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ANALYTICAL METHOD DEVELOPMENT TECHNIQUES OF TEDIZOLID: A REVIEW

Naresh Panigrahi[1]* and Mehul H. Jain[2]

[1]Assistant Professor, Department of Pharmaceutical Chemistry, GITAM Institute of Pharmacy, GITAM Deemed to be University, Visakhapatnam.

[2]GITAM Institute of Pharmacy, GITAM Deemed to be University, Visakhapatnam.

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***Corresponding Author**
Dr. Naresh Panigrahi
Assistant Professor, Department of Pharmaceutical Chemistry, GITAM Institute of Pharmacy, GITAM Deemed to be University, Visakhapatnam.

ABSTRACT

Tedizolid is an oxazolidinone antibiotic with a wide antibacterial action against gram-positive bacteria, including methicillin-resistant *Staphylococcus aureus* (MRSA). Tedizolid is a pyridine substituted at position 2 by a 2-methyl-2H-tetrazole-5-yl group and at position 5 by a 2-fluoro-4-[(5R)-5-(hydroxymethyl)-2-oxo-1,3-oxazolidin-3-yl] phenyl group. (5*R*)-3-[3-fluoro-4- [6-(2-methyltetrazole-5-yl) pyridin-3-yl]phenyl]-5-(hydroxymethyl)-1,3-oxazolidine-2-one is the IUPAC name of Tedizolid. It is administered as a phosphate prodrug to treat acute bacterial skin and skin structure infections (ABSSSI) caused by susceptible bacteria such as *Staphylococcus aureus* (including MRSA and methicillin-susceptible strains), *Streptococcus* species, and *E. faecalis*. It serves as an antibacterial, a pharmacological metabolite, and a protein synthesis inhibitor, among other things. It is a carbamate ester, a pyridine, a tetrazole, an organofluorine molecule, an oxazolidinone, and a primary alcohol. In this work, a quick overview of the analytical methodologies developed to estimate this drug is reviewed.

KEYWORDS: Oxazolidinone antibiotic, Tedizolid, Tedizolid Phosphate, Analytical Techniques, Spectroscopy, Chromatography.

INTRODUCTION

Tedizolid phosphate (TZDP) is a potential second-generation oxazolidinone antibiotic used to treat skin and skin structure infections caused by Gram-positive microorganisms such as methicillin-resistant *Staphylococcus aureus* and vancomycin-resistant *enterococci*.[1] It's a

prodrug that is readily metabolized into its active metabolite, Tedizolid (TDZ), due to the phosphate group being hydrolyzed. Gram-positive bacteria are responsible for the most prevalent form of ABSSSI. Oral and intravenous (IV) routes are used to give Tedizolid phosphate (TDZP).[2,3]

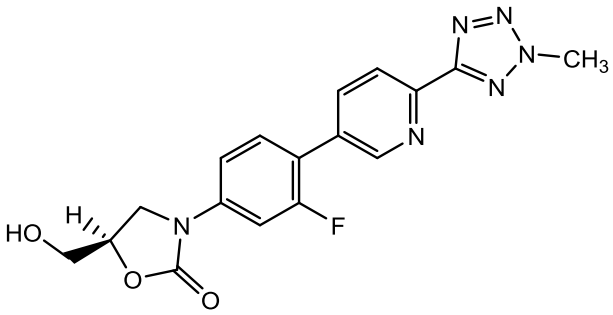

Fig. 1: Tedizolid structure.

Mechanism of action

Oxazolidinone antibiotics' spectrum of activity revealed that they impede a stage in the commencement of protein synthesis. Tedizolid bind to the A site of the peptidyl transferase centre (PTC) by interacting with the 23S rRNA component, which restricts the uptake of charged aminoacyl-tRNAs and renders the formation of peptide bonds. As a result, tedizolid works by preventing bacteria from synthesizing proteins.[4-8]

Analytical method development

Analytical analysis of bulk drug materials, intermediates, drug products, drug formulations, contaminants and degradation products, as well as biological samples containing medicines and their metabolites, is critical in pharmaceutical research. Analytical assay techniques have been included in compendial monographs from the beginning of the formal pharmaceutical analysis to characterize the quality of bulk medicinal materials by defining active component concentration limits. In recent years, titrimetry, spectrometry, chromatography, and capillary electrophoresis have been included in monographs; likewise, electroanalytical procedures have been mentioned in the literature.

