

Overview on Development and Validation of Analytical and Bioanalytical Methods for the Estimation of Linezolid in Bulk and **Pharmaceutical Dosage Form.**

¹Dr. Pratap Y. Pawar, ²Suvarna P. Bodkhe*, ³Dayanedeo B. Sumbre, ⁴Vidya S. Jadhav, ⁵Rutuja D. Bhangare

1.2.4.5 Pharmaceutical Chemistry Department, DR Vithalrao Vikhe Patil Foundations College of Pharmacy, Vilad Ghat, PO.MIDC, Ahmednagar, Maharashtra, India. ³*MVPs College of Pharmacy, Nashik- 422 002, Department of Pharmaceutical Chemistry.*

Corresponding Author: Suvarna P. Bodkhe*

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ABSTRACT:

Linezolid is an antibacterial medication that has been licenced by the US Food and Drug Administration. It's used to treat Gram-positive bacteria infections that have become resistant to other antibiotics. It is also used to treat skin infections and pneumonia, while it can also be used to treat a range of other infections, such as drugresistant tuberculosis. Several analytical and bioanalytical procedures have been established for the resolution of linezolid in dose form and bulk form, including HPTLC, UV, HPLC, UPLC, and LC-MS/MS. For linezolid. methods for determining human plasma stability and impurity profiling are also outlined. The preceding analytical procedures were employed for the qualitative and quantitative evaluation of linezolid, and they can also be used for similar degradants in bulk formulations and biological fluids. The supporting research demonstrates.

KEYWORDS: Linezolid, Antibiotic, Pneumonia, RP-HPLC, Human plasma.

I. **INTRODUCTION:**

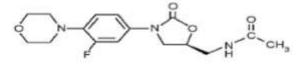
The United States Food and Drug Administration has approved linezolid for the treatment of infections caused by Gram-positive bacteria that are resistant to other antibiotics. The

Structure:

antibiotic linezolid is the first of the oxazolidinone class of antibiotics. The substance is a synthetic antibiotic that binds to rRNA and inhibits bacterial protein production. Most Gram-positive bacteria that cause disease, such as streptococci, vancomycin-resistant enterococci (VRE), and methicillin-resistant Staphylococcus auras, are susceptible to linezolid (MRSA). It is also used to treat skin infections and pneumonia, while it can also be used to treat a range of other infections, such as drug-resistant tuberculosis. The USFDA has approved the antibiotic linezolid for the treatment of illnesses caused by Gram-positive bacteria.

1.1 LINEZOLID:

1.1.1 Description: Linezolid was approved by the United States Food and Drug Administration (FDA) on April 18, 2000. Linezolid has been approved to treat infections caused by vancomycinresistant Enterococcus faecium, hospital-acquired pneumonia caused by Staphylococcus aureus, complicated skin and skin structure infections (SSSIs). uncomplicated SSSIs caused bv methicillin-susceptible S.aureus or Streptococcus pyogenes, and community-acquired pneumonia caused by Streptococcus pneumonia.





Chemical name	(S)-N-[[3-[3-Fluoro-4-(4-morpholinyl)phenyl]-2-oxo-5- oxazolidinyl] methyl] acetamide		
Generic name	Linezolid		
Brand name	Zyvox		
Class	Synthetic antibiotic, antimicrobial called oxazolidinones		
Mol. Formula	$C_{16}H_{20}FN_{3}O_{4}$		
Mol. Weight	337.35 g/mol		
CAS Registry Number	165800-03-3		
Antimicrobial spectrum	Mainly active against gram- positive organisms		
pH value	4.3 to 5.3		
pKa value	1.8		
Polarity	Log P 0.232		
solubility	Water-soluble (approximately 3mg/ml), it is also soluble in organic solvents such as methanol, ethanol, DMSO, dimethyl formamide.		
bioavailability	~100% (oral)		
Protein binding	Low (31%)		
metabolism	Hepatic (50-70%, CYP not involved)		
Dose	Oral or i.v. 600 mg every 12 hours for serious infections & 400 mg every 12 hours for uncomplicated infection [FDA Label]		
Half life	4.2- 5.4 hours (shorter in children)		
Excretion	Non renal, renal, and fec		
Melting point	181.5 to 182.5 Ċ		
Storage	Store at RT		
U.V. spectrum	$\lambda \max 252-259 \ \text{nm}$		

Therapeutic category: Linezolid is used to treat infections, including pneumonia, and infections of the skin

l, chloroform, methanol, DMSO, and dimethyl formamide.

