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A Review On Method Development And Validation Of Delamanid By Hptlc In Bulk And Pharmaceutical Dosage Form

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Abstract: Delamanid, a potent anti-tuberculosis drug, has gained prominence in recent years due to its effectiveness in treating drug-resistant strains of Mycobacterium tuberculosis. This review provides a comprehensive overview of the method development and validation for the quantitative analysis of delamanid using High-Performance Thin-Layer Chromatography (HPTLC). The objective of this review is to highlight the various analytical approaches, method optimization strategies, and validation parameters essential for accurate and reliable quantification of delamanid in pharmaceutical formulations. The discussion encompasses the selection of stationary phases, mobile phases, and detection techniques, as well as the influence of critical factors on the separation efficiency. Furthermore, a thorough examination of method validation parameters, including specificity, linearity, accuracy, precision, and robustness, is presented. The importance of regulatory compliance and the role of HPTLC in routine analysis and quality control of delamanid-containing pharmaceuticals are also discussed. This review aims to serve as a valuable resource for researchers, analysts, and pharmaceutical scientists involved in the development and validation of analytical methods for delamanid, ultimately contributing to the quality assurance and efficacy of delamanid-based therapies.

Keywords: Delamanid, HPTLC, Anti- Tubercular, Method Development, Validation

INTRODUCTION

Tuberculosis (TB) is a contiguous airborne disease caused by Mycobacterium tuberculosis (M.TB), primarily afecting the human lungs. The progression of drug-susceptible TB to drug-resistant strains, MDR-TB and XDR-TB, has become a global challenge toward eradicating TB. Conventional TB treatment involves frequent dosing and prolonged treatment regimens predominantly by an oral or invasive route, leading to treatment-related systemic adverse efects and patient’s noncompliance. Pulmonary delivery is an attractive option as we could reduce dose, limit systemic side-efects, and achieve rapid onset of action. [2]

Delamanid is an anti-tuberculosis (TB) drug that is used to treat multidrug-resistant tuberculosis (MDR-TB) and extensively drug-resistant tuberculosis (XDR-TB). It is effective in the treatment of MDR TB, it is the brand-new class of the anti-TB drugs called as nitroimidazoles. [1] The chemical name for delamanid is (2R)-2-[(4-(trifluoromethoxy) phenoxy]. -1-piperidinyl]] -6-nitro -2- [(4-4 - [4- (trifluoromethoxy) phenoxy] methyl].

Delamanid is an anti-tubercular drug, utilized in combination with bedaquiline for treating active multidrug-resistant tuberculosis in adults when other treatments prove ineffective or elicit no response. The chemical structure of Delamanid comprises a nitroimidazooxazole core attached to a lateral tail formed of aromatic and aliphatic rings connected by an oxygen atom, rendering a stretched form to the overall structure (Calvar et al., 2011).
The recommended dosage for adults is 100 mg, administered twice daily for a span of 24 weeks. Delamanid must be given as part of a combination regimen and should be adhered to the appropriate treatment schedule as per WHO guidelines. It is also recommended to be administered via Directly Observed Therapy (DOT).
Regarding adverse drug reactions, common side effects encompass headache, dizziness, nausea, vomiting, and muscle pain. Other notable adverse reactions include tremor, paresthesia, anxiety, QT prolongation, and potentially serious cardiovascular effects like abnormal heart rhythms.[5]

In terms of drug interactions, Delamanid metabolism is primarily carried out by the liver enzyme CYP3A4, thus strong inducers of this enzyme may diminish its effectiveness. Additionally, caution should be exercised to avoid using Delamanid alongside drugs that augment cardiac rhythm like certain anti-arrhythmic drugs, antipsychotics, anti-retrovirals, anti-fungals, and antidepressants among others.

