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Research Article

Formulation Development and Evaluation Studies of Linezolid Inhaler in the Treatment of Tuberculosis

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ABSTRACT

The primary objective of this study was to prepare and evaluate a linezolid inhaler. Dry powder inhaler liposomes were formulated to investigate the efficacy of pulmonary delivery of linezolid for tuberculosis. The liposomes were prepared using soya lecithin and cholesterol in different weight ratios, constant amounts of drugs, and two methods: physical dispersion and ethanol injection. The F9 formulation was characterized for physical and chemical properties such as vesicle size, shape, and zeta potential. The results of physical characterization, *in-vitro* testing, and stability studies indicate that liposomes containing linezolid can be used for the treatment of tuberculosis. The evaluated batch exhibited favorable physicochemical properties, with spherical liposomes having a mean size below 100 nm and high entrapment efficiency (98.8%). The prepared liposomal dry powder inhalers (DPIs) sustained drug release for up to 8 hours. Liposome stability was assessed 90 days after storage at room temperature, revealing its stability. The liposomal formulation had steady zeta potential, good entrapment efficiency, improved stability, and an extended drug release time. In conclusion, linezolid-loaded liposomal inhalers were successfully formulated.

INTRODUCTION

The primary goal is the development of a liposomal inhaler for treating tuberculosis by extending the dosage form's release. Another purpose of a drug delivery system is to transport a medicine effectively, especially to the site of action, and achieve increased efficacy while limiting harmful effects when compared to conventional drugs. Tuberculosis is a persistent granulomatous illness that causes significant public health problems in developing countries. Linezolid is an antibiotic prescribed for the treatment of pneumonia. It is also used as a secondary treatment for tuberculosis. It is considered an effective third-line drug for managing multidrug-resistant and extensively drug-resistant TB. Linezolid is a synthetic antibiotic that is an antibacterial oxazolidinone derivative that is active. Linezolid works by inhibiting bacterial

protein synthesis, thereby preventing the growth and spread of bacteria.^[1,2]

When a drug is administered into the body, it undergoes several chemical and metabolic changes that reduce its availability at its final site of action in the body. The choice of route of drug delivery is vastly dependent on drug properties, disease states, site of action, and patient compliance. For example, when a drug is administered orally, it has to pass through the digestive system before it reaches the bloodstream. During this process, some of the drugs may be metabolized by the liver or excreted, reducing the amount of drug available for therapeutic effects. On the other hand, when a drug is administered through the pulmonary route, it bypasses the digestive system and directly enters the bloodstream through the lungs. This allows for faster absorption and higher

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bioavailability of the drug.^[3] DPIs are favored delivery devices for inhalation therapy due to their higher stability, lack of propellants, and ease of use. Well-designed dry powder inhalers are highly efficient drug-delivery systems. Inhalation powders, also known as DPIs, are made up of a combination of active pharmaceutical ingredients (APIs) and a carrier; all formulation components are in a finely split solid state and are packaged in an appropriate container closure system. The dry powder inhaler approach provides various advantages, including improved liposomal formulation stability.^[4]

Liposomes are colloidal, bilayered, micro-spherical vesicles having an aqueous core surrounded by phospholipid molecules (Fig. 1). Liposomes are useful dosage forms for pulmonary medication delivery because they may solubilize poorly soluble medicines, making them aerosol-friendly. Because of their biodegradability, they may remain in the lungs for longer periods without producing allergies or other adverse effects.^[5]

The deposition of particles at the site of action is a significant disadvantage for inhaled medicine. Due to mucociliary clearance, the drug deposited at the site of action has a low residence duration. Barriers such as lung lining fluid, airway macrophages, and lung epithelial cells reduce the duration of action of such medicine. To overcome these drawbacks, innovative techniques such as liposomes represent a potential plan to deliver the medicine at the site of action. When compared to free drugs, liposomal encapsulation has been found to reduce the agent's absorption into the systemic circulation and provide dispersion across the lung airways. The resulting decrease in medicine dose frequency will improve the quality of life and reduce healthcare expenses.^[6] The backbone of liposomes is phosphatidylcholine, which has a hydrophilic head and hydrophobic tail. Phospholipids play an important role in forming bilayers in liposomes. Cholesterol enhances the stability of liposome membranes, reduces drug leakage, and modulates membrane fluidity, elasticity, and permeability. Organic solvents used in liposome preparation can help dissolve lipids and aid in liposome formation.^[7]