1.1.2. Pharmacokinetics:

Absorption: Linezolid is well absorbed in healthy individuals, having a mean absolute bioavailability of 100%. After oral doses, maximum blood concentrations (C max) take 0.5-2 hours to attain. When a high-fat meal is given with linezolid, the mean time to attain (C max) is delayed from 1.5 to 2.2 hours, and (C max) is reduced by 15-20%; nevertheless, the area under the plasma concentration-time curve is unaffected. Oral suspension absorption is comparable to film-coated tablet absorption. Linezolid is well absorbed in healthy individuals, having a mean absolute (C max) is delayed from 1.5 to 2.2 h.

Distribution: In healthy adults, the volume of distribution at steady state is 30-50 L, or 0.5–0.6 L/kg, which approximates total body water. Protein binding is about 31% and isn't affected by concentration.

Metabolism: The metabolism of linezolid is relatively complex, producing two primary metabolites and a slew of smaller ones. The aminoethoxyacetic acid metabolite (PNU-142300) and the hydroxyethyl glycine metabolite are the two major metabolites formed by oxidation of the morpholine ring, resulting in two inactive openring carboxylic acid derivatives (PNU-142586). The most common human metabolite, PNU-



142586, is produced by a non-enzymic process and can thus be found throughout the body.

Elimination: Linezolid is primarily excreted through urine. The metabolites of linezolid are eliminated in the urine as they are produced. Non-renal clearance accounts for 65 percent of overall linezolid clearance. At steady state, 30% of linezolid is excreted in the urine unaltered. Under single-dose and steady-state settings, the elimination half-life was 4.5-5.5 hours.

1.1.3. Pharmacology:

Linezolid is an antibiotic oxazolidinone that is effective against most aerobic Gram-positive bacteria and mycobacteria. It seems to be bacteriostatic against staphylococci and enterococci, as well as bactericidal against most streptococci isolates.

Mechanism of action: Bacterial ribosomes are made up of two subunits, 30S and 50S, each of which is made up of RNAs encased in proteins. These two units link together to start the process of protein synthesis and then separate after the process is finished. The ribosomal 30S subunit binds to mRNA to make formylmethionyl-tRNA, which subsequently forms an initiation complex with GTP and three initiation factors ([IFs] 1-3). After binding to the ribosomal 50S subunit to form the 70S ribosome, protein synthesis can commence. Oxazolidinones have been demonstrated to attach to the 50S ribosomal subunit within domain V of the 23S RNA peptidyl transferase centre near the contact with the 30S subunit, preventing the 50S subunit from binding to the 30S subunit.

Indication and clinical use: Infections caused by susceptible Gram-positive bacteria, such as nosocomial pneumonia, community-acquired pneumonia, skin and skin structure infections, and vancomycin-resistant Enterococcus faecium infections, are treated with linezolid in both adults and children. Linezolid isn't approved to treat gram-negative infections or infections at catheter sites.

Contraindication: If you're taking MAO inhibitors like phenelzine, don't take it within two weeks. Tyramine-containing meals and serotonergic medicines should be avoided since they can cause a hypertensive emergency. Aged cheese, cured or smoked meats, draught beer, fava beans, and soy products are examples of tyramine-containing foods.

Adverse reaction: Reduced platelets, haemoglobin, and white blood cell counts, headache, nausea, diarrhoea, raised pancreatic enzymes, elevated liver function tests, and neuropathy are the most prevalent side effects of linezolid use. $^{[1-6]}$

Drug interaction: interactions with other medicine

1. Serotonin syndrome

Changes in mental state, ataxia, restlessness, and lower extremities hyper-reflexia or diaphoresis are all symptoms of serotonin syndrome, which can progress to medical problems such as delirium, generalised tonic-clonic seizures, shock, or even coma. Excess 5-HT levels caused by the use of two or more serotonergic medicines are the cause of serotonin syndrome. Linezolid is a nonselective nonreversible MAO inhibitor that reduces serotonin breakdown by inhibiting the MAO-B isoform. Patients on serotonergic antidepressants should only use linezolid if no other options are available, according to the ZYVOX full prescribing information, and serotonergic antidepressants should be stopped. Furthermore, patients should be closely monitored for signs and symptoms of serotonin syndrome or antidepressant cessation.

