A Review on Analytical techniques for the estimation of Bedaquiline in pharmaceutical dosage form.

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***Abstract*- Pharmaceutical medications serve an important role in human life by aiding in the treatment of numerous illnesses. As a result, creating analytical procedures has become the primary focus of analysis. People have been looking for safe and effective ways to treat viral infections since ancient times. Due to the rise of new fungal infections, the identification of drugs for their treatment is becoming increasingly relevant in the modern setting. These medications should be confirmed before they are placed into the market. High-performance liquid chromatography (HPLC) in combination with ultraviolet (UV), photodiode array detectors (PDA), mass spectrophotometer (MS) detectors, and other technologies is one of the quickest, safest, and most precise methods for determining and separating pharmaceutical drugs, impurities, and biological samples. When compared prior to liquid chromatography techniques, HPLC is more adaptable and requires less time to quantify drugs. Bedaquiline is a diarylquinoline antimycobacterial used in combination with other antibacterials to treat pulmonary multidrug resistant tuberculosis (MDR-TB).. The current study found that the HPLC technique, as well as the spectroscopic approach, have been the most frequently used for analysis. The investigatory review may provide detailed information to researchers involved in the Bedaquiline analytical investigation.**

***Key Words*: Bedaquiline, HPLC, Spectroscopy, LC-MS, Pharmaceutical analysis.**

INTRODUCTION

Pharmaceutical analysis is a field of practical chemistry that includes a number of procedures for identifying, determining, quantifying, and purifying a substance, separating the components of a solution or mixture, and determining the structure of chemical compounds. The drug might be a single component or a mixture of compounds, and it can be administered in any dose form. Pharmaceutical substances include animals, plants, microbes, minerals, and a variety of synthetic items. [(1,2)]. The primary purpose of the pharmaceutical industry is to provide drug products of adequate quality, efficacy, and safety. The development and production of a new medication product include numerous pharmaceutical processes, including analytical testing. The obtained analytical data enable additional decisions on how to proceed development or provide information on whether a therapeutic product should be released. [(3)] Analytical procedures are one of the most important stages in drug product development and production. They play an important role in assisting other development and manufacturing activities across the whole life cycle of a medicinal product. An analytical method must be exact, accurate, and dependable so that it can be used for its intended purpose. [(4,5)].

In most cases, the separation of analytes found in a sample is the primary operational principle of an analytical technique. Liquid chromatography procedures such as HPLC or UPLC are commonly utilized, usually in reversed-phase mode and with UV absorbance detection. The goals of analysis differ depending on the number, significance, and relationship of analytes to be discovered. The most common analytical procedures are those employed to test an active pharmaceutical ingredient (API) or to determine its related chemicals and degradation products(3,4). An analytical approach for assessing stressed condition-maintained products must be capable of detecting their rise during the product's shelf life, while the assay method must be capable of detecting any decrease in the drug substance's content during the product's shelf life. Such approaches [(7-9)].

Since 2000, Tuberculosis (TB) is an ancient infectious disease caused by Mycobacterium tuberculosis and other closely related species. It is the second leading cause of death worldwide, with an estimated incidence of 5,00,000 cases and two million to three million deaths annually.[(11,12,13)]. Bedaquiline is a bactericidal antimycobacterial medication in the diarylquinoline class. Bedaquiline antimycobacterial effect is mediated by its quinolinic core heterocyclic nucleus, which contains alcohol and amine side chains. [(10)]. Although the current standard of TB therapy of anti-TB medications for two months, including two important drugs, isoniazid and rifampin, is highly effective, the advent of multidrug-resistant TB (MDR-TB) to isoniazid and rifampin has significantly deteriorated patients' outcomes.[(14)]. BDQ belongs to the diarylquinoline class of compounds, which is a novel class of anti-TB drugs. BDQ includes a quinolinic core

heterocyclic nucleus with alcohol and amine side chains that are responsible for its anti-TB action, Chemically Bedaquiline is known as 4C32H31BrN2O2 (Figure. 1), The structural formula of BDQ shows two major components: (i) a hydrophobic part containing single bond N(CH3)2, which has a vital role in binding to the ATP synthase; and (ii) an H2-bonding acceptor/donor that provides stability. However, BDQ's anti-TB activity is linked to the diarylquinoline ring, the side chain with the N,N-dimethyl amino terminus, the hydroxyl group, and the naphthalene moiety. [15,16].

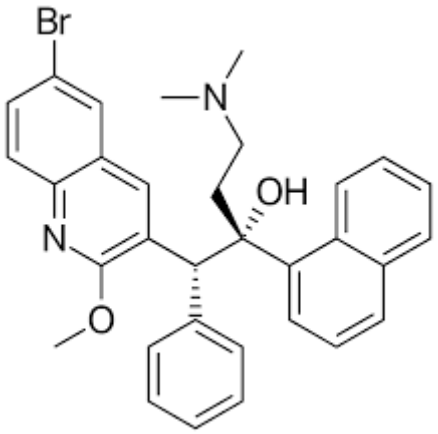

Figure 1: Structure of Bedaquiline

Quantitative & Qualitative Analytical Techniques for Bedaquiline

Quantitative & Qualitative analysis techniques help to determine precisely the concentration of each variable and type of medication present in the sample.

