Section A-Research paper
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STABILITY INDICATING RP-HPLC METHOD DEVELOPMENT FOR TRILACICLIB IN PHARMACEUTICAL SUBSTANCE AND ITS VALIDATION

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ABSTRACT

A simple, precise, accurate, sensitive, and specific RP-HPLC method for the determination of Trilaciclib in the pharmaceutical dosage form. Chromatogram was run through Inertsil C18 150 x 4.6 mm, 5µ. Mobile phase containing 0.01N KH2PO4: Acetonitrile taken in the ratio 60:40 was pumped through the column at a flow rate of 1.0ml/min. The temperature was maintained at 30°C. The optimized wavelength selected was 220.0 nm. The retention time of Trilaciclib was found to be 2.347 min. %RSD of the Trilaciclib was found to be 1.3%. %RSD of Method precision of Trilaciclib was found to be 0.7. %. Recovery was obtained as 99.29% for Trilaciclib. The LOD and LOQ values obtained from the regression equation of Trilaciclib were 0.29, and 0.89. The Regression equation of Trilaciclib is y = 100035x + 16845. Retention times were decreased and that run time was decreased, so the method developed was simple and economical that can be adopted in regular Quality control tests in Industries.

Key Words: Trilaciclib, Method development, Validation, RP-HPLC

INTRODUCTION

Trilaciclib is a CDK4 and CDK6 inhibitor to reduce the risk of chemotherapy-induced myelosuppression [1]. Trilaciclib, or G1T28, is a CDK4 and CDK6 inhibitor, indicated to reduce the incidence of chemotherapy-induced myelosuppression in patients before topotecan-containing or platinum and etoposide-containing chemotherapy for extensive stage small cell lung cancer [2]. CDK4 and CDK6 inhibitors have been investigated since the mid-1990s for their use in tumorigenesis and chemotherapy. Trilaciclib was first described in the literature in 2016. Trilaciclib was granted FDA approval on 12 February 2021[3].

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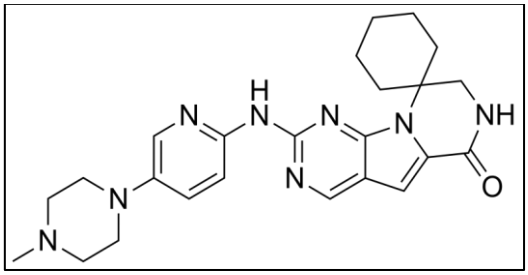

Figure.1: Structure of Trilaciclib

The chemical name of Trilaciclib is 12'-{[5-(4-methylpiperazin-1-yl)pyridin-2-yl]amino}-2',5',11',13'-tetraazaspiro[cyclohexane-1,3'-tricyclo[7.4.0.0^{2,7}]tridecane]-1'(9'),7',10',12'-tetraen-6'-one[4]. Trilaciclib is indicated to reduce the incidence of chemotherapy-induced myelosuppression in patients prior to receiving platinum and etoposide-containing or topotecan-containing chemotherapy regimens for extensive-stage small cell lung cancer [5-7]. Trilaciclib is inhibits cyclin-dependant kinase 4 (CDK4) at a concentration of 1 n mol/L and cyclin-dependent kinase 5 (CDK5) at 4 nmol/L.1,6 Inhibition of CDK2, CDK5, and CDK7 is over 1000-fold less at these concentrations and inhibition of CDK9 is 50-fold less. CDK4 and CDK5 are expressed in hematopoietic stem cells and progenitor cells [8-10]. The literature review reveals that only one RP-HPLC [11] determination of pure Trilaciclib has been reported for identification and quantification. Thus, the goal of the study is to develop a more precise, accurate, and sensitive method for Trilaciclib, which is a pharmaceutical component, using RP-HPLC.

Materials: Trilaciclib pure drug (API), Trilaciclib formulation (**SCEMBLIX**), Distilled water, Acetonitrile, Phosphate buffer, Methanol, Potassium dihydrogen orthophosphate buffer, Ortho-phosphoric acid. All the above chemicals and solvents are from Rankem.

Instruments:

Electronics Balance-Denver, p^H meter -BVK enterprises, India, Ultrasonicator-BVK enterprises, WATERS HPLC 2695 SYSTEM equipped with quaternary pumps, Photo Diode Array detector and Auto sampler integrated with Empower 2 Software. UV-VIS spectrophotometer PG Instruments T60 with special bandwidth of 2mm and 10mm and matched quartz cells integrated with UV win 6 Software was used for measuring absorbance of Trilaciclib solution.

