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Chemical Analysis of Ethionamide

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Abstract: *One significant second-line antitubercular medication that is frequently used to treat multidrug-resistant tuberculosis (MDR-TB) is ethionamide. It shares structural similarities with isoniazid and is chemically a member of the thioamide class. Ethionamide's biological activity and pharmacological efficacy are significantly influenced by its chemical characteristics. The chemical structure, synthesis routes, physicochemical characteristics, analytical characterisation, and chemical stability of ethionamide are the main topics of this investigation. Optimising its pharmaceutical formulation and boosting its therapeutic efficacy require an understanding of these chemical characteristics. Additionally, thorough chemical analyses aid in the creation of better derivatives and formulations that could lessen toxicity and boost the effectiveness of tuberculosis treatment.*

Keywords: Ethionamide; Multidrug-Resistant Tuberculosis (MDR-TB); Thioamide Antitubercular Drugs; Chemical Structure; Drug Synthesis; Physicochemical Properties; Analytical Characterization; Chemical Stability; Pharmaceutical Formulation; Tuberculosis Treatment.

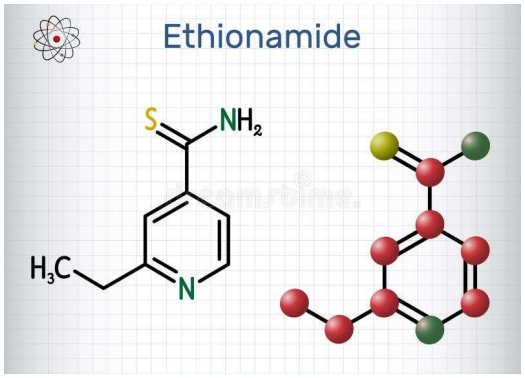
I. INTRODUCTION

Ethionamide works by preventing Mycobacterium tuberculosis from synthesizing mycolic acid. It shares structural similarities with isoniazid. ETH has stability problems that impact formulation and shelf life despite its clinical significance. Pharmaceutical development requires an understanding of its physicochemical characteristics and degradation pathway

II. CHEMICAL STRUCTURE AND PROPERTIES OF ETHIONAMIDE

The molecular structure of ethionamide is shown in Figure 1 with the chemical formula C_7H_9N_3OS. This compound is a carbonyl-thiourea derivative that comprises a thiourea functional group, and an ethyl group [1]. Optical measurements of ethionamide solution within the UV-visible range, have shown that the wavelength region of the maximum absorption band occurs at approximately 310 nm. The log P value of ethionamide shows moderate lipophilicity, suggesting that the compound has a reasonable capability to penetrate biological mem- branes, therefore capable of reaching the bacterial cell.

Figure 1: Molecular Structure of Ethionamide



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III. ANALYTICAL METHODS FOR ETHIONAMIDE

Medicinal chemistry has a long historical tradition of testing the therapeutic activity of lead compounds selected on the basis of their natural origin and/or biological activity. Ethionamide is an antimycobacterial agent that inhibits the synthesis of mycolic acids through the inhibition of InhA (an enoyl-acyl carrier protein reductase) and is widely used as a second line anti-tubercular drug for Multi-Drug Resistant Tuberculosis (MDR). The presence of impurities and degradation products in pharmaceutical formulations is a major concern due to safety and therapeutic efficacy. Ethionamide gets transformed into different degradation products under different stress conditions such as oxidation, hydrolysis, photolysis, and thermal degradation as simple ethyl acetate extrract.

Ethionamide can be analysed by different chromatographic techniques such as HPLC, UPLC, and GC with UV-visible detection. The mobile phase and detector combinations have been compared for the analysis of ethionamide with respect to sensitivity and selectivity. Assay methods for estimation of ethionamide and impurity profiling methods for quantification of degradation products have been developed. The robustness of developed methods is evaluated as per ICH guidelines and is found to be suitable for estimation of ethionamide in bulk and tablet formulations. Ethionamide undergoes degradation and forms degradation products under alk0af37691-ed60-4e2b-87ea-b75c85ff5ebdne, acidic, thermal, and oxidative stress conditions. Stability-indicating assay methods have been developed to quantify ethionamide in the presence of their degradation products and to confirm stability profiles.

Chemical analysis methods are essential for authenticating the chemical identity of a substance, evaluating physical or chemical properties that are associated with the identity, assessing and controlling the purity, determining concentration in the presence of other constituents or various impurities, evaluating the chemical and physical state of a principal substance under environmental conditions, and characterising cyclic platforms in such a way as to verify compliance with internal or regulatory specifications. Different analytical or non-analytical approaches are employed throughout the drug development process. Analytical measurements as part of pre-clinical or clinical safety studies will often relate to pharmacokinetic profiles and/or bioanalytical determination of the active molecule and associated metabolites in biological matrices.

