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Research

Stability-indicating RP-HPLC method for palbociclib: validation and stress-degradation kinetics

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Abstract

A stability-indicating reversed-phase high-performance liquid chromatography (RP-HPLC) method was developed and validated for the quantitative determination of palbociclib in bulk drug and capsule dosage form. Separation was achieved on a C18 column (250 × 4.6 mm, 5 µm) using an isocratic mobile phase of acetonitrile and 0.02 M potassium dihydrogen phosphate buffer (60:40, v/v; pH 3.2 ± 0.1) at 1.0 mL/min with UV detection at 267 nm. The palbociclib peak eluted at approximately 4.8 min with acceptable system suitability. The method was linear over 0.5–25 µg/mL and demonstrated adequate sensitivity (LOD 0.15 µg/mL; LOQ 0.45 µg/mL). Accuracy and precision complied with typical ICH acceptance criteria, and robustness was confirmed by deliberate variations in flow rate, mobile phase composition, and wavelength. Forced degradation under acidic, alkaline, oxidative, thermal and photolytic conditions confirmed specificity by resolving palbociclib from degradation products. First-order kinetic behavior under acidic and oxidative stress was evaluated using ln(% remaining) versus time. The method is suitable for routine quality control and stability testing in accordance with ICH guidance.

Keywords: Palbociclib; stability-indicating assay; RP-HPLC; forced degradation; ICH Q2(R1); degradation kinetics; capsule analysis.

1. Introduction

Palbociclib is an orally active cyclin-dependent kinase 4/6 inhibitor used in the management of hormone receptor–positive advanced breast cancer [1–4]. Accurate quantification in drug substance and finished products is essential for routine release testing and to ensure dose uniformity. Moreover, regulatory expectations for stability assessment require stability-indicating analytical procedures capable of separating the active pharmaceutical ingredient from potential degradation products generated under stress conditions [5–6].

Although several chromatographic methods have been reported for palbociclib determination. The published information indicates that palbociclib is susceptible to oxidative and photolytic degradation and may undergo structural changes under extreme pH conditions [7–12], analytical laboratories benefit from a simple, rapid, isocratic RP-HPLC method using widely available UV detection that also supports forced-degradation studies and kinetic evaluation within a short run time.

Accordingly, this work aimed to develop and validate an RP-HPLC-UV method for palbociclib in bulk drug and marketed capsules, demonstrate stability-indicating capability through forced-degradation studies, and evaluate degradation kinetics under selected stress conditions.

2. Materials and Methods

2.1. Chemicals and reagents

Palbociclib reference standard and marketed palbociclib capsules (label claim: 125 mg; brand: “PALBOCIB”) were used. Acetonitrile and methanol (HPLC grade), potassium dihydrogen phosphate (analytical reagent grade), orthophosphoric acid, hydrochloric acid, sodium hydroxide, hydrogen peroxide, and purified water were used for mobile phase preparation and stress studies. [Information required for journal submission: supplier name(s), city, and country for each chemical and reference standard].

2.2. Instrumentation

Chromatographic analysis was performed using an HPLC system with UV detection (Shimadzu LC-20AD) controlled by LabSolutions software. Separation was carried out on an Inertsil ODS-3 C18 column (250 × 4.6 mm, 5 µm). Ancillary equipment included an analytical balance (Shimadzu AY220), ultrasonic bath (Microclean), and pH meter (Thermo). [Information required for journal submission: manufacturer location (city, country) for each instrument].

2.3. Chromatographic conditions

Optimized chromatographic conditions are summarized in Table 1. The mobile phase was filtered and degassed prior to use.

Table 1. Chromatographic conditions used for palbociclib RP-HPLC analysis.

Parameter	**Condition**
Column	C18, 250 × 4.6 mm, 5 µm
Mobile phase	Acetonitrile : 0.02 M KH_2PO_4 buffer (60:40, v/v)
Buffer pH	3.2 ± 0.1 (orthophosphoric acid)
Flow rate	1.0 mL/min
Detection wavelength	267 nm
Column temperature	30 °C
Injection volume	20 µL
Run time	10 min

2.4. Preparation of standard and sample solutions

A standard stock solution (1000 µg/mL) was prepared by dissolving 25 mg of palbociclib in methanol and diluting to 25 mL. Working solutions for calibration (0.5–25 µg/mL) were prepared by dilution with the mobile phase. For capsule assay, capsule contents were weighed and an amount equivalent to 25 mg palbociclib was dissolved in methanol, sonicated, and diluted to 25 mL. An aliquot was diluted with mobile phase to obtain 10 µg/mL, filtered, and injected (20 µL).