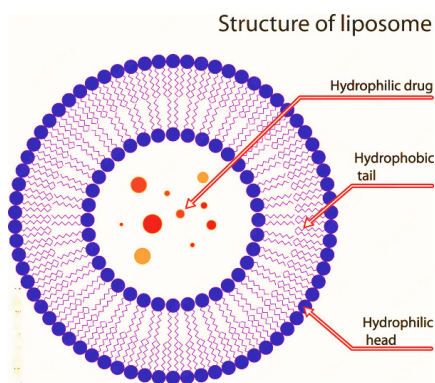


Fig. 1: Structure of liposome encapsulating drug by forming bilayer from phospholipids

In the current study, a liposomal dry powder inhaler formulation containing linezolid was developed to achieve site-specific targeted delivery with prolonged residence time in the lungs and to achieve maximum respirable fraction with improved dispersibility, which may play a promising role in tuberculosis management. Another purpose of a drug delivery system is to transport a medicine effectively, especially to the site of action, and achieve increased efficacy while limiting harmful effects when compared to conventional drugs in the case of tuberculosis.

MATERIALS AND METHOD

Materials

Linezolid was obtained from Lupin Ltd., Aurangabad. Soya lecithin was purchased from HiMedia Laboratory, Mumbai, and cholesterol and chloroform were purchased from Loba Chemie. Ethanol was purchased from Mxradly Lab Solutions Pvt. Ltd. All the chemicals, reagents, and solvents used were of analytical reagent grade.

Methods

Preformulation studies^[8-12]

Preformulation is a link between drug discovery and drug development. It is the fundamental step in the rational development of dosage forms. It can also be defined as an investigation of a drug substance's physical and chemical properties alone and when combined with excipients.

Organoleptic characteristics

The drug powder is examined by using organoleptic properties like color, odor, and appearance.

Melting determination

The melting point was determined using the melting point apparatus [Veego (VMP-D)]. A small amount of the pure drug linezolid was taken in a capillary tube and kept in the melting point apparatus, and the readings were taken in triplicate.

Solubility

The solubility of the drug in water and the organic solvent was determined at room temperature with the help of a magnetic stirrer.

Analytical Profile

Determination of analytical wavelength

Accurately weighed, 10 mg of linezolid was dissolved in 10 mL of methanol and then diluted to 100 mL with distilled water (conc. 100 µg/mL). From this solution, 1-mL was pipetted out into 10 mL volumetric, and the volume was made up with distilled water to make 10 µg/mL. The solution containing 10 µg/mL of linezolid in methanol and distilled water was scanned over the range of 400–200 nm

against distilled water as a blank using a UV-visible spectrophotometer. The λ_{max} for the pure drug was then determined.

Calibration Curve of Linezolid

In 1, 2, 3, 4, and 5 mL from the standard solution were withdrawn in a 10 mL volumetric flask and diluted to 10 mL with distilled water, respectively. The solution was analyzed by a UV-visible spectrophotometer [JASCO (V-630)] at 251 nm, and results were recorded. The calibration graph was plotted as concentration on the x-axis and absorbance on the y-axis.

Fourier transform infrared

Preparation of potassium bromide disc: Grind 200 mg of potassium bromide to a fine powder in a pestle and mortar. Add 2–3 mg of the substance under investigation and grind to a fine powder again. Combine the contents thoroughly. The dry drug sample was treated in a 1:1 ratio with IR-grade potassium bromide (KBr). This combination was compacted into a pellet. The pellets were scanned in an FTIR instrument [Jasco (FTIR 4100)] throughout a wave number range of 4000 to 400 cm^{-1} and spectral analysis was performed.