High performance liquid chromatography:

HPLC gives a constant quantitative accuracy and precision for the determination of active pharmaceutical compounds and associated substances employing a range of colonnade, solvents, and detectors in the same phase and may be accomplished on fully automated equipment using HPLC System. HPLC has good replicability and may be applied to a wide range of various chemical forms by carefully selecting the HPLC column chemistry. Chiral molecules are also possible to be isolated by HPLC into their respective enantiomers. HPLC is the most effective method for meeting the majority of the quantitative analytical needs for a variety of drugs. Today, HPLC, particularly reversed HPLC, is widely used. It is primarily a fluid chromatographic method for isolating and quantifying complicated mixtures of resolved elements (17). Various HPLC methods and its characteristics available in literature has shown in table 1.

Table 1: Performance attributes of HPLC method[17-21]

Author	Drug	Stationary phase	Mobile phase	Application	Wave length
Vishwas Pardhi.et.al	Bedaquiline	Sunfire C18 column (250 mm × 4.6 mm, 5 µm particle size)	10 mM ammonium acetate buffer as aqueous phase (A) and methanol as organic phase (B)_ 15:85 v/v (A:B)	To evaluate its forced degradation behaviour and stability in official dissolution media	226nm
Dubey Nitin. et.al.	Bedaquiline	Thermos C18 analytical column (250mm4.6 mm ,5.0µm)	10mM Ammonium acetate: methanol in the ratio 15:85	Bedaquiline (BDQ) Using RP-HPLC	232nm
Arti Mohan.et.al.	Bedaquiline	Shim-pack C8 (250 × 4.6 mm; 5 µm)	Acetonitrile and 0.1% trifluoroacetic acid	Dosage Form	242nm

Michal Dousa.et.al.	Bedaquiline	Sunfire C18 (5 µm 4.6 ×150 mm)	10mM buffer of triethylamine/phosphoric acid pH 7.0 and acetonitrile (40 : 60; v/v)	Polysaccharide-based Chiral Stationary Phases in RP-HPLC	227nm
Snehal.R. Dhamodkar.et.al.	Bedaquiline	HPLC column (250 mm × 4.6 mm)	Methanol: Ammonium acetate buffer (pH 4) (90: 10, v/v)	In tablet dosage form	240nm

UV Visible spectroscopy

Spectrophotometric approaches based on UV absorption and chemical reactions are useful in pharmacopoeia. Spectrophotometry is the quantitative examination of a material's reflection or transmission qualities as a function of wavelength. These techniques have the benefit of requiring less time and work. These approaches are likewise incredibly precise and precise. In recent years, there has been a tremendous increase in the use of UV-vis spectrophotometry, particularly in the approach of generating pharmacological doses. EMR spectrum areas supply numerous forms of information because of such interactions [(22)]. Different UV methods and its characteristics available in literature has shown in table 2.

Table 2: Performance attributes of UV spectroscopy method[(23,24)]

Author	Drug	Buffer & Diluent	Linearity range (µg/ml)	Application	Wave length
Vineela Parvathaneni. et.al	Bedaquiline	Methanol and phosphate buffer(6.8)	2.5- 60 µg/mL	In raw material	285nm
B.S.Pooja.et. al.	Bedaquiline	Acetonitrile	15-75µg/ml	In raw material	275 to 295nm

High Performance Thin-Layer chromatography:

As technology advanced, high-performance chromatography with a thin layer (HPTLC) emerged as an essential pharmaceutical analysis method. HPTLC is a quick and versatile separation method for analysing a large number of samples. This approach is advantageous in many ways since it is simple to handle and needs less time for analysis of the raw sample clean-up difficult. HPTLC evaluates all chromatograms without regard to time restrictions using a variety of criteria. Furthermore, several samples and standards are created concurrently yet individually on each plate, resulting in higher performance dependability. HPTLC is used to quantify the administration of drugs such as ethinyl estradiol, cyproterone, alfuzosin, and pentazocine. Available HPTLC methods and its characteristics in literature has shown in table 3.

Table 3: Performance attributes of HPTLC method [(25)]

Author	Drug	Stationary phase	Mobile phase	Application	Wave length
M. C. Damle. et.al.	Bedaquiline	silica gel 60 F254TLC plates	Acetonitrile: Ethyl acetate (7:3v/v)	Stability Indicating	229nm

Ultra-Performance Liquid Chromatography

UPLC for particles with diameter less than 2mm achieves higher resolution, velocity and sensitivity than high-performance liquid chromatography (HPLC). In the pharmaceutical markets of the twenty-first century, new methodologies are being investigated, and medication production times are being reduced. Meanwhile, UPLC analysis provides enhanced product consistency, and this expansion is not limited to analytical laboratories. Under extremely

high pressure, the UPLC is isolated and measured (up to 100M Pa)[26]. As no method as developed in UPLC as normal method they have gone with some hyphenated techniques.

