RESEARCH ARTICLE

Release Kinetic of Sustained Release Matrix Tablet of Linezolid Containing Polymer Blend

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ABSTRACT

Tuberculosis (TB) is a bacterial infection mainly affecting the lungs. TB is a major health problem worldwide and the occurrence of extensively drug-resistant TB (XDR-TB) and multidrug-resistant TB (MDR-TB) offers considerable hurdles to effective treatment and disease management. The growth of treatment-resistant Mycobacterium TB strains has prompted the investigation of alternate therapeutic techniques, including the application of sustained drug delivery. Sustained-release drugs reduce the need for frequent dosing can extend the effects of linezolid by 8 to 12 hours, thus improving the patient's adherence to the treatment. The objective of this study is to formulate oral sustained-release linezolid tablets employing blends of polymers like hydroxy propyl methyl cellulose (HPMC)- K100M, ethyl cellulose, xanthan gum, and chitosan to provide sustained drug release. Linezolid was made into a sustained-release tablet by employing the direct compression method using different drug-polymer ratios. Formulated tablets were compared with marketed formulations to assess the similarity factor. The formulation was assessed for drug-excipient interaction, solubility, flow properties, etc. The diameter, friability, thickness, hardness, weight variation, *in-vitro* drug release, and drug release kinetics of compressed tablets were examined. Drug release research proved that all polymers were able to sustain drug release. Formulation (F5) with HPMC (100mg) and ethyl cellulose (100mg) resulted in 49.89% drug release after 8 hours, making it the optimal formulation. According to the kinetic model of the drug release, the Higuchi model was selected, which indicates the diffusion of the drug from an insoluble matrix. The optimized formulation showed a similarity factor of 52% with the marketed formulation, suggesting similarity in drug release between these two formulations.

Keywords: Linezolid, Tuberculosis, Matrix tablet, Sustained release, Kinetics.

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INTRODUCTION

Tablets are a commonly utilized solid dose form primarily taken orally. Oral medication bioavailability is influenced by the drug's gastrointestinal permeability and *in-vitro* dissolution.[1,2] Medicinal formulations intended to release their active ingredients gradually over a prolonged time after intake are called sustained-release, extended-release, or controlled-release tablets.[3-5] Since the drug is formulated to enter the bloodstream gradually, the drug concentration occupies the therapeutic range for a longer period.[2,6,7] Tuberculosis (TB) is a major worldwide health concern, affecting millions of people each year despite intense attempts to eradicate it.[8,9] The emergence of drug-resistant strains of Mycobacterium TB, the tuberculosis-causing bacteria, challenges treatment efforts and emphasizes the crucial need for novel therapeutic approaches. According to the WHO report for 2022, tuberculosis killed 1.3 million people, including 167,000 HIV-positive adults. After COVID-19, TB is the second most prevalent infectious killer

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worldwide, exceeding HIV and AIDS.[10] Linezolid (LNZ), an oxazolidinone antibiotic, has demonstrated potential action against drug-resistant tuberculosis strains and is used to treat MDR- and XDR-TB infections off-label.[11] However, the appropriate use of linezolid in tuberculosis treatment regimens is still being researched and debated. To guarantee the safe and effective use of this medicine, factors such as optimal dose, treatment duration, and side effect management need to be investigated further. One method to address these issues is to create sustained-release linezolid formulations.[12] Sustained-release drug delivery systems can provide various benefits, including increased patient compliance, reduced dose frequency, and possible therapeutic effectiveness. The goal of the current study was to create and evaluate a linezolid tablet with sustained release employing synthetic polymers like HPMC K100M, EC, XG, and chitosan. The rationale for this approach is to use the biocompatibility, biodegradability, cost-effectiveness, and controlled drug-release properties of synthetic polymers to create an optimized sustained-release linezolid formulation for tuberculosis treatment.

MATERIALS AND METHODS

Materials

Linezolid was obtained from Optrix. Pvt. Ltd. HPMC K100M, ethyl cellulose, xanthan gum, and chitosan were obtained from the Central Drug House (CDS), New Delhi, India. All the chemicals were of analytical grade.