Differential scanning calorimetry

Differential scanning calorimetry (DSC) is a common method for studying the melting and recrystallization of pharmacological compounds. Properties measured by DSC techniques include glass transitions, “cold” crystallization, phase changes, melting, crystallization, product stability, and oxidative stability. It is a thermo-analytical approach for determining the thermodynamic characteristics of materials by providing information on the polymorphic changes that occur when they are exposed to a regulated heat flux.

Preparation of Liposomes

Physical dispersion method^[13]

The preparation of liposomes with soybean lecithin and cholesterol was prepared by the physical dispersion method. Different weight ratios of soya lecithin and cholesterol were weighed and dissolved in chloroform. (Table 1) It was spread over a flat-bottomed conical flask and evaporated at room temperature to form a lipid film without disturbing the solution. The drug was dissolved in phosphate buffer (pH 7.4), an aqueous medium. The lipid film was then hydrated with an aqueous medium. Then the conical flask was kept in a water bath, and the temperature was maintained at $37 \pm 2^\circ\text{C}$ for 2 hours to complete hydration. The conical flask was gently shaken until the lipid layer was removed from the wall of the flask. Then the formed liposomal suspension was stored at 4°C for one day for the maturation of liposomes. The formulations were subjected to centrifugation. The

precipitates are collected and diluted with distilled water for further studies.

Ethanol injection method^[14]

A modified ethanol injection approach was used to create liposomes. In ethanol, the different weight ratios of phospholipids and cholesterol were dissolved. The resultant organic phase was injected into a fixed volume of distilled water using a syringe pump while magnetic stirring was going on. Spontaneous liposome production occurred when the ethanolic solution came into contact with the aqueous phase. The liposome suspension was then stirred at room temperature for 15 minutes. Finally, rotary evaporation under lower pressure was used to extract the ethanol and some water. The lipophilic drug was introduced into the organic phase (Table 1), while if a drug is hydrophilic, it will be introduced into the aqueous phase. The unloaded medication was removed by centrifuging the liposome suspension for 1-hour at 45,000 rpm. Phosphate buffered saline (PBS) was used for dispersing the pellets, which were stored in amber-colored vials and then kept at 4°C .

Evaluation of liposomes^[15-19]

Liposomes were evaluated by studying their physicochemical properties like angle of repose, drug content, entrapment efficiency, *in-vitro* drug release, particle size, zeta potential, and SEM.

Angle of repose

The angle of repose can measure the fractional force in a loose powder, θ . It is indicative of the flow properties of the powder. It is defined as the maximum angle between the surface of a pile of powder and the horizontal plane.

$$\tan \theta = \frac{h}{r}$$

Where,

θ = Angle of Repose

h = Height of the pile

r = Radius in cm

Table 1: Formulation of linezolid liposomes

Formulation Code	Drug (mcg)	Soya lecithin (mg)	Cholesterol (mg)	Ethanol (mL)	Chloroform (mL)
F1	250	100	75	-	5
F2	250	150	75	-	5
F3	250	200	75	-	5
F4	250	250	75	-	5
F5	250	100	100	3	-
F6	250	150	100	3	-
F7	250	200	100	3	-
F8	250	250	100	3	-
F9	250	300	100	3	-



Drug content

The equivalent weight formulation was dissolved in 10 mL of methanol and make-up with distilled water in a 100 mL volumetric flask. From the standard solution, 2 or 3 mL were withdrawn in a 10 mL volumetric flask and diluted to 10 mL with distilled water, respectively. The solution was analyzed by a UV-visible spectrophotometer [JASCO V-630] at 251 nm, and results were recorded in triplicate.

