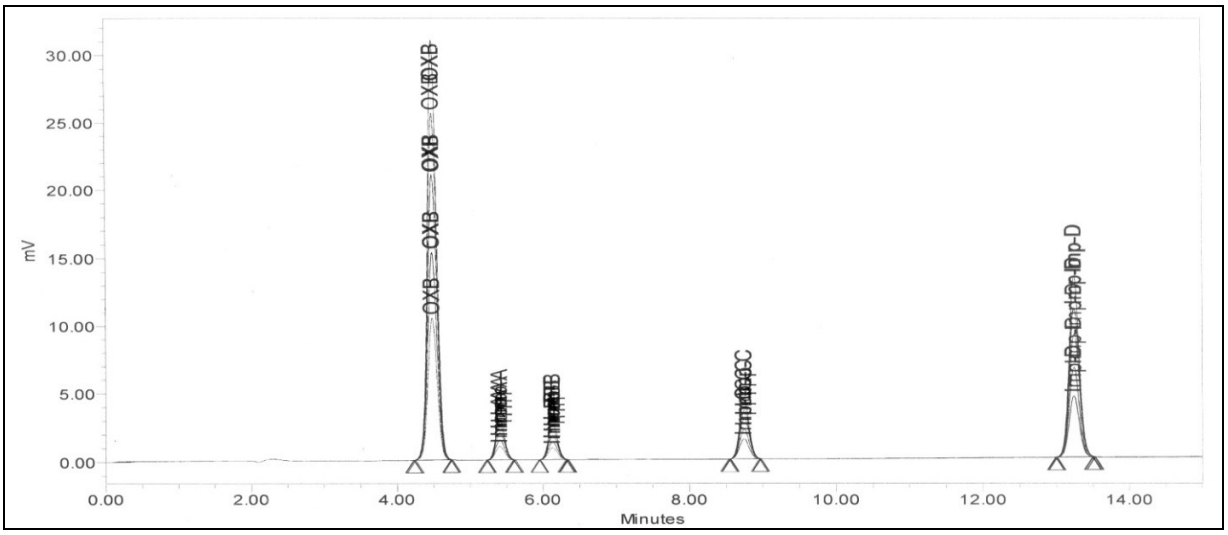

Figure 16: The chromatogram of different levels of standard solution for linearity

CONCLUSION

- Correlation coefficient found 0.9996 within acceptance limit for Oxcarbazepine as shown in fig.11 and the data shown in table 6.
- Correlation coefficient found 0.9997 within acceptance limit for impurity A as shown in fig.12 and the data shown in table 7.
- Correlation coefficient found 0.9997 within acceptance limit for impurity B as shown in fig.13 and the data shown in table 8.
- Correlation coefficient found 0.9998 within acceptance limit for impurity C as shown in fig. 14 and the data shown in table 9.
- Correlation coefficient found 0.9998 within acceptance limit for impurity D as shown in fig.15 and the data shown in table 10.

ACCURACY

The accuracy of an analytical procedure expresses the closeness of agreement between the value which is accepted either as a conventional true value or an accepted reference value and the value found. The accuracy of the method was determined by recovery studies. The known amount of impurities were spiked as per table in triplicate to the samples and the recovery of the drug was calculated. The accuracy of the method was calculated at three levels such as 50%, 100%, and 150% of considered target limit. The results indicated that the mean recovery of impurity A, impurity B, impurity C, and impurity D are 102.70%, 101.73%, 102.01%, 100.91% respectively. The recovery experiments of the method are depicted in the table. The chromatograms for 50%, 100 and 150% of impurities spiking is given in the figure 17-19.

Accuracy study for Impurity A

Table 11: Accuracy data for Impurity A

Recovery levels	Amount added (µg/ml)	Amount recovered (µg/ml)	% Recovery	Mean	SD	% RSD
50%	0.269	0.271	100.63	101.84	0.875	0.859
	0.269	0.275	102.22			
	0.269	0.276	102.67			
100%	0.538	0.554	103.04	103.15	0.104	0.101
	0.538	0.555	103.29			

	0.538	0.554	103.12			
150%	0.806	0.834	103.44	103.12	0.225	0.218
	0.806	0.831	103.00			
	0.806	0.830	102.93			
Overall				102.70	0.40	0.39

