



FORMULATION AND CHARACTERIZATION OF BIFONAZOLE ELASTIC LIPOSOMES FOR EFFECTIVE TOPICAL FUNGAL INFECTION

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ABSTRACT

Bifonazole is a broad-spectrum antifungal agent widely used for the treatment of superficial fungal infections; however, conventional topical formulations may suffer from inadequate drug retention and limited penetration into the skin. The present study aimed to develop and evaluate bifonazole-loaded elastic liposomal gel to improve topical drug delivery and provide sustained drug release. Six elastic liposomal formulations (F1–F6) were prepared using phosphatidylcholine and Tween 80 as vesicle-forming and edge-enhancing components, respectively. The formulations were evaluated for vesicle size and entrapment efficiency, and formulation F5 was selected as the optimized elastic liposome based on its desirable characteristics. F5 exhibited a vesicle size of 146.8 nm, entrapment efficiency of $86.52 \pm 0.84\%$, and zeta potential of -30.25 mV. The optimized elastic liposomes were incorporated into gel formulations (ELG1–ELG3), which were evaluated for drug content, pH, spreadability, and viscosity. ELG2 demonstrated the most desirable characteristics, with drug content of $98.76 \pm 0.22\%$, pH of 6.48 ± 0.07 , spreadability of 12.46 ± 1.08 g·cm/sec, and viscosity of 3425 ± 19 cps. The *in-vitro* drug-release study of ELG2 showed a sustained release of bifonazole, reaching 98.36% at 10 h. Release-kinetic analysis indicated that the Korsmeyer–Peppas model provided the best fit ($R^2 = 0.9955$), followed by the Higuchi model ($R^2 = 0.9910$), suggesting a diffusion-associated release mechanism. Stability studies demonstrated that ELG2 retained its homogeneous and smooth appearance with only minor changes in drug content during four weeks of storage at $4 \pm 0.5^\circ\text{C}$ and $28 \pm 0.5^\circ\text{C}$. The findings suggest that bifonazole-loaded elastic liposomal gel, particularly ELG2, represents a promising topical delivery system capable of providing efficient drug incorporation and sustained drug release.

Keywords: Bifonazole, Elastic liposomes, Liposomal gel, Phosphatidylcholine, Tween 80, Topical drug delivery, Sustained drug release, Antifungal delivery.

INTRODUCTION

Fungal skin infections, or superficial mycoses, are common dermatological disorders caused by pathogenic fungi and are associated with itching, inflammation, scaling, irritation, and discomfort (Kaushik *et al.*, 2015). Although a variety of antifungal agents are available for

topical therapy, successful treatment depends not only on the intrinsic antifungal activity of the drug but also on its ability to remain at the site of infection and penetrate sufficiently into the affected skin layers. Conventional topical preparations such as creams, ointments, and lotions may have limitations including

inadequate skin retention, poor drug penetration, rapid removal from the application site, and the need for frequent administration. These limitations have encouraged the development of advanced topical drug-delivery systems capable of improving drug localization and maintaining therapeutic concentrations at the site of infection (Sharma and Nonzom, 2021).

Bifonazole is a broad-spectrum imidazole antifungal agent used for the treatment of dermatological fungal infections. It exerts its antifungal activity primarily by interfering with fungal ergosterol biosynthesis, thereby affecting the integrity and function of the fungal cell membrane (Ivanov *et al.*, 2022). Despite its established therapeutic usefulness, conventional delivery of bifonazole may not provide optimal drug deposition within the skin because the stratum corneum acts as a major barrier to drug permeation. Therefore, incorporation of bifonazole into a suitable vesicular delivery system may improve its localization, penetration, and residence time within the skin while potentially reducing the frequency of application (Patel and Mastiholimath, 2025).

Elastic liposomes are deformable vesicular carriers composed mainly of phospholipids and membrane-modifying surfactants. Their flexible bilayer enables them to undergo deformation and pass through narrow intercellular pathways, making them attractive carriers for enhanced topical and transdermal drug delivery (Jamshidfar *et al.*, 2026). The incorporation of surfactants such as Span 80 or Tween 80 can impart greater membrane flexibility and facilitate vesicle penetration into the skin. In addition, the lipidic environment of elastic liposomes can improve

the incorporation of poorly water-soluble drugs and provide a controlled reservoir for drug release. Vesicle size, lipid concentration, surfactant concentration, entrapment efficiency, and surface charge are important formulation parameters that influence the performance and stability of elastic liposomes (Loushambam *et al.*, 2026).