Methods:

Diluent: Based up on the solubility of the drugs, diluent was selected, Acetonitrile and Water taken in the ratio of 50:50.

Preparation of Standard stock solutions: Accurately weighed 15mg of Trilaciclib is transferred to 50 ml volumetric flask. 3/4 th of diluents was added to the flask and sonicated for 10 minutes. Flask was made up with diluents and labeled as Standard stock solution. (300µg/ml of Trilaciclib)

Preparation of Standard working solutions (100% solution): 1ml from each stock solution was pipetted out and taken into a 10ml volumetric flask and made up with diluent. (30µg/ml of Trilaciclib)

Preparation of Sample stock solutions: 10 tablets were weighed and the average weight of each tablet was calculated, then the weight equivalent to 1 tablet was transferred into a 100ml volumetric flask, 50ml of diluents was added and sonicated for 25 min, further the volume was made up with diluent and filtered by HPLC filters (3000µg/ml of Trilaciclib).

Preparation of Sample working solutions (100% solution): 0.1ml of filtered sample stock solution was transferred to 10 ml volumetric flask and made up with diluent. (30µg/ml of Trilaciclib)

Preparation of buffer:

0.01N KH_2PO_4 Buffer: Accurately weighed 1.36gm of Potassium dihydrogen Ortho phosphate in a 1000ml of Volumetric flask add about 900 ml of milli-Q water added and degas to sonicate and finally make up the volume with water then PH adjusted to 4.8 with dil. Orthophosphoric acid solution.

0.1%OPA Buffer: 1ml of ortho phosphoric acid was diluted to 1000ml with HPLC grade water.

Validation:

The developed method has been validated as per ICH guidelines for the following parameters [12- 14].

System suitability parameters:

The system suitability parameters were determined by preparing a standard solution of Trilaciclib (30ppm) and the solution was injected six times and the parameters like peak tailing, resolution and USP plate count were determined.

The % RSD for the area of six standard injections results should not be more than 2%.

Specificity: Checking of the interference in the optimized method. We should not find interfering peaks in blank and placebo at retention times of these drugs in this method. So this method was said to be specific.

Precision:

Preparation of Standard stock solutions: Accurately weighed 15mg of Trilaciclib is transferred to 50 ml volumetric flask. 3/4 th of diluents was added to the flask and sonicated for 10 minutes. Flask was made up with diluents and labeled as Standard stock solution. (300µg/ml of Trilaciclib)

Preparation of Standard working solutions (100% solution): 1ml from each stock solution was pipetted out and taken into a 10ml volumetric flask and made up with diluent. (30µg/ml of Trilaciclib)

Preparation of Sample stock solutions: 10 tablets were weighed and the average weight of each tablet was calculated, then the weight equivalent to 1 tablet was transferred into a 100ml volumetric flask, 50ml of diluents was added and sonicated for 25 min, further the volume was made up with diluent and filtered by HPLC filters (3000µg/ml of Trilaciclib)

Preparation of Sample working solutions (100% solution): 0.1ml of filtered sample stock solution was transferred to 10 ml volumetric flask and made up with diluent. (30µg/ml of Trilaciclib)

Linearity:

Preparation of Standard stock solutions: Accurately weighed 15mg of Trilaciclib is transferred to 50 ml volumetric flask. 3/4 th of diluents was added to the flask and sonicated for 10 minutes. Flask was made up with diluents and labeled as Standard stock solution. (400µg/ml of Trilaciclib)

25% Standard solution: 0.25ml each from two standard stock solutions was pipetted out and made up to 10ml. (7.5µg/ml of Trilaciclib)

50% Standard solution: 0.5ml each from two standard stock solutions was pipetted out and made up to 10ml. (15µg/ml of Trilaciclib)

75% Standard solution: 0.75ml each from two standard stock solutions was pipetted out and made up to 10ml. (22.5µg/ml of Trilaciclib)

100% Standard solution: 1.0ml each from two standard stock solutions was pipetted out and made up to 10ml. (30µg/ml of Trilaciclib)

125% Standard solution: 1.25ml each from two standard stock solutions was pipetted out and made up to 10ml. (37.5µg/ml of Trilaciclib)

150% Standard solution: 1.5ml each from two standard stock solutions was pipetted out and made up to 10ml (45µg/ml of Trilaciclib)

Accuracy:

Preparation of Standard stock solutions: Accurately weighed 15mg of Trilaciclib is transferred to 50 ml volumetric flask. 3/4 th of diluents was added to the flask and sonicated for 10 minutes. Flask was made up with diluents and labeled as Standard stock solution. (300µg/ml of Trilaciclib)

Preparation of 50% Spiked Solution: 0.5ml of sample stock solution was taken into a 10ml volumetric flask, to that 1.0ml from each standard stock solution was pipetted out, and made up to the mark with diluent.