Analytical techniques are used throughout the drug development process, from determining the drug's physical and chemical stability to influencing dosage form selection and design, assessing the strength of drug molecules, quantifying impurities and identifying those that are above the established threshold, and evaluating the toxicity profiles of these impurities to

distinguish the safe from the harmful. In pharmacokinetic investigations, the examination of the medication and its metabolite, which can be quantitative or qualitative, is often used.

The role of numerous analytical techniques and their associated analytical procedures in the pharmaceutical analysis is highlighted in this study.

1. UV/vis spectrophotometric method

In laboratories where advanced and expensive equipment such as those required for GC or HPLC are not accessible, spectrophotometric procedures such as UV-spectroscopy can be utilized to determine the medicines. UV-spectrophotometric methods are adaptable and cost-effective, especially in under-developed nations. This method offers various advantages over other approaches, including simple, straightforward, low-cost, and time-consuming.[9] Table 1 lists the UV-spectrophotometric techniques for determining the concentration of Tedizolid alone or in combination with other medicines.[3]

Table 1: Determination of tedizolid by UV spectrophotometric method.

Solvent/Reagent	λ_{max} (nm)	Linearity (µg/ml)	Reference
Phosphate buffer solution (PBS) pH 7.4	330	20-120	[3]
Ethanol: DMSO (6:4 v/v)	330	20-120	[3]

2. Fluorimetry method

Pharmaceutical companies are always on the lookout for sensitive analytical procedures that use a low quantity of samples. Fluorescence spectrometry is one of the methods that may achieve great sensitivity without sacrificing accuracy or specificity. In the recent past, there has been a progressive growth in the use of fluorimetry[10,11] in the quantitative study of different drugs in dosage forms and biological fluids. Table 2 lists the fluorimetry techniques for determining the concentration of Tedizolid alone or in combination with other medicines.[12]

Table 2: Determination of tedizolid by fluorescence method.

Parameter	Solvent system	LOD (ng/ml)	LOQ (ng/ml)	Reference
λ_{ex} (nm) 300 λ_{em} (nm) 395	Ethanol	5.27	15.97	[12]

3. Thin layer chromatography (TLC)

In thin-layer chromatography, a solid phase, the adsorbent, is deposited as a thin layer onto a solid support, commonly glass, plastic, or aluminium. Several parameters determine this sort

of chromatographic separation's efficiency. The adsorbent must be very selective toward separating compounds, resulting in substantial differences in elution rates. Some adsorbents may adsorb too strongly or too weakly for the separation of any particular combination. Thin-layer chromatography is a common technique for analyzing a wide range of organic and inorganic compounds due to its unique benefits, such as minimum sample preparation, a large selection of mobile phases, sample differentiation flexibility, high sample loading capacity, and low cost. TLC is an effective method for detecting unknown substances in bulk medicines.[13] It ensures that all possible drug components are isolated to a great degree. Using spot elution followed by spectrophotometric measurement, TLC's high specificity has been used for quantitative analytical purposes. TLC is critical in the early stages of drug development because knowledge of contaminants and degradation products in the drug substance and drug product is limited. TLC has been used to identify and quantify specific pharmaceutical contaminants.[14,15] Table 3 lists the TLC techniques for determining the concentration of Tedizolid alone or in combination with other medicines.[16]

Table 3: Determination of tedizoid by TLC method.

Mobile Phase	Rf	References
Methanol: Butanol: Ethyl acetate: Ammonia (60:20:20:10 v/v)	0.19 ± 0.02	[16]

4. High Performance Thin Layer Chromatography (HPTLC)

As the technology has progressed, high-performance thin-layer chromatography (HPTLC) has become an essential tool in drug analysis. HPTLC is a quick separation method that may be used to evaluate a wide range of materials. This procedure is helpful in many ways, including its ease of use and the fact that it takes a short amount of time to examine the complicated or crude sample cleaning. HPTLC assesses the complete chromatogram in real-time using a range of factors. Furthermore, numerous samples and standards are developed simultaneously yet independently on each plate, resulting in more excellent dependability.[17] Table 4 lists the HPTLC techniques for determining the concentration of Tedizolid alone or in combination with other medicines.[18]

Table 4: Determination of tedizolid by HPTLC Method.