Further incorporation of optimized elastic liposomes into a suitable gel base can provide additional advantages for topical administration. A gel formulation can improve residence time on the skin, facilitate uniform application, enhance patient acceptability, and provide a convenient dosage form. The combination of elastic liposomes with a gel matrix therefore offers the possibility of integrating enhanced vesicular delivery with prolonged contact at the site of infection. The physicochemical characteristics of the resulting formulation, including pH, viscosity, spreadability, drug content, vesicle size, entrapment efficiency, and *in-vitro* drug-release behavior, are essential for establishing its suitability as a topical antifungal delivery system (Elias *et al.*, 2020).

Accordingly, the present study was undertaken to formulate and characterize bifonazole-loaded elastic liposomes using phospholipid and surfactant components and to identify an optimized formulation based on vesicle size and drug-entrapment efficiency. The optimized elastic liposomes were subsequently incorporated into a topical gel and evaluated for physicochemical properties and *in-vitro* drug-release characteristics. The study was aimed at developing a promising topical delivery system capable of improving bifonazole delivery to the skin and providing

sustained drug release for effective management of superficial fungal infections.

MATERIALS AND METHODS

Material

The materials used for the formulation development of bifonazole-loaded elastic liposomes and liposomal gel included Soya Phosphatidylcholine obtained from Ash Chemie India, Thane, as the principal drug and lipid components, respectively. Disodium hydrogen phosphate, dipotassium hydrogen orthophosphate, hydrochloride, methanol, ethanol, chloroform, Carbopol 934P, methyl paraben, propyl paraben, and propylene glycol were procured from S. D. Fine Chem. Ltd., Mumbai, Qualigens Fine Chemicals, Mumbai, and other specified suppliers. Span 80 and sodium hydroxide were obtained from Thomas Baker (Chemicals) Pvt. Ltd., Mumbai. All materials were of suitable pharmaceutical/analytical grade and were used as received for formulation development and evaluation.

Methods

Formulation of Bifonazole loaded elastic liposomes

Bifonazole-loaded elastic liposomes were prepared by the thin-film hydration method using rotary evaporation, with slight modification of the method reported by Tuitou et al. (2000). Phosphatidylcholine was used as the main vesicle-forming lipid, while Tween 80 was incorporated as an edge activator to impart elasticity and deformability to the vesicles. Bifonazole was used as the model antifungal drug.

Accurately weighed quantities of Bifonazole, phosphatidylcholine, and Tween 80 were transferred into a clean, dry round-bottom flask. The drug and lipid components were

dissolved in a minimum quantity of an organic solvent mixture consisting of chloroform and methanol (2:1, v/v). The flask was attached to a rotary evaporator and rotated at approximately 60 rpm at $40 \pm 2^\circ\text{C}$ under reduced pressure. The organic solvent was slowly evaporated until a thin, uniform lipid film was formed on the inner wall of the flask.

The resulting lipid film was further dried under vacuum for overnight to remove residual solvent. The dried lipid film was then hydrated with an appropriate volume of phosphate buffer pH 6.8 containing the required concentration of ethanol, which also facilitated incorporation of Bifonazole into the vesicular system. Hydration was performed at $40 \pm 2^\circ\text{C}$ with continuous rotation at 60 rpm for 60 min. The hydrated vesicular dispersion was subsequently subjected to probe/bath sonication at 4°C for three cycles of 10 min, with a 5-s interval between successive cycles, to reduce vesicle size and obtain a relatively uniform dispersion.

The prepared elastic liposomal dispersions were allowed to equilibrate at room temperature and were subsequently stored in tightly closed containers at $4 \pm 2^\circ\text{C}$ until further characterization. The formulations were evaluated for vesicle size, polydispersity index, zeta potential, entrapment efficiency, deformability, drug content, morphology, and *in-vitro* drug release/permeation.