Entrapment efficiency

Prepared liposomes were centrifuged at 2000 rpm for 15 minutes to collect supernatant liquid. The liquid was filtered to measure the amount of free drug concentration after a suitable dilution with methanol. The absorbance was measured at 251 nm in a UV spectrophotometer. The percent of entrapment efficiency (EE%) was calculated using the following equation:

$$EE (\%) = \frac{\text{Total drug} - \text{Free drug}}{\text{Total drug}} \times 100$$

In-vitro release studies

An *in-vitro* release study was carried out using a Franz diffusion cell, and the temperature was adjusted to $37 \pm 0.5^\circ\text{C}$. Samples were withdrawn at periodic intervals for 8 hours and replaced with a fresh buffer solution to maintain sink conditions. The drug content was analyzed by using a UV-visible spectrophotometer at 251 nm using phosphate buffer (pH 7.4).

Particle size

The diluted liposomal suspension was added to the sample cuvette before placing it in a zeta sizer [Horiba Scientific (SZ-100)]. The sample was stabilized for 2 minutes before taking the reading. The average particle size and polydispersity index were calculated by experimenting with triplicate.

Zeta potential analysis

The zeta potential of developed liposomes was determined using the Horiba Scientific zeta sizer SZ-100.

Scanning electron microscopy

The particle size of liposomes was determined by using a scanning electron microscope (SEM). The optimized batch of liposomes was viewed under a microscope to study their size. The size of liposomal vesicles was measured at different locations on a slide by taking a small drop

of liposomal dispersion on it, and the average size of liposomal vesicles was determined.

Stability studies

The physical appearance of the liposomes was measured. The formulations were stored at 4°C , room temperature, and physiologic temperature (40°C). At specific time intervals of three months, the samples were taken, and their physical appearance was examined.

RESULTS

Preformulation Studies

Organoleptic Characteristics

- Color: White
- Odor: Odorless
- Appearance: Crystalline

Determination of Melting Point

The melting point of linezolid was found to be 180°C (practically), as reported in the literature, thus indicating the purity of the sample.

Solubility Study

The solubility of the drug in water and the organic solvent was determined (Table 2).

Analytical Profile

Determination of analytical wavelength

The spectra of linezolid in methanol and distilled water (10:90) v/v, respectively, at a concentration of 10–50 $\mu\text{g/mL}$, λ_{max} of linezolid was observed at 251 nm, as shown in Fig. 2, respectively.

Calibration curve of linezolid

The study of linearity was performed as per ICH guidelines. The linearity study for the proposed method was established by least squares linear regression analysis. Linezolid standards were found to be linear in the 10–50 $\mu\text{g/mL}$ range, respectively, with $R^2 = 0.997$ found at a selected wavelength, as shown in Fig. 3 and Table 3.

IR spectroscopy

The FTIR spectra of pure drug and mixtures of drug and excipients are shown in Figs 4, 5, and 6, respectively. From

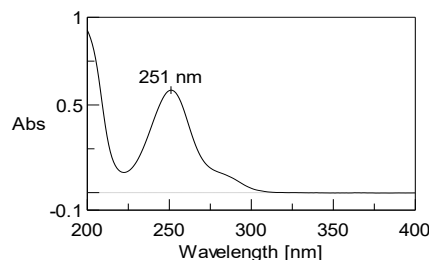


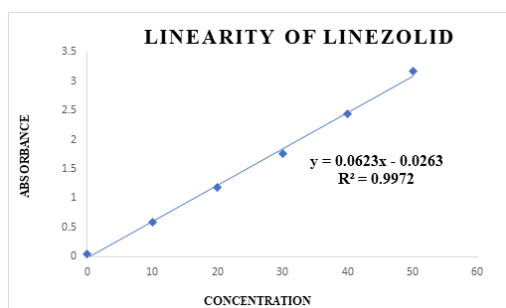
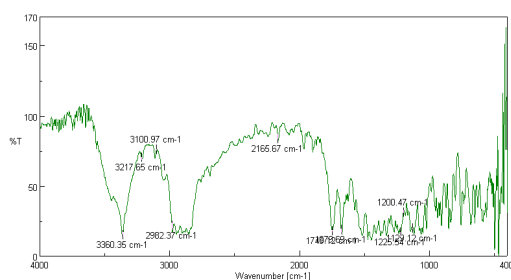
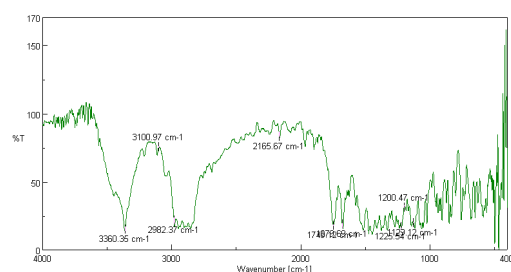
Fig. 2: UV spectrum of Linezolid - The λ_{max} for the pure drug was found to be 251 nm