Accuracy study for Impurity B

Table 12: Accuracy data for Impurity B

Recovery levels	Amount added (µg/ml)	Amount recovered (µg/ml)	% Recovery	Mean	SD	%RSD
50%	0.260	0.250	96.18	96.45	0.195	0.203
	0.260	0.251	96.52			
	0.260	0.252	96.64			
100%	0.521	0.542	104.11	104.11	0.017	0.016
	0.521	0.542	104.13			
	0.521	0.542	104.09			
150%	0.781	0.820	104.95	104.62	0.328	0.313
	0.781	0.814	104.17			
	0.781	0.818	104.74			
Overall				101.73	0.18	0.18

Accuracy study for Impurity C

Table 13: Accuracy data for Impurity C

Recovery levels	Amount added (µg/ml)	Amount recovered (µg/ml)	% Recovery	Mean	SD	% RSD
50%	0.251	0.235	93.34	95.09	1.463	1.538
	0.251	0.239	95.02			
	0.251	0.244	96.92			
100%	0.503	0.485	96.52	96.72	0.287	0.297
	0.503	0.485	96.51			
	0.503	0.488	97.12			
150%	0.754	0.862	114.35	114.23	0.135	0.118
	0.754	0.860	114.04			
	0.754	0.862	114.29			
Overall				102.01	0.63	0.65

Accuracy study for Impurity D

Table 14: Accuracy data for Impurity D

Recovery levels	Amount added (µg/ml)	Amount recovered (µg/ml)	% Recovery	Mean	SD	% RSD
50%	0.247	0.248	100.17	100.04	0.101	0.101
	0.247	0.247	100.01			
	0.247	0.247	99.93			
100%	0.495	0.502	101.37	101.29	0.131	0.129
	0.495	0.502	101.40			
	0.495	0.500	101.11			
150%	0.742	0.753	101.47	101.40	0.063	0.062
	0.742	0.753	101.42			
	0.742	0.752	101.32			
Overall				100.91	0.10	0.10