Method

Preformulation parameters

- *Organoleptic properties*

Using the appropriate technique, the drug's organoleptic qualities such as its color, odor, and physical form, were identified.[13]

Melting point

The capillary tube technique determined the melting point of the active excipient. The medication was put in a narrow capillary tube. The temperature at which the sample starts melting is noted as the melting point. The mean value was reported after the melting point was measured three times.[14]

Solubility

A rotary flask shaker was used to measure the drug's aqueous solubility. A saturated solution of LNZ was made by placing an excess quantity of LNZ in a conical flask containing 25 mL solvent. A rotary flask shaker was used to agitate the solution for a full day. After filtering and diluting the solution, it was examined in a UV-vis spectrophotometer.[15]

Determination of λ max and preparation of calibration curve in 0.1N HCl

To measure the λ max of linezolid in 0.1N HCl, the drug is dissolved in the 0.1N HCl and scanned using a UV-visible spectrophotometer to determine the wavelength of maximum absorption. Once λ_{max} is determined, a calibration curve is created by measuring the absorbance of linezolid solutions at different concentrations. The curve is created by plotting these absorbance values against their respective concentrations. Finally, the calibration curve is tested to verify its precision and dependability in quantitative analysis.[16]

Drug excipient compatibility study

FTIR was used to identify the drug and to determine the compatibility of the drug and the excipient utilized in the formulation. A pinch of the sample is taken, combined with KBr, and crushed in a mortar and pestle. The drug and excipients are taken either separately or in combination. Pellets are created by pressing this mixture under a hydraulic press. These pellets are further scanned for compatibility testing.[17]

Tablet compression

The direct compression approach was utilized to manufacture a sustained-release tablet of linezolid. To formulate tablets of linezolid, accurately weighed quantity of the drug and other excipients were taken in varied concentrations as shown in Table 1. All the excipients were combined and blended homogeneously in mortar and pestle. The powdered mixture was mixed for five minutes with the lubricant (magnesium stearate) and glidant (talc) before the compression. Using a rotary press, the powdered mixture was compressed, and the tablets were punched.[14]

Evaluation Parameters

Pre-compression evaluation

A crucial factor in ensuring dosage consistency in the tablets is the flow property. Flow property is determined by measuring the angle of repose, Carr's Index and Hausner's ratio. The fixed funnel method was used to calculate the powder's angle of repose. The powder was taken via a funnel after being precisely weighed. The funnel's height was modified such that the tip of the funnel just touched the top of the powder pile. The powder was let to freely pour onto the surface through the funnel.[18] The powder cone's height and diameter were measured, and the following equation was used to determine the angle of repose:

$$\tan \theta = h / r$$

Where, h = height of the pile, r = radius of the pile base, θ = angle of repose

To calculate the Hausner's ratio and Carr's compressibility index, the bulk and tapped densities were measured as follows.[19]

$$\text{Hausner ratio} = \text{Tapped density}/\text{Bulk density}$$

$$\text{Carr's index (\%)} = \text{tapped density} - \text{bulk density} / \text{tapped density} \times 100$$

Post-compression Evaluation of Tablet

Thickness and diameter of tablet

The thickness and diameter of the tablet are measured using a vernier caliper. A tablet is placed between the jaws of the

Table 1: Formulation code

Formulation	F_1 *(mg)*	F_2 *(mg)*	F_3 *(mg)*	F_4 *(mg)*	F_5 *(mg)*	F_6 *(mg)*	F_7 *(mg)*	F_8 *(mg)*	F_9 *(mg)*	F_{10} *(mg)*
Linezolid	600	600	600	600	600	600	600	600	600	600
HPMC	200	-	-	-	100	100	100	-	-	-
Ethylcellulose	-	200	-	-	100	-	-	100	100	-
Xanthan gum	-	-	200	-	-	100	-	100	-	100
Chitosan	-	-	-	200	-	-	100	-	100	100
Magnesium stearate	2	2	2	2	2	2	2	2	2	2
talc	5	5	5	5	5	5	5	5	5	5
Total weight (mg)	800	800	800	800	800	800	800	800	800	800

caliper. The reading displayed on the caliper represents the thickness and diameter of the tablet.[20]