Preparation of 100% Spiked Solution: 1.0ml of sample stock solution was taken into a 10ml volumetric flask, to that 1.0ml from each standard stock solution was pipetted out, and made up to the mark with diluent.

Preparation of 150% Spiked Solution: 1.5ml of sample stock solution was taken into a 10ml volumetric flask, to that 1.0ml from each standard stock solution was pipetted out, and made up to the mark with diluent.

Acceptance Criteria:

The % Recovery for each level should be between 98 to 102.

Robustness: Small deliberate changes in method like Flow rate, mobile phase ratio, and temperature are made but there were no recognized changes in the result and are within range as per ICH Guidelines.

Robustness conditions like Flow minus (0.9ml/min), Flow plus (1.1ml/min), mobile phase minus, mobile phase plus, temperature minus (25°C) and temperature plus (35°C) were maintained and samples were injected in a duplicate manner. System suitability parameters were not much affected and all the parameters were passed. %RSD was within the limit.

LOD sample Preparation: 0.25ml each from two standard stock solutions was pipetted out and transferred to two separate 10 ml volumetric flasks and made up with diluents. From the above solutions 0.1ml each of Trilaciclib, solutions respectively were transferred to 10ml volumetric flasks and made up with the same diluents

LOQ sample Preparation: 0.25ml each from two standard stock solutions was pipetted out and transferred to two separate 10 ml volumetric flasks and made up with diluent. From the above solutions 0.3ml each of Trilaciclib, solutions respectively were transferred to 10ml volumetric flasks and made up with the same diluent.

Degradation studies[15-38]:

Oxidation:

To 1 ml of stock solution of Trilaciclib, 1 ml of 20% hydrogen peroxide (H2O2) was added separately. The solutions were kept for 30 min at 60^0c. For HPLC study, the resultant solution was diluted to obtain 30µg/ml solution and 10µl were injected into the system and the chromatograms were recorded to assess the stability of the sample.

Acid Degradation Studies:

To 1 ml of stock solution Trilaciclib, 1 ml of 2N Hydrochloric acid was added and refluxed for 30 mins at 60^0c. For HPLC study, the resultant solution was diluted to obtain 30µg/ml solution and 10µl were injected into the system and the chromatograms were recorded to assess the stability of the sample.

Alkali Degradation Studies:

To 1 ml of stock solution Trilaciclib, 1 ml of 2N sodium hydroxide was added and refluxed for 30 mins at 60^0c. For HPLC study, the resultant solution was diluted to obtain 30µg/ml solution and 10µl were injected into the system and the chromatograms were recorded to assess the stability of the sample.

Dry Heat Degradation Studies:

The standard drug solution was placed in the oven at 105°C for 6h to study dry heat degradation. For HPLC study, the resultant solution was diluted to obtain 30µg/ml solution and 10µl were injected into the system and the chromatograms were recorded to assess the stability of the sample.

Photostability studies:

The photochemical stability of the drug was also studied by exposing the 300µg/ml solution to UV Light by keeping the beaker in UV Chamber for 7 days or 200 Watt hours/m^2 in photo stability chamber. For HPLC study, the resultant solution was diluted to obtain 30µg/ml solution and 10µl were injected into the system and the chromatograms were recorded to assess the stability of the sample.

Neutral Degradation Studies:

Stress testing under neutral conditions was studied by refluxing the drug in water for 6hrs at a temperature of 60º. For HPLC study, the resultant solution was diluted to obtain 30µg/ml solution and 10µl were injected into the system and the chromatograms were recorded to assess the stability of the sample.