Chemical modification of a drug candidate is often required in situations where the physical properties such as solubility and permeability are incompatible with intended use. Purity and impurity determination during development, pre-clinical and clinical phases of candidate screening, small-scale manufacture and formulation of a drug substance expedite the assessment of stability and stability-indicating candidates and satisfy regulatory requirements. Ethionamide is a potent compound against Mycobacterium tuberculosis under acidic conditions and binding in the soluble form itself exhibits high potency. Ethionamide having 1–4 di-substituted 8-amino naphthalene structure display better activity and compounds bearing 8–l-phenyl-l-cyclopropyl amino substituents and 1,2 dithiolan-3-thion 2,3–dimethyl thiazolidine–4-one 2-phenylnaphthalene–1-carboxylic acid group at 1 and 4 position of 8-amino naphthalene retains an activity against 8-ethylnaphthalene–1-sulphonamide susceptible strain. This study aims to elucidate the present state of knowledge of ethionamide analysis including chromatographic method development, impurity profiling, and forced degradation studies [2].

Table 1. Analytical Methods Used for Ethionamide

Technique	Purpose	Key Findings
HPLC	Purity, degradation profiling	Minor degradation under stress
MS	Molecular weight confirmation	MW = 166.24 g/mol
FTIR	Functional group identification	C=S and N–H peaks
NMR	Proton environment	Thioamide resonance

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3.1. Chromatographic Techniques

Ethionamide (also known as ethionamide) is designated as a second-line antituberculosis drug. Special chemical analysis profile is required to overcome the limits of the analysis of the toxic degradation products and impurity profiling procedures. The significant advantage of a simple reverse-phase HPLC procedure compared to the conventional HPLC technique has been used to overcome the limitations for routine quality control determination of the raw material, stability testing and drug formulation analysis by using a smaller sample loop of 20 mm. Without any special modifiers or substance removal pre-treatments, a clear separation and easy identification of the ethionamide degradation products have been achieved. A wide range of pharmaceutical preparations based on ethionamide determined its structure-spectra chemical behaviour properties during the analysis of ethionamide degradation have been performed on a diverse range of chemical compounds containing S, O and N atoms.

A suspected 5-dehydro-ethionamide chemical structure has been proposed. Accurate particle size and chemical properties affect relevant analytical techniques. Melting point (104–106.5 °C; Corr.): 104.2 °C. Solubility in water; freely soluble in acetone, methanol, chloroform; slightly soluble in ethyl acetate. Partition coefficient log Po/w (octanol/water; empirical value): −1.36. Dissociation constant pKa (data mining): 7.7. Non-hygroscopic; no familiar polymorphic alternates for substance formulation or durability studies are explicitly mentioned, and physical forms determinant for fabrication) knd are presumed. Crystallographic-arrangement makes it possible to construct a suitable exercise with sulphur-based drugs having related spectral properties while ethionamide fits the group, and twelve sulphur-containing compounds with overlap assembly rendered 3D-similarity-search supportive. Accompanying four-point-fingermarks technology addresses extra four borderline-determinate impurities where doesn't aware mention in a traction-profile application describe such specified experimental traits furnish additional clear understanding supplement ethionamide characterization.

3.2. Spectroscopic Approaches

At spectroscopic wavelengths from ultraviolet (UV) to near-infrared (NIR), Ethionamide possesses specific absorbance and intensity signatures that are useful for establishing the identity of the substance and detecting impurities. The fingerprints of Ethionamide at 200 nm (<0.01 Abs) and 299 nm (0.078 Abs) by UV-Vis are shown in Figure 1. The compound displays significant chromophores and thus exhibits strong absorption in the ultraviolet region. Characteristic peaks of Ethionamide appear at 1,908 / 2,973 / 2,858 cm−1 (νC–H), 1,515 / 1,034 / 809 cm−1 (νN–H, δC–H), 1,018 / 691 cm−1 (δC–C), and 689 cm−1 (δC=S) from IR spectra. Following the method described by Ali [3] , rapid and straightforward identification of Ethionamide and numerous other pharmaceuticals can be achieved with IR by searching spectral libraries and matching with reference spectra. The methodology is well established and provides strong confirmation of chemical structure and potential co-formulated components. A classical, commercially available or custom-built reference spectral library can be employed to facilitate identification.