2.5. Method validation

Validation was performed using ICH Q2(R1) terminology for analytical procedure validation [6]. System suitability was evaluated using replicate injections. Specificity was assessed using blank, placebo, standard, and stressed samples. Linearity was evaluated using least-squares regression. Accuracy was determined by recovery at 50%, 100%, and 150% levels. Precision was assessed as intra-day and inter-day repeatability and expressed as %RSD. Sensitivity was reported as LOD and LOQ. Robustness was evaluated by small deliberate changes in flow rate (±0.1 mL/min), mobile phase composition (±2% organic), and wavelength (±2 nm).

2.6. Forced degradation and kinetic studies

Forced degradation was performed under acidic (1 N HCl, 60 °C), alkaline (0.1 N NaOH, 60 °C), oxidative (3% H_2O_2, 60 °C), thermal (60 °C), and photolytic conditions to demonstrate stability-indicating capability [5]. After stressing, samples were neutralized where appropriate, diluted to 10 µg/mL, and injected. For kinetic studies, stressed samples were withdrawn at predefined time points and degradation was modeled by regression of ln(% remaining) versus time to evaluate first-order behavior.

3. Results and Discussion

3.1. System suitability

System suitability met typical acceptance criteria for an isocratic RP-HPLC-UV assay (e.g., %RSD $\leq$ 2.0%, tailing factor $\leq$ 2.0, and theoretical plates > 2000). The palbociclib peak eluted at approximately 4.8 min with symmetric peak shape (Table 2).

Table 2. System suitability parameters for palbociclib (n = 6).

Parameter	**Mean ± SD**	**%RSD**	**Acceptance criterion**
Retention time (min)	4.80 ± 0.04	0.83	—
Theoretical plates (N)	6800 ± 200	2.94	N ≥ 2000
Tailing factor (T)	1.12 ± 0.03	2.68	T ≤ 2.0
Peak area	210000 ± 1400	0.67	%RSD ≤ 2.0

3.2. Specificity and forced degradation behavior

No interference from blank or placebo was observed at the palbociclib retention time, indicating specificity. Under stress, palbociclib exhibited variable susceptibility depending on condition. The largest degradation was reported under oxidative stress (3% H_2O_2, 60 °C), followed by alkaline hydrolysis (0.1 N NaOH, 60 °C). Acidic hydrolysis (1 N HCl, 60 °C) produced moderate degradation, whereas thermal and photolytic stresses resulted in comparatively low degradation (Table 6). Representative chromatograms under stress are shown in Figures 1–2, illustrating separation of palbociclib from degradation products.

3.3. Linearity and sensitivity

The method was linear over 0.5–25 µg/mL. The calibration equation relating concentration (x) to peak area (y) was $y = 21000x + 0$ with $R^2 = 1.000$. LOD and LOQ were 0.15 and 0.45 µg/mL, respectively.

Table 3. Calibration data for palbociclib.

Concentration (µg/mL)	**Mean peak area (mAU·s)**
0.5	10500.0
1.0	21000.0
2.5	52500.0
5.0	105000.0
10.0	210000.0
15.0	315000.0
25.0	525000.0

3.4. Accuracy and precision

Accuracy by standard addition at 50%, 100%, and 150% levels showed acceptable recoveries, and precision expressed as intra-day and inter-day %RSD complied with typical ICH expectations (Table 4).

Table 4. Accuracy (recovery) and precision results for palbociclib.

Accuracy (standard addition).

Level (%)	Amount added (µg/mL)	Amount found (µg/mL)	% Recovery	SD	%RSD
80	8.0	7.91	98.88	0.06	0.61
100	10.0	9.96	99.60	0.07	0.70
120	12.0	12.14	101.17	0.09	0.74

Precision.

