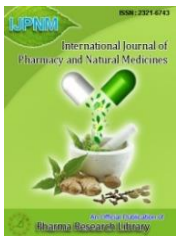

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Quality by design (QBD) based Development and Validation of RP-HPLC method for palbociclib in capsule dosage form

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A B S T R A C T

A robust and reliable RP-HPLC method was developed and validated for the estimation of Palbociclib in bulk and pharmaceutical dosage forms, in accordance with ICH Q2(R1) guidelines**.** Method optimization using statistical design revealed that flow rate, buffer pH, and temperature significantly influenced chromatographic responses. Separation was achieved on an Intersil C18-EP column (4.6×250 mm, 5 µm) with a mobile phase of acetonitrile and phosphate buffer (70:30, pH 5) at a flow rate of 1.0 mL/min, detection at 270 nm, and injection volume of 20 µL. Palbociclib showed a sharp, symmetrical peak at ~3.3 min with excellent system suitability parameters (tailing factor ~1.1, plate count >6700).Validation studies confirmed the method's performance, with linearity over 25–120 µg/mL (R^2 = 0.9999)**,** high precision (%RSD < 1%), and accuracy with recoveries within 98–102%. Sensitivity was established with LOD 1.08 µg/mL and LOQ 3.62 µg/mL. Accuracy studies at multiple concentration levels yielded recoveries between 98.3–100.7%. Robustness testing showed no significant effect of small changes in flow rate and mobile phase composition on chromatographic performance. The developed RP-HPLC method is simple, precise, accurate, sensitive, and stability-indicating, making it suitable for routine quality control, batch release, and regulatory applications of Palbociclib formulations in the pharmaceutical industry.

Keywords: Palbociclib, RP-HPLC, Method Validation, ICH Q2(R1), Stability-indicating, Quality Control.

A R T I C L E I N F O

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C O N T E N T S

1. Introduction

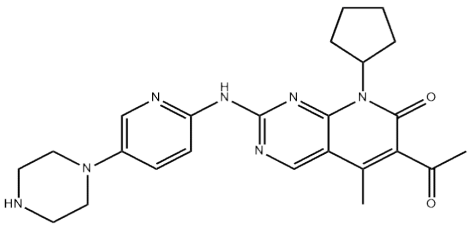

Fig.1: Palbociclib

Table.1: Palbociclib drug profile

Molecular Formula	$C_{38}H_{50}N_6O_5$
Molecular Weight	670.86 g/mol
IUPAC Name	(2S)-N-[(2S,3R)-4-[(3S)-3-(tert-butylcarbamoyl)-3-pyridin-2-ylpropyl]-3-hydroxy-1-phenylbutan-2-yl]-2-(quinolin-2-ylcarbonylamino)butanediamide
Chem Spider ID	4449
Density	1.23 g/cm3

Boiling Point	720.4°C
Vapour Pressure	1.15E-13 mmHg
Flash Point	386.4°C
Refractive Index	1.56
Polar Surface Area	173.2 Å2
LogP	4.7 **(Octanol/Water)**
Generic Name	Palbociclib
Brand Names	Invirase, Fortovase
Drug category	HIV Protease Inhibitor
Indications	Treatment of HIV-1 infection in combination with other antiretroviral agents
Pharmacology	Inhibition of HIV-1 protease, preventing viral replication
Potency	High potency against HIV-1 protease
Tolerability	Generally well-tolerated, but may cause gastrointestinal disturbances, diarrhea, and nausea
Contraindications	Hypersensitivity to Palbociclib or any component of the formulation
Adverse Effects	Gastrointestinal disturbances, diarrhea, nausea, vomiting, abdominal pain
Availability	Prescription-only medication, available in oral capsules or tablets
Mechanism of Action	1. Binding to HIV Protease: Palbociclib binds to the active site of the HIV protease enzyme, which is essential for the maturation of viral particles. 2. Inhibition of Proteolytic Cleavage: By binding to the active site, saquinavir prevents the protease enzyme from cleaving viral polyprotein precursors into functional proteins, such as gag, pol, and env.. 3. Prevention of Viral Maturation: The inhibition of proteolytic cleavage prevents the maturation of viral particles, thereby inhibiting the replication of HIV. 4. Reduction of Viral Load: The reduction in viral replication leads to a decrease in viral load, which slows down the progression of HIV disease.

