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"Formulation And Evaluation of Terbinafine Glycerosomal Gel as Novel Vesicular Drug Delivery System"

Narayan Prasad Patel[1]*, Pratyush Jain[2]
[1]ResearchScholar- RKDF College of Pharmacy, Bhopal, Madhya Pradesh
[2]Professor- RKDF College of Pharmacy, Bhopal, Madhya Pradesh

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ABSTRACT

The present study aimed to formulate and evaluate a Terbinafine-loaded glycerosomal gel as a novel vesicular drug delivery system for enhanced topical antifungal therapy. Preformulation studies confirmed the purity and suistability of Terbinafine, exhibiting characteristic organoleptic properties, acceptable pH (4.81), and melting point (197.09°C). The drug showed poor aqueous solubility and good solubility in organic solvents, indicating its lipophilic nature. UV–Visible spectrophotometric analysis revealed a λmax at 283 nm, and the calibration curve demonstrated good linearity in the concentration range of 20–120 µg/mL.Glycerosomal formulations (GF1–GF5) were successfully prepared and found to be homogeneous and stable. Among them, GF5 exhibited the smallest particle size (172.15 nm), highest zeta potential (−15.8 mV), and maximum entrapment efficiency (92.15%), indicating superior stability and drug-loading capacity. SEM analysis confirmed the formation of spherical nanosized vesicles with uniform distribution. The optimized glycerosomal gel showed desirable physicochemical properties, including suitable viscosity (4119 cps), pH (6.70), and good spreadability (11.50 g·cm/s), ensuring effective topical application. In vitro drug release studies demonstrated sustained release up to 92.53% over 13 hours, following zero-order kinetics (R^2 = 0.980), indicating controlled drug delivery. Stability studies conducted for 90 days under both ambient and accelerated conditions showed no significant changes in appearance, pH, or viscosity, confirming the formulation's stability. Overall, the developed Terbinafineglycerosomal gel, particularly formulation GF5, exhibited enhanced stability, controlled drug release, and improved potential for topical antifungal therapy.

Keywords: Terbinafine, Glycerosomes, Vesicular drug delivery system, Topical gel, Entrapment efficiency, Zeta potential, In vitro drug release, Antifungal therapy

I. INTRODUCTION

Glycerosomes are bilayer vesicles used for dermal and transdermal drug delivery. These vesicles differ from conventional liposomes in bilayer fluidity, formed by the addition of phospholipids and varying concentrations of glycerol (10-30 % v/v)**(Gupta *et al.,* 2020).**These are so named, as they contain high amount of glycerol. These vesicles deliver the active ingredients to skin with high efficiency **(Ashtiani*et al.,*2016).**Glycerosomes are found to be more stable and possess greater fluidity then liposomes and hence are predominantly used as topical drug delivery systems. Glycerol ameliorates the deformability index of liposomal bilayers, thus enhancing skin penetration **(Zhang *et al.,* 2017).**

Compared to conventional liposomes, glycerosomes exhibit improved deformability, stability, and drug loading capacity. The high glycerol content also acts as a humectant, increasing skin hydration and thereby enhancing drug permeation. These properties make glycerosomes particularly suitable for the delivery of antifungal agents like Terbinafine, where effective penetration and prolonged retention in the skin are crucial for therapeutic success **(Akhtar *et al.,* 2015).** Incorporation of glycerosomal dispersion into a gel base further enhances the applicability of the formulation. Gels are preferred for topical delivery due to their non-greasy nature, ease of application, better patient compliance, and ability to provide controlled drug release. Carbopol-based gels, in particular, are widely used owing to their excellent rheological properties, biocompatibility, and stability **(Aishwarya *et al.,* 2024).**

Terbinafine hydrochloride is a broad-spectrum antifungal agent belonging to the allylamine class, widely used in the treatment of superficial fungal infections. It exerts its antifungal action by inhibiting the enzyme squalene epoxidase, thereby disrupting ergosterol biosynthesis, an essential component of the fungal cell membrane. Despite its potent antifungal activity, Terbinafine

exhibits limited solubility and permeability when applied topically, which can reduce its therapeutic efficiency(**Elmataeeshy*et al.*, 2018).**Therefore, there is a need to develop advanced drug delivery systems that can enhance its penetration and sustain its release at the site of infection. Terbinafine is increasingly administered by topical route may increase the bioavailability. Terbinafine is very slightly soluble in water so because of its hydrophobicity, emulsion can formulate(**Hossain *et al.*, 2019).**

Despite its strong antifungal efficacy, the topical delivery of Terbinafine faces several challenges. The drug is highly lipophilic in nature and exhibits poor aqueous solubility, which limits its diffusion through the aqueous layers of the skin(**Shaker *et al.*, 2019).**Furthermore, the outermost layer of the skin, the stratum corneum, acts as a major barrier to drug penetration, reducing the amount of drug reaching the deeper layers where the infection resides. Conventional topical formulations such as creams and gels often show limited skin retention and require frequent application to maintain therapeutic levels(**Mohiuddin *et al.*, 2019).**

The present study is therefore aimed at the formulation and evaluation of Terbinafine-loaded glycerosomal gel as a novel vesicular drug delivery system. The developed formulation is evaluated for various physicochemical and performance parameters, including vesicle size, entrapment efficiency, drug release, and antifungal activity, to establish its potential as an effective topical drug delivery system.

