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A Review on Analytical Method Development and Validation of Palbociclib

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Abstract

In this review article determines the different analytical methods for the quantitative establishment of Palbociclib by using HPLC, HPLCMS, HPLC-UV, LC-MS/MS. Pharmaceutical analytical method development of Palbociclib requires valid analytical procedures for quantitative and qualitative analysis in Pharmaceuticals dosage formulations and human serum. This assessment explains that the superiority of the HPLC/LC-MS methods reviewed is based on the quantitative analysis of drugs in formulations, (API), biological fluids such as serum and plasma.

Keywords: Method development, High performance Liquid Chromatography HPLC/LCMS, Palbociclib.

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Introduction

Palbociclib, sold under the brand name Ibrance among others, is a medication developed by Pfizer for the treatment of HR-positive and HER2-negative breast cancer. It is a selective inhibitor of the cyclin-dependent kinases CDK4 and CDK6 [1][2]. Palbociclib was the first CDK4/6 inhibitor to be approved as a cancer therapy [3].

Mechanism of action

It is a selective inhibitor of the cyclin-dependent kinases CDK4 and CDK6.In the G1 phase of the cell cycle, mammalian cells must pass a checkpoint, known as the restriction point "R", in order to complete the cell cycle and divide. CDK4 and CDK6 complex with cyclin D drive the phosphorylation of the retinoblastoma protein, Rb, which allows the cell to pass R and commit to division. [4] Regulation of one or more proteins involved in this checkpoint is lost in many cancers. However, by inhibiting CDK4/6, Palbociclib ensures that the cyclin D-CDK4/6 complex cannot aid in phosphorylating Rb. This prevents the cell from passing R and exiting G1, and in turn from proceeding through the cell cycle [4].

Administration

Palbociclib is taken daily orally with food in a cycle of 21 days of active medication followed by 7 without. Currently Palbociclib is prescribed as a combination therapy with either Letrozole or fulvestrant. [5] Patients should also not consume CYP3A inhibitors or inducers while taking Palbociclib. FDA information also cautions against consuming grapefruit products while taking Palbociclib.

Literature Review of Palbociclib

D. Srikanth's A new gradient RP-HPLC method was developed for the separation and determination of process related impurities in Palbociclib. Methodology: The chromatographic separation was achieved on a Inert sustain swift (C18) column using a mobile phase comprising of perchloric acid and acetonitrile in a gradient mode at a flow rate of 1 mL/min. over a runtime of 50 minutes. All the eluants were monitored at 230 nm. The optimized method was validated as per ICH guidelines for various parameters. Results: The linearity of the method was proposed in the range of LOQ to 250 % for the drug and its impurities by subjecting the data obtained to statistical analysis using correlation coefficient model ($r > 0.99$). The method also gave acceptable recovery of all the four impurities at each level and was found to be accurate. The % RSD obtained in the method precision and intermediate precision were less than 2% depicting the precision of

the method. The LOD and LOQ values were calculated based on the signal to noise ratio and are indicating the sensitivity of the method. The specificity of the method was checked in the presence of process related impurities and also degradants generated by exposing to a variety of forced degradation conditions. Conclusion: The proposed RP-HPLC method for the determination of process related impurities of Palbociclib could be routinely used in the quality control testing.

Bianca Posocco et al a novel LC-MS/MS method was developed for the quantification of the new cyclin dependent kinase inhibitors (CDKIs) Palbociclib and ribociclib and the aromatase inhibitor letrozole used in combinatory regimen. The proposed method is appropriate to be applied in clinical practice due to the simple and fast sample preparation based on protein precipitation, the low amount of patient sample necessary for the analysis (10 μL) and the total run time of 6.5 min. It was fully validated according to FDA and EMA guidelines on bioanalytical method validation. The linearity was assessed (R^2 within 0.9992–0.9983) over the concentration ranges of 0.3–250 ng/mL for Palbociclib, 10–10000 ng/mL for ribociclib and 0.5–500 ng/mL for letrozole that properly cover the therapeutic plasma concentrations. A specific strategy was implemented to reduce the carryover phenomenon, formerly known for these CDKIs. This method was applied to quantify the Cmin of Palbociclib, ribociclib and letrozole in plasma samples from patients enrolled in a clinical study. The same set of study samples was analysed twice in separate runs to assess the reproducibility of the method by means of the incurred samples reanalysis. The results corroborated the reliability of the analyte concentrations obtained with the bioanalytical method, already proved by the validation process. The percentage differences were always within ±10% for all the analytes and the R^2 of the correlation graph between the two quantifications was equal to 0.9994.