Tablet hardness

Hardness is measured as the force needed to shatter the table. It determines the ability of the tablet to withstand mechanical shock. A Monsanto hardness tester was used to determine the tablet's hardness. A tablet is placed in the tester and force is applied until the tablet breaks or fractures. The force required to break the tablet is its hardness.[21]

Weight variation test

Using an Indian Pharmacopoeia protocol, the test was conducted on a Digital Electronic Balance. Each batch had twenty tablets selected at random, each of which was weighed separately before being weighed as a group. The weight variation was examined for each tablet separately, and the provided formula can be used to calculate the deviation.[22]

% Weight variation = (weight of single tablet-Average weight of 20 tablets) × 100%

The average weight of 20 tablets

Friability

Twenty tablets were weighed and shaken in a friability apparatus (Electro lab, model EF1W, Mumbai) for four minutes at 25 rpm to ascertain friability. After the pills were weighed and dusted, the reduction in weight due to the proportion of total weight loss that was lost due to fracture or abrasion was determined.[23]

In-vitro dissolution studies

The matrix tablet was examined for *in-vitro* dissolution in 0.1N HCl at 50 rpm using the USP paddle type II apparatus. Throughout the research, the dissolving media was kept at 37°C. An adequate sample volume was obtained regularly. Following each sampling, the jar was filled with dissolving liquid in the same volume as the removed samples. The concentration of the medication in the samples was determined at 244 nm using the UV-visible spectrophotometer.[24]

Kinetics of drug release

The DD solver was used to investigate the kinetics of drug release in the improved formulations[25] Using Microsoft Excel 2007, the zero-order, first-order, Higuchi, Hixson-Crowell cube root, and Korsmeyer-Peppas equations were fitted to the *in-vitro* release data to define the drug release kinetics for each formulation.[26] To describe the drug release mechanisms, the model with the best R^2 value, lowest sum of square (SS), and highest Model selection criteria (MSC) values was adopted.

RESULTS AND DISCUSSION

Pre-formulation Studies

The drug was a white or nearly white crystalline powder with no taste and odor. The melting point of LNZ was found to be between 181.5 and 182.5°C.

Solubility Study

The drug is completely soluble in water. Linezolid solubility in water was 0.57 mg/mL as given in Table 2.

UV-visible Spectrophotometer

The standard curve of LZ in 0.1N HCl was plotted between absorbance and concentration and results are mentioned in Figure 1. The regression value (R^2) of 0.9794 indicates the linearity in the results.

Drug-excipients compatibility study

FTIR spectra were utilized to assess drug-polymer compatibility. Figures 2 and 3 show the FTIR spectra of linezolid and optimized formulation (F5). The FTIR-spectrum test findings revealed that the drug and polymer did not interact. The FTIR spectrum of LNZ (Fig. 2) revealed distinct peaks for aromatic C-H at 3055 cm^{-1}, ester at 1747 cm^{-1}, aromatic N-H at 3363 cm^{-1}, aromatic C-F at 1023 cm^{-1}, and aromatic C-H out of plain at 1143 cm^{-1}. The FTIR spectrum of the formulation demonstrates that the drug's FTIR peaks remain unchanged, as shown in Figure 3.

Table 2: Solubility studies of linezolid

Solvent	*Observation Solubility (mg/mL)*			*Average (mg/mL)*	*Standard deviation*
	1	*2*	*3*		
Distilled water	0.5626	0.5841	0.5689	0.5718666	0.011053