2. Materials and Methods

Table.1: List of Instrument Used

S.No	Instrument	Model
1	HPLC	WATERS, software: Empower, 2695 separation module.2487 UV detector.
2	UV/VIS	LABINDIA UV 3000+
3	pH meter	Adwa – AD 1020
4	Weighing machine	Afcoset ER-200A
5	Pipettes and Burettes	Borosil
6	Beakers	Borosil

Table 2: Chemicals used

S.No	Chemical	Brand
1	Palbociclib	Supplied by MSN LAB
2	KH_2PO_4	FINAR chemical LTD
3	Water and Methanol for HPLC	Standard solutions Ltd
4	Acetonitrile for HPLC	Standard solutions Ltd
5	HCl, H_2O_2, NaOH	MERCK

HPLC Method Development:

Wave length selection:

UV spectrum of 10µg/ml Palbociclib in diluent (mobile phase composition) was recorded by scanning in the range of 200nm to 400nm. From the UV spectrum wavelength selected as 220nm. At this wavelength both the drugs show good absorbance.

Optimized chromatographic conditions:

Instrument used : High performance liquid chromatography equipped with Auto Sampler and PDA detector
Temperature : Ambient
Column : INTERSIL C18-EP (4.6 x 250mm, 5µm)
Mobile phase : ACN: KH2PO4 PH 5 (70:30ml)
Flow rate : 1ml/min
Wavelength : 270 nm
Injection volume : 20µl
Run time : 10 min.

Preparation of buffer and mobile phase:

Preparation of Phosphate buffer pH 5:

To prepare potassium phosphate buffer solution, by adding 6.4gm of phosphate buffer in 1000ml water. Adjust this solution to pH 5 by using Ortho Phosphoric Acid.

Preparation of mobile phase: Mix a mixture of above CAN 700ml (70%) and 300 ml KH2PO4 (30%) and degas in ultrasonic water bath for 5 minutes. Filter through 0.45µ filter under vacuum filtration.

Diluent Preparation: ACN: KH2PO4 buffer PH 5 (70:30) ratio.

System Suitability: Tailing factor for the peaks due to Palbociclib in Standard solution should not be more than 2.0
Theoretical plates for the Palbociclib peaks in Standard solution should not be less than 2000

Calculation: (For Palbociclib)

$$\%\ Assay = \frac{AT}{AS} * \frac{WS}{DS} * \frac{DT}{WT} * \frac{Average\ weight}{Label\ Claim} * \frac{P}{100} * 100$$

Where:

AT = average area counts of sample preparation.
AS = average area counts of standard preparation.
WS= Weight of working standard taken in mg.
P= Percentage purity of working standard
LC= Label Claim mg/ml.

System Suitability Results:

- Tailing factor Obtained from the standard injection is 1.16
- Theoretical Plates Obtained from the standard injection is 3338

Validation parameters:

1. Assay:

Standard Solution Preparation: Accurately weigh and transfer 25 mg of Palbociclib working standard into a 25 ml clean dry volumetric flask add Diluents and sonicate to dissolve it completely and make volume up to the mark with the same solvent. (Stock solution)**.** Further pipette 0.75ml of the above stock solution into a 10ml volumetric flask and dilute up to the mark with Diluents. (30ppm)

Sample Solution Preparation: Accurately weigh and transfer equivalent to 25 mg of Palbociclib equivalent weight of the sample into a 25 ml clean dry volumetric flask add about 7ml of Diluents and sonicate to dissolve it completely and make volume up to the mark with the same solvent. (Stock solution). Further pipette 0.75ml of the above stock solution into a 10ml volumetric flask and dilute up to the mark with Diluents.

Procedure: Inject 10 mL of the standard, sample into the chromatographic system and measure the areas for the Palbociclib peaks and calculate the % Assay by using the formulae.

2. Linearity:

Preparation of stock solution:

Accurately weigh and transfer 25 mg of Palbociclib working standard into a 25 ml clean dry volumetric flask add Diluents and sonicate to dissolve it completely and make volume up to the mark with the same solvent. (Stock solution)

Preparation of Level – I (10ppm of Palbociclib):

0.1ml of stock solution has taken in 10ml of volumetric flask dilute up to the mark with Diluents.

Preparation of Level – II (20ppm of Palbociclib):

0.2ml of stock solution has taken in 10ml of volumetric flask dilute up to the mark with Diluents.

Preparation of Level – III (30ppm of Palbociclib):

0.3ml of stock solution has taken in 10ml of volumetric flask dilute up to the mark with Diluents.