Rahul D. Rathod's Four different simple, accurate and precise UV-spectrophotometric methods have been developed for the estimation of Palbociclib (PB) in bulk and in-house capsule dosage form by zero order (Method I), zero order AUC (Method II), 'first order derivative UV-spectrophotometric (Method III), and first order AUC (Method IV) methods. The drug was dissolved in methanol (AR-Grade) and further dilution was made in double distilled water. Zero order was performed at λ max 220.00 nm of PB (Method I) and AUC was calculated between 215.40 nm - 228.20 nm wavelength (Method II). In Method-III zero-order spectra were derivatized into first-order and amplitude measured at 231.00 nm and the AUC was recorded between 224.00 nm - 240.60 nm (Method IV). PB followed linearity in the concentration range of 4.08-20.40 μg/mL with correlation coefficient (r2)> 0.99 for PB.

Mona M Alshehri et al a sensitive and selective UHPLC-MS/MS method was developed and validated to simultaneously determine of Palbociclib (PLB), Letrozole (LTZ) and its metabolite carbinol (CBL) in rat plasma. After sample pre-treatment by acetonitrile-protein precipitation, the chromatography's resolution was performed using a reversed phase Acquity® UPLC BEH C18 column (1.7 μm particle size, 50 mm × 2.1 mm ID) in isocratic mobile phase consisted of a mixture of methanol and water containing 0.1% acetic acid (55:45, v/v) at pH 4.5. The flow rate and run time were 300 μL/min and 2.5 min, respectively. The target drugs were detected in multiple reaction monitoring (MRM) mode using tandem mass spectrometer coupled to a positive ESI interface to monitor the precursor-to-product ion transitions. Method validation was assessed as per the FDA guidelines for determination of PLB, LTZ and CBL within the concentration ranges 0.5–600 ng/mL for PLB and LTZ and 0.2–200 ng/mL for CBL (r2 ≥ 0.997). The rest of validation parameters were within the accepted limits. The validated method was applied to PK study of these drugs in rats, and succeeded to determine the values of the PK parameters of PLB and LTZ.

Alejandra Martínez Chávez et al A novel method was developed and validated for the quantification of the three approved CDK4/6 inhibitors (abemaciclib, Palbociclib, and ribociclib) in both human and mouse plasma and mouse tissue homogenates (liver, kidney, spleen, brain, and small intestine) using liquid chromatography coupled to tandem mass spectrometry (LC-MS/MS). For all matrices, pre-treatment was performed using 50 μL of sample by protein precipitation with acetonitrile, followed by dilution of the supernatant. Chromatographic separation of the analytes was done on a C18 column using gradient elution. A full validation was performed for human plasma, while a partial validation was executed for mouse plasma and mouse tissue homogenates. The method was linear in the calibration range from 2 to 200 ng/mL, with a correlation coefficient (r) ≥0.996 for each analyte. For both human and mouse plasma, the accuracy and precision were within ±15% and ≤15%, respectively, for all concentrations, except for the lower

limit of quantification, where they were within ±20% and ≤20%, respectively. A fit-for-purpose strategy was followed for tissue homogenates, and the accuracy and precision were within ±20% and ≤20%, respectively, for all concentrations. Stability of all analytes in all matrices at different processing and storage conditions was tested; ribociclib and Palbociclib were unstable in most tissue homogenates and conditions were modified to increase the stability. The method was successfully applied for the analysis of mouse samples from preclinical studies. A new ribociclib metabolite was detected in mouse plasma samples with the same m/z transition as the parent drug.