Table 2: Solubility of drug

Solubility Media	Solubility of Drug
Sparingly soluble	Water
Soluble	Methanol
Soluble	Chloroform
Soluble	Ethanol
Soluble	DMSO

Table 3: Calibration curve of linezolid

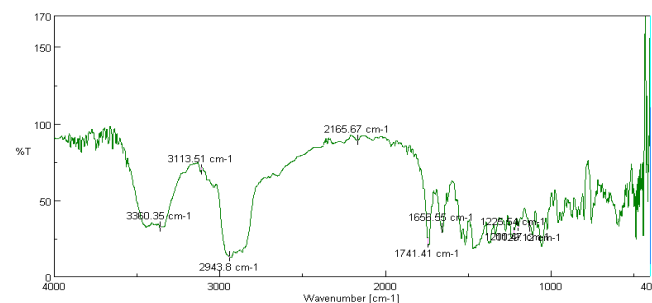
S. No.	Concentration ($\mu\text{g/mL}$)	Absorbance (251 nm)
1	0	0.0403
2	10	0.5800
3	20	1.1908
4	30	1.7605
5	40	2.4432
6	50	3.1666

**Fig. 3:** Calibration curve of linezolid in distilled water**Fig. 4:** IR spectrum of Linezolid**Fig. 5:** IR spectrum of drug and excipients**Table 4:** Characteristic ir peaks of linezolid

S. No.	Functional group	Standard frequency (cm^{-1})	Observed frequency (cm^{-1})
1	N - H	3500–3300	3360.35
2	Aromatic (Benzene)	3150–3050	3100.97
3	C = O (Ester)	1800–1600	1749.12
4	C = O (Amide)	1680–1630	1679.69
5	C - F	1400–1000	1129.12
6	C - N (Morpholine)	1350–1000	1200.47
7	C - N (Aromatic)	1350–1000	1225.54

Table 5: Characteristic ir peaks of drug and excipients

S. No.	Functional group	Standard frequency (cm^{-1})	Observed frequency (cm^{-1})
1	N - H	3500–3300	3360.35
2	Aromatic (Benzene)	3150–3050	3100.97
3	C = O (Ester)	1800–1600	1749.12
4	C = O (Amide)	1680–1630	1679.69
5	C - F	1400–1000	1129.12
6	C - N (Morpholine)	1350–1000	1200.47
7	C - N (Aromatic)	1350–1000	1225.54

**Fig. 6:** IR spectrum of formulation**Table 6:** Characteristics IR peaks of formulation

S. No.	Functional group	Standard frequency (cm^{-1})	Observed frequency (cm^{-1})
1.	N - H	3500–3300	3360.35
2.	Aromatic (Benzene)	3150–3050	3113.51
3.	C = O (Ester)	1800–1600	1741.41
4.	C = O (Amide)	1680–1630	1656.55
5.	C - F	1400–1000	1129.12
6.	C - N (Morpholine)	1350–1000	1200.47
7.	C - N (Aromatic)	1350–1000	1225.54

the spectral study, as shown in Tables 4, 5, and 6, there were no significant changes in the peak of pure drug and drug-polymer mixtures. Hence, no specific interaction was found between the drug and the polymers used in the formulations.