RESULTS AND DISCUSSION

Optimized method:

Chromatographic conditions:

Mobile phase **:**60% 0.01N Kh2po4: 40% Acetonitrile

Flow rate **:** 1.0ml/min

Column **:** Inertsil C18 (4.6 x 150mm, 5µm)

Detector wavelength : 220 nm
Column temperature : 30°C
Injection volume : 10µL
Run time : 10 min
Diluent : Water and Acetonitrile in the ratio 50:50
Results : Trilaciclib peak has good resolution, tailing Factor, theoretical plate count and resolution.

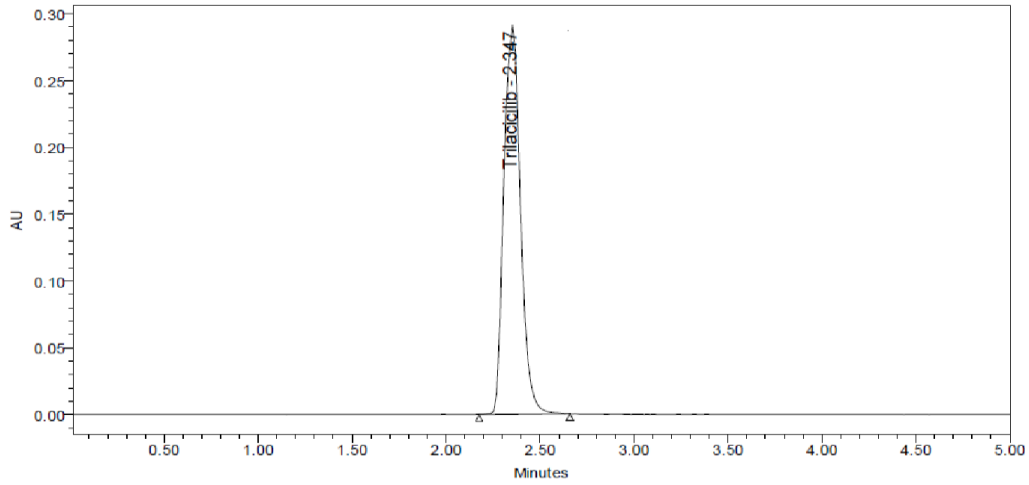

Figure 2: Optimized chromatogram

Observation: Trilaciclib were eluted at 2.347min with good resolution. Plate count and tailing factor was very satisfactory, so this method was optimized and to be validated.

System suitability: All the system suitability parameters were within the range and satisfactory as per ICH guidelines

Table 1 : System suitability parameters for Trilaciclib

S no	**Trilaciclib**		
Inj	RT(min)	USP Plate Count	Tailing
1	2.349	6419	1.31
2	2.349	6419	1.31
3	2.354	6694	1.30
4	2.364	6610	1.30
5	2.373	6400	1.30
6	2.379	6528	1.30

Discussion: According to ICH guidelines plate count should be more than 2000, tailing factor should be less than 2 and resolution must be more than 2. All the system suitable parameters were passed and were within the limits.

Validation:

Specificity:

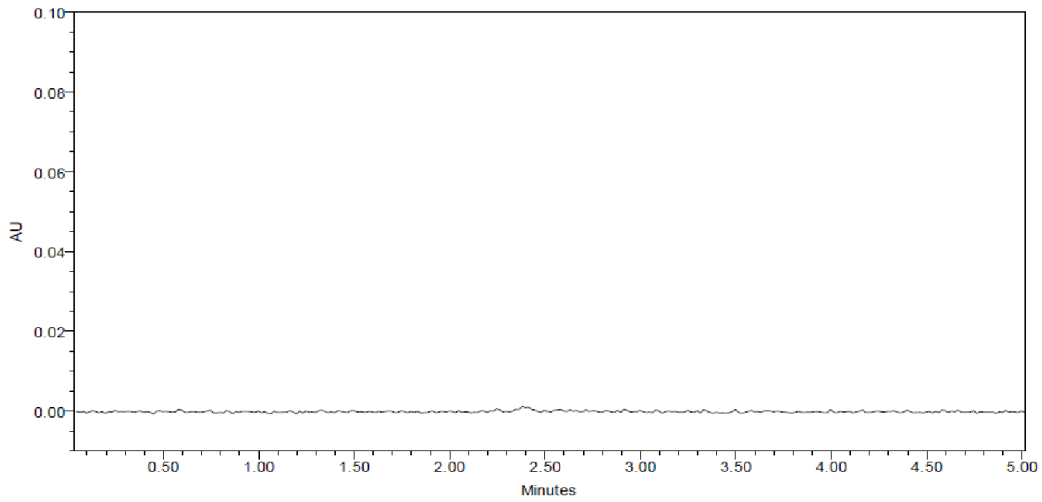

Figure 3: Chromatogram of blank

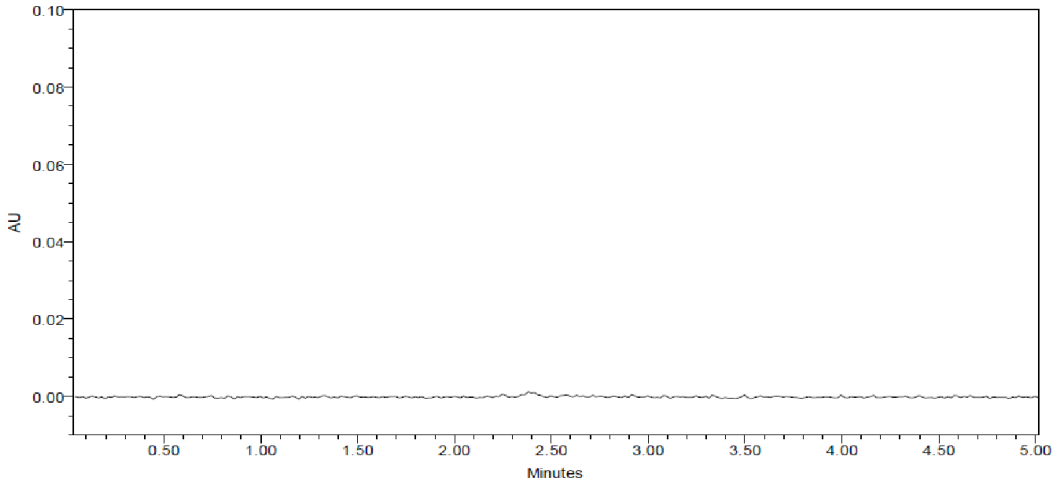

Figure 4: Chromatogram of placebo

Discussion: Retention time of Trilaciclib was 2.347 min. We did not find any interfering peaks in blank and placebo at retention times of these drugs in this method. So this method was said to be specific.

Linearity:

Table 2: Linearity table for Trilaciclib

Trilaciclib	
Conc (µg/mL)	**Peak area**
0	0
7.5	755762
15	1534853
22.5	2283529
30	3055085

37.5	3734046
45	4510206

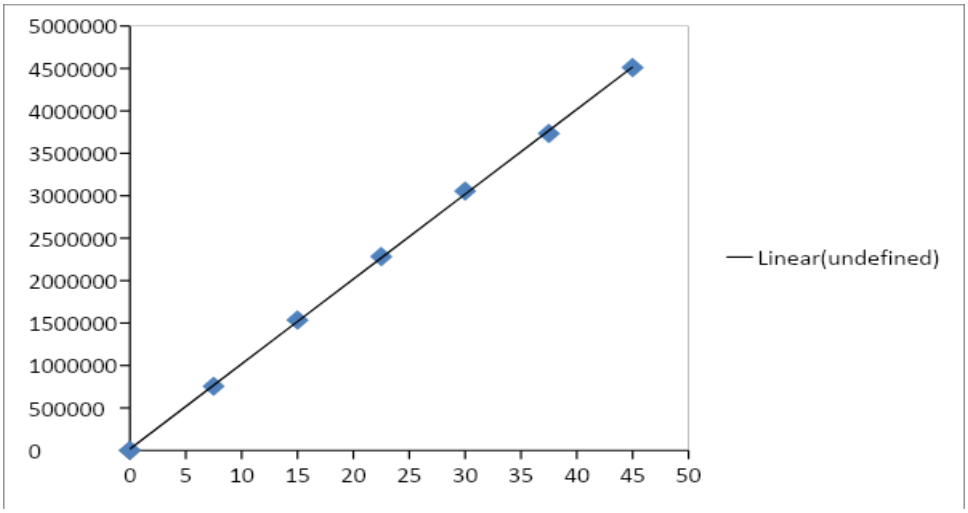

Figure 5: Calibration curve of Trilaciclib

Discussion: Six linear concentration of Trilaciclib (7.5-45µg/ml) were injected in a duplicate manner. Average areas were mentioned above and linearity equations obtained for Trilaciclib was y = 100035x + 16845. Correlation coefficient obtained was 0.999 for the two drugs.