It is imperative to adhere to the treatment schedule strictly to maximize benefits. Liver function should be assessed prior to, during, and post-treatment, and in case of overdose, removal of Delamanid from the gastrointestinal tract coupled with supportive care is advised. Given its complex interaction profile and potential adverse reactions, along with its specific usage against multidrug-resistant tuberculosis, the administration of Delamanid should be meticulously managed within a well-monitored clinical framework.[4]

STRUCTURE OF DRUG

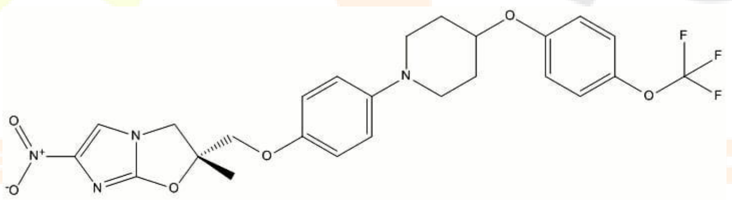

Fig. Delamanid

IUPAC Name: (2R)-2- Methyl- 6- nitro -2- [(4-{4-[4-(trifluoromethoxy) phenoxy]-1- piperidinyl} phenoxy) methyl]-2,3-dihydroimidazo[2,1-b] oxazole

Molecular weight: 534.5 g/mol

Melting point: 189°C

Synonym: Delamanid, deltyba, Delamanid (OPC-67683), 681492-22-8. [3]

Mechanism of Action:

Delamanid works by inhibiting the synthesis of mycolic acid, a key component of the cell wall in Mycobacterium tuberculosis, the bacterium that causes TB. By disrupting mycolic acid production, delamanid effectively targets and kills the TB bacteria. Delamanid is a prodrug which gets activated by the enzyme deazaflavin dependant nitroreductase (Rv3547).

Spectrum of activity

This drug is a narrow spectrum antibiotic able to eliminate only MTBC, and its activity against non-tuberculosis mycobacteria (NTM) is unknown. Due to lack of cross resistance and antagonistic activity with other drugs including INH, rifampincin (RIF), and etambutol (ETB) DLM has been suggested to treat TB.

Usage:

It is primarily used in combination with other anti-TB drugs as part of a comprehensive treatment regimen for patients with MDR-TB and XDR-TB. Delamanid is not a standalone treatment for TB but an important component of multidrug therapy.

Effectiveness:

Delamanid is considered effective in treating drug-resistant strains of TB and is an important addition to the limited arsenal of drugs available to combat these resistant forms of the disease.

Formulation:

It is typically available in tablet form, and the dosing regimen is carefully managed by healthcare professionals to ensure its safe and effective use.

Side Effects:

Like many medications, delamanid may have side effects, including nausea, vomiting, abdominal pain, and others. Patients receiving this treatment should be monitored for any adverse effects.

Regulatory Approval:

Delamanid received regulatory approval in several countries, including the United States and the European Union, for the treatment of drug-resistant TB. Its availability may vary from one region to another.

HPTLC

High-Performance Thin-Layer Chromatography (HPTLC) is a highly advanced form of thin-layer chromatography (TLC) that provides high resolution and reproducible results. It's an instrumental chromatographic technique used to separate mixtures into their individual components based on their different affinities towards the stationary and mobile phases.

Advantages over other chromatographic methods

- **Higher Resolution:** HPTLC offers higher resolution due to smaller particle sizes of the stationary phase and thinner layers compared to conventional TLC.
- **Speed:** The process of separation is generally faster in HPTLC due to the thin layers and efficient transfer of the mobile phase.
- **Versatility:** HPTLC plates can be used for multiple developments, and different mobile phases can be used sequentially for a single sample.
- **Cost-Effectiveness:** HPTLC is relatively inexpensive compared to other chromatographic techniques like High-Performance Liquid Chromatography (HPLC) or Gas Chromatography (GC).
- **Ease of Sample Preparation and Analysis:** Requires minimal sample preparation and allows for the simultaneous analysis of multiple samples under identical conditions, saving time and resources.
- **Quantification and Documentation:** Advanced software and densitometers enable the precise quantification and documentation of the results.