Preparation of Level – IV (40ppm of Palbociclib):

0.4 ml of stock solution has taken in 10ml of volumetric flask dilute up to the mark with Diluents.

Preparation of Level – V (50ppm of Palbociclib):

0.5ml of stock solution has taken in 10ml of volumetric flask dilute up to the mark with Diluents.

Procedure:

Inject each level into the chromatographic system and measure the peak area: Plot a graph of peak area versus concentration (on X-axis concentration and on Y-axis Peak area) and calculate the correlation coefficient.

3. Precision:

Preparation of stock Solution:

Accurately weigh and transfer 25 mg of Palbociclib working standard into a 25 ml clean dry volumetric flask add Diluents and sonicate to dissolve it completely and make volume up to the mark with the same solvent. (Stock solution). Further pipette 0.75ml of the above stock solution into a 10ml volumetric flask and dilute up to the mark with Diluents.

Procedure: The standard solution was injected for six times and measured the area for all six injections in HPLC. The %RSD for the area of six replicate injections was found to be within the specified limits.

4. Intermediate precision/ruggedness:

To evaluate the intermediate precision (also known as Ruggedness) of the method, Precision was performed on different day within the laboratory.

Preparation of stock solution:

Accurately weigh and transfer 25 mg of Palbociclib working standard into a 25 ml clean dry volumetric flask add Diluents and sonicate to dissolve it completely and make volume up to the mark with the same solvent. (Stock solution). Further pipette 0.75ml of the above stock solution into a 10ml volumetric flask and dilute up to the mark with Diluents.

Procedure: The standard solution was injected for six times and measured the area for all six injections in HPLC. The %RSD for the area of six replicate injections was found to be within the specified limits.

5. Accuracy:

For accuracy determination, three different concentrations were prepared separately i.e. 50%, 100% and 150% for the analyte and chromatograms are recorded for the same.

Preparation of Standard stock solution: Accurately weigh and transfer 25 mg of Palbociclib working standard into a 25 ml clean dry volumetric flask add Diluents and sonicate to dissolve it completely and make volume up to the mark with the same solvent. (Stock solution). Further pipette 0.75ml of the above stock solution into a 10ml volumetric flask and dilute up to the mark with Diluents.

Preparation Sample solutions:

For preparation of 50% solution (With respect to target Assay concentration): Accurately weigh and transfer 12.5mg of Palbociclib working standard into a 25 ml clean dry volumetric flask add Diluents and sonicate to dissolve it completely and make volume up to the mark with the same solvent. (Stock solution). Further pipette 0.3ml of the above stock solution into a 10ml volumetric flask and dilute up to the mark with Diluents.

For preparation of 100% solution (With respect to target Assay concentration): Accurately weigh and transfer 25 mg of Palbociclib working standard into a 25 ml clean dry volumetric flask add Diluents and sonicate to dissolve it completely and make volume up to the mark with the same solvent. (Stock solution). Further pipette 0.75ml of the above stock solution into a 10ml volumetric flask and dilute up to the mark with Diluents.

For preparation of 150% solution (With respect to target Assay concentration): Accurately weigh and transfer 37.5 mg of Palbociclib working standard into a 25ml clean dry volumetric flask add Diluents and sonicate to dissolve it completely and make volume up to the mark with the same solvent. (Stock solution). Further pipette 0.75ml of the above stock solution into a 10ml volumetric flask and dilute up to the mark with Diluents.

Procedure:

Inject the standard solution, Accuracy -50%, Accuracy -100% and Accuracy -150% solutions. Calculate the Amount found and Amount added for Palbociclib and calculate the individual recovery and mean recovery values.

6. Limit of Detection:

Preparation of 1.08µg/ml solution: Accurately weigh and transfer 25 mg of Palbociclib working standard into a 25 ml clean dry volumetric flask add Diluents and sonicate to dissolve it completely and make volume up to the mark with the same solvent. (Stock solution)**.** Further pipette 0.75ml of the above stock solution into a 10ml volumetric flask and dilute up to the mark with Diluents. Further pipette 1 ml of the above stock solution into a 10ml volumetric flask and dilute up to the mark with Diluent. Further pipette 1.44ml of the above stock solution into a 10ml volumetric flask and dilute up to the mark with Diluents.