2. Interactions with adrenergic agents

Because linezolid is a nonselective MAO inhibitor, it can also block the MAO-A isoform, resulting in reduced norepinephrine breakdown and increased adrenergic activity. Linezolid should not be given to patients who are receiving directly or indirectly acting sympathomimetic medicines, vasopressive agents, or dopaminergic agents unless they are monitored for potential rises in blood pressure.^[7]

1.1.4. Dosage and administration:

In adults and adolescents (12 years and older) patients with infection caused by VRE or MRSA, the recommended dosage of linezolid is 600 mg every 12 hours. The drug may be given through IV infusion or orally. The recommended duration of treatment for VRE infections is 14 to 28 days. In patients with MRSA treated with linezolid in clinical trials, the duration of treatment, ranged from 7 to 28 days. The recommended dosage of linezolid for the treatment of patients with nosocomial or community- acquired pneumonia, or complicated SSTIs is 600 mg every 12 hours for 10 to 14 days. In patients with uncomplicated SSTIs, the recommended dosage of linezolid is 400mg every 12 hours for 10 to 14 days. The



recommended dosage of linezolid for the treatment of children (below 11 years of age) with infection caused by VRE, or nosocomial or communityacquired pneumonia, or complicated SSTIs is 10 mg/kg intravenously or orally, every 8 hours.

1.1.5. Available dosage form:

Linezolid single-dose, ready-to-use flexible plastic infusion bags in a foil laminate overwrap for ZYVOX I.V. Injection: 200 mg/100 ml (2 mg/ml) and 600 mg/300 ml (2 mg/ml) linezolid singledose, ready-to-use flexible plastic infusion bags in a foil laminate overwrap

ZYVOX 600 mg pill is a white, capsule-shaped, film-coated tablet with the letters "ZYV" and "600" debossed on one side and "600" on the other.

ZYVOX for oral suspension is a dry, white to offwhite granule/powder with an orange flavour. Each bottle will provide 150 ml of a suspension containing the equivalent of 100 mg of linezolid per 5 ml when prepared as indicated.

1.1.6. Storage and Handling:

Keep it at 25 degrees Fahrenheit. Protect from the light. To avoid moisture, keep bottles securely closed. The infusion bags should be kept wrapped in the overwrap until ready to use. Also, keep infusion bags away from the freezer.^[8]

II. ANALYTICAL METHODS:

Different chromatographic procedures are utilised to enhance and validate the medication in its bulk and dose form in solvent employing analytical methodologies. According to a review of the literature, numerous analytical methods for estimating linezolid have been published, including UV, LC-UV, HPLC-UV, RP-HPLC, and HPTLC.

2.1. Chromatographic methods for analytical development:

Spectrophotometric method:

The quantitative measurement of linezolid in pharmaceutical dosage forms was reported using a UV spectroscopic approach. The new procedures were simple, precise, specific, and accurate, and statistical analysis revealed that they are reproducible and selective for linezolid analysis in bulk medication and tablet formulations. UV spectrophotometry is mostly utilised for technique improvement and validation, as well as stability testing.

HPTLC Method:

A simple, selective, precise, and stabilityindicating high-performance thin layer chromatographic technique for analysing linezolid was developed and validated in pharmaceutical dosage form. The method used TLC aluminium plates precoated with silica gel 60F-254 as the stationary phase and an appropriate mobile phase, and all validation parameters were investigated at maximum absorbance, with results presented in the form of bands. HPTLC has the potential to be used in the pharmaceutical business. This technique was discovered to produce compact linezolid spots. The degraded products were likewise clearly distinguished from the pure medication.

RP-HPLC Method:

The most commonly used methodology linezolid is RP-HPLC, which for is а straightforward, sensitive, and accurate approach for drug development and method validation. It's employed in drug development and method validation in API and formulation, and the majority of the work on linezolid stability is done with RP-HPLC, as well as force degradation and stress testing. The RP-HPLC technology has been certified and developed for linezolid impurity profiling. To demonstrate the medication's identity, the drug substance was subjected to a variety of stress conditions, including oxidation, hydrolysis (acidic and basic), thermal degradation, and photolysis, all of which followed the ICH criteria for stress conditions. A considerable change was detected during acid base hydrolysis and thermic degradation. By using NMR and FTIR and LC-MS spectral analysis the vital degradants were known.