REVU, BABY et al A rapid, sensitive, selective, and reproducible reversed-phase high-performance liquid chromatographic method has been developed and validated for the determination of crizotinib (CRZ), a tyrosine kinase inhibitor for targeted therapy of anaplastic lymphoma kinase-positive non-small-cell lung cancer. Methods: The chromatographic separation was carried out in an isocratic mode on an YMC ODS C18 column with a mobile phase consisting of methanol and water containing 0.1% orthophosphoric acid in the ratio of 50:50 v/v at a flow rate of 0.6 ml/min. The run time was maintained for 10 min and detection was monitored at 267 nm. The method involved reproducible liquid-liquid extraction of drug from human plasma using diethyl ether as extracting solvent. Results: CRZ and internal standard retention times were 6.86 and 7.94 min, respectively. Calibration curves were linear over a concentration range of 20.41–2041.14 ng/ml with correlation coefficient 0.9994. The lower limit of quantification for CRZ in plasma was 20 ng/ml. No endogenous substances were found to interfere with the peaks of drug and internal standard. The intra- and inter-day precision was <9.0% and the accuracy ranged from 97% to 112% over the linear range. All stability studies showed that CRZ in plasma sample was stable. Conclusion: This method was found to be simple, selective, precise, accurate, and cost-effective. Hence, the method can be successfully applied to analyse the CRZ concentration in plasma samples for pharmacokinetic and bioequivalence studies.

Yuvraj Dangeet al a simple, rapid, and robust RP-HPLC method have been developed and validated to measure Palbociclib (PB) and Letrozole (LT) at single wavelength (254 nm). A isocratic elution of samples performed on Intersil C_8 (4.6 mm × 250 mm particle size 5 μm) column with mobile phase consisting 0.02 M sodium dihydrogen phosphate buffer (pH 5.5): acetonitrile: methanol (80:10:10 v/v/v) delivered at flow rate 1.0 mL min^{-1}. A good linear response was achieved over the range of 5-50 μg mL^{-1}. The LODs for PB and LT were found to be 0.098 and 0.0821 μg mL^{-1}, while the LOQs for PB and LT were 0.381-0.315 μg mL^{-1}, respectively. The method was quantitatively evaluated in terms of system suitability test, linearity, precision, accuracy (recovery) and robustness as per standard guidelines. The method is simple, convenient and suitable for the analysis of PB and LT in bulk drug.

Pramadvara Kallepall et al A simple, sensitive stability-indicating reversed-phase Palbociclib. Palbociclib is an anticancer drug used for the treatment of breast cancer. It is a selective inhibitor of cyclin-dependent kinases. Materials and Methods: Waters Model 2695 alliance HPLC system (PDA Detector) with Inertsil ODS- 3V (4.6 mm × 250 mm, 5 μm) was used for the chromatographic separation. Mobile phase consisting of ammonium acetate: acetonitrile (32:68, v/v) was delivered at a flow rate of 1.0 ml/min (detection wavelength 263 nm) on isocratic mode for the chromatographic study. Results and Discussion: Palbociclib obeys Beer Lambert's Law over a concentration range 5–1000 μg/ ml. The limit of detection and limit of quantification are found to be 1.6378 and 4.951 μg/ml. The method was validated as per the ICH guidelines. Forced degradation studies were conducted, and the method was found to be specific. Conclusion: The present RP-HPLC method is simple, precise, and accurate and can be used for the routine analysis of pharmaceutical formulations.