Level	Intra-day mean assay (%)	Intra-day %RSD	Inter-day mean assay (%)	Inter-day %RSD	Acceptance criterion
80%	99.1	0.85	98.7	1.10	≤ 2.0
100%	99.4	0.78	99.0	1.05	≤ 2.0
120%	99.8	0.72	99.3	1.00	≤ 2.0

3.5. Robustness

Deliberate variations in chromatographic conditions produced minimal changes in retention time, peak area, efficiency, and peak symmetry, indicating robustness within the tested ranges (Table 5).

Table 5. Robustness study results.

Condition	Flow / Composition / λ	Rt (min)	Tailing factor	%Assay	%RSD
Flow 0.9 mL/min	-0.1 mL/min	5.05	1.14	99.5	0.90
Flow 1.1 mL/min	+0.1 mL/min	4.60	1.11	99.2	0.92
ACN 58%	-2% ACN	5.00	1.13	99.6	0.88
ACN 62%	+2% ACN	4.65	1.11	99.3	0.91
λ = 265 nm	-2 nm	4.80	1.12	99.4	0.86
λ = 269 nm	+2 nm	4.80	1.12	99.7	0.89

Table 6. Forced degradation results for palbociclib under stress conditions.

Stress condition	**% Assay remaining**	**% Degradation**	**Major degradant Rt (min)**	**Mass balance (%)**
Acidic (1 N HCl, 60 °C, 2 h)	78.0	22.0	2.4	99.0
Alkaline (0.1 N NaOH, 60 °C, 1 h)	82.5	17.5	5.9	98.8
Oxidative (3% H_2O_2, RT, 2 h)	72.0	28.0	3.2	98.5
Neutral (water, 80 °C, 4 h)	94.2	5.8	—	100.0
Thermal (80 °C, solid, 24 h)	96.0	4.0	—	100.0
Photolytic (1.2 M lux h, solid)	93.0	7.0	—	99.6

Figure 1. Representative chromatogram of palbociclib under optimized conditions (UV 267 nm).

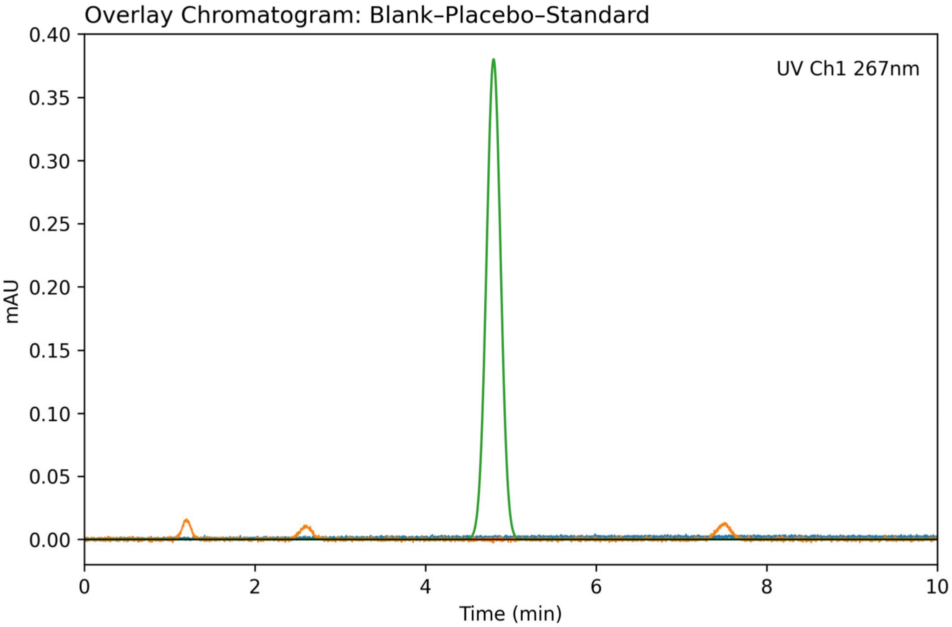


Figure 2. Representative chromatograms of palbociclib under stress conditions: (A) acidic hydrolysis, (B) alkaline hydrolysis, (C) oxidative degradation (UV 267 nm).