LC-MS Method:

LC-MS is a less used technique for an analytical method development, it is used for stress testing of linezolid.

III. BIOANALYTICAL METHODS:

It is the process used to establish that a quantitative analytical method is suitable for biomedical applications.

3.1 Chromatographic methods for bioanalytical development:

RP-HPLC Method:

For bioanalytical studies, the RP-HPLC method is utilised, which is a simple, easy, and cost-effective chromatographic method. In RP-HPLC, a research of linezolid and its metabolite was performed, for which different biological fluids of different species were employed and sample pretreatment was done using different extraction techniques. In comparison to LC-MS/MS, sensitivity is modest. LC-MS/MS method:



Sr. No.	Title of Article	Name Of Journal	Analytical conditions	References
1	UV- Spectrophotomet ric method development and validation for determination of linezolid in pharmaceutical dosage form.	Research and reviews: Journal of pharmaceutical analysis	Solvent- 0.05N HCl Concentration range- 1-6 mcg/ml. Correlation coefficient (r²)- 0.997 λmax- 252 nm LOD- 0.36 mcg/ml LOQ- 1.11 mcg/ml Recovery- 98.30-101.09%	Nagaraju PT, 2014
2	Method development and validation of spectrophotomet ric method for the estimation of linezolid in pure and tablet dosage form	Asian Journal of pharmaceutical analysis and medicinal chemistry	Solvent- Distilled water Concentration range- 1-6 mcg/ml Correlation coefficient (^{r²})-0.999 λmax- 251 nm LOD- 0.603 LOQ- 0.830 Recovery- 97.44 - 102.52 %	Sushma S, 2015
3	Development and validation of UV spectrophotomet ric method for simultaneous estimation of cefixime and linezolid in combined dosage	International journal for pharmaceutical Research scholars	Solvent- Methanol Concentration range of Cefixime- $5-40\mu g/ml$ Linezolid-10- $30\mu g/ml$ Correlation coefficient (r^2) of Cefixime- 0.9998 Linezolid- 0.9998 λ max of - Cefixime- 289.0 nm Linezolid- 257.0 nm Recovery of- Cefixime-100.51% Linezolid- 100.23% LOD- Cefixime- 0.46 $\mu g/ml$ Linezolid- 0.75 $\mu g/ml$ LOQ- Cefixime- 1.42 $\mu g/ml$ Linezolid- 2.27 $\mu g/ml$	Patel DP,2012



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4.	Validation of a new HPLC-UV method for determination of the antibiotic linezolid in human plasma and in bronchoalveolar lavage	Biomedical chromatography	Column-C18 Mobile phase- dihydrogen phosphate buffer 50 mm (PH 3.5) and acetonitrile (60:40 v/v) Concentration range -25-25,600 ng/ml Correlation coefficient - 0.9997 Flow rate- 1ml/min Detector-2996 photodiode array detector λ max-254 nm R.T For linezolid - 3.78 min For IS- 10.91 min	Serena fortuna,2013
5.	Validated stability indicating RP- HPLC method for the estimation of linezolid in a pharmaceutical dosage form	Journal of liquid chromatography & Related technologies, Taylor & Francis	Column- Model Hypersil ODS C18 Solvent- water: methanol (50:50 v/v) Flow rate- 1ml/min λ max- 254 nm R.T- 5.1 min Concentration range- 0.001 -3.4 mg/ml Correlation coefficient-0.9999 Degradation- acidic, basic, hydrogen peroxide, thermal degradation	Sharmistha Mohapatra, 2011
6.	RP- HPLC method development and validation for the analysis of pharmaceutical drugs- linezolid	International journal of science and research (IJSR)	Elution- Isocratic Mobile phase- Acetonitrile:0.1 M Acetic Acid 50:50 (v/v) Concentration range- 100 ppm- 140 ppm Correlation coefficient-0.9733 pH- 3.0 column- C18 λmax- 254 nm flow rate- 1.2 ml/min R.T- 3.35	Bhaskarrav Makwana, 2014
7.	UV spectroscopic method for estimation of linezolid in tablets	International journal of pharmaceutical, chemical and biological sciences	Concentration range-2-16 mcg/ml λmax-251 nm correlation coefficient- 0.998 sol vent- Phosphate buffer pH- 7.2	BH.saikiran, 2013