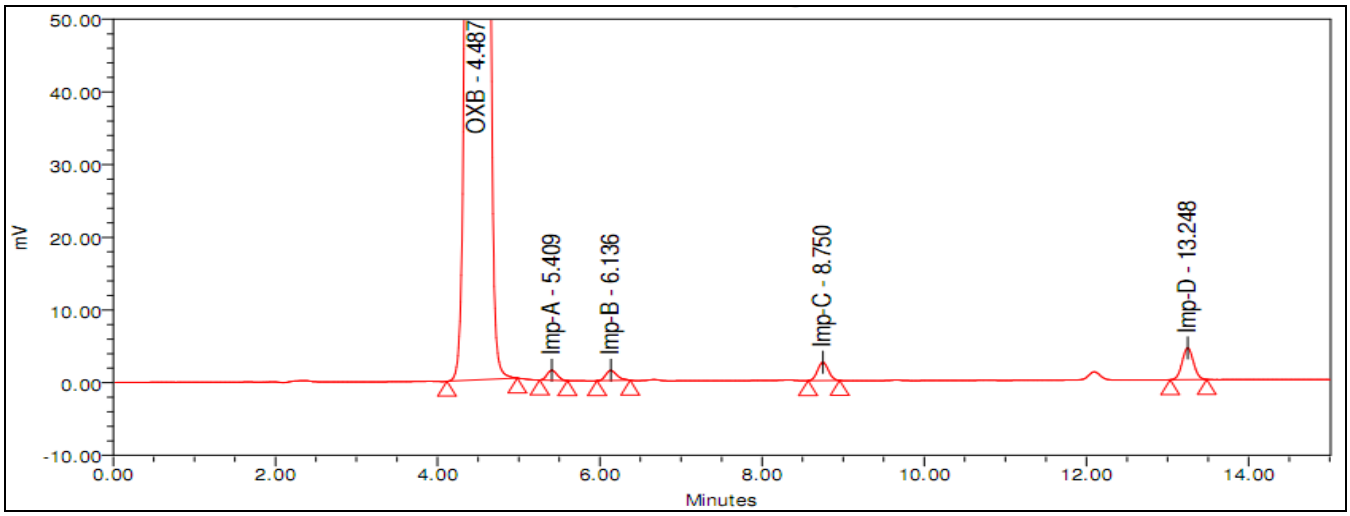

Figure17: The chromatogram for Accuracy at 50% level

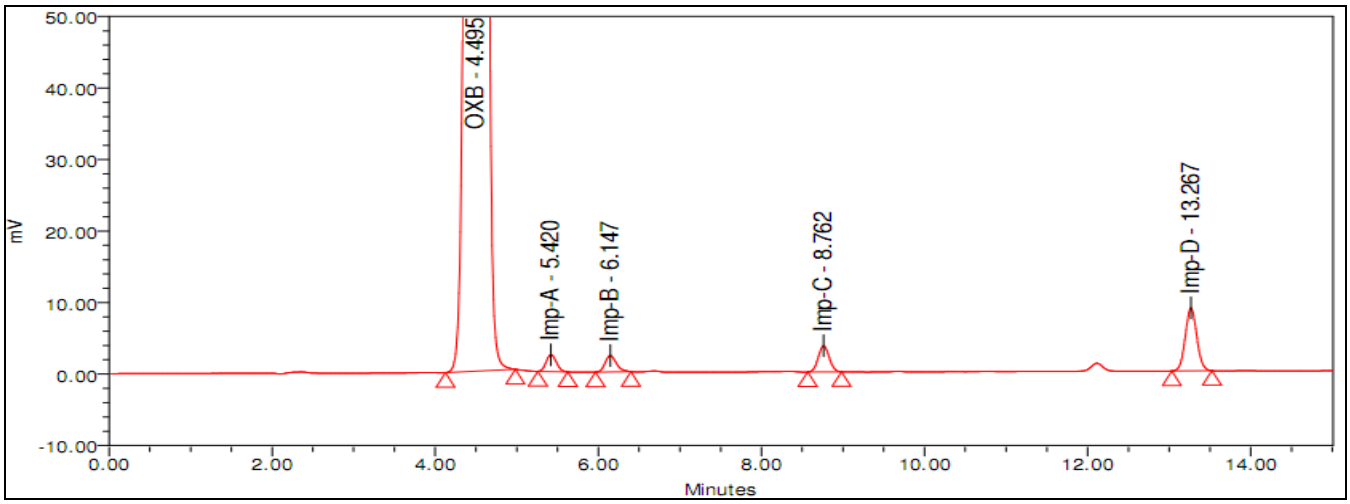

Figure18: The chromatogram for Accuracy at 100% level

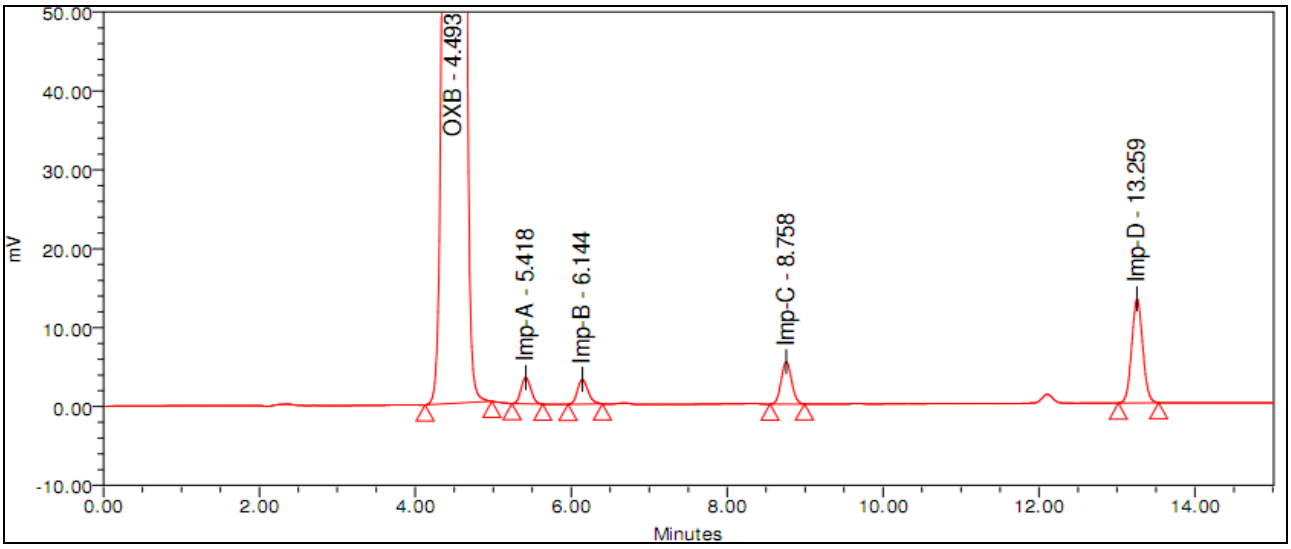

Figure 19: The chromatogram for Accuracy at 150% level

CONCLUSION

- The % Recovery of impurity A was found 102.70% within the acceptance limit i.e. in between 80-120%(data shown in table 11)
- The % Recovery of impurity B was found 101.73% within the acceptance limit i.e. in between 80-120%(data shown in table 12)
- The % Recovery of impurity C was found 102.01% within the acceptance limit i.e. in between 80-120%(data shown in table 13)
- The % Recovery of impurity D was found 100.91% within the acceptance limit i.e. in between 80-120%(data shown in table 14)
- The chromatograms representing accuracy of all impurities at 50%, 100% and 150% (data shown in fig.17-19.)

SUMMARY AND CONCLUSION

SUMMARY

The summary of the work done

Method Development

Table 15: Chromatographic condition

	Inertsil ODS3V, (250 X 4.6 mm), 5.0 micron		
Column Temperature	35° C		
Flow Rate	1.0 mL per minute		
Gradient Program	Time (Min)	M P-A, %	M P-B, %
	0.0	50	50
	15	20	80
	15.1	50	50
Injection Volume	20 µL		
Next Injection Delay	5.0 minutes		
Detector wavelength	256 nm		
Run Time	15 n		

Method Validation

Table 16: Impurity A

Parameters	**Observed Value**	**ICH Specification**
Specificity	Peak was pure	Peak purity should pass
Linearity	0.9997	Not less than 0.999
System precision	%RSD 0.10	< 1 %
Repeatability	%RSD 0.42	< 2 %
Intermediate precision	%RSD 3.13	< 10%
Accuracy	102.70%	80-120%
LOD	%RSD 10.05	< 33%
LOQ	%RSD 3.24	< 10%
Robustness	RSD was < 2 %	< 2%

Table 17: Impurity B

Parameters	Observed Value	ICH Specification
Specificity	Peak was pure	Peak purity should pass