Differential scanning calorimetry

The pre-formulation study of drug-excipient interaction was carried out by DSC, which shows interactions between the drug and excipients. Fig. 7 shows an endothermic peak at 183.25°C, which indicates the purity of the drug. As shown in Fig. 8, the sample finally melted at 174.8°C, producing a strong melting endothermic peak in the DSC image. As shown in Fig. 9, formulation shows a peak at 148.6°C. It indicates the compatibility between drug and excipients.



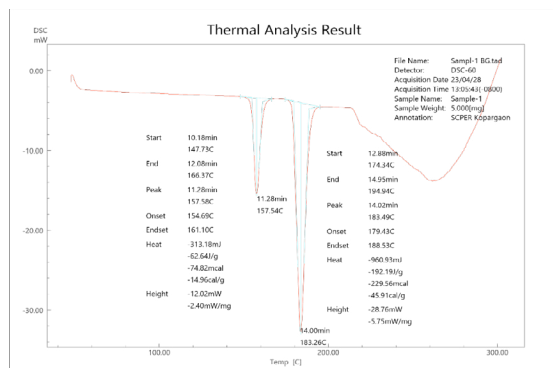


Fig. 7: DSC graph of Linezolid

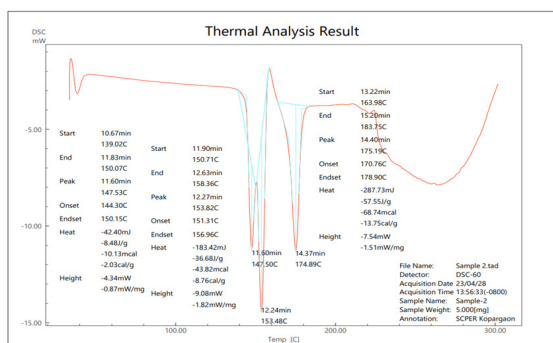


Fig. 8: DSC graph of drug and excipients

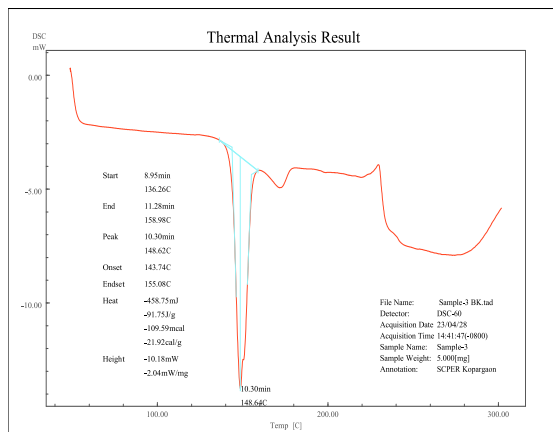


Fig. 9: DSC graph of formulation

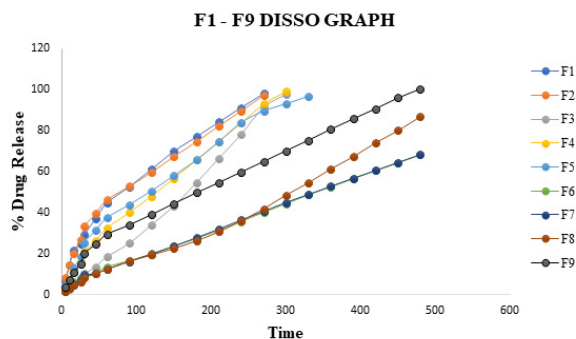


Fig. 10: Percentage of drug release of linezolid liposomes at periodic time intervals for 8 hrs of all formulations

Evaluation of Liposomes

Visual appearance and pH

Formulations of odor, nature, and appearance were evaluated. The pH of all formulations was in the range of 7.1 to 7.4. The formulation was found to be 7.3 of batch (F9).

- Color: Off-white
- Odor: Odorless
- Nature: Solid

Angle of repose

The angle of repose was found in a range of 15.35–24.67°, respectively. The results are given in Table 7.