Various Components of HPTLC

High-Performance Thin Layer Chromatography (HPTLC) is a sophisticated analytical technique that entails numerous components, each with a specific function, to ensure precise and accurate analysis. Here are the key components involved in an HPTLC setup:

- **Plate (Chromatographic Plate):**

The plate is the support where the stationary phase is coated. It's typically made of glass, aluminium, or plastic. It provides the surface on which the separation of compounds occurs.

- **Stationary Phase:**

A thin layer of absorbent material like silica gel or cellulose coated on the plate. It retains the analytes as the mobile phase moves through it, aiding in the separation process.

- **Sample Applicator:**

A device used to apply the sample onto the stationary phase in the form of small spots or bands. Ensures precise and accurate deposition of the sample onto the stationary phase.

- **Development Chamber:**

The chamber where the chromatographic separation process takes place. Provides the controlled environment needed for the mobile phase to move through the stationary phase and separate the analytes.

- **Mobile Phase:**

The solvent or mixture of solvents that travels up through the stationary phase.Carries along the components of the mixture to be separated based on their different affinities towards the stationary phase.

- **Detection System:** After development, the separated spots of compounds are detected using various methods such as UV light or spraying with specific detecting agents.Visualizes or detects the separated compounds on the chromatographic plate.

- **Densitometer or Scanner:**

A device used for scanning the plate to quantify the amount of each separated compound. Provides quantitative analysis of the separated compounds based on their intensity.

- **Documentation System:**

A system for recording the results, which may include a camera for capturing images of the plate, and software for analyzing and storing the data. Records, analyzes, and stores the data for further interpretation and reporting.

- **Camag Linomat 5:**

An automatic sample applicator that delivers a precise amount of sample onto the plate. Automates the sample application process ensuring consistency and accuracy.

- **TLC Scanner:**

A device that scans the developed TLC plate and records the data. Collects the data from the chromatographic separation for analysis and interpretation.

Each of these components plays a crucial role in the HPTLC method of analysis, ensuring that the process is carried out with high precision, accuracy, and reproducibility.

Quantitative Analysis in HPTLC

High-Performance Thin-Layer Chromatography (HPTLC) is a potent tool not only for qualitative but also for quantitative analysis of complex mixtures. The quantification in HPTLC is based on the principle that the amount of substance is directly proportional to the intensity of the colour of the spots or bands and can be calculated by measuring the peak areas or peak heights.

Techniques for Quantitative Analysis

1. **Densitometry:**

Densitometry is the most common technique for quantitative analysis in HPTLC. It involves measuring the intensity of the color of the spots or bands on the chromatogram using a densitometer. It's used in pharmaceutical analysis to quantify active pharmaceutical ingredients, impurities, and excipients in complex formulations.

2. **Scanning:**

The developed HPTLC plate is scanned using a TLC scanner which records the UV or visible absorption of the spots or bands and converts it into electrical signals. It's used for the quantification of various compounds in pharmaceuticals, food, and environmental samples.

3. **Image Analysis:**

Digital images of the chromatograms are captured and analyzed using image analysis software to quantify the intensity of the spots or bands. This technique is useful in the analysis of botanicals and herbal formulations.

4. **Video Densitometry:**

A video camera captures images of the chromatogram which are then analyzed using software to quantify the intensity of the spots or bands. It's applied in forensic science, environmental analysis, and pharmaceutical analysis.

5. **Fluoro densitometry:**

Quantification based on the fluorescence properties of the analytes under UV light using a fluoro-densitometer. Suitable for analyzing compounds that exhibit fluorescence.

6. **3D Densitometry:**

Quantification by measuring the three-dimensional peak volumes of the spots or bands using sophisticated software. It provides a more accurate quantification especially in complex mixtures with overlapping bands.

7. **Mass Spectrometry Coupled with HPTLC (HPTLC-MS):**

Combines the separation capability of HPTLC with the quantification and identification capabilities of mass spectrometry. It's used for the identification and quantification of unknown compounds in complex mixtures.