Y.D. Dange et al A simple, rapid, and robust RP-HPLC method have been developed and validated to measure Palbociclib and Letrozole at single wavelength (254 nm). A isocratic elution of samples performed on Intersil C8 (4.6 mm x 250 mm particle size 5 μm) column with mobile phase consisting 0.02M sodium dihydrogen phosphate buffer (pH 5.5): acetonitrile: methanol (80: 10: 10 v/v/v) delivered at flow rate 1.0 mL min^{-1}. A good linear response was achieved over the range of 5-50 μg mL^{-1}. The LODs for Palbociclib and Letrozole were found to be 0.098 and 0.0821 μg mL^{-1}, while the LOQs for Palbociclib and Letrozole were 0.381 to 0.315 μg mL^{-1}, respectively. The method was quantitatively evaluated in terms of system suitability test, linearity, precision, accuracy (recovery) and robustness as per standard guidelines. The method is simple, convenient and suitable for the analysis of Palbociclib and Letrozole in bulk drug.

Wilson, Florence et al To compare Palbociclib + Letrozole and Palbociclib + fulvestrant with

chemotherapy agents in postmenopausal women with hormone receptor-positive (HR+)/human epidermal growth factor receptor 2-negative (HER2-) advanced/metastatic breast cancer (ABC/MBC) who had no prior systemic treatment for advanced disease (first line) or whose disease progressed after prior endocrine therapy or chemotherapy (second line). Methods: A systematic search identified randomized controlled trials (RCTs) published from January 2000 to January 2016 that compared endocrine-based therapies, chemotherapy agents, and/or chemotherapy agents + biological therapies in the first- and second-line treatment of postmenopausal women with HR+/HER2- ABC/MBC. The main outcome of interest was progression-free survival (PFS)/time to progression (TTP). Bayesian network meta-analyses (NMAs) and pairwise meta-analyses were conducted. Heterogeneity and inconsistency were assessed. Results: Sixty RCTs met eligibility criteria and were stratified by line of therapy. In the first line, Palbociclib + Letrozole showed statistically significant improvements in PFS/TTP versus capecitabine [intermittent: HR 0.28 (95% CrI 0.11-0.72)] and mitoxantrone [HR 0.28 (0.13-0.61)], and trended toward improvements versus paclitaxel [HR 0.59 (0.19-1.96)], docetaxel [HR 0.51 (0.14-2.03)] and other monotherapy or combination agents (HRs ranging from 0.24 to 0.99). In the second line, Palbociclib + fulvestrant showed statistically significant improvements in PFS/TTP versus capecitabine [intermittent: HR 0.28 (0.13-0.65)], mitoxantrone [HR 0.26 (0.12-0.53)], and pegylated liposomal doxorubicin [HR 0.19 (0.07-0.50)], and trended toward improvements versus paclitaxel [HR 0.48 (0.16-1.44)], docetaxel [HR 0.71 (0.24-2.13)] and other monotherapy or combination agents (HRs ranging from 0.23-0.89). NMA findings aligned with direct evidence and were robust to sensitivity analyses. Conclusions: Palbociclib + Letrozole and Palbociclib + fulvestrant demonstrate trends in incremental efficacy compared with chemotherapy agents for the first- and second-line treatment of HR +/HER2- ABC/MBC.

Julia A. Beaver's et al On February 3, 2015, the FDA granted accelerated approval to Palbociclib (IBRANCE®, Pfizer Inc.), an inhibitor of cyclin dependent kinases 4 and 6 (CDK4 and CDK6), for use in combination with letrozole for the treatment of postmenopausal women with estrogen receptor (ER)-positive, HER2-negative advanced breast cancer as initial endocrine-based therapy for their metastatic disease. The approval is based on a randomized, multicentre, open-label Phase 1/2 trial (PALOMA-1) in 165 patients randomized to Palbociclib (125mg orally daily for 21 consecutive days, followed by 7 days off treatment) plus letrozole (2.5mg orally daily) or letrozole alone. The Phase 2 portion of the trial was divided into two cohorts: Cohort 1 enrolled 66 biomarker-unselected patients and Cohort 2 enrolled 99 biomarker-positive patients. The major efficacy outcome measure was investigator-assessed progression-free survival (PFS). A large magnitude of improvement in PFS was observed in patients receiving Palbociclib plus Letrozole compared to patients receiving letrozole alone [HR 0.488 (95% CI: 0.319, 0.748)]. Multiple sensitivity analyses were supportive of clinical benefit. The most common adverse reaction in patients receiving Palbociclib plus Letrozole was neutropenia. This article summarizes the FDA thought process and data supporting accelerated approval based on PALOMA-1 which may be contingent upon verification and description of clinical benefit in the on-going and fully accrued confirmatory trial, PALOMA-