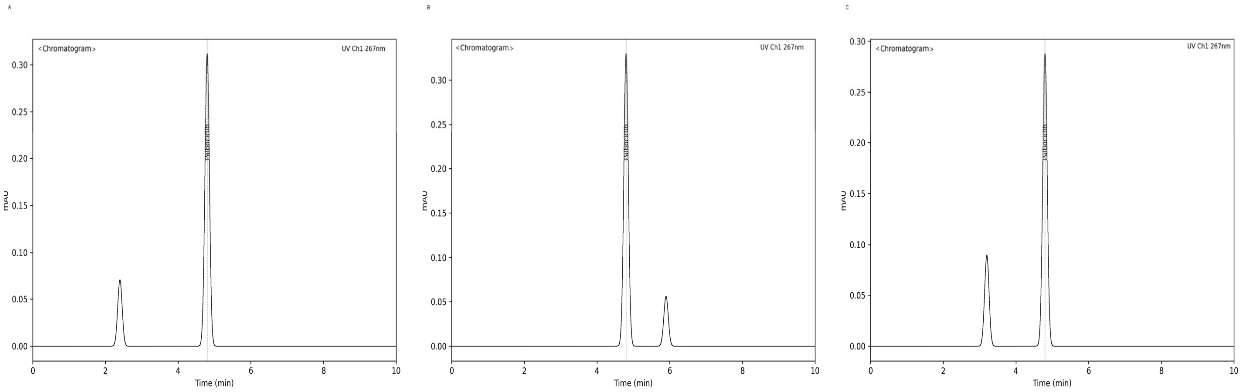
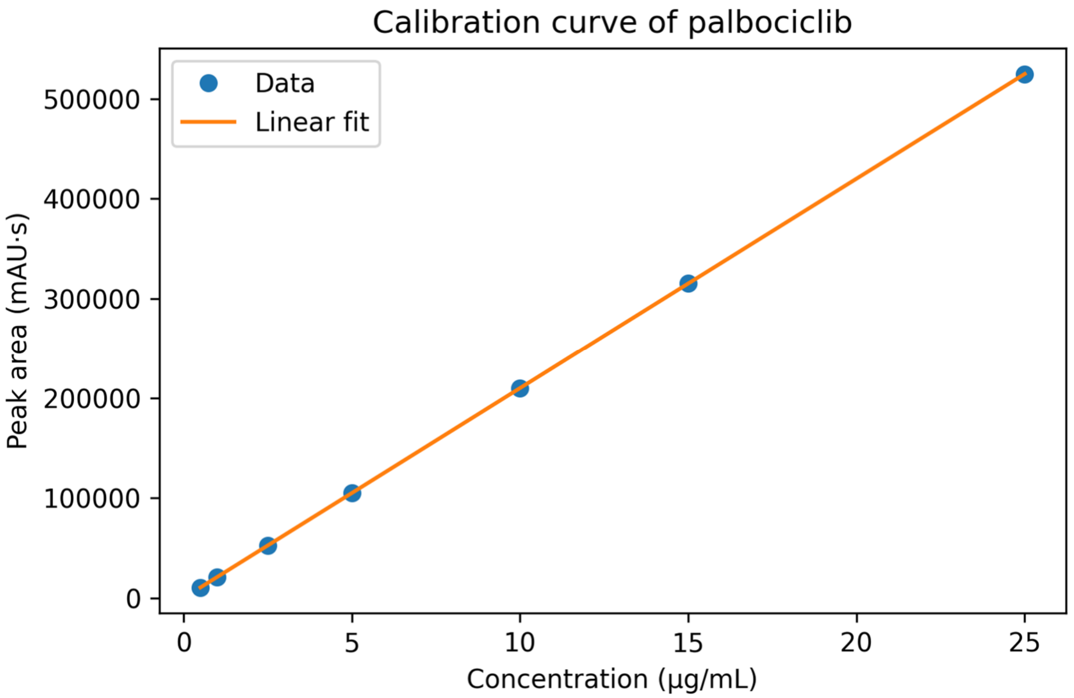


Figure 3. Calibration curve of palbociclib over 0.5–25 µg/mL.



3.6. Degradation kinetics

Kinetic evaluation was performed for acidic and oxidative degradation by linear regression of ln(% remaining) versus time, consistent with pseudo-first-order behavior under the experimental conditions. Kinetic parameters derived from the tabulated results are summarized in Table 7, and the corresponding kinetic plots are shown in Figures 4–5. [Note: the thesis narrative reports a first-order rate constant for acidic degradation; regression of the tabulated values yields a slightly different estimate, which should be verified against the original non-rounded data prior to submission.]