7. Limit of Quantification:

Preparation of Palbociclib solution:

Preparation of 3.62µg/ml solution: Accurately weigh and transfer 25 mg of Palbociclib working standard into a 25 ml clean dry volumetric flask add Diluents and sonicate to dissolve it completely and make volume up to the mark with the same solvent. (Stock solution)**.** Further pipette 0.75ml of the above stock solution into a 10ml volumetric flask and dilute up to the mark with Diluents. Further pipette 1ml of the above stock solution into a 10ml volumetric flask and dilute up to the mark with Diluents. Further pipette 1.61ml of the above stock solution into a 10ml volumetric flask and dilute up to the mark with Diluents.

8. Robustness:

As part of the Robustness, deliberate change in the Flow rate, Mobile Phase composition, Temperature Variation was made to evaluate the impact on the method.

a) The flow rate was varied at 0.8 ml/min to 1.2 ml/min. Standard solution 75 µg/ml of Palbociclib prepared and analyzed using the varied flow rates along with method flow rate.

b) The Organic composition in the Mobile phase was varied from 63% to 77%

Standard solution 75 µg/ml of Palbociclib was prepared and analyzed using the varied Mobile phase composition along with the actual mobile phase composition in the method.

Table 3: Development by QBD Optimization

		Factor 1	Factor 2	Factor 3	Response 1	Response 2
Std	Run	A:Flow rate	B: Buffer PH	C:Temperature	Retention time mins	Plate count
6	1	1.00	4.50	15.00	3.2	7560
8	2	1.00	4.50	25.00	3.2	7560
9	3	0.90	4.00	15.00	3.1	7554
17	4	0.90	4.50	20.00	3.1	7557
5	5	0.80	4.50	15.00	3.1	7556
13	6	0.90	4.50	20.00	3.1	7557
1	7	0.80	4.00	20.00	3	7555
4	8	1.00	5.00	20.00	3.3	7566
7	9	0.80	4.50	25.00	3.1	7556
2	10	1.00	4.00	20.00	3.3	7566
3	11	0.80	5.00	20.00	3.1	7550
10	12	0.90	5.00	15.00	3.4	7562
16	13	0.90	4.50	20.00	3.1	7562
11	14	0.90	4.00	25.00	3.1	7554
15	15	0.90	4.50	20.00	3.1	7557
12	16	0.90	5.00	25.00	3.2	7560
14	17	0.90	4.50	20.00	3.1	7557

Table 4: Software Information

File Version	22.0.4.0		
Study Type	Response Surface	Subtype	Randomized
Design Type	Box-Behnken	Runs	17
Design Model	Quadratic	Blocks	No Blocks
Build Time (ms)	4.00		

Table 5: Factors

Factor	Name	Type	Low Actual	High Actual	Low Coded	High Coded	Mean	Std. Dev.
A	Buffer PH	Numeric	0.80	1.00	-1.000	1.000	0.900	0.069
B	Flow rate	Numeric	4.00	5.00	-1.000	1.000	4.500	0.343
C	Temperature	Numeric	15.00	25.00	-1.000	1.000	20.000	3.430

Table 6: Responses

Response	Name	Obs	Analysis	Minimum	Maximum	Mean	Std. Dev.	Ratio	Trans	Model
Y1	RT	17	Polynomial	3.00	3.40	3.15	0.098	1.13	None	Linear
Y2	Plate count	17	Polynomial	7550.00	7566.00	7558.18	4.12	1.00	None	Linear