0	Development of	Characteratio	Column C19 5 250 mm × 4.(Cristiani C. C.
8.	Development of a validated	Chromatographia	Column- C18, 5μm, 250 mm × 4.6	Cristiani C. G.
			mm Mabila phone 10/ apotia acid:	O. Lopes, 2008
	stability-		Mobile phase- 1% acetic acid:	
	indicating LC		methanol: acetonitrile (50:25:25,	
	Assay and Stress		v/v/v	
	degradation		Concentration range - 6-16 µg/ml	
	studies of		R.T - 4.6 min	
	linezolid in		Flow rate- 1.0 ml/ min	
	tablets		LOD - 0.21 µg/ml	
			LOQ - 0.63 μg/ml	
			Degradation- acid, base, oxidation,	
			dry heat and photolytic degradation	
9.	Development	Indian journal of	Column- C18, 250×4.6 mm, 5 μm	Patel, et al.
	and validation of	pharmaceutical	Mobile phase-phosphate buffer	2014
	stability-	sciences	(pH7):methanol (60:40 v/v)	
	indicating HPLC		Concentration range-	
	method for		For cefixime-2-12µg/ml	
	simultaneous		For linezolid-6-36µg/ml	
	estimation of		Flow rate- 1ml/min	
	cefixime and		R.T-	
	linezolid		For cefixime-3.12 min	
			For linezolid-11.9 min	
			λ max-276nm	
			degradation - acid and base	
			hydrolysis, thermal and photo	
			degradation	
10.	Spectrophotomet	National	Concentration range - 5-40µg ml	Lories I.
10.	ric and HPLC	organization for	λ max-240 nm	Bebawy, 2003
	determination of	drug control and	Mobile phase- methanol and water	Debawy, 2005
	linezolid in	research, Egypt	(65:35v/v)	
		research, Egypt		
	presence of its		pH- 3.5	
	alkaline- induced		flow rate- 2 ml/min	
	degradation		degradation product	
	products and in		preparation-	
	pharmaceutical		sodium hydroxide, methanol, 2 M	
	tablets		HC1	
			Mobile phase- Isobutanol:	
			ammonia 25% (9:1 v/v)	
			λ max-254nm	
11.	Determination of	Ther Drug Monit,	Column- C18 (4.6 mm × 150 mm),	Cattaneo et al,
	linezolid in	Volume 32	3.5 μm	2010
	human plasma		Mobile phase- phosphoric acid	
	by high –		0.05% :acetonitrile (75:25, v/v)	
	performance		Flow rate- 1ml/min	
	liquid		λmax- 254 nm	
	chromatography		Run time - 12 min	
	with ultraviolet		R.T - 4.0- 10.6 min	
	detection		Concentration range- 0.2- 48 mg/l	
			Drug recovery- 99.8%	



12.	High performance thin layer chromatographic method for estimation of linezolid in tablets	Indian journal of pharmaceutical sciences	Stationary phase- silica gel 60 F_{254} TLC plate (10×10 cm, layer thickness 0.2 mm) Mobile phase- methanol : benzene (2:8 v/v) Rf- 0.45 ± 0.03 λ max- 258 nm LOD- 16.7 ng/spot LOQ- 50.7 ng/spot Aliquots- 2-14 µl of Std linezolid solution (100 µg/ml). Linearity range for linezolid was found in the concentration range of 200 to 1400 ng/spot Correlation coefficient- 0.9945 % recovery- 97.8- 100.4	S. A. Patel, 2007
13.	Stability indicating HPTLC determination of linezolid as bulk drug and in pharmaceutical dosage form	Drug development and industrial pharmacy	Stationary phase-TLC aluminium plates percoated with silica gel 60 F-254 TLC scanner III Solvent- toluene- acetone(5:5, v/v) Rf value- 0.29 ± 0.01 λ max- 254 nm correlation coefficient- $0.997\pm$ 0.001 concentration range- 300- 800 ng/spot LOD- 20 ng/spot LOQ- 50 ng/spot Degradation- acidic, alkali hydrolysis, oxidation and photo degradation	Agrawal et al, K. R. Mahadik, 2003
14.	Development of a sensitive LC- MS/MS method for quantification of linezolid and its primary metabolites in human serum	Journal of pharmaceutical and biomedical analysis	Column- (C18, 150× 4.6 mm, 3.5 µm) at 25Ċ Mass analysis- positive electrospray ionization. Mobile phase- 1.water with 0.1% formic acid 2.acetonitrile with 0.1% formic acid Flow rate- 0.6 ml/min Run time- 15 min Correlation coefficient- ≥ 0.99 Concentration ranges- 0.1-50 µg/ml for LZD and PNU-142300, and 0.1-25 µg/ml for PNU-142586 Calibration curves to be linear for LZD- 0.2- 50 µg/ml Curves were linear at 0.2-20 µg/ml for both metabolites. Correlation coefficient- (r^2 >0.99)	Ernane souza, 2019
15.	Determination of residual solvents in linezolid by	Journal of chromatographic science, 2015	Solvents- petrolium ether, acetone, tetrahydrofuran, ethyl acetate, methanol, dichloromethane and	Xiao- Zhen Feng, 2015