Table 7. First-order kinetic parameters for palbociclib degradation.

Condition	**Regression (ln% vs time)**	**R^2**	**k_1 (min^{-1})**	**t½ (min)**
Acidic (1 N HCl, 60 °C)	ln% = -0.002838·t + 4.5867	0.99366	0.002838	244.18
Oxidative (3% H_2O_2, 60 °C)	ln% = -0.003382·t + 4.5654	0.98338	0.003382	204.91

Figure 4. Acidic degradation kinetics (ln% remaining vs time).

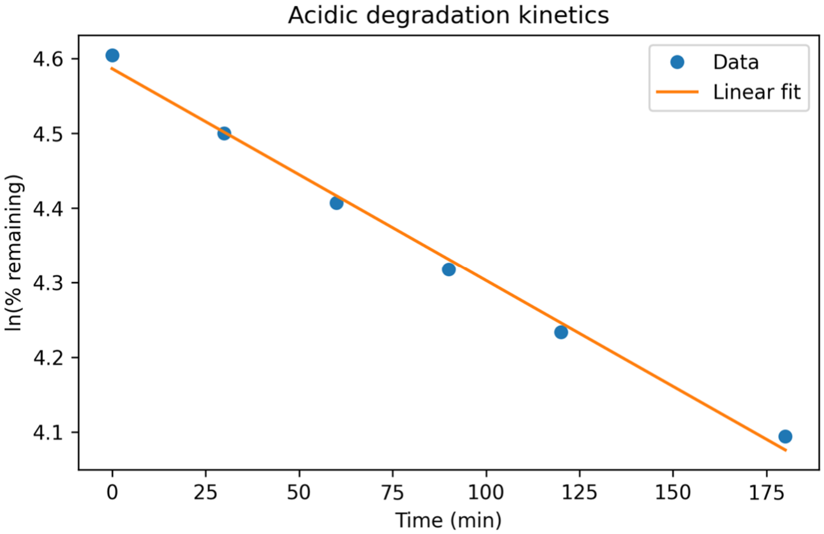
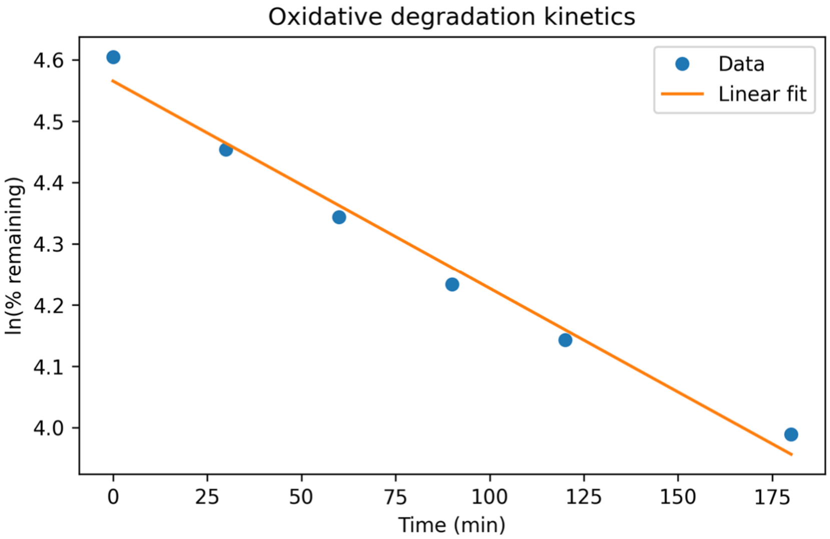


Figure 5. Oxidative degradation kinetics (ln% remaining vs time).



4. Conclusion

A rapid and stability-indicating RP-HPLC-UV method was developed for palbociclib assay in bulk drug and capsules. Validation results met ICH Q2(R1) expectations for system suitability, specificity, linearity, accuracy, precision, sensitivity, and robustness. Forced degradation demonstrated that the method can resolve palbociclib from degradation products, supporting its application in stability testing. Kinetic evaluation under acidic and oxidative stress further characterized degradation behavior relevant to stability studies and regulatory submissions.

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