3. Results and Discussion

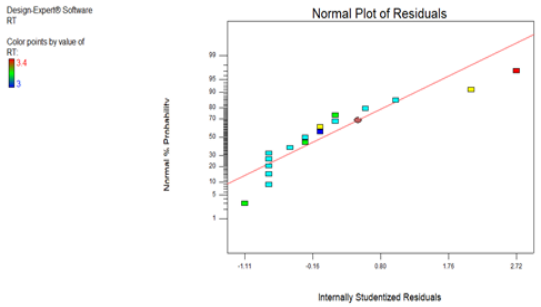

Figure 6: Normal plot of Residuals for Palbociclib

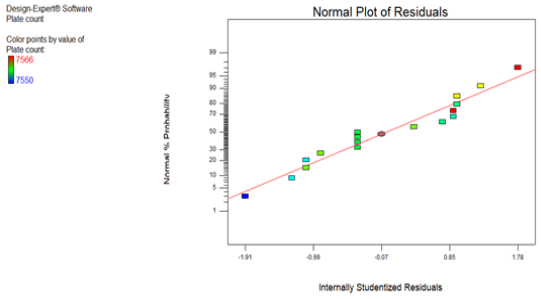

Figure 11: Normal plot of Residuals for Palbociclib

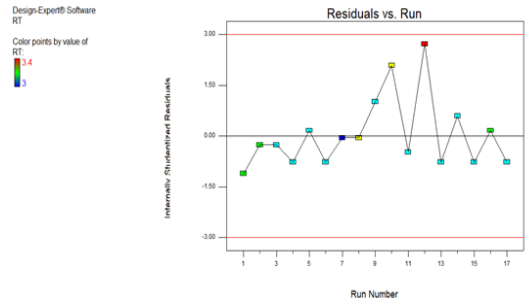

Figure 7: Residuals vs. Run for Palbociclib

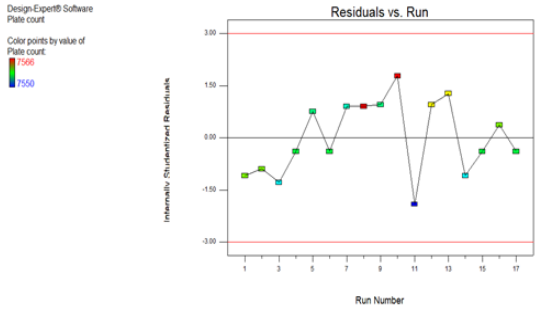

Figure 12: Residuals vs. Run for Palbociclib

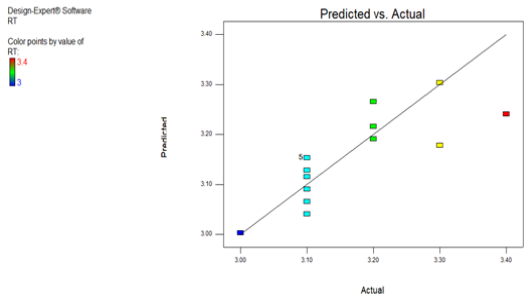

Figure 8: Predicted vs. Actual for Palbociclib

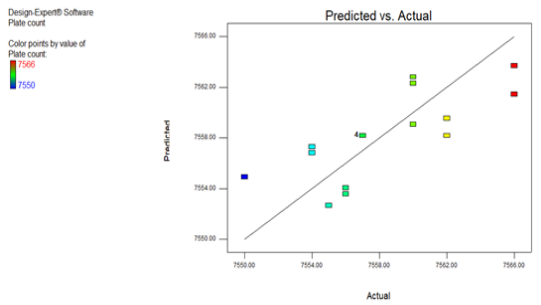

Figure 13: Predicted vs. Actual for Palbociclib

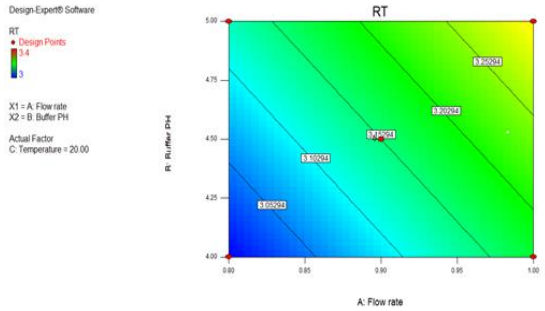

Figure 9: Retention time for Palbociclib

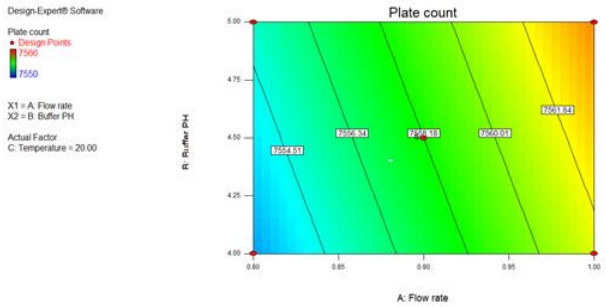

Figure 14: Plate count factor for Palbociclib

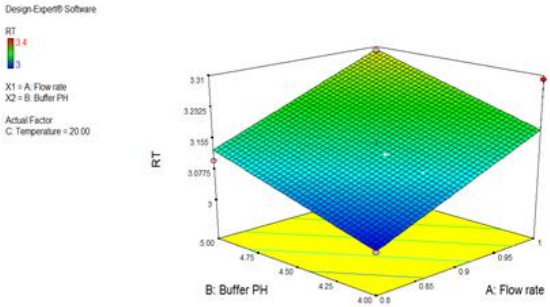

Figure 10: 3D Surface for Palbociclib

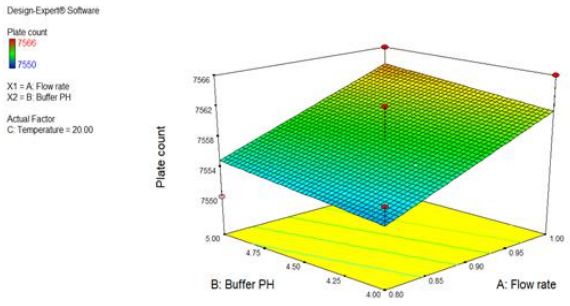

Figure 15: 3D Surface for Palbociclib

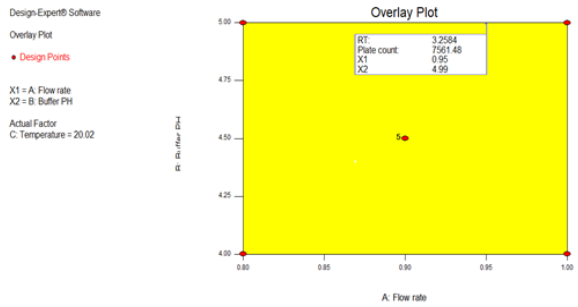

Figure 16: Overlay plot for Palbociclib

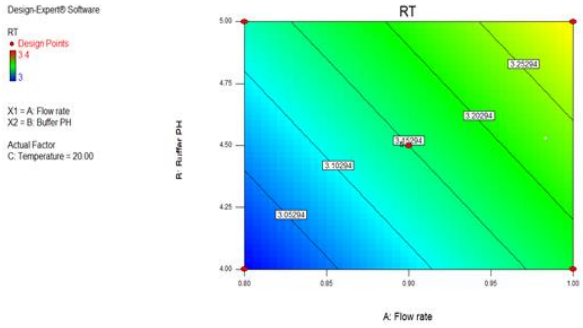

Figure 17: Retention Time for Palbociclib

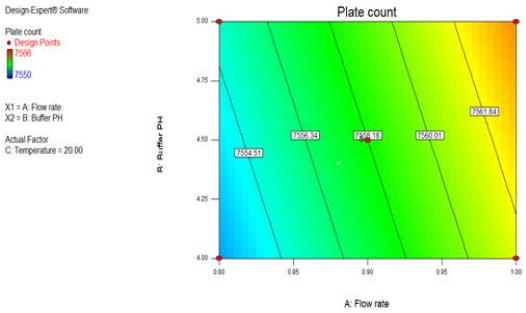

Figure 18: Plate count factor for Palbociclib

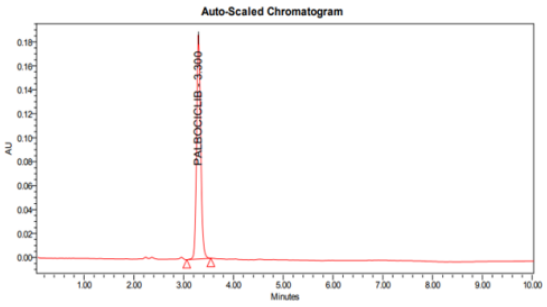

Figure 20: Chromatogram for system suitability

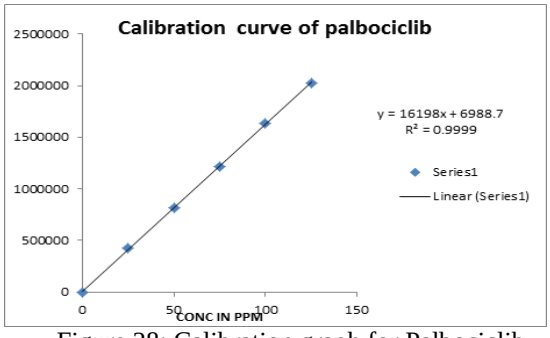

Figure 28: Calibration graph for Palbociclib