Preparation of Gel Base

The required quantity of Carbopol 934 was accurately weighed and slowly dispersed in approximately 80 ml of double-distilled water with continuous stirring to avoid lump formation. The dispersion was allowed to hydrate for approximately 1 hour with gentle

mechanical stirring. After complete hydration of Carbopol 934, propylene glycol (10 ml) was added gradually with continuous stirring to improve the moisturizing properties and spreadability of the gel.

The hydrated polymer dispersion was then allowed to stand until a uniform polymeric dispersion was obtained. The dispersion was neutralized gradually with 0.05 N sodium hydroxide solution added dropwise under continuous stirring, until a clear and homogeneous gel with suitable consistency was formed. The pH was adjusted to approximately 6.0–6.5, which is appropriate for topical application.

The previously prepared Bifonazole-loaded elastic liposomal dispersion, corresponding to 0.75% w/w Bifonazole, was incorporated slowly into the prepared Carbopol gel base with gentle and uniform stirring to minimize vesicle disruption and air entrapment. The final volume/weight of the formulation was adjusted with double-distilled water. The resulting elastic liposomal gel was subjected to mild sonication using a bath sonicator for approximately 5–10 min to remove entrapped air bubbles. The prepared formulations were allowed to equilibrate and were stored in well-closed containers at $4 \pm 2^\circ\text{C}$ until further evaluation.

Characterization of elastic liposomes

Vesicle size

Microscopic analysis was performed to determine the average size of prepared Liposomes. Formulation was diluted with distilled water and one drop was taken on a glass slide and covered with cover slip (Wertz *et al.*, 1986). The prepared slide was examined under trinocular microscopic at 400 X. The diameters of more than 150 vesicles

were randomly measured using calibrated ocular and stage micrometer. The average diameter was calculated using the flowing formula:

$$\text{Average Diameter} = \frac{\sum n.d}{\sum n}$$

Where n = number of vesicles; d = diameter of the vesicles

Surface charge and vesicle size

The vesicles size and size distribution and surface charge were determined by Dynamic Light Scattering method (DLS) (Malvern Zetamaster, ZEM 5002, Malvern, UK). Zeta potential measurement of the liposomes was based on the zeta potential that was calculated according to Helmholtz–Smoluchowsky from their electrophoretic mobility (Alam *et al.*, 2008). For measurement of zeta potential, a zetasizer was used with field strength of 20 V/cm on a large bore measures cell. Samples were diluted with 0.9 % NaCl adjusted to a conductivity of 50 IS/cm.

Entrapment efficiency

Bifonazole entrapped within the liposomes was estimated after removing the unentrapped drug (Zheng *et al.*, 1992). The unentrapped drug was separated from the liposomes by subjecting the dispersion to centrifugation in a cooling centrifuge (Remi Equipments, Mumbai) at 18000 rpm at a temperature of 4°C for 45 minutes, where upon the pellets of liposomes and the supernatant containing free drug were obtained. The liposomes pellets were washed again with phosphate buffer to remove any unentrapped drug by centrifugation. The combined supernatant was analyzed for the drug content after suitable dilution with phosphate buffer solution by measuring absorbance at 252 nm using Labindia 3000+ spectrophotometer.

$$\% \text{ Entrapment Efficiency} = \frac{\text{Theoretical drug content} - \text{Practical drug content}}{\text{Theoretical drug content}} \times 100$$

Characterization of elastic Liposomes containing gel

Measurement of viscosity

Viscosity measurements of prepared topical liposomes based gel were measured by Brookfield viscometer using spindle no. 63 with the optimum speed of 10rpm.

pH measurements

pH of selected optimized formulations was determined with the help of digital pH meter. Before each measurement of pH, pH meter should be calibrated with the help of buffer solution of pH 4, pH 7 and pH 9.2. After calibration, the electrode was dipped into the vesicles as long as covered by the vesicles. Then pH of selected formulation was measured and readings shown on display were noted (Wen, *et al.*, 2006).

Drug content

Accurately weighed equivalent to 100 mg of topical liposome gel was taken in 10 ml volumetric flask, add 5 ml of methanol and sonicate it for 10 min and after sonication volume was made upto 10 ml with methanol (Monica and Gautami, 2014). This solution was mixed thoroughly and filtered using Whatman filter paper no.1. Then 0.1mL of filtered solution was taken in 10 mL capacity of volumetric flask and volume was made upto 10 mL with methanol. This solution was analyzed using UV-Spectroscope at $\lambda_{\max}$ 252 nm. Drug content of topical liposome based gel is shown in table no 7.7.

