Int J. Curr Inn Adv Res, Vol: 6, Issue: 1, 2023; 30-35

Review Article

International Journal of Current Innovations in Advanced Research

Content Available at www.ijciar.com ISSN (O) 2636-6282 ISSN (P) 2659-1553

OVERALL REVIEW ON ANNALYTICAL METHOD DEVELOPMENT AND VALIDATION OF CABOZANTINIB

Mohana Vamsi Nuli*

Associate Professor, Raghavendra Institute of Pharmaceutical Education and Research K.R. Palli Cross, Dist Anantapuramu, Chiyyedu, Andhra Pradesh 515721

***Corresponding Author**

Mohana Vamsi Nuli

DOI: https://doi.org/10.47957/ijciar.v6i1.147

Received: 29 Jan 2023 Revised: 11 Mar 2023 Accepted: 28 March 2023

Abstract

In this review article determines the different analytical methods for the quantitative establishment of Cabozantinib by using HPLC, HPLCMS, HPLC-UV, LC-MS/MS. Pharmaceutical analytical method development of Cabozantinib 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, Cabozantinib**.**

Introduction

Cabozantinib, sold under the brand names Cometriq and Cabometyx among others, is a medication used to treat medullary thyroid cancer, renal cell carcinoma, and hepatocellular carcinoma. It is a small molecule inhibitor of the tyrosine kinases c-Met and VEGFR2, and also inhibits AXL and RET. It was discovered and developed by Exelixis Inc.

In November 2012, Cabozantinib in its capsule formulation was approved by the U.S. Food and Drug Administration (FDA) under the name Cometriq for treating patients with medullary thyroid cancer. [1][2] The capsule form was approved in the European Union for the same purpose in 2014. [3]

In April 2016, the FDA granted approval for marketing the tablet formulation (Cabometyx) as a second line treatment for kidney cancer [4][5] and the same was approved in the European Union in September of that year. [9]The brands Cometriq and Cabometyx have different formulations and are not interchangeable.

Interactions

Grapefruit and grapefruit juice should be avoided as they may increase the concentration of the drug in the blood.

Cabozantinib is a substrate of CYP3A4 and multidrug resistance-associated protein 2; drugs that inhibit these enzymes will increase the half-life of Cabozantinib and potentially increase its adverse effects; drugs that activate them may cause Cabozantinib to be less effective. [10]

It inhibits P-glycoprotein, so will change the availability of other drugs that depend on this transporter.

Pharmacology

It inhibits the following receptor tyrosine kinases: MET (hepatocyte growth factor receptor protein) and VEGFR, RET, GAS6 receptor (AXL), KIT), and Fms-like tyrosine kinase-3 (FLT3).

History

Cabozantinib was granted orphan drug status by the U.S. Food and Drug Administration (FDA) in November 2010, and in February 2017.

Exelixis filed a new drug application with the FDA in the first half of 2012, and on November 29, 2012, Cabozantinib in its capsule formulation was granted marketing approval by the U.S. FDA under the name Cometriq for treating patients with medullary thyroid cancer. The capsule form was approved in the European Union for the same purpose in 2014.

In March 2016 Exelixis licensed to Ipsen worldwide rights (outside the US, Canada, and Japan) to market Cabozantinib.

Exelixis' Phase III trial results of testing the drug in renal cancer published in the NEJM in 2015. In April 2016 the FDA granted approval for marketing the tablet formulation as a second line treatment for kidney cancer and the same was approved in the European Union in September of that year.

In December 2017, the FDA granted approval to Cabozantinib (Cabometyx, Exelixis, Inc.) for treatment of people with advanced renal cell carcinoma (RCC). The approval was based on data from CABOSUN (NCT01835158), a randomized, open-label phase II multicenter study in 157 participants with intermediate and poor-risk previously untreated RCC.

In January 2019, the FDA approved Cabozantinib (Cabometyx, Exelixis, Inc.) for people with hepatocellular carcinoma (HCC) who have been previously treated with sorafenib. The approval was based on CELESTIAL (NCT01908426), a randomized (2:1), double-blind, placebo-controlled, multicenter trial in participants with HCC who had previously received sorafenib and had Child Pugh Class A liver impairment.