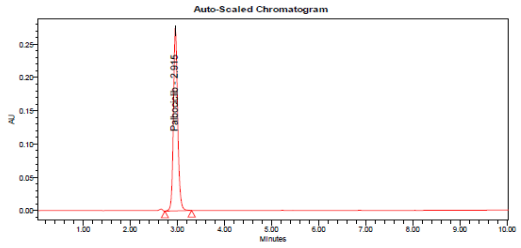

Figure 34: Chromatogram for Precision -6

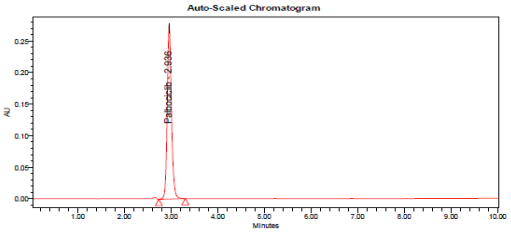

Figure 40: Chromatogram for ID Precision -6

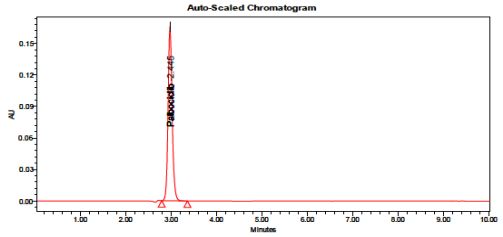

Figure 43: Chromatogram for Accuracy 50%-3

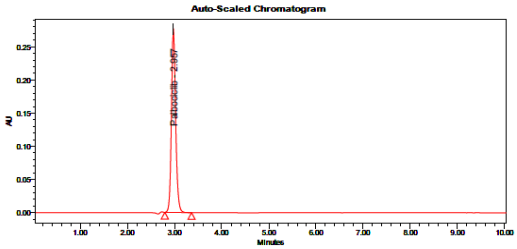

Figure 46: Chromatogram for Accuracy100%-3

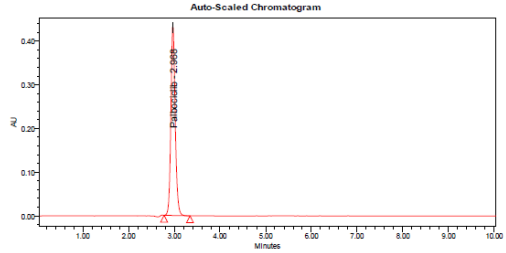

Figure 49: Chromatogram for Accuracy 150%-3

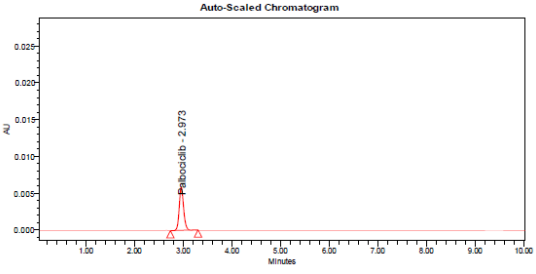

Figure 50: Chromatogram of Palbociclib showing LOD

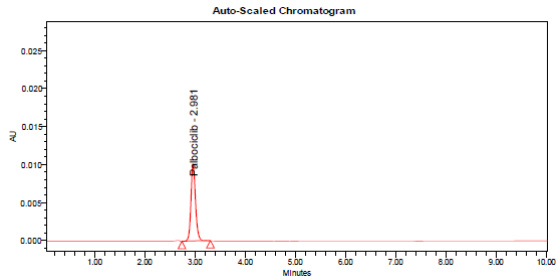

Figure 51: Chromatogram of Palbociclib showing LOQ

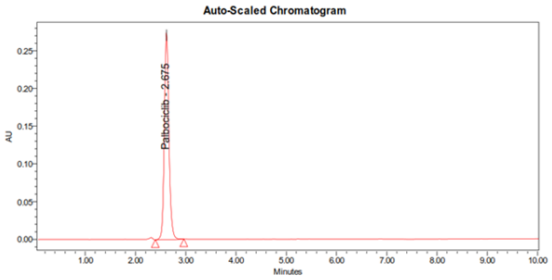

Figure 53: Chromatogram showing more flow

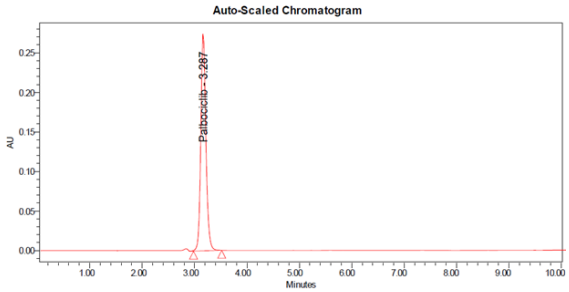

Figure 52: Chromatogram showing less flow

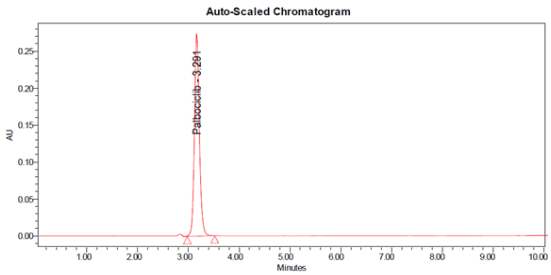

Figure 54: Chromatogram showing less organic composition

Table 7: FIT Summary Response-1 Retention Time of Palbociclib

Source	**Sum of Squares**	**df**	**Mean Square**	**F-Value**	**p-value Prob>F**	
Mean vs Total	169.00	1	169.00			
Linear vs Mean	0.097	3	0.032	6.51	0.0063	Suggested
2FI vs Linear	0.013	3	4.167E-003	0.80	0.5237	
Quadratic vs 2FI	0.025	3	8.284E-003	2.11	0.1875	
Cubicvs Quadratic	0.027	3	9.167E-003	6.366E+007	< 0.0001	Aliased
Residual	0.000	4	0.000			
Total	169.16	17	9.95			