Spreadability

Spreadability of formulation is necessary to provide sufficient dose available to absorb from skin to get good therapeutic response

(Keerthana and Sandeep, 2022). An apparatus in which a slide fixed on wooded block and upper slide has movable and one end of movable slide tied with weight pan. To determine spreadability, placing 2-5 g of gel between two slide and gradually weight was increased by adding it on the weight pan and time required by the top plate to cover a distance of 6cm upon adding 20g of weight was noted, good spreadability show lesser time to spread.

$$S = M \times L / T$$

Where:

- **S** = Spreadability (g·cm/sec)
- **M** = Weight placed on the upper slide (g)
- **L** = Length travelled by the slide (cm)
- **T** = Time required to travel the specified distance (sec)

In vitro drug diffusion study

The *in-vitro* diffusion study is carried by using franz diffusion cell. Egg membrane is taken as semi permeable membrane for diffusion (Higuchi, 1963; Korsmeyer *et al.*, 1983). The Franz diffusion cell has receptor compartment with an effective volume approximately 60 mL and effective surface area of permeation 3.14sq.cms. The egg membrane is mounted between the donor and the receptor compartment. A two cm² size patch taken and weighed then placed on one side of membrane facing donor compartment. The receptor medium is phosphate buffer pH 7.4. The receptor compartment is surrounded by water jacket so as to maintain the temperature at 32 ± 0.5°C. Heat is provided using a thermostatic hot plate with a magnetic stirrer. The receptor fluid is stirred by Teflon coated magnetic bead which is placed in the

diffusion cell. During each sampling interval, samples are withdrawn and replaced by equal volumes of fresh receptor fluid on each sampling. The samples withdrawn are analyzed spectrophotometrically at wavelength 252nm of drug.

Stability studies

Stability study was carried out for drug loaded liposomes at two different temperatures i.e. refrigeration temperature ($4.0 \pm 0.2^\circ\text{C}$) and at room temperature ($25-28 \pm 2^\circ\text{C}$) for 3 weeks. The formulation subjected for stability study was stored in borosilicate container to avoid any interaction between the formulation and glass of container. The formulations were analyzed for any physical changes and drug content.

RESULTS AND DISCUSSION

The composition of the bifonazole-loaded elastic liposomal formulations is presented in Table 1. Six formulations (F1–F6) were prepared by varying the concentrations of phosphatidylcholine and Tween 80 while maintaining bifonazole at 10 mg and ethanol at 10%. The aqueous phase was adjusted to a final volume of 10 mL. Increasing the phosphatidylcholine concentration from 100 to 200 mg and varying Tween 80 from 10 to 20 mg allowed assessment of their influence on vesicle characteristics and drug entrapment. This systematic variation was useful for identifying a formulation with desirable vesicle size and entrapment efficiency.

The vesicle size and entrapment efficiency of the prepared elastic liposomes are shown in Table 2. The vesicle size ranged from 146.8 ± 2.9 to 182.6 ± 4.8 nm, while entrapment efficiency ranged from $72.45 \pm 1.32\%$ to $86.52 \pm 0.84\%$. Formulation F1 exhibited the

largest vesicle size (182.6 ± 4.8 nm) and comparatively lower entrapment efficiency ($72.45 \pm 1.32\%$). With increasing phosphatidylcholine concentration, a progressive reduction in vesicle size and improvement in entrapment efficiency were observed. F5 showed the smallest vesicle size of 146.8 ± 2.9 nm and the highest entrapment efficiency of $86.52 \pm 0.84\%$. However, F6 showed an increase in vesicle size to 163.5 ± 3.7 nm and a decrease in entrapment efficiency to $81.68 \pm 1.11\%$, indicating that excessive Tween 80 concentration was not advantageous. Based on these findings, F5 was selected as the optimized elastic liposomal formulation.