Research

Cabozantinib is being researched[23] for efficacy as a treatment for renal cell carcinoma (RCC), hepatocellular carcinoma (HCC), cervical cancer, colorectal cancer (CRC), urothelial cancer, prostate cancer, gastric and gastroesophageal cancer, bladder cancer, melanoma, merkel cell carcinoma, brain cancers (including glioblastoma multiforme and anaplastic astrocytoma), non-small cell lung cancer (NSCLC), adrenocortical carcinoma, various sarcomas, head and neck squamous cell carcinomas (HNSCC), breast cancer, endometrial cancer, neuroendocrine cancers, and neurofibromatosis type 1.[24]

Literature Review of Cabozantinib

Punna Venkateshwarlu et., al Reported that the objective of this method is to be simple, precise, and economical performed by LC-MS/MS instrument. The mass spectrometric determination was performed using electrospray ionization in the positive mode with multiple reaction monitoring (MRM) mode and precursor to product ion transition to product ion of m/z 502.2 > 323 for Cabozantinib. The effective separation of Cabozantinib was achieved X-Bridge (2.1 mm × 100 mm, 3.5 µ) column and the mobile phase composition is 0.2% formic acid: acetonitrile (40:60 v/v), pumped at 0.12 ml/min flow rate. The Rt of Cabozantinib was found to be 1.34 minutes. The LOD and LOQ were found at 1.5 ng/ml and 5 ng/ml concentrations and linearity concentrations were in a range of 5 ng/ml to 75 ng/ml with a regression correlation coefficient of 0.999. The % RSD value of accuracy was observed at 1.2–2.0. The marketed formulation assay was found to be 99.82%. The developed method and validation parameters were accepted as per USFDA guidelines.

K.E.Pravallika et., al reported that A simple, sensitive and rapid chromatographic method was developed and validated for simultaneous quantification of Cabozantinib and Nivolumab in rat plasma using Alectinib as internal standard. The samples were assayed by the Waters alliance e-2695 HPLC instrument using Symmetry C18 column (150x4.6mm, 3.5µ) under isocratic condition. Here the buffer was Triethyl amine at pH 2.5 adjusted with OPA. Mobile phase used was 0.1% TEA and Acetonitrile (70:30) with a flow rate of 1ml/min. The eluent was monitored at 219nm for simultaneous measurement of Cabozantinib and Nivolumab. The calibration curves were linear over the range of 1- 20µg/ml of Cabozantinib and 0.1-2µg/ml of Nivolumab. The method was validated in terms of system suitability, selectivity, sensitivity, accuracy, precision, recovery, matrix effect, linearity and stability. The % RSD of peak areas of all measurements always less than 2. The proposed method was specific for the simultaneous determination of Cabozantinib and Nivolumab in rat plasma.

Gopinath k, et.al reported that The present paper describes a simple, accurate, and precise reversed-phase high-performance liquid chromatography (HPLC) method for rapid and simultaneous quantification of Cabozantinib (CZT) and Nivolumab (NVM) in bulk and pharmaceutical dosage form. The chromatographic separation was achieved on Luna C18 (150 mm×4.6 mm, 3.5 µm). Mobile phase contained a mixture of 0.1% orthophosphoric acid and acetonitrile in the ratio of 50:50 v/v, flow rate 1.0 ml/min, and ultraviolet detection at 222 nm. The proposed method shows a good linearity in the concentration range of 20–300 µg/ml for CZT and 5–75 µg/ml for NVM under optimized conditions. Precision and recovery study results are in between 98 and 102%.

Srikanth Inturi et., al reported thatA simple, sensitive and specific liquid chromatography–tandem mass spectrometry (LC-MS/MS) method was developed for the quantification of Cabozantinib (CZ) in human plasma using cabozantinib-d4 (CZD4) as an internal standard (IS). Chromatographic separation was performed on Xbridge C18, 50 x 4.6 mm, 5 mm

column with an isocratic mobile phase composed of 10mM Ammonium formate and Methanol in the ratio of (20:80 v/v), at a flow-rate of 0.7 mL/min. CZ and CZD4 were detected with proton adducts at m/z 502.2 → 391.1 and 506.3 → 391.2 in multiple reaction monitoring (MRM) positive mode respectively. Liquid-Liquid extraction method was used to extract the drug and IS. The method was validated over a linear concentration range of 5.0-5000.0 pg/mL with correlation coefficient (r2) ≥ 0.9994. This method demonstrated intra and inter-day precision within 1.95 to 2.37 and 2.93 to 9.3 % and Accuracy within 101.4 to 102.4 and 99.5 to 104.8 %. Cabozantinib was found to be stable throughout freeze-thawing cycles, bench top and postoperative stability studies.

Amruta A. Chaudhary et,al reported that A specific, accurate Rp-Hplc (reversed-phase high performance liquid chromatographic) method was developed for the quantification of Cabozantinib. The effective separation was achieved through reversed-phased C18 column 4.6 x 250 mm, 5µm using a mobile phase Methanol: phosphate buffer (ph. 3.00) with orthophosphoric acid (OPA) (55:45 % v/v). The flow rate of the mobile phase was found to be 0.8 mL/min. The detection was carried at a wavelength of 244 nm. The retention time of Cabozantinib was found to be 3.702 min. The correlation coefficient was found to be 0.9999. The developed method was accurately validated in the terms of accuracy, linearity range, precision, system suitability, robustness, limit of detection and limit of quantification. The details presented in this test will be useful for industrial application for determining Cabozantinib in active pharmaceutical ingredient and pharmaceutical dosage form.