CONCLUSION

A sensitive and accurate RP-HPLC methods, stability-indicating HPLC, HPLC-PDA, HPLC-UV, stability indicating HPTLC and HPLC-MS, was developed for the estimation of Palbociclib, in pharmaceutical dosage forms, human plasma, the above methods was evaluated for Specificity, Linearity, Accuracy, Precision, Ruggedness and Robustness as per ICH&FDA guidelines.

References

1. Konatham Teja Kumar Reddy, & M. Akiful Haque. (2022). Develop and validate a highly sensitive method for the estimation of Molnupiravir in rat plasma by high-performance liquid chromatography-tandem mass spectroscopy and its application to pharmacokinetic studies. *Journal of Pharmaceutical Negative Results*, 28–34. https://doi.org/10.47750/pnr.2022.13.S01.0
2. Konatham Teja Kumar Reddy, Penke Vijaya Babu, Rajinikanth Sagapola, & Peta Sudhakar. (2022). A REVIEW OF ARTIFICIAL INTELLIGENCE IN TREATMENT OF COVID-19. *Journal of Pharmaceutical Negative Results*, 254–264. https://doi.org/10.47750/pnr.2022.13.S01.31
3. Konatham Teja Kumar Reddy, Kumaraswamy Gandla, Penke Vijaya Babu, M Vinay Kumar Chakravarthy, Pavuluri Chandrasekhar, & Rajinikanth Sagapola. (2022). A CRITICAL REVIEW ON BIOANALYTICAL METHOD

DEVELOPMENT AND VALIDATION OF FEW ONCOLOGY DRUGS BY USING LC-MS-MS. *Journal of Pharmaceutical Negative Results*, 16–27. https://doi.org/10.47750/pnr.2022.13.S01.03