The characterization of the optimized formulation F5 is presented in Table 3. F5 exhibited a vesicle size of 146.8 nm, with an entrapment efficiency of $86.52 \pm 0.84\%$ and a zeta potential of -30.25 mV. The relatively small vesicle size is desirable for improving the deposition and penetration of the formulation, whereas the high entrapment efficiency indicates effective incorporation of bifonazole within the lipid vesicles. The negative zeta potential of -30.25 mV suggests adequate electrostatic repulsion between vesicles, which may contribute to improved physical stability by reducing vesicle aggregation. The vesicle-size distribution of the optimized formulation is depicted in Figure 1, while its zeta-potential profile is presented in Figure 2.

The evaluation results of the elastic liposomal gel formulations are presented in Table 4. ELG1, ELG2, and ELG3 exhibited drug contents of $97.24 \pm 0.38\%$, $98.76 \pm 0.22\%$, and $97.93 \pm 0.31\%$, respectively, indicating good drug uniformity. The pH values ranged

from 6.42 ± 0.09 to 6.51 ± 0.11 , which suggests that the formulations were within a suitable range for topical application. Spreadability decreased from 14.28 ± 1.15 g·cm/sec for ELG1 to 10.18 ± 1.26 g·cm/sec for ELG3, accompanied by an increase in viscosity from 2856 ± 21 to 4018 ± 24 cps. ELG2 showed a balanced viscosity of 3425 ± 19 cps and spreadability of 12.46 ± 1.08 g·cm/sec, together with the highest drug content of $98.76 \pm 0.22\%$. Therefore, ELG2 was selected as the optimized liposomal gel formulation.

The *in-vitro* drug-release profile of optimized ELG2 is presented in Table 5. The formulation exhibited a gradual and sustained release of bifonazole over the studied period. Drug release increased from 15.65% at 0.5 h to 98.36% at 10 h. The progressive release pattern indicates that incorporation of bifonazole into elastic liposomes followed by incorporation into the gel matrix effectively prolonged drug release. The release of 98.36% after 10 h also indicates efficient drug availability from the optimized formulation while maintaining a sustained-release pattern. The release-kinetic analysis of ELG2 is presented in Table 6. The coefficient of determination (R^2) values were 0.9854 for the zero-order model, 0.8307 for the first-order model, 0.9910 for the Higuchi model, and 0.9955 for the Korsmeyer–Peppas model. Among the evaluated models, the Korsmeyer–

Peppas model showed the highest R^2 value, followed by the Higuchi model. This indicates that drug release from ELG2 was best described by the Korsmeyer–Peppas model, suggesting that diffusion from the lipidic vesicles and gel matrix played an important role in controlling bifonazole release. The high R^2 value obtained for the Higuchi model further supports the contribution of diffusion-controlled release.

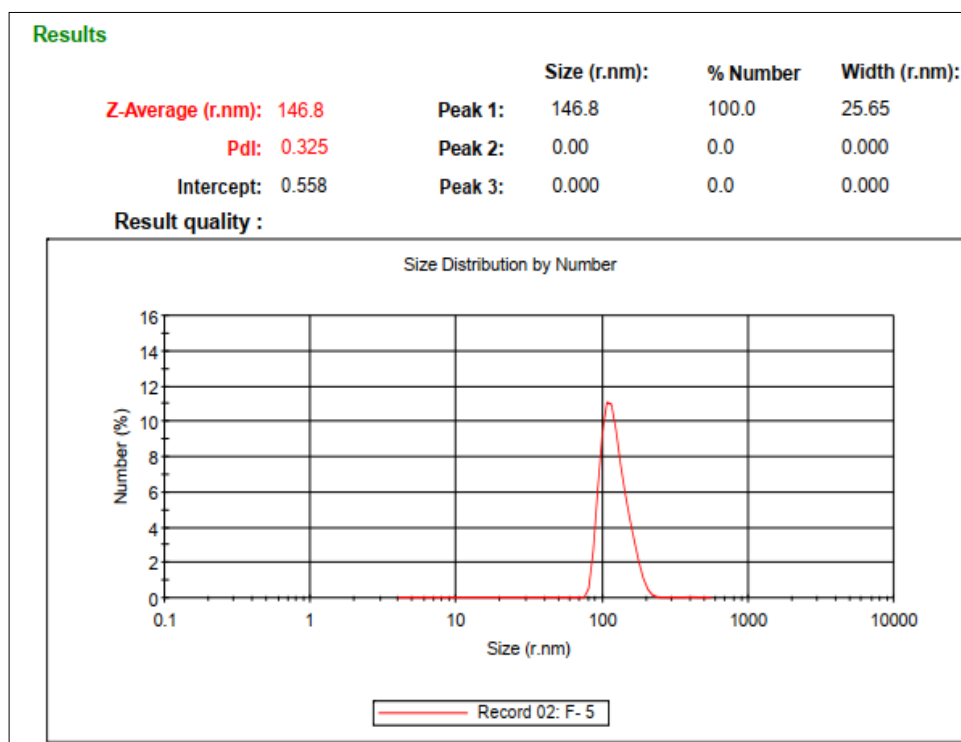
The stability results of optimized ELG2 under refrigerated and room-temperature conditions are shown in Table 7. The formulation retained a homogeneous and smooth appearance throughout the four-week study at both $4 \pm 0.5^\circ\text{C}$ and $28 \pm 0.5^\circ\text{C}$. At $4 \pm 0.5^\circ\text{C}$, drug content decreased only slightly from $98.76 \pm 0.22\%$ initially to $98.21 \pm 0.31\%$ after four weeks. Similarly, at $28 \pm 0.5^\circ\text{C}$, drug content decreased from $98.76 \pm 0.22\%$ to $97.96 \pm 0.33\%$. The relatively small changes in drug content and absence of visible physical changes indicate that ELG2 maintained satisfactory physical and chemical stability during the investigated storage period. The optimized ELG2 demonstrated suitable physicochemical properties, high drug entrapment, sustained drug release, and satisfactory short-term stability, supporting its potential as a topical bifonazole delivery system.

