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ANALYTICAL METHOD DEVELOPMENT AND VALIDATION OF BEDAQUILINE: REVIEW

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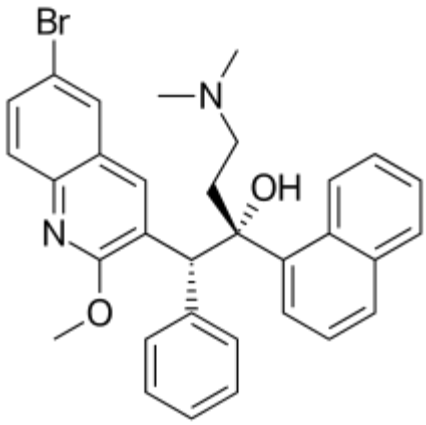
ABSTRACT

Analytical method development and Validation are the continuous and inter-dependent task associated with the research & development, quality control and quality assurance departments. Analytical procedures play a critical role in equivalence and risk assessment, management. It helps in establishment of product-specific acceptance criteria and stability of results. Validations determine that the analytical procedure is suitable for its intended purpose. Literature survey reveals that the analytical methods based on UV spectrometry, RP-HPLC and LC\MS for the determination of Bedaquiline personally and in combination with different drugs. The parameters were validated according to ICH guideline in terms of accuracy, precision, robustness, and other components of analytical validation. The developed methods are simple, sensitive and reproducible and can be used for the analysis of Bedaquiline in bulk and Tablet dosage form.

KEYWORDS: Bedaquiline, Literature Survey, UV, HPLC, LC\MS, Validation, ICH Guidelines.

INTRODUCTION

Bedaquiline is a new antitubercular drug belonging to the diarylquinoline class that efficiently inhibits the adenosine triphosphate synthase enzyme of Mycobacterium tuberculosis. Bedaquiline offers a new mechanism of anti-TB action by specifically inhibiting mycobacterial adenosine triphosphate (ATP) synthase.[1]



Bedaquiline is chemically known as (1R,2S)-1-(6-Bromo-2-methoxy-3-quinolyl)-4-dimethyla-mino-2-(1-naphthyl)-1-phenylbutan-2-ol with a molecular formula of $C_{32}H_{31}BrN_2O_2$ and a molecular weight of 555.516 $g \cdot mol^{-1}$. Bedaquiline drug substance is White Crystalline powder and it is soluble in organic solvents such as ethanol and dimethyl formamide.

REVIEW OF LITERATURE

1. **B. S. Pooja**[2] ***et al***., have developed an simple, accurate and precise zero order derivative method and area under curve method for the estimation of Bedaquiline and validation according to ICH Q2(R1) guideline. The absorbance maxima was determined at 285nm using Acetonitrile as solvent. The area selected for the estimation of Bedaquiline was between 275 to 295nm. The method represented the correlation coefficient (R2 = 0.999 for Zero order & R 2 = 0.999 for First order Derivative methods) at concentration range 15- 75µg/ml. The methods were validated for the parameters such as linearity, accuracy, precision, and limit of quantification & limit of detection as per ICH guidelines. The proposed methods were thus found suitable for estimation of Bedaquiline in bulk and tablet formulations without any interference of the exciepients.

2. **Michal Douša**[3] ***et al.,*** have developed a sensitive and specific high-performance liquid chromatography method for the separation and determination of bedaquiline stereoisomers. Ten different chiral columns were tested in a reversed-phase system. Excellent enantioseparation with a resolution of all isomers >2.0 was achieved for all stereoisomers on a Chiralcel OJ-3R column, using a mixture of 10 mM buffer of triethylamine/phosphoric acid pH 7.0 and acetonitrile (40 : 60; v/v). Bedaquiline stereoisomers were detected using UV–vis detector at a wavelength of 227nm. The

influence of mobile phase composition, namely buffer type, mobile phase pH and acetonitrile content in mobile phase, on retention and enantioseparation was studied. Validation of the developed method including linearity, limit of detection, limit of quantification, precision, accuracy and selectivity was performed according to the International Conference on Harmonisation guidelines.

3. **Vishwas Pardhi**[4] ***et al***., have developed a simple, rapid and accurate reverse phase RP-HPLC method for the validation of antitubercular drug bedaquiline fumarate. The stability and forced degradation behaviour of bedaquiline fumarate in official dissolution media (0.01 N HCl) and methanol were assessed. The developed method has significant applicability for the qualitative and quantitative determination of in different pharmaceutical formulations in the official dissolution media in routine quality control analysis.