Drug content

The drug content of all formulations was found in the range of 65 to 98%. The drug content was higher for formulation F9 (97%), as shown in Table 7.

Entrapment efficiency

The percentage entrapment efficiency of linezolid in liposomes was found to be in the range of 73 to 98%, as shown in table 7. The entrapment efficiency was higher for formulation F9 (98.8%), as shown in Table 7.

In-vitro drug release of linezolid liposomal powder

In-vitro release studies were carried out using Franz diffusion cells. The samples were withdrawn at periodic intervals for 8 hours and replaced with a fresh buffer solution to maintain sink conditions. The drug content was analyzed using a UV-visible spectrophotometer at 251 nm using phosphate buffer (pH 7.4) as a blank.

The percentage of drug release from various liposomal formulations is shown in Fig. 10. The experimental studies show the drug release rate depends on the concentration of the formulation's contents. Formulation F9 showed a higher drug release than other formulations. Hence, it was chosen to be an optimized formulation.

Particle size

The particle size of the liposomes was determined using a zeta sizer, and the Z-average of the liposomes was found to be 199.1 nm, and the polydispersity index (PDI) was found to be 0.494, as shown in Fig. 11.

Zeta potential

The zeta potential of the liposomes was determined using a zeta sizer, and the value of the liposomes was found to be 10.3 mV, as shown in Fig. 12.

SEM

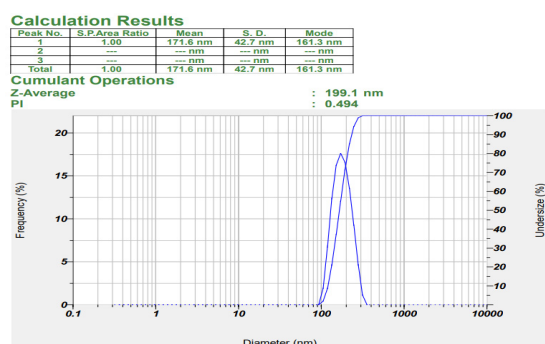
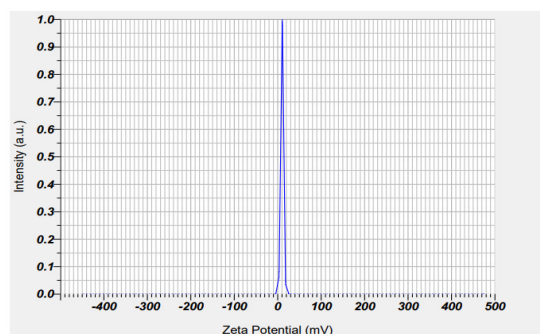
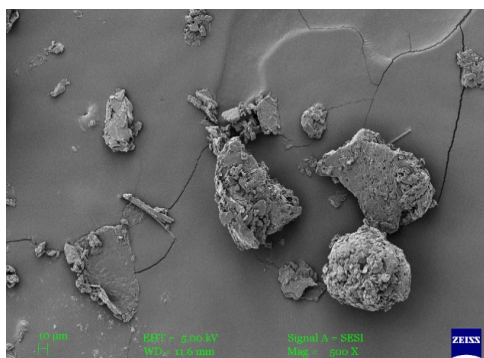
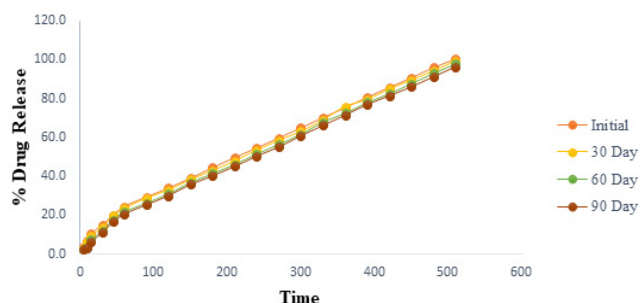
SEM, the microscopic evaluation shown in Fig. 13.

