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A REVIEW ON ANALYTICAL METHOD DEVELOPMENT AND VALIDATION OF CAPMATINIB IN BULK AND DOSAGE FORM

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ABSTRACT

Capmatinib is the first FDA-approved therapy for the treatment of non-small cell lung cancer cells with specific mutations (leading to a mesenchymal-epithelial junction such as exon 14 MET skipping). This work classifies a new rapid, accurate, and accurate analytical method for the determination of capmatinib in most and indeterminate amounts of pharmaceutical products. Analytical techniques play an important role in providing solutions such as development. This article will provide an overview and classification of the various analytical methods most commonly used to identify common supply problems. Pharmaceutical analysis has a unique role in quality assurance as well as in the internal control of most pharmaceutical drugs and preparations. The rapid rise of the pharmaceutical and pharmaceutical industries in many parts of the world has led to an increase in demand for new analytical methods in the pharmaceutical industry. As a result, the development of analytical methodology has become an important learning activity. Recent advances in analytical methods have resulted from advances in analytical tools.

KEYWORDS Introduction of Capmatinib, Pharmacology, Pharmacokinetics, HPLC Method.

INTRODUCTION

Capmatinib is a kinase inhibitor that targets the c-Met receptor tyrosine kinase in the treatment of small cell lung cancer by exon 14 MET bypass. Capmatinib is a small molecule kinase inhibitor targeted to c-Met (aka hepatocyte growth factor receptor [HGFR]), a receptor tyrosine kinase that activates signaling cascades associated with organ regeneration and tissue repair in healthy individuals. Aberrant activation of c-Met - due to mutations, amplification and / or overexpression - occurs in many types of cancer and leads to overactivation of many downstream signaling pathways, such as STAT3, PI3K / ATK and RAS / MAPK. MET mutations were detected in small cell lung cancer (NSCLC), and the prevalence of MET amplification in NSCLC patients not previously treated with epidermal growth factor receptor tyrosine kinase inhibitor (EGFR-TKI) was reported to be 1.4% - 21%. This co-occurrence makes c-Met a desirable target in the treatment of NSCLC. Capmatinib, manufactured by Novartis and sold under the tradename Tabrecta, received accelerated FDA approval on May 6, 2020 for the treatment of NSCLC in patients whose tumors have mutations that lead to mesenchymal-epithelial transition (MET) skip exon 14. [16]

The presence of the mutation must be confirmed an FDA-approved test, such as the FoundationOne CDx test (manufactured by Foundation Medicine, Inc.), which is approved by the FDA on the same day. Because this

indication is provided on a rapid approval basis, ongoing approval depends on verifying the benefit of capmatinibes in confirmation problems..

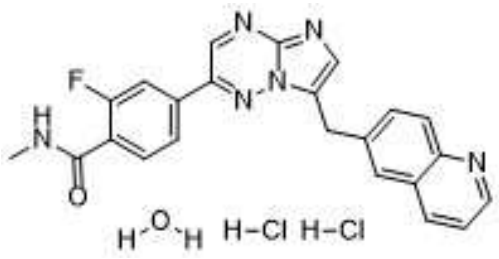

Fig. 1. Structure of Capmatinib HCL.

Drug profile:

Drug	Capmatinib HCL
IUPAC Name	2-fluoro-N-methyl-4-{7-[(quinolin-6-yl)methyl]imidazo[1,2-b][1,2,4]triazin-2-yl}benzamide hydrate dihydrochloride
Chemical Formula	$C_{23}H_{21}Cl_2FN_6O_2$
Molecular Mass	503.36
Solubility	Capmatinib hydrochloride is slightly soluble in acidic aqueous solutions at pH 1 and 2 and of further decreasing solubility towards neutral condition
pKa	12.77
Half Life	6.5
Therapeutic Use	used to treat a certain type of non-small cell lung cancer (NSCLC)

PHARMACOLOGY

Indication : Capmatinib is indicated for the treatment of adult patients with metastatic non-small cell lung cancer (NSCLC) whose tumors have mutations leading to skipping exon 14 of the mesenchymal-epithelial junction (MET), as determined by an FDA-approved test.

Pharmacodynamics : Capmatinib inhibits the overactive activity of c-Met, a receptor tyrosine kinase encoded by the MET proto-oncogene. MET mutations are associated with the proliferation of many cancers, including smallpox lung cancer. cells (NSCLC).
Capmatinib may cause photosensitivity reactions in patients after exposure to ultraviolet (UV) radiation - Patients undergoing treatment with capmatinib should be instructed to use sunscreen and protective clothing to reduce UV exposure. Cases of interstitial lung disease / pneumonitis could be fatal. in patients treated with capmatinib. Patients with signs or symptoms of lung disease (eg cough, dyspnoea, fever) should be discontinued immediately and capmatinib should be discontinued permanently if no other possible cause of lung-related symptoms is known..

Mechanism of action : Aberrant c-Met activation has been documented in many cancers, including non-small cell lung cancer (NSCLC). Mutations that bypass MET-exon 14 lead to c-Met mutants with a lost regular domain - these mutant proteins have a reduced ability to down-regulate, leading to a pathological increase in their downstream activity.

Capmatinib inhibits phosphorylation of wild-type and mutant variants of c-Met due to binding to endogenous ligand, hepatocyte growth factor-on-action, inhibits c-Met-mediated phosphorylation of downstream signaling proteins, as well as proliferation and survival of c-Met-dependent tumor cells.