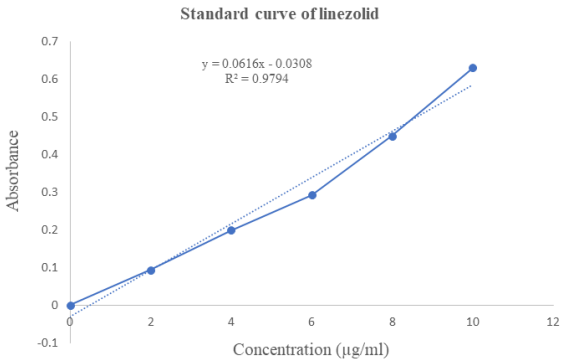

Figure 1: Standard curve of linezolid

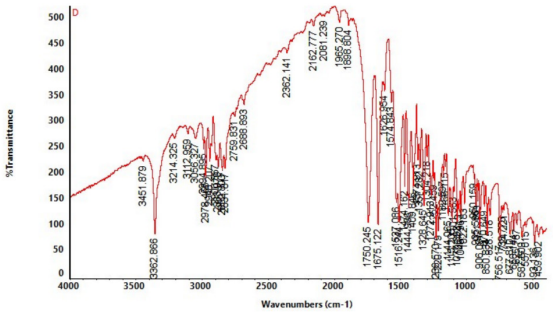

Figure 2: FTIR spectrum of linezolid

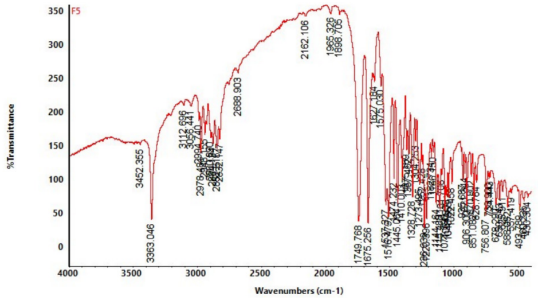

Figure 3: FTIR spectrum of F5

Table 3: Flow properties of the powder blend

Formulations	*Angle of repose*	*Carr's index*	*Hausner's ratio*	*Flow property*
F1	24 ± 0.54	10 ± 0.95	1.11 ± 0.05	Excellent
F2	26 ± 0.19	11 ± 0.23	1.12 ± 0.03	Excellent
F3	24 ± 0.11	11 ± 0.51	1.12 ± 0.15	Excellent
F4	26 ± 0.95	12 ± 0.34	1.14 ± 0.52	Excellent
F5	25 ± 0.52	15 ± 0.11	1.20 ± 0.11	Excellent
F6	23 ± 0.46	10 ± 0.19	1.11 ± 0.21	Excellent
F7	22 ± 0.17	13 ± 0.78	1.13 ± 0.59	Excellent
F8	24 ± 0.54	14 ± 0.67	1.15 ± 0.06	Excellent
F9	22 ± 0.19	12 ± 0.95	1.12 ± 0.12	Excellent
F10	21 ± 0.11	10 ± 0.55	1.11 ± 0.13	Excellent

Table 4: *In-vitro* release of linezolid

Time (minutes)	*%Drug release (Linowal^{TM})*	*%Drug release (F5)*
30	24.77	9.5
60	25.25	16.47
90	27.68	20.91
120	28.17	24.39
150	30.91	26.92
180	32.86	27.02
210	33.53	29.04
240	35.50	29.13
270	37.32	30.22
300	41.32	33.49
330	45.52	35.10
360	50.32	38.56
390	52.72	41.43
420	55.12	43.65
450	57.44	47.32
480	60.05	49.89

Evaluation of Matrix Tablets

Pre-compression evaluation

The flow parameters of the powder mix were evaluated before tablet compression using the angle of repose, Carr's compressibility index, and Hausner's ratio. The powder blend's flow properties were found satisfactory, with Hausner's ratio ranging from 1.11 to 1.20, angle of repose values ranging from 21 to 26, and Carr's compressibility index ranging from 10-15, as seen in Table 3.

Post-compression evaluation of matrix tablet

All batches of compressed tablets were successfully manufactured utilizing direct compression. The formulation generated satisfactory results for all criteria, fulfilling the approval requirements. Tablets were analyzed for thickness, diameter, weight fluctuation, hardness, and friability. The average tablet diameter and thickness were 1 and 0.9 cm, respectively. The tablets had an average hardness of 9 kg. The tablets passed the friability test, with less than 1% friability across all tables. The weight variance in every batch of formulation was within the acceptable range of ± 5%.

In-vitro drug release study

Figure 4 displays data from *in-vitro* drug release experiments compared to marketed products. The percentage of drug release for the test formulation was 49.89% in 480 minutes (8 hours), suggesting sustained drug release when compared to the marketed formulation (60%) as shown in Table 4.