Stability studies of optimized formulation

Stability studies were performed as per ICH guidelines at an accelerated temperature of $25 \pm 2^\circ\text{C}$ and humidity of $60\% \text{ RH} \pm 5\% \text{ RH}$ for three months and evaluated

Table 7: Percentage entrapment efficiency and drug content of linezolid in liposomes

Formulations	Angle of Repose	Drug Content	Entrapment Efficiency
F1	22.34 ± 0.8	65.2 ± 0.45	73.1 ± 0.19
F2	22.45 ± 1.5	82.2 ± 0.87	86.6 ± 0.91
F3	24.67 ± 0.3	75.8 ± 0.36	79.9 ± 0.45
F4	24.59 ± 1.2	83.2 ± 0.65	88.5 ± 0.70
F5	21.23 ± 0.7	77.9 ± 0.48	82.5 ± 0.53
F6	19.97 ± 1.8	82.5 ± 0.30	90.5 ± 0.33
F7	15.35 ± 0.6	95.9 ± 0.24	97.4 ± 0.11
F8	16.45 ± 0.9	85.8 ± 1.38	91.3 ± 0.82
F9	19.45 ± 0.4	97 ± 1.3	98.8 ± 0.41

**Fig. 11:** Particle size of linezolid liposomes**Fig. 12:** Zeta potential of linezolid liposomes**Fig. 13:** SEM image of liposomal solution for F9 formulation**STABILITY DISSO GRAPH****Fig. 14:** Stability study of formulation - Stability testing parameters for optimized batch F9 at 25°C ± 2°C and humidity of 60% RH ± 5% RH for 3 months**Table 8:** Stability data of linezolid liposomal powder

Sampling time interval	Drug content	Entrapment efficiency
Initial	97 ± 1.3	98.8 ± 0.41
30 days	96.8 ± 0.65	98.2 ± 0.52
60 days	95.9 ± 0.69	96.1 ± 0.87
90 days	93.52 ± 0.86	94.8 ± 0.36

for EE, drug content, and *in-vitro* drug release, which were determined every 30 days for 3 months (Fig. 14). It was observed that there was no change in the physical appearance of the formulation. The drug content was analyzed, and there was a marginal difference between the formulations kept at different temperatures, as shown in Table 8. Liposome formulations retained good stability throughout the study.

DISCUSSION

Preformulation investigations revealed that the drug is pure with a $\lambda_{\max}$ of 251 nm. The FTIR spectrum of the pure drug revealed the substance's characteristic functional groups and their wave number. The compatibility study of the drug and excipients was determined, and it was discovered that all excipients are compatible with linezolid.



The angle of repose of the F1-F5 batches was found to be between 20–30°, indicating that the formulations have good flow properties. The angle of repose of the F6-F9 batches was found to be less than 20°, indicating that the formulations had excellent flow properties. The percent drug content values for all formulations were determined to be between 65 and 98%. All formulations had *in-vitro* drug deposition tests performed. The results show that batch F9 is the best formulation of all since it has a better-sustained release. A zeta sizer was used to determine the particle size and zeta potential of the F9 batch. The F9 batch's mean diameter was determined to be 199.1 nm, and its average zeta value is 10.3 mV, indicating stability. Liposomes containing linezolid may be utilized to treat tuberculosis, according to physical characterization, *in-vitro* testing, and stability investigations. The liposomal formulations were spherical, had a steady zeta potential, and were monodisperse without aggregating. Therefore, it was established from the study that the liposomal formulation of linezolid had good entrapment efficiency and an improved stability profile. linezolid-loaded liposomal inhalers were successfully formulated. The liposomal inhaler extends the drug's release time in a sustained manner. As a result, it is expected to maximize the therapeutic index while decreasing systemic adverse effects, dosage and dose frequency, and, most likely, therapy cost. With the potential for new prospects for the pulmonary application of linezolid in antitubercular activity, the liposomal formulation has a promising option for targeted delivery.

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