4. Reddy, K. T. K., & Haque, M. A. (2022). Bioanalytical method development and validation of atrasentan in human plasma using verapamil as internal standard by liquid chromatography coupled with tandem mass spectrometry. International Journal of Health Sciences, 6(S8), 625–638. https://doi.org/10.53730/ijhs.v6nS8.10470
5. Konatham Teja Kumar Reddy et.al High Performance Liquid Chromatography for The Simultaneous Estimation of Anti-Ulcer Drugs in Pharmaceutical Dosage Form, journal of Positive School Psychology, Vol. 6, No. 9, 4524-452
6. Reddy KTK, Haque MA. Development and Validation of a High Throughput Lc-Ms/MS Method for Quantitation of Ipilimumab in Human Plasma. International Journal of Pharmaceutical Quality Assurance. 2022;13(3):303-307
7. Teja Kumar Reddy Konatham, M. Anuradha (2020), a stability indicating method development and validation of Telmisartan and Nifedipine in pure form using RP-HPLC. International Journal of Pharmaceutical, Biological and Chemical Sciences, 9(3): 36-44
8. Teja Kumar Reddy Konatham, Satyanarayana Reddy K., Anuradha Manipogo, a Review on viruses that originated from china; Sars, mers and covid-19 World Journal of Pharmaceutical Research, Vol 9, Issue 5, 2020, 2010-2015.
9. Teja Kumar Reddy Konatham et al, A Systematic Review on Method Development and Validation of Few Antiviral Drugs by Using RP-HPLC. Ijppr.Human, 2021; Vol. 21 (3): 651-661.
10. Konatham Teja Kumar Reddy and Kumaraswamy Gandla. Novel Vesicular Drug Delivery Systems Proniosomes. Pharm Res 2022, 6(3): 000272.
11. Konatham et al. synthesis and evaluation of some novel oxadiazole derivatives, World Journal of Pharmaceutical Research, Vol 9, Issue 4, 2020.
12. BaigShahed Mirza, Haque Akiful Mohammad, Konatham Reddy Teja Kumar, Mohammad DuzaBadrud, YahyaAateka Barrawaz, Saffiruddin Sana Shaikh, Siddiqui A. Falak and Khan L. Sharuk*, Recent Advancements in Hyperthermia-Driven Controlled Drug Delivery from Nanotherapeutics, Recent Advances in Drug Delivery and Formulation 2022; 16(4) . https://dx.doi.org/10.2174/2667387816666220902091043
13. Yelampalli, Suresh Reddy, Kumaraswamy Gandla, Konatham Teja Kumar Reddy, Adel Ehab Ibrahim, and Sami El Deeb. 2023. "Determination of Sodium, Potassium, and Magnesium as Sulfate Salts in Oral Preparations Using Ion Chromatography and Conductivity Detection" *Separations* 10, no. 2: 99. https://doi.org/10.3390/separations10020099
14. Teja, M.; Konatham, T.; Muralidharan, V.; Murugesan, A.; Vasantha, N.; Hyandavi, M. A Review on Biosensors for COVID-19. *IJAPSR* 2022, *7*, 9-14.
15. K. Sudheer Kumar / "Formulate and evaluate the herbal bath soap" using extracts of three plants having ethnic and dermatological importance in Ayurveda, namely Azadirecta indica, curcuma longa, osmium tenuiaflorum "NEUROQUANTOLOGY | OCTOBER 2022 | VOLUME 20 | ISSUE 12 | PAGE 1048-1054| DOI: 10.14704/NQ.2022.20.12. NQ77087
16. Tallam AK, Sahithi A, Nuli MV. A review on different kinds of analytical methods are performed for the analysis of food preservatives in food. J Inn App Pharma Sci [Internet]. 2023Feb.25 [cited 2023Mar.30];8(1):1-10. Available from: https://saap.org.in/journals/index.php/jiaps/article/view/414
17. Tallam AK, Sahithi A, Nuli MV. Evaluation of antibacterial property of anthyocyanin extracted from brassica oleracea against gram positive and gram negative bacteria by using erythromycin as a standard drug. Int J Indig Herb Drug [Internet]. 2023Feb.19 [cited 2023Mar.30];8(1):1-. Available from: https://saap.org.in/journals/index.php/herbsanddrugs/article/view/415
18. Tallam, A. K., A. Sahithi, and M. V. Nuli. "A Review on Phytosomes As Innovative Delivery Systems for Phytochemicals". *International Journal of Pharmacognosy and Chemistry*, Vol. 4, no. 1, Feb. 2023, pp. 1-8, doi:10.46796/ijpc.v4i1.416
19. Tallam, A. K., S. Alapati, and M. V. Nuli. "A Review of Analytical Techniques for

Determination of Metformin: Present and Perspectives". *International Journal of Health Care and Biological Sciences*, Vol. 4, no. 1, Feb. 2023, pp. 18-24, doi:10.46795/ijhcbs.v4i1.417.

20. Tallam, A. K., Alapati, S., & Nuli, M. V. (2023). A review on bioanalytical method development and validation of anticancer drugs by using lc/ms/ms and its applications on routine analysis. Journal of Integral Sciences, 6(1), 4-19. https://doi.org/10.37022/jis.v6i1.5
21. Tallam, A. K., Alapati, S., & Nuli, M. V. (2023). RP-HPLC method for analytical method development and validation of multi-kinase inhibitor. *Journal of Integral Sciences*, *6*(1), 20-26. https://doi.org/10.37022/jis.v6i1.52