A. K. Kuna et., al reported that A simple, specific, accurate reversed-phase high performance liquid chromatographic method was developed for the quantification of Cabozantinib. Although extensive studies on Cabozantinib have been developed for determining Cabozantinib in human place and urine by LC-MS, studies on the pharmaceutically active ingredient and formulation are scarce. The effective separation was achieved through BDS C18 150 × 4.6 mm, 5m using a mobile phase KH_2PO_4 Buffer and ACN (55:45% v/v). The flow rate of the mobile phase was 1.0 mL/min, and the detection was carried at a wavelength of 210 nm. The retention time of Cabozantinib was 2.932 nm. The correlation coefficient is 0.9998. The developed method was validated in terms of system suitability, specificity, linearity range, precision, accuracy, limits of detection and quantification. Degradation studies were performed on Cabozantinib to indicate the stability property and specificity of the proposed method. The information presented in this study will be useful for industrial application for determining Cabozantinib in active pharmaceutical ingredient and pharmaceutical dosage form.

Bhavani Podili et.al reported thatThe present work describes the development and subsequent validation of a novel, simple, selective and stability indicating gradient reversed phase high performance liquid chromatography method for the quantitative determination of related substances, assay of Cabozantinib and Nivolumab and its application to dissolution studies. The chromatographic method was optimized using the impurity-spiked solution. A good resolution between the peaks was achieved under selected chromatographic conditions. The separation was accomplished on an X-Bridge C18, 150×4.6 mm, 3.5 µ column connected to a photo diode array detector using 0.1 % orthophosphoric acid in water as mobile phase A and acetonitrile as mobile phase B, under gradient elution. The mobile phase flow rate was maintained at 1.0 ml/min. The detection of the constituents was done at 216 nm using a ultra-violet detector. Recovery studies were satisfactory and the correlation coefficient for two active pharmaceutical ingredients and their related substances, 0.999 indicates the linearity of the method within the limits. Limit of detection and limit of quantification for all impurities and Cabozantinib and Nivolumab were established with respect to the test concentration. Specificity, accuracy, precision, ruggedness and robustness were determined as part of the method validation. The performance of the method was validated according to the current International Council for Harmonization requirements. Moreover, the dissolution study was performed on active pharmaceutical ingredients to estimate the recovery using the same method. Validation of the developed reversed phase high performance liquid chromatography procedure revealed that all the degradation products formed during stress conditions and related impurities were well separated from their active pharmaceutical ingredients and peaks were well resolved from each other with appropriate retention time. The method was characterized by good linearity, specificity, low values of limit of detection and quantization, accuracy, precision, ruggedness and robustness. All statistical results were within the acceptance criteria and the proposed method is simple, fast, accurate, precise and reproducible hence, it can be applied for routine dissolution analysis and employed for quality control of drug samples during stability studies.

Jadhav, Anil G. et.,al reported that A specific, accurate Rp-Hplc (reversed-phase high performance liquid chromatographic) method was developed for the quantification of Cabozantinib. The effective separation was achieved through reversed-phased C18 column 4.6 x 250 mm, 5µm using a mobile phase Methanol: phosphate buffer (ph. 3.00) with

orthophosphoric acid (OPA) (55:45 % v/v). The flow rate of the mobile phase was found to be 0.8 mL/min. The detection was carried at a wavelength of 244 nm. The retention time of Cabozantinib was found to be 3.702 min. The correlation coefficient was found to be 0.9999. The developed method was accurately validated in the terms of accuracy, linearity range, precision, system suitability, robustness, limit of detection and limit of quantification. The details presented in this test will be useful for industrial application for determining Cabozantinib in active pharmaceutical ingredient and pharmaceutical dosage form.