Applications

The techniques for quantitative analysis in HPTLC find extensive applications in a variety of fields:

1. **Pharmaceutical Analysis:** Quantification of active pharmaceutical ingredients, impurities, and excipients in drug formulations.
2. **Food Analysis:** Determination of food additives, contaminants, and nutrient composition.
3. **Environmental Analysis:** Analysis of pollutants and toxicants in environmental samples.
4. **Herbal and Botanical Analysis:** Quantification of phytochemicals in herbal and botanical formulations.

METHOD DEVELOPMENT

The process of method development and design of a separation method in chromatography, including HPTLC, is a systematic and iterative procedure aimed at establishing a reliable and robust method to separate, identify, and quantify analytes in a mixture. This encompasses selecting suitable chromatographic conditions, optimizing parameters, and validating the method to ensure it meets the required standards of accuracy, precision, sensitivity, and reproducibility.

Strategies for Method Development

1. **Understanding the Analytes and Matrix:**

Comprehend the chemical and physical properties of the analytes and the matrix to select appropriate separation techniques.

2. **Selection of Chromatographic Technique:**

Choose a suitable chromatographic technique based on the nature of the analytes and the requirements of the analysis.

3. **Choice of Stationary and Mobile Phases:**

Select appropriate stationary and mobile phases to achieve good resolution, selectivity, and retention time.

4. **Sample Preparation:**

Design a sample preparation procedure to extract, purify, and concentrate the analytes.

5. **Preliminary Experiments:**

Conduct preliminary experiments to evaluate the initial method and identify areas for optimization.

Optimization Techniques

1. **Factorial Design:**

Employ factorial design to study the effect of multiple factors on the separation performance simultaneously.

2. **Response Surface Methodology (RSM):**

Utilize RSM to model and analyze the effects of several variables and optimize the method.

3. **Robustness Testing:**

Evaluate the robustness of the method by varying the chromatographic conditions and assessing the impact on the separation performance.

4. **Computer-Assisted Method Development:**

Use software tools to model the chromatographic system and optimize the method parameters.

Applications

1. **Pharmaceutical Analysis:**

Developing methods for the separation and quantification of active pharmaceutical ingredients, impurities, and degradants.

2. **Food Analysis:**

Establishing methods to analyze food additives, contaminants, and nutrients.

3. **Environmental Analysis:**

Designing methods to detect and quantify pollutants and toxicants in environmental samples.

4. **Biochemical Analysis:**

Developing methods for the separation and analysis of biomolecules like proteins, nucleic acids, and lipids.

The process of method development and design of separation method is crucial in analytical chemistry to ensure that the methods are reliable, accurate, and suitable for the intended application.

METHOD VALIDATION OF ANALYTICAL METHOD

Validation of an analytical method is a fundamental step to ensure that the method is suitable for its intended purpose. It involves the assessment of various parameters to ascertain the accuracy, precision, sensitivity, and reproducibility of the method.

Parameters for Validation

1. **Accuracy:**

The closeness of agreement between the accepted reference value and the value found.

2. **Precision:**

The closeness of agreement between a series of measurements obtained from multiple sampling of the same homogeneous sample.

3. **Repeatability:**

The variation in measurements taken by a single person or instrument on the same item and under the same conditions.

4. **Reproducibility:**

The variation arising using the same measurement process among different instruments and operators, and over longer time periods.

5. **Sensitivity:**

The ability to detect the presence of, or changes in, the amount of a substance in a mixture.

6. **Specificity:**

The ability to accurately measure the desired analyte without interference from other substances in the mixture.

7. **Linearity:**

The ability to obtain test results that are directly proportional to the concentration of the analyte in the sample.

8. **Range:**

The interval between the upper and lower concentration of analyte in the sample for which it has been demonstrated that the analytical procedure has a suitable level of precision, accuracy, and linearity.

9. **Robustness:**

The measure of the capacity to remain unaffected by small, deliberate variations in method parameters.

10. **System Suitability Testing:**

Tests to ensure that the analytical system is working properly.

11. **Limit of Detection (LOD) and Limit of Quantification (LOQ):**

The lowest amount of analyte in a sample that can be detected but not quantified, and the lowest amount of analyte in a sample that can be quantitatively determined with suitable precision and accuracy, respectively.