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static headspace GC	pyridineLOD-0.12µg/ml (petroleum ether)and 3.56 µg/ml (DCM)LOQ-0.41 µg/ml (petroleumether) and 11.86µg/ml (DCM)GC-FID analysis-Column-ZB-WAX capillarycolumn (30 m length × 0.53 mmi.d. and 1.0 µm film thickness andDB-FFAP capillary columnTemp. of injector-90ĊDetector temperature-280ĊCarrier gas-NitrogenFlow rate-1ml/minInjection volume of sample-1ml	

In the development of bioanalytical methods, the most commonly utilised approach is LC-MS/MS, which is a quick and sensitive method for drug bioanalysis. Interference of biological

fluid is avoided in this procedure, and the drug and its metabolite are easily detected in biological fluid, with an internal standard used to compare the drug to a reference.^[9-25]

BELOW TABLE INCLUDES OVERVIEW OF ARTICLES: [9-25]

16.	Development and validation of a new UPLC-PDA method to quantify linezolid in plasma and in dried plasma spots.	Journal of chromatograph y B	Linezolid extraction from plasma was obtained using- acetonitrile. Internal standard- quinoxaline Analysis was performed by – (UPLC) system coupled with (PDA) detector, at 254 nm. Analytical methods were linear ($r^2 > 0.999$) over the calibration range of 30-0.117 mg/l. LOQ-0.117mg/L LOD-0.058 mg/L R.S.D% and accuracy% were <15%.	L. Baietto et al. (2013)



17.	Measurement uncertainty of a UPLC stability indicating method for determination of linezolid in dosage forms.	Measurement Journal homepage: www. Elsevier. com/locate/me asurement	Linezolid was degraded after exposed to light and oxidation. The UPLC method was linear (range from 8.0 to 12.0 μ g/ml, with r^2 =0.9985), showed good precision (repeatability of 0.89% and intermediate precision of 0.66%0, accuracy rate (recovery from 98.07% to 99.03) and robust. 72% overall uncertainty	A. Saviano al. 2015	M. et	_
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IV. DISCUSSION:

Many methods have been published for the identification and quantification of linezolid, which is utilised against gram-positive bacteria and in many pharmaceutical formulations and biological substances. For method development and stability investigations, UV spectrophotometry, RP-HPLC, and HPTLC can be concluded to be the most simple, easy, and commonly utilised procedures. The UPLC method and LC-MS/MS techniques are also commonly employed in stability investigations, while the RP-HPLC method is used for stress testing and impurity profiling. While HPLC-UV and LC-MS/MS are commonly used to detect linezolid in biological fluids such as plasma and serum, a novel technique called dried blood/plasma spot is also utilised for linezolid bioanalytical studies. As a result, the current evaluation will assist scholars in broadening their perspectives on various improved elements and generating new ideas.

V. CONCLUSION:

This review covered the basics of UV spectroscopy, HPTLC, HPLC, LC-MS/MS, and UPLC as analytical and bioanalytical procedures for determining linezolid. We looked at references on analytical and bioanalytical topics from 2003 to 2019, with a focus on newly developed analytical methods for development and validation, as well as bioanalytical methods for application in biological samples for pharmacokinetic investigations in animals and people. The majority of work in analytical techniques is focused on method development and linezolid stability testing. In addition, the HPLC-UV method remains a powerful analytical tool with a low instrument cost in bioanalytical. In comparison to HPLC-UV, LC-MS (MS) delivers improved specificity and sensitivity for measuring linezolid with simpler and newer sample preparation processes and smaller sample quantities to inject, as per the present demand.

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