LC -MS Techniques

LC/MS is a popular approach for liquid chromatography that is constantly changing. The recommended chromatographic tool is LC-MS [Liquid chromatographic mass spectrometry]. Analytical chemistry combines the capacity to physically isolate compound using liquid chromatography (or HPLC) with mass spectrometry for mass analysis. LC-MS/MS is widely utilized in qualitative and quantitative analysis in laboratory research for medicinal components, medical goods, and biological samples. It has been utilized repeatedly in drug development at several levels, including metabolic stability screening, metabolite detection, live drug screening, impurity discovery, peptide mapping, and glycoprotein mapping. LC-MS has been effectively used in a variety of applications, including therapeutic medicinal monitoring (TDM), clinical and forensic toxicology, and doping control. This advancement in LC-MS was initially and continues to be inspired by the demand for more powerful analytical and bio-analytical methods that are sensitive and selective in correctly and precisely distinguishing target analytes from high complexity mixtures. With the advancement of two-dimensional hyphenated (2D) apparatus, the use of liquid (LC) and mass spectrometric (MS) chromatography has become a powerful approach [27].Table 4 shows LC-MS & UPLC-MS Characteristics methods available in literature.

Table 4: Performance attributes of LC-MS/UPLC-MS methods[28-31]

Author	Drug	Column	Mobile phase	Application
Pragati.J Vanavi .et .al.	Bedaquiline	Acquity BEH C8 (150 × 2.1 mm, 5 µm)	0.1% Formic acid in Milli Q water (pH = 2.70 ± 0.5) and B) 0.1%Formic acid in Milli Q water: acetonitrile (10:90).	Rs method
Pankul Kotwal.et.al.	Bedaquiline	ChromolithC18 column	Acetonitrile or methanol in different proportion with formic acid or acetic acid or trifluoroacetic acid in water	Quantification In Human plasma
Jan-Willem C Alffenaar.et. al.	Bedaquiline	Simple protein precipitation with acetonitrile, UPLC BEH C18 column	0.1% aqueous formic acid and acetonitrile	Bioanalytical method
Wesley A Gray et al..,	bedaquiline and rifabutin	2.1-mm by 30-mm Acquity UPLC C18 1.7-µm analytical column	10mM Ammonium formate in ultrapure water plus 0.1% FA (solvent A) and acetonitrile plus 0.1% FA (solvent B)	Quantification In Human plasma

Electrophoresis

In advancement of the life sciences, capillary electrophoresis (CE) played a major role. This method is now used to analyze large and small molecules in applications in which it works better than liquid chromatography or is complementary to them. Routine CE analyzes and latest advances in metabolomic methods are explored for profiling small molecules in biological samples [32]. Table 5 shows Capillary electrophoresis Characteristic method

Table 5: Performance attributes of Capillary electrophoresis method[33]

Author	Drug	Detection	Buffer	Application

Diana. A. Aguilar Ayala . et.al.	Bedaquiline	field-amplified sample stacking (FASS)	1.25 M formic acid as the background electrolyte and 0.2 M formic acid in 95% (v/v) methanol	Determination in patient plasma

Nuclear Magnetic Resonance technique

NMR Spectroscopy, also known as Magnetic Resonance Spectroscopy, is a spectroscopic method that monitors local magnet fields surrounding atomic nuclei (MRS). The sample is placed in a magnetic field, and the NMR signal is produced by a nuclear-resonant stimulation of the sample's nuclei with radio waves that sensitive radio receivers detect. The intramolecular magnetic field surrounding an atom in a molecule alters the frequency of the resonance, revealing information on the electronic structure and functional groups of the molecule[(42)]. Table 6 shows NMR Characteristic method.

Table 6: Performance attributes of NMR method[(43)]

Author	Drug	Detection	Application
Dr. Chun Xian He.et. al.	Bedaquiline	field-amplified sample stacking (FASS)	Molecular Interactions

CONCLUSION:

The current review covered several analytical approaches used to evaluate TDF, FTC, and EFV. Numerous tests have been performed, including bio-analytical, HPLC, HPTLC, UV/Vis-Spectroscopy, LC-MS, LC-ESI-MS, and others. for evaluation of Bedaquiline in bulk and in its combination with other drugs from pharmaceutical formulations and also biological fluids. Bedaquiline in bulk and in combination with other medications from pharmaceutical formulations and biological fluids was evaluated using LC-MS, LC-ESI-MS, and other techniques. The most researched approach for estimating Bedaquiline in pharmaceutical dosage forms was liquid chromatography with UV detection, whereas hyphenated LS-MS and LSMS/MS methods were described for determining Bedaquiline and its metabolite in plasma and other biological fluids. A few chromatography techniques, such as HPTLC and Stability-indicating HPLC, UPLC, and HPTLC, are also included. A few basic UV-Spectrophometric techniques can be utilized for regular Bedaquiline analysis.

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