Linearity	0.9997	Not less than 0.999
System precision	%RSD 0.10	< 1 %
Repeatability	%RSD 1.04	< 2 %
Intermediate precision	%RSD 0.00	< 10%
Accuracy	101.73%	80-120%
LOD	%RSD 11.35	< 33%
LOQ	%RSD 3.56	< 10%
Robustness	RSD was < 2 %	< 2%

Table 18: Impurity C

Parameters	Observed Value	ICH Specification
Specificity	Peak was pure	Peak purity should pass
Linearity	0.9998	Not less than 0.999
System precision	%RSD 0.10	< 1 %
Repeatability	%RSD 1.45	< 2 %
Intermediate precision	%RSD 2.67	< 10%
Accuracy	102.01%	80-120%
LOD	%RSD 4.83	< 33%
LOQ	%RSD 1.75	< 10%
Robustness	RSD was < 2 %	< 2%

Table 19: Impurity D

Parameters	Observed Value	ICH Specification
Specificity	Peak was pure	Peak purity should pass
Linearity	0.9998	Not less than 0.999
System precision	%RSD 0.10	< 1 %
Repeatability	%RSD 0.22	< 2 %
Intermediate precision	%RSD 1.06	< 10%
Accuracy	100.91%	80-120%
LOD	%RSD 9.66	< 33%
LOQ	%RSD 5.35	< 10%
Robustness	RSD was < 2 %	< 2%

Table 20: Oxcarbazepine

Parameters	Observed Value	ICH Specification
Specificity	Peak was pure	Peak purity should pass
Linearity	0.9996	Not less than 0.999
System precision	%RSD 0.10	< 1 %
Repeatability	%RSD 0.46	< 1 %
Intermediate precision	%RSD 0.01	< 10%
Robustness	RSD was < 2 %	< 2%

CONCLUSION

The proposed HPLC method enables quantitative determination of related substances of Oxcarbazepine API. UV detection at 256nm was found to be suitable without any interference. The result of linearity, precision, specificity and ruggedness were within limits. Preparation of samples is easy and efficient. From the results of related substances of Oxcarbazepine analysis it can be concluded that the proposed HPLC method is precise, linear and robust that can be used for routine analysis.

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