Table 8: Response 1: Retention time ANOVA for Quadratic model

		Factor 1	Factor 2	Factor 3	Response 1	Response 2
STD	Run	A:Flow rate	B: Buffer PH	C:Temperature	Retention time mins	Plate count
6	1	1.00	4.50	15.00	3.2	7560
8	2	1.00	4.50	25.00	3.2	7560
9	3	0.90	4.00	15.00	3.1	7554
17	4	0.90	4.50	20.00	3.1	7557
5	5	0.80	4.50	15.00	3.1	7556
13	6	0.90	4.50	20.00	3.1	7557
1	7	0.80	4.00	20.00	3	7555
4	8	1.00	5.00	20.00	3.3	7566
7	9	0.80	4.50	25.00	3.1	7556
2	10	1.00	4.00	20.00	3.3	7566
3	11	0.80	5.00	20.00	3.1	7550
10	12	0.90	5.00	15.00	3.4	7562
16	13	0.90	4.50	20.00	3.1	7562
11	14	0.90	4.00	25.00	3.1	7554
15	15	0.90	4.50	20.00	3.1	7557
12	16	0.90	5.00	25.00	3.2	7560
14	17	0.90	4.50	20.00	3.1	7557

Table 17: Results of LOD

Drug name	**Baseline noise(µV)**	**Signal obtained(µV)**	**S/N ratio**	**Conc.**
Palbociclib	90	266	2.96	1.08µg/ml

4. Conclusion

A simple, precise, and robust RP-HPLC method was successfully developed and validated for the estimation of Palbociclib in bulk and pharmaceutical dosage forms in accordance with ICH Q2(R1) guidelines. The method optimization using a statistical design confirmed that flow rate, buffer pH, and temperature significantly influenced retention time and plate count. Chromatographic separation was achieved on an Intersil C18-EP column (4.6 × 250 mm, 5 µm) with a mobile phase of acetonitrile and phosphate buffer (70:30, pH 5), at a flow rate of 1.0 mL/min, detection wavelength of 270 nm, and injection volume of 20 µL. The method produced a sharp and symmetrical peak for Palbociclib at a retention time of ~3.3 minutes with excellent system suitability results (tailing factor ~1.1 and plate count >6700). Validation studies demonstrated that the method was accurate, precise, and sensitive. The assay results showed recoveries within 98–102%, confirming accuracy. Linearity was excellent over the range of 25–120 µg/mL with R^2 = 0.9999. The precision study yielded %RSD values below 1%, while intermediate precision confirmed ruggedness across different days and systems. The LOD (1.08 µg/mL) and LOQ (3.62 µg/mL) established method sensitivity. Accuracy studies at 50%, 100%, and 150% concentration levels confirmed recoveries between 98.3–100.7%. Robustness evaluation further confirmed that deliberate variations in flow rate and mobile phase composition did not significantly affect chromatographic performance. Overall, the developed RP-HPLC method proved to be simple, cost-effective, accurate, reproducible, and stability-indicating, making it highly suitable for routine quality control, batch release, and regulatory applications for Palbociclib formulations in the pharmaceutical industry.

5. References

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