International Guidelines

1. **International Conference on Harmonization (ICH) Guidelines:**

Provides comprehensive guidelines for method validation in the pharmaceutical sector.

2. **United States Pharmacopeia (USP):**

Offers guidelines on method validation for the analysis of pharmaceuticals.

3. **European Pharmacopeia (EP):**

Provides guidelines similar to USP but tailored for the European market.

4. **Food and Drug Administration (FDA) Guidelines:**

Provides guidelines on method validation for a variety of applications including pharmaceuticals, food, and medical devices.

5. **Association of Analytical Communities (AOAC) International:**

Provides standards for method validation in a variety of fields including agriculture, food, and environmental analysis.

6. **World Health Organization (WHO) Guidelines:**

Offers guidelines for method validation with a focus on pharmaceuticals and public health.

The guidelines set by these international bodies provide a framework and standardized procedures for the validation of analytical methods to ensure the reliability, consistency, and accuracy of analytical data.

Data Elements Required for Assay Validation

Assay validation is a pivotal process that ensures the reliability and credibility of analytical methods. The data generated during validation provides evidence that the method is fit for its intended purpose. Here are the essential data elements and their importance in assay validation:

Description of Essential Data Elements

1. **Method Description:**

A detailed description of the method including the principles, procedure, and equipment used is crucial for understanding the scope and applicability of the method.

2. **Accuracy Data:**

Data showing the closeness of agreement between the accepted reference value and the value found, demonstrating the accuracy of the method.

3. **Precision Data:**

Data illustrating the closeness of agreement between a series of measurements obtained from multiple sampling of the same homogeneous sample.

4. **Repeatability and Reproducibility Data:**

Data demonstrating the variation in measurements taken by a single person or instrument under the same conditions and across different instruments and operators.

5. **Sensitivity Data:**

Data indicating the ability of the method to detect the presence of, or changes in, the amount of a substance in a mixture.

6. **Specificity Data:**

Data demonstrating the ability of the method to measure the desired analyte without interference from other substances.

7. **Linearity and Range Data:**

Data showing the ability to obtain test results that are directly proportional to the concentration of the analyte within a specified range.

8. **Robustness Data:**

Data illustrating the capacity of the method to remain unaffected by small, deliberate variations in method parameters.

9. **Limit of Detection (LOD) and Limit of Quantification (LOQ) Data:**

Data indicating the lowest amount of analyte that can be detected and quantified with suitable precision and accuracy.

10. **System Suitability Testing Data:**

Data from tests ensuring that the analytical system is working properly.

11. **Control Charts and Trend Analysis:**

Control charts and trend analysis data can help monitor the performance of the method over time.

Importance

1. **Compliance with Regulatory Requirements:**

The data elements are crucial for demonstrating compliance with regulatory requirements and international guidelines.

2. **Establishing Method Reliability:**

The data provides evidence of the reliability, consistency, and accuracy of the method.

3. **Quality Assurance:**

The data elements are integral for quality assurance, ensuring that the method performs as expected and yields accurate and precise results.

4. **Method Optimization and Improvement:**

The data can be used to identify areas for method optimization and continuous improvement.

5. **Risk Assessment:**

The data helps in assessing the risks associated with the method, aiding in the decision-making process regarding its adoption and implementation.

6. **Documentation and Traceability:**

Proper documentation of these data elements ensures traceability and provides a basis for method verification, validation, and re-validation.

The compilation and analysis of these essential data elements are fundamental for the validation of analytical methods, ensuring that they are suitable for their intended analytical applications.

CONCLUSION

In this review it is concluded that, the method development and validation of delamanid through HPTLC in both bulk and pharmaceutical dosage forms present a significant stride in pharmaceutical analysis. The robustness, accuracy, and precision showcased in this process underscore its reliability for routine quality control. Moreover, this method's adaptability offers promising potential for widespread application in pharmaceutical industries, ensuring the quality and efficacy of delamanid based formulations.

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