Precision:

System Precision:

Table 3: System precision table of Trilaciclib

S. No	Area of Trilaciclib
1.	3025584
2.	2985584
3.	2993557
4.	3076485
5.	2980389
6.	3058927
Mean	3020088
S.D	40471.5
%RSD	1.3

Discussion: From a single volumetric flask of working standard solution six injections were given and the obtained areas were mentioned above. Average area, standard deviation and % RSD were calculated. % RSD obtained as 1.3% for Trilaciclib. As the limit of Precision was less than "2" the system precision was passed in this method.

Method precision:

Table 4: Method precision table of Trilaciclib

S. No	Area of Trilaciclib
1.	3001432
2.	3015547
3.	3026742
4.	3003912
5.	2987168
6.	3048815
Mean	3013936
S.D	21709.4
%RSD	0.7

Discussion: Multiple sampling from a sample stock solution was done and six working sample solutions of same concentrations were prepared, each injection from each working sample solution was given and obtained areas were mentioned in the above table. Average area, standard deviation and % RSD were calculated and obtained as 0.7% for Trilaciclib. As the limit of Precision was less than "2" the system precision was passed in this method.

Intermediate precision (Day_Day Precision):

Table 5: Intermediate precision table of Trilaciclib

S. No	Area of Trilaciclib
1.	3042970
2.	3032813
3.	3049637
4.	3045454
5.	3049250
6.	3043708
Mean	3043972
S.D	6127.7
%RSD	0.2

Discussion: Multiple sampling from a sample stock solution was done and six working sample solutions of same concentrations were prepared, each injection from each working sample solution was given on the next day of the sample preparation and obtained areas were mentioned in the above table. Average area, standard deviation and % RSD were calculated and obtained as 0.2% for Trilaciclib. As the limit of Precision was less than "2" the system precision was passed in this method.

Accuracy:

Table 6: Accuracy table of Trilaciclib

% Level	**Amount Spiked (µg/mL)**	**Amount recovered (µg/mL)**	**% Recovery**	Mean %Recovery
\50%	15	14.86	99.09	99.28%
	15	14.76	98.41	
	15	14.97	99.81	
100%	30	29.65	98.85	
	30	30.20	100.65	
	30	29.84	99.46	
150%	45	44.68	99.28	
	45	44.53	98.96	
	45	44.60	99.11	

Discussion: Three levels of Accuracy samples were prepared by standard addition method. Triplicate injections were given for each level of accuracy and mean %Recovery was obtained as 99.28% for Trilaciclib.

Sensitivity:

Table 7: Sensitivity table of Trilaciclib

Molecule	**LOD**	**LOQ**
Trilaciclib	0.29	0.89

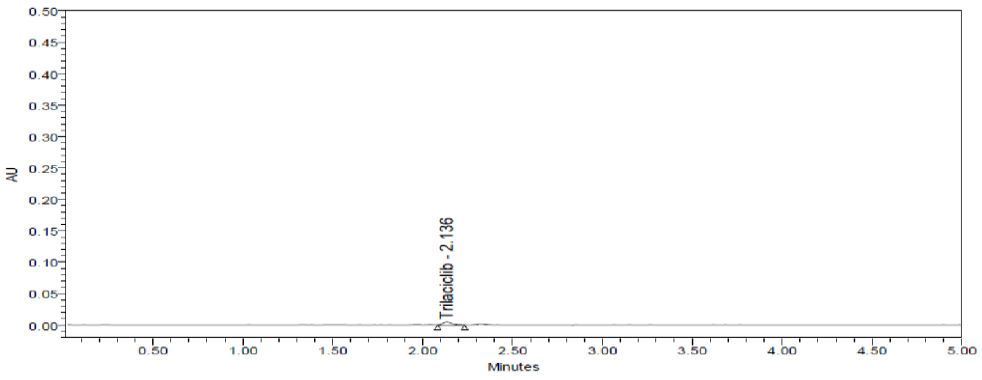

Figure 6: LOD Chromatogram of Standard

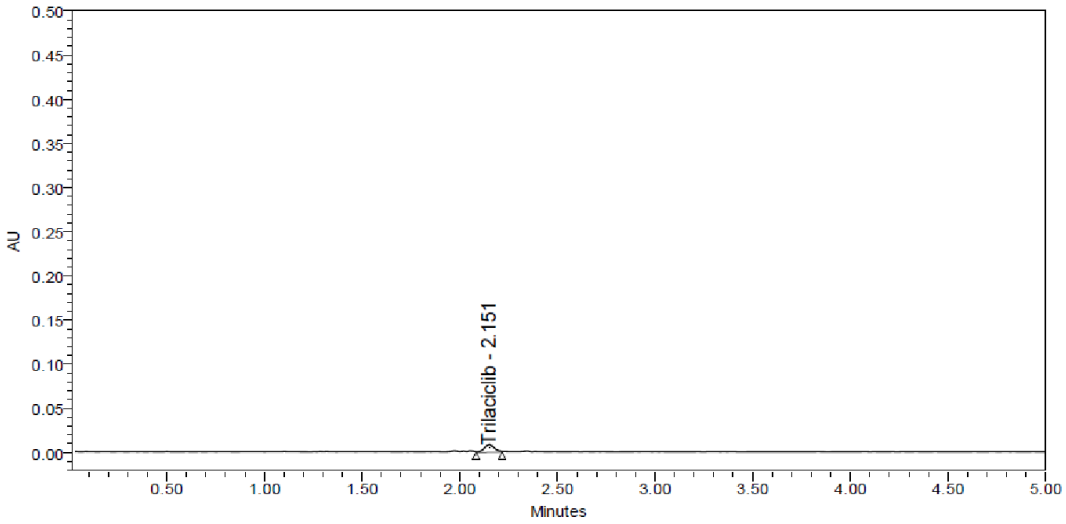

Figure 7: LOQ Chromatogram of Standard

Robustness:

Table 8: Robustness data for Trilaciclib

S.no	Condition	%RSD of Trilaciclib
1	Flow rate (-) 0.9ml/min	1.0
2	Flow rate (+) 1.1ml/min	1.2
3	Mobile phase (-) 75B:25A	0.2
4	Mobile phase (+) 65B:35A	0.4
5	Temperature (-) 27°C	0.9
6	Temperature (+) 33°C	1.3

Discussion: Robustness conditions like Flow minus (0.9ml/min), Flow plus (1.1ml/min), mobile phase minus (55:45A), mobile phase plus (65B:35A), temperature minus (27°C) and temperature plus (33°C) was maintained and samples were injected in duplicate manner. System suitability parameters were not much affected and all the parameters were passed. %RSD was within the limit.

Assay: Lenvima bearing the label claim Trilaciclib 10mg. Assay was performed with the above formulation. Average % Assay for Trilaciclib obtained was 99.60%.

Table 9: Assay Data of Trilaciclib

S.no	Standard Area	Sample area	% Assay
1	3025584	3001432	99.18
2	2985584	3015547	99.65
3	2993557	3026742	100.02
4	3076485	3003912	99.27
5	2980389	2987168	98.71
6	3058927	3048815	100.75
Avg	3020088	3013936	99.60
Stdev	40471.5	21709.4	0.72
%RSD	1.3	0.7	0.7

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DEGRADATION

Degradation Studies: Degradation studies were performed with the formulation and the degraded samples were injected. Assay of the injected samples was calculated and all the samples passed the limits of degradation

Table 10: Degradation Data of Trilaciclib

S.NO	Degradation Condition	% Drug Un Degraded	% Drug Degraded
1	Acid	96.21	3.79
2	Alkali	95.53	4.47
3	Oxidation	95.80	4.20
4	Thermal	97.87	2.13
5	UV	98.64	1.36
6	Water	99.37	0.63

Discussion: Regarding the pH adjustment in mobile phase for the acid and base degradation studies have movement in retention time of drugs. But due to neutralized acid sample with 2N Base solution and base sample with 2N Acid solution there will be no change in retention time.

CONCLUSION

A simple, precise, accurate, sensitive, and specific RP-HPLC method for the determination of Trilaciclib in the pharmaceutical dosage form. The retention time of Trilaciclib was found to be 2.347 min. %RSD of the Trilaciclib was found to be 1.3%. %RSD of Method precision of Trilaciclib was found to be 0.7. %Recovery was obtained as 99.29% for Trilaciclib. LOD, and LOQ values obtained from the regression equation of Trilaciclib were 0.29, 0.89. The

Regression equation of Trilaciclib is y = 100035x + 16845. Retention times were decreased and that run time was decreased, so the method developed was simple and economical that can be adopted in regular Quality control tests in Industries.

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