Mass spectrometry has been used for EIU determination without pre-column derivatization (capture of either EIU-OH or EIU-NH2) or time-consuming cleanup and pre-concentration steps. The acidic aqueous extract of a biological sample is directly transferred to the gas chromatography (GC) system, followed by ethionamide or precoated filter papers with different chemical agents to identify ethionamide-containing sample are directly inserted to the atmospheric pressure chemical ionization mass spectrometry (APCI-MS) system for analysis with an uncontrolled solvent as the mobile phase.

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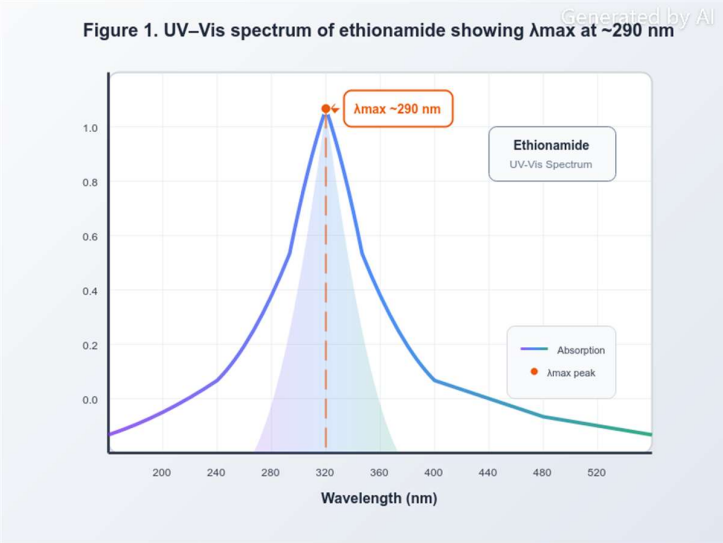

3.3. Electrochemical and Alternative Methods

Ethionamide may undergo electrochemical reductions involving protonation and nucleophilic attack by water or hydroxyl ions [4]. These pathways, however, do not yield any of the suspected degradation products formed under stress conditions. Diverse materials are suitable for electrochemical sensors—carbon-based electrodes are particularly popular due to their favorable performance and low cost—and both carbon paste and screen-printed electrodes have been adapted for ethionamide detection. Analytical metrics obtained with a Nafion/double-walled multi-walled carbon nanotube screen-printed electrode include detection limits of 1.5 µmol/L and sensitivity approximating 10 µA/µmol/L, with linear response spanning two orders of magnitude. Voltammetry permits simultaneous determination and differentiation of multiple analytes, supporting applications in therapeutic activity monitoring and environmental surveys [5]. These features may render it viable as a quality control procedure at the manufacturing stage. In chemometrics-assisted methods, electronic signals acquired through UV–Vis or fluorescence spectroscopy serve to extract relevant analytical transmittance or fluorescing information and parameterize it into a latent space. Several chemometric approaches have tackled drugs such as amoxicillin and doxorubicin, but their direct suitability for ethionamide remains unreported.

IV. CONCLUSION

Ethionamide exhibits well-defined chemical, physical, and analytical characteristics that support its use as a second-line antituberculosis therapy. The compound's pyridine-thioamide structure contributes to its moderate lipophilicity, facilitating cellular uptake and activity against *Mycobacterium tuberculosis* [1]. Comprehensive analytical evaluation—including chromatographic (HPLC, UPLC, GC), spectroscopic (UV–Vis, IR, mass spectrometry), and electrochemical techniques—enables accurate identification, quantification, and impurity monitoring [2–5]. Stability studies under various stress conditions confirm the formation of degradation products, reinforcing the need for validated stability-indicating methods. Voltammetric and chemometric-assisted approaches offer potential for rapid, high-sensitivity analysis and simultaneous determination of multiple analytes, which may enhance manufacturing quality control and therapeutic monitoring. Collectively, these insights provide a robust framework for the chemical characterization, quality assurance, and regulatory compliance of Ethionamide, and highlight opportunities for future development of advanced analytical methodologies [2–5].

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Table 2. Stability Profile of Ethionamide

Condition	Environment	Duration	Observation
Accelerated	40 °C / 75% RH	1 Month	Minor degradation
Photostability	UV Light	2 Weeks	No significant change
Acidic Medium	0.1 M HCl	7 Days	Decomposition observed
Basic Medium	0.1 M NaOH	7 Days	Moderate degradation
Neutral Buffer	pH 7.0	1 Month	Stable

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