Pharmacokinetic :

Absorption : The oral bioavailability of capmatinib is estimated to be> 70%. Following oral administration, peak plasma concentrations are reached within 1 to 2 hours (Tmax). Co-administration with a high fat diet increased the AUC of capmatinib by 46% without altering Cmax (compared to solid conditions) and co-administration of a low fat diet did not show any significant clinical effect of exposure. **Volume of distribution :** The apparent

volume of distribution at steady-state is 164 L. **Metabolism :** Capmatinib is metabolised by CYP3A4 and aldehyde oxidase. The specific pathways of biotransformation and metabolic products are not yet known. **Route of elimination :** Following oral administration of radiolabelled capmatinib, approximately 78% of the radioactivity was recovered in faeces, of which ~42% was unchanged compared to parenteral medication and 22% was recovered in urine, of which a small amount did not change with parenteral medication.[16,17]

LITERATURE REVIEW

1. **Shubhada Dalvi, Pankaj Thakur -** The work aims to develop a simple, accurate, correct and reproducible method of reverse phase high performance liquid chromatography (RP-HPLC) for the quantitative determination of the antineoplastic drug Capmatinib in large and in the form of tablets. Chromatography was performed on a Zorbax Eclipse XDB-C18 column (4.6 mm X 150 mm, 5 µm) with a mobile phase composed of phosphate buffer and methanol in a ratio of 50:50 v / v. in isocratic mode. Detection was performed at 255 nm with a UV detector, 20 ynl of injection volume was selected at a flow rate of 1 ml / min. The continuation time was found to be about 6.5 minutes. The method is linear in the range of 5-45 µg / ml with a regression coefficient of 0.9997. The method was validated according to ICH instructions. The developed method is better in terms of theoretical levels and has a small cooling factor. The method can be used for routine analysis of capmatinib quality control in a tablet formulation.[2]
2. **Chunling Zhou, Jinmiao Tian** - After precipitation of the egg white with acetonitrile, chromatographic separation was performed using an Acquity UPLC BEH C18 column and subsequently found to have positive electrospray ionization using a triple quadrupole tandem mass spectrometer. The target quantitative ion pairs m / z were 412.99 → 381.84 for capmatinib and 387.00 → 355.81 for the internal pattern. The calibration curve for the test was linear in the range of 1.0-4000 ng / ml. Conclusions: The method demonstrated excellent performance in linearity, accuracy, precision, robustness and was successfully used in a pharmacokinetic study after oral administration of capmatinib in three doses (5, 10 and 20) mg / kg) in mice.[3]
3. **Xiaoguang Fan, Guanghu Yang -** A highly sensitive, specific and simple LC-MS / MS method for the quantification of capmatinib (INC280) in rat plasma is presented. The LC-MS / MS method was validated for specificity and selectivity, linearity, accuracy and precision, matrix effect, extraction gain, dilution integrity, transfer and stability according to the US Food and Drug Administration's bioanalytical method validation guidelines. A validated test was used to quantify capmatinib from an oral pharmacokinetic study in mice at doses of 1.0, 3.0 and 9.0 mg / kg. The calibration curve ranged from 1 to 2000 ng / ml with the required linearity and r2> 0.99. Intra-dose and inter-dose accuracy ranged from 99.24-103.59 and 97.76-102.83% with coefficients of variation of 5.08-7.36 and 3.18-4.99%, respectively. No significant interference was observed during the endogenous peak retention period of capmatinib and IS. The test was independent of any matrix effect and showed an accurate recovery of the entire calibration curve and the samples were robust under all experimental conditions. The validated assay was successfully used to analyze plasma samples in a rat pharmacokinetic study to determine capmatinib concentrations. In summary, the new method of analysis of capmatinib in rat plasma has been successfully validated and is now used to calculate capmatinib from preclinical studies.[4]

Sr. No.	Authors	Method	Description	Reference
1	Shubhada Dalvi, Pankaj Thakur	RP- HPLC	**Column :** Zorbax Eclipse XDB- C18 (4.6 mm X 150 mm, 5 µm) **M.P :** phosphate buffer : methanol (50:50 v/v) **F.R :** 1 ml/min **Linearity :** 5-45 µg/ml **Lambda max :** 255 nm **R.T. :** 6.5 min	2

2	Chunling Zhou, Jinmiao Tian	UPLC-MS/MS	**Column :** Acquity UPLC BEH C_{18} column **Linearity :** 1.0-4000 ng/ml	3
3	Xiaoguang Fan, Guanghu Yang	LC–MS/MS	**Linearity :** 1 to 2000 ng/ml	4

Validation Parameter :[1,5,13]

Validation is an essential part of any good analytical practice. The method for a specific test is suitable for its intended use. The validation method used to assess the quality, reliability and consistency of analytical results is the process used to confirm that the analytical method is used. For method validation, the USP has issued a specific method describing eight validation steps :

1. Accuracy:
2. Precision
3. Specificity
4. Linearity
5. Range
6. Detection limit
7. Quantitation limit
8. Robusteness
9. Ruggedness
10. Sensitivity
11. Repeatability
12. Reproducibility

CONCLUSION

Capmatinib is the first therapy approved by the US Food and Drug Administration (FDA) to treat non-small cell lung cancer with a specific mutation. The above study provides analytical methods for the analysis of capmatinib bulk and tablet dosage forms. A review of the literature revealed that different approaches to the development and validation of different drugs have been reported. This review describes the various analytical methods used to evaluate capmatinib, various studies have been performed including HPLC, UPLC, bulk LC-MS / MS, and pharmaceutical dosage forms. These methods have been described for the development and validation of various drugs.

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