Kinetics of drug release

The kinetics of drug release from the sustained release tablet were calculated using DD-Solver 1.0. The drug release data was fitted into multiple models, and the results are presented in Table 5. The results suggest that the drug release follows the Higuchi model, which indicates that the drug is released by diffusion from the insoluble table matrix.

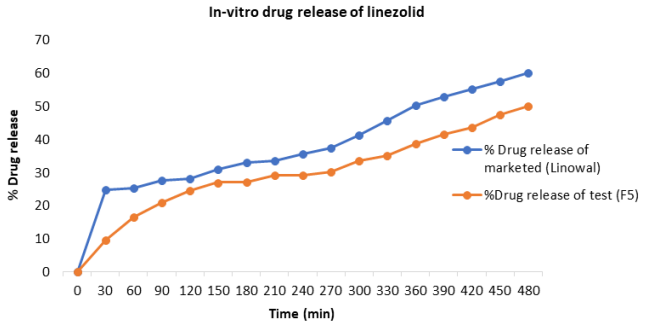

Figure 4: *In-vitro* drug release of marketed and test formulation

Table 5: Kinetics of drug release

Fitting release	R^2	R^2 *adjusted*	*SS*	*MSC*
Zero-order	0.6706	0.6706	602.2054	0.9856
First order	0.8753	0.8753	344.0178	1.5823
Higuchi	0.9705	0.9705	81.3908	3.0238
Korsmeyer-peppas	0.9700	0.9712	74.5058	2.9945
Hixon-cornwell	0.8497	0.8497	414.5186	1.3959

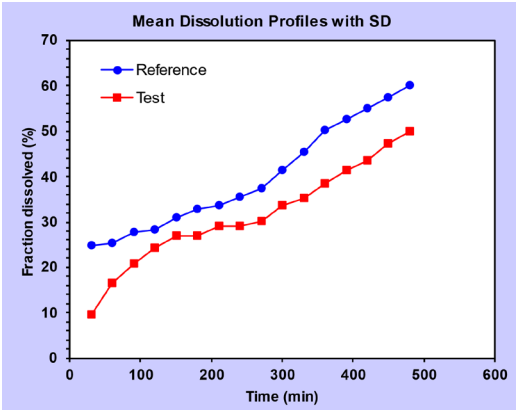

Figure 5: similarity between test and marketed formulation (reference)

Similarity factor

The *in-vitro* dissolution profile of the test formulation (F5) is compared with the *in-vitro* data of the marketed formulation (LinowalTM) using DDSolver 1.0 to determine the similarity factor. The similarity factor (f2) of 52.09 was obtained, suggesting a similarity between the test and marketed formulation as shown in Figure 5.

DISCUSSION

Linezolid sustained-release matrix tablets were prepared using different polymer blends by direct compression methods. All tablets were evaluated for the pre-compression and post-compression parameters. The powder blend for tablet formulation showed good flow properties. FTIR spectra of formulation confirmed the compatibility between the drug and polymers. The formulation generated satisfactory results for all criteria, such as thickness, diameter, weight variation, hardness, and friability. *In-vitro* drug release experiments revealed that the formulations delivered consistent drug release for more than 8 hours. The %drug release for the optimized formulation containing HPMC and EC blend was found to be 49.89% in 480 minutes (8 hours), indicating sustained drug release in comparison to the marketed formulation (LinowalTM), showing 60% drug release. In the first hour of the study, only 16.47% of the drug was released from the test formulation. It is assumed that the tablet got swelled by wetting with the dissolution medium giving initial burst release from the outer layer of the tablet. The erosion of tablet proceeds with time, showing an increase in drug release. To better understand the release kinetics and mechanism, mathematical models are utilized to assess dissolution study release data 25. It has been found that the drug release follows the Higuchi model of drug release, indicating the release of the drug through diffusion from the insoluble table matrix. The formulated tablet showed an excellent way to provide sustained action of linezolid in comparison to an available market.[27]

CONCLUSION

The findings of this study add to continuing attempts to identify effective and long-term treatment alternatives for tuberculosis, particularly in the setting of medication-resistant strains.

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AUTHOR CONTRIBUTION

All author contributed equally to this manuscript.

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