Table 1: Composition of Bifonazole-Loaded Elastic Liposomal Formulations

Formulation	Bifonazole (mg)	Phosphatidylcholine (mg)	Tween 80 (mg)	Ethanol (%)	Aqueous phase* (ml)
F1	10	100	10	10	q.s. to 10 ml
F2	10	100	20	10	q.s. to 10 ml
F3	10	150	10	10	q.s. to 10 ml
F4	10	150	20	10	q.s. to 10 ml
F5	10	200	10	10	q.s. to 10 ml
F6	10	200	20	10	q.s. to 10 ml

Table 2: Evaluations of elastic liposomes for vesicle size and entrapment efficiency

Formulation	Vesicle Size (nm)	Entrapment Efficiency (%)
F1	182.6 ± 4.8	72.45 ± 1.32
F2	169.4 ± 3.9	76.82 ± 1.15
F3	158.7 ± 3.6	80.36 ± 1.08
F4	151.3 ± 3.2	83.74 ± 0.96
F5	146.8 ± 2.9	86.52 ± 0.84
F6	163.5 ± 3.7	81.68 ± 1.11

**Figure 1: Vesicle Size of Optimized liposomes formulation F5**

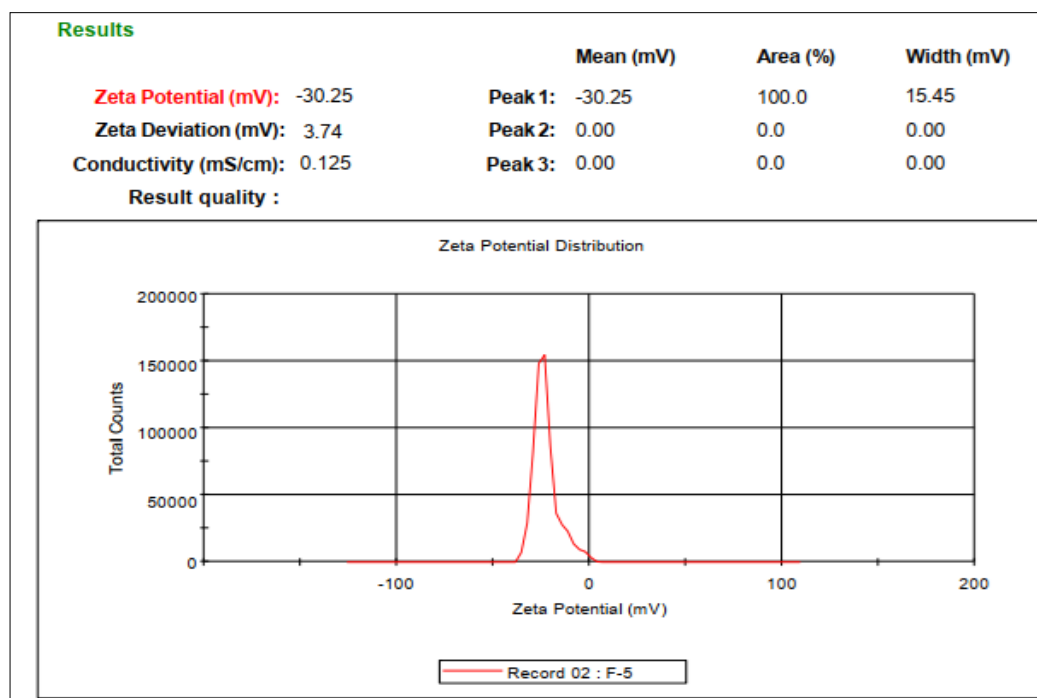


Figure 2: Zeta potential of Optimized liposomes formulation F5

Table 3: Vesicle size and entrapment efficiency of optimized formulation

Formulation Code	Vesicle Size (nm)	Entrapment Efficiency (%)	Zeta potential (mV)
F5	146.8	86.52 ± 0.84	- 30.25

Table 4: Results of liposomes gel formulations

Code	Drug Content (%)	pH	Spreadability (g·cm/sec)	Viscosity (cps)
ELG1	97.24 ± 0.38	6.42 ± 0.09	14.28 ± 1.15	2856 ± 21
ELG2	98.76 ± 0.22	6.48 ± 0.07	12.46 ± 1.08	3425 ± 19
ELG3	97.93 ± 0.31	6.51 ± 0.11	10.18 ± 1.26	4018 ± 24

Table 5: *In-vitro* drug release data for ELG2

Time (h)	Square Root of Time(h) ^{1/2}	Log Time	Cumulative* % Drug Release	Log Cumulative % Drug Release	Cumulative % Drug Remaining	Log Cumulative % Drug Remaining
0.5	0.70711	-0.301	15.65	1.195	84.35	1.926
1	1	0	22.36	1.349	77.64	1.890
2	1.41421	0.301	39.98	1.602	60.02	1.778
4	2	0.602	55.78	1.746	44.22	1.646
6	2.44949	0.778	69.98	1.845	30.02	1.477