T N V S S Satyadev et,al reported that A reliable, accurate and simple RP-HPLC method was developed for the simultaneous estimation of Cabozantinib and Nivolumab, validated according to ICH guidelines. A column of X-bridge phenyl (150x4.6mm, 3.5µm) with a flow rate of 1ml/min was used. The combination of 0.1% Tri ethyl amine and Acetonitrile in 70:30 ratios was used as a mobile phase. Cabozantinib and Nivolumab peaks were eluted at a retention time of 4.358min, 7.744min respectively. The total run time was 10min. Standard solutions were prepared by dissolving in acetonitrile first and then make up to the mark with mobile phase. The method shows a good linearity in the concentration range of 6-90µg/ml of Cabozantinib and 4-60µg/ml of Nivolumab with correlation coefficient 0.999. This method was validated in terms of specificity, linearity, accuracy, LOD, LOQ, robustness and forced degradation

Adnan A Kadiet,al reported that To develop a simple, adequately sensitive, and practical liquid chromatographic-mass spectrometric method to simultaneously quantify three tyrosine kinase inhibitors, viz, tofacitinib (TOF), Cabozantinib (CBZ) and afatinib (AFB) after their extraction from both human plasma and urine. Blood and urine samples were obtained from healthy volunteers who admitted to not being on any medications. The investigated analytes were chromatographically separated on a C18 column (Luna®-PFP 100Å column, 50 mm × 2.0 mm i.d., 3.0 µm) with the aid of a mobile phase containing A; acetonitrile (ACN) and B; 0.01 M ammonium formate buffer (pH 4.1) pumped at a rate of 0.3 mL.min-1 in the ratio A:B, 50:50 v/v. Analyte monitoring was achieved by tandem mass spectrometry interfaced with an electrospray ionization source with the aid of multiple reaction monitoring (MRM) mode for analytes quantification. Results: The proposed method permitted a specific and sensitive determination of the investigated TKIs in the linear range of 1.0 - 100 ng mL-1 with correlation coefficient (r2) of 0.9991, 0.9997, and 0.9998 for TOF, CBZ and AFB, respectively. The method was validated with regard to its limits of quantification (ranging from 0.91 to 1.24 ng mL-1 for the 3 analytes), intra- and inter assay accuracy (in the range -1.85 to 1.22 %) and precision (0.71 - 5.12 %). The method was also validated in terms of recovery from both studied matrices, robustness and matrix effect. The results obtained reveal that the developed method is simple, specific and highly efficient for routine determination of the studied analytes in human plasma and urine. It can be reliably applied for high throughput analysis of clinical samples containing the investigated analytes.

Conclusion

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

Conflict of Interest

Authors are declared No Conflict of Interest

Acknowledgement

Not Applicable

Author Contribution

All Authors Contributed equally

Ethical Considerations

Not Applicable

Inform Consent

Not Applicable

Reference

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. Shiv Chandra Singh, A., Yu, A., Chang, B., Li, H., Rosenzweig, A. and Roh, J.D., 2021. Exercise Training Attenuates Activin Type II Receptor Signaling in the Aged Heart. Circulation, 144(Suppl_1), pp.A14259-A14259.
7. 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
8. 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
9. 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.
10. Singh, A., Kumar, A. and Kalaiselvi, P., 2018. Aegeline, targets LOX1, the receptor for oxidized LDL to mitigate hypercholesterolemia: a new perspective in its anti-atherosclerotic action. Free Radical Biology and Medicine, 128, p.S41.
11. 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.
12. Singh, A., 2022. Role of microbial metabolites in cardiovascular and human health. In Microbiome, Immunity, Digestive Health and Nutrition (pp. 137-148). Academic Press.
13. Konatham Teja Kumar Reddy and Kumaraswamy Gandla. Novel Vesicular Drug Delivery Systems Proniosomes. Pharm Res 2022, 6(3): 000272.
14. Konatham et al. synthesis and evaluation of some novel oxadiazole derivatives, World Journal of Pharmaceutical Research, Vol 9, Issue 4, 2020.
15. Singh, A., Gowtham, S., Chakrapani, L.N., Ashokkumar, S., Kumar, S.K., Prema, V., Bhavani, R.D., Mohan, T. and Sathyamoorthy, Y.K., 2018. Aegeline vs Statin in the treatment of Hypercholesterolemia: A comprehensive study in rat model of liver steatosis. Functional Foods in Health and Disease, 8(1), pp.1-16.
16. 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

17. 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
18. Teja, M.; Konatham, T.; Muralidharan, V.; Murugesan, A.; Vasantha, N.; Hyandavi, M. A Review on Biosensors for COVID-19. *IJAPSR* 2022, *7*, 9-14.
19. Singh, A., Srinivasan, A.K., Chakrapani, L.N. and Kalaiselvi, P., 2019. LOX-1, the common therapeutic target in hypercholesterolemia: a new perspective of antiatherosclerotic action of aegeline. Oxidative medicine and cellular longevity, 2019.
20. 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, ocimum tenuiaflorum "NEUROQUANTOLOGY | OCTOBER 2022 | VOLUME 20 | ISSUE 12 | PAGE 1048-1054| DOI: 10.14704/NQ.2022.20.12.NQ77087