4. **Mohammad A.M Mommin**[5] ***et al.,*** have developed a reversed phase high performance liquid chromatography method for the simultaneous quantification of bedaquiline (TMC207), moxifloxacin and pyrazinamide in a pharmaceutical powder formulation for inhalation. The powder was simply dissolved in methanol and the analytes separated in a run time of 20 min on a Luna C_{18} (2) (150 × 4.6 mm, 5 µm) column using gradient elution with methanol and triethylamine phosphate buffer (pH 2.5) delivered at 1.2ml/min. The detection (with retention time) was carried out at 269 nm (2.9 min) for pyrazinamide, 296nm (7.0 min) for moxifloxacin and 225nm (16.3 min) for bedaquiline, respectively. The method was accurate and precise.

5. **K. Heamanth kumar**[6] ***et al.,*** have developed a specific, simple and sensitive high-performance liquid chromatographic method for the estimation of Bedaquiline and Delamanid in human plasma. The method involved deproteinization and further extracted the analyte using Solid Phase Extraction cartridge and analysed using C_{18} column with the wavelength set at 231nm. The isocratic mobile phase consisted of 10 mol ammonium acetate buffer containing 0.25% acetic acid and 0.02% trifluoroacetic acid and acetonitrile in the ratio of 20:80(v/v). The validation parameters were evaluated. The method was applied to estimate plasma Bedaquiline and Delamanid collected from five MDR-TB patients. A specific and sensitive method for simultaneous determination of Bedaquiline and Delamanid in plasma using high-performance liquid chromatography was developed. This method can be used in clinical studies to evaluate drug exposure.

6. **John Metcalfe**[7] ***et al.,*** have developed a Sample preparation consisted of hair pulverization using an Omni Bead Ruptor homogenizer (Omni Inc, Kennesaw, GA, USA), extraction with methanol, evaporation, and reconstitution to 20% (v/v) methanol with 1% formic acid. After injection of the sample extract (10 µl) into the LC-MS/MS, the analytes were separated by gradient elution on a Phenomenex Synergi Polar RP column (2.1 × 100 mm, 2.5 µm particle size; Phenomenex, Torrance, CA, USA) using water with 1% formic acid as mobile phase A (MPA) and acetonitrile with 0.4% formic acid as mobile phase B (MPB). The gradient for analyte separation consisted of 5% MPB at 0–0.3 min, gradient to 100% MPB from 0.3 to 6.8 min, and 5% MPB at 6.81–14 min. Mass spectrometric detection was achieved with electrospray ionization in positive polarity, and mass scanning was performed via multiple reaction monitoring. Bedaquiline was monitored using two transitions (quantifier 557.1–58.1 m/z; qualifier 557.1–329.9 m/z), and retention time. Quantitation was performed by isotope dilution using deuterium-labeled standard, Bedaquiline d6, monitored using the transition 562.2–64.1 m/z. have developed an assay to accurately and non-invasively determine long-term exposure to Bedaquiline in small hair samples as a metric of adherence and exposure. Full analytic validation of this assay and testing of its utility in clinical settings are underway.

7. **Jan-Willem C. Alffenaar**[8] ***et al.,*** have developed a simple, new method using a quadrupole mass spectrometer for analysis of bedaquiline and N-monodesmethyl bedaquiline (M2) in human serum, using deuterated bedaquiline as the internal standard. A simple liquid chromatography-tandem mass spectrometry method to quantify bedaquiline and M2 levels in human serum using a deuterated internal standard has been validated. This method can be used in clinical studies and daily practice.The method was validated as per ICH guidelines.

8. **Pragati J. Vanavi**[9] ***et al.,*** have been developed a first stability indicating RP-HPLC (reverse phase-high performance liquid chromatography) method to analyze the Bedaquiline in presence of its degradation products. Another UPLC/ESI–MS (ultra performance liquid chromatography/electron spray ionization–mass spectrometry) method was developed for the identification of different degradation based and process related impurities and the third, preparative HPLC method was developed for the isolation of major degradation products. Eleven degradation products and one process related impurity were identified using UPLC/ESI–MS whereas preparative HPLC was

used to isolate two degradation products and their chemical structure was elucidated using nuclear magnetic resonance, mass and infra-red spectral data.

CONCLUSION

Literature survey suggested that various UV, HPLC and few LC\MS methods were developed and reported. The published methods were validated for various parameters as per ICH guidelines. Statistical analysis proved that the published methods were reproducible and selective. Thus it can be concluded that the reported and published methods can be successfully applied for the estimation of the Bedaquiline in pure and pharmaceutical dosage form.

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