8	2.82843	0.903	78.85	1.897	21.15	1.325
10	3.16228	1	98.36	1.993	1.64	0.215

Table 6: Regression analysis data of liposomes gel formulation

Batch	Zero Order	First Order	Higuchi's Model	Korsmeyers Peppas Equation
	R ²	R ²	R ²	R ²
ELG2	0.9854	0.8307	0.9910	0.9955

Table 7: Stability study of optimized Bifonazole-loaded elastic liposomal gel (ELG2) at different storage conditions

Storage condition	Time (weeks)	Physical appearance	Drug content (%)
4 ± 0.5°C	0	Homogeneous, smooth	98.76 ± 0.22
	1	Homogeneous, smooth	98.61 ± 0.24
	2	Homogeneous, smooth	98.48 ± 0.26
	3	Homogeneous, smooth	98.35 ± 0.28
	4	Homogeneous, smooth	98.21 ± 0.31
28 ± 0.5°C	0	Homogeneous, smooth	98.76 ± 0.22
	1	Homogeneous, smooth	98.52 ± 0.25
	2	Homogeneous, smooth	98.34 ± 0.27
	3	Homogeneous, smooth	98.12 ± 0.30
	4	Homogeneous, smooth	97.96 ± 0.33

CONCLUSION

Bifonazole-loaded elastic liposomes were successfully formulated and characterized as a potential topical antifungal delivery system. The optimized formulation F5 showed a vesicle size of 146.8 nm, entrapment efficiency of $86.52 \pm 0.84\%$, and zeta potential of -30.25 mV. Incorporation into the optimized gel ELG2 provided satisfactory drug content, pH, spreadability, viscosity, and sustained *in-vitro* drug release up to 10 h. The formulation also demonstrated acceptable short-term stability, indicating that bifonazole elastic liposomal gel may be a promising approach for effective topical management of fungal infections.

DECLARATION OF INTEREST

The authors declare no conflicts of interests. The authors alone are responsible for the content and writing of this article.

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