Mobile Phase	λ (nm)	Stationary Phase	Linearity Range (ng/ml)	LOD (ng/ml)	LOQ (ng/ml)	Reference
Chloroform: Methanol (90:10 v/v)	300	Silica gel 60 F_{254S}	10-2000	3.41	10.23	[18]

5. High Performance Liquid Chromatography (HPLC)

A robust separation process must be capable of resolving mixtures, including a high number of identical analytes. Each component in the combination has its unique elution time (the moment the signal shows on the screen) under a particular set of circumstances. The area and height of each signal are proportional to the quantity of the associated substance. This example demonstrates the efficiency of high-performance liquid chromatography (HPLC), which produces excellent separations in a short amount of time. Martin and Synge, the "inventors" of contemporary chromatography, recognized as early as 1941 that, in theory, the stationary phase requires highly tiny particles and that, as a result, high pressure is required to force the mobile phase through the column. As a result, HPLC was termed "high-pressure liquid chromatography" at one point.[19] Table 5 lists the HPLC techniques for determining the concentration of TDZ alone or in combination with other medicines.[16, 20-22]

Table 5: Determination of Tedizolid by HPLC Method.

Technique	Mobile Phase	Flow rate	LOD (µg/ml)	LOQ (µg/ml)	References
RP-HPLC	Disodium hydrogen phosphate buffer (pH 7.0) with additive β-cyclodextrin, triethylamine and acetonitrile	1.0 ml/min	0.10	0.30	[20]
HPLC	Phosphate buffer (50mM, pH 6.5): Acetonitrile (70:30 v/v)	1.0 ml/min	0.25	1.0	[16]
HPLC in Human Plasma	20mM sodium phosphate: Acetonitrile with pH 7.1–7.25	0.4 ml/min	-	-	[21]
HPLC in Human Plasma	Sodium acetate buffer: Acetonitrile	1.0 ml/min	-	-	[22]
HPLC in Human Serum	Sodium acetate buffer: Acetonitrile	1.0 ml/min	-	-	[22]
HPLC in Saline	Sodium acetate buffer: Acetonitrile	1.0 ml/min	-	-	[22]
HPLC in Mouse Plasma	Sodium acetate buffer: Acetonitrile	1.0 ml/min	-	-	[22]

6. Hyphenation techniques

The creation of a hyphenated technique occurs when a separation technique and an online separation technique are combined. A range of hyphenated methods, such as LC-MS,[23,24] have been used in examining medicines. Drug detection in biological materials is a vital stage

in the drug research and development process. In combination with various forms of detection such as ultraviolet, fluorescence, and mass spectrometry, HPLC has emerged as the preferred approach for developing bioanalytical methods. [25] Table 6 lists the hyphenation techniques for determining the concentration of TDZ alone or in combination with other medicines.[26-33]

Table 6: Determination of Tedizolid by UPLC-MS/MS Method.

Matrices	Mobile Phase	Column	Method	Flow Rate	LOQ (ng/ml)	Reference
Rat Plasma	Acetonitrile: 20mM Ammonium Acetate (85:15 v/v)	UPLC BEH C18 column	Isocratic	0.3 ml/min	0.74	[26]
Rabbit Aqueous Humor	Acetonitrile: 20mM Ammonium Acetate (85:15 v/v)	HILIC column	Isocratic	0.3 ml/min	1.97	[27]
Rat Plasma	0.1% Formic Acid: Acetonitrile	UPLC BEH C18 column	Gradient	0.4 ml/min	5.0	[28]
Human Plasma	0.1% Formic Acid, 2mM Ammonium Formate and Acetonitrile	UHPLC CSH C18 column	Gradient	0.4 ml/min	-	[29]
Human Plasma	0.1% Formic Acid, 2mM Ammonium Formate and Acetonitrile	BEH C18 column	Gradient	0.5 ml/min	2.0	[30]
-	10mM Ammonium Acetate Buffer (pH 6.5): Acetonitrile	XR-ODS column	Gradient	0.4 ml/min	-	[31]
-	0.05 M ammonium bicarbonate buffer (pH 7.8): Acetonitrile	Gemini C18 Column	Gradient	0.8 ml/min	-	[32]
Mouse Plasma	20mM ammonium formate (pH 8.0): methanol	Gold C18 column	Gradient	0.5 ml/min	-	[33]

CONCLUSION

According to the current study, a broad range of analytical techniques such as spectrophotometry, spectrofluorimetry, and chromatography methods are available to determine Tedizolid. However, because of their ability to identify materials with low concentrations, high-performance liquid chromatography (HPLC) and ultra-performance liquid chromatography (UPLC) technologies are often utilized in biological matrices research. To sum up, the analyst and experienced formulators will work together shortly to create more environmentally friendly ways for estimating Tedizolid that use less harmful solvents. More LC-MS/MS-based approaches might open the path for drug determination in biological fluids, which could be more critical for Tedizolid therapeutic monitoring.

CONFLICT OF INTEREST

There isn't any potential for a conflict of interest.

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