II. MATRIALS AND METHODS

2.1 Chemicals

Terbinafine, were obtained from Mankind Pharma Ltd. Amitex Agro Products Pvt. Ltd provided the Soya Lecithin. Merck Ltd.provided the CholesterolwhileGlycerol, were procured from alaxy Surfactants Ltd, a well-known provider of high-quality laboratory chemicals. Methanolwas supplied by Simalin Chemical Industries Pvt. Ltd.All other solvents, Chemicals and reagents used were of analytical (AR) grade and purchased from MeruChemPvt. Ltd**,** Oryn Healthcare Llp, Vizag Chemicals, Joshi Pharma, Emco Dyestuff Pvt Ltdand Zygene Biotechnologies.

2.2 Pre-formulation study

2.2.1 Organoleptic Properties

The Terbinafine drug sample was visually inspected under normal laboratory lighting to observe its color, shape, and crystalline form. The odor and texture of the drug were also examined by careful sensory evaluation(**Kumineke*et al.*, 2013).**

2.2.2 Solubility study

One milligram of Terbinafine was added to separate test tubes containing 1 mL of water, methanol, DMSO, PBS (pH 7.4), ethanol, and chloroform. Each test tube was shaken or vortexed to mix the contents and left at room temperature for a few minutes. The solutions were observed directly in the test tubes for dissolution. Based on the appearance, the solubility of Terbinafine was classified as soluble (completely dissolved), moderately soluble (partially dissolved with some particles), or insoluble (undissolved solid visible **(Li *et al.*, 2021).**

2.2.3 pH Determination

The pH of Terbinafine was determined to evaluate its acid–base properties, which are essential for assessing its stability and compatibility within the intended formulation. A calibrated digital pH meter was used for all measurements to ensure accurate and reproducible results(**Behnood*et al.*, 2018).**

2.2.4 Melting Point

The melting point of Terbinafine was determined to assess its thermal properties and purity, which are important for formulation development. The analysis was performed using the capillary method **(Karaipekli*et al.*, 2017).**

2.2.5 Determination of Lambda max and calibration curve of Terbinafine

- **Lambda (λ) max analysis**

The wavelength of maximum absorbance (λmax) of Terbinafine was determined using UV–Visible spectrophotometry by scanning its methanolic solution over the range of 200–400 nm. The λmax was selected at the point of highest absorbance to ensure accurate analysis. A standard stock solution (1 mg/mL) was prepared, followed by suitable dilutions. The absorbance of these solutions was measured at λmax, and a calibration curve was plotted between absorbance and concentration. The curve showed good linearity, complying with Beer–Lambert's law, and was used for quantitative estimation of the drug **(Orteganet *al.*, 2025).**

- **Standard calibration curve analysis**

A calibration curve of Terbinafine was prepared for quantitative analysis. A stock solution (1 mg/mL) was made in methanol, followed by serial dilutions

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to obtain concentrations in the range of 20–100 µg/mL. The absorbance of each solution was measured at the predetermined λmax using a UV–Visible spectrophotometer. A calibration graph of absorbance versus concentration was plotted, showing good linearity in accordance with Beer–Lambert's law. The regression equation and correlation coefficient (R^2) confirmed the method's accuracy. All measurements were performed in triplicate, and the calibration curve was used for estimation of drug content in formulations and release studies **(Zhao *et al.,* 2017).**

2.2.6 Fourier transmission Infra-Red Spectroscopy

FTIR spectroscopy was used to analyze the functional groups and confirm the chemical structure of Terbinafine. The drug was mixed with dry KBr (1:100) and compressed into a transparent pellet, which was scanned over the range of 4000–400 cm^{-1}. The obtained spectrum showed characteristic peaks corresponding to functional groups, confirming the identity and purity of the drug. The results were compared with standard literature values. All measurements were performed under dry conditions to avoid interference.

2.3 Formulation of Terbinafine -Loaded Glycerosomes via Thin-Film Hydration

Terbinafine-loaded glycerosomes were prepared using the thin film hydration method. Soy lecithin, cholesterol, and Terbinafine (1%) were dissolved in chloroform and evaporated using a rotary evaporator at 45°C to form a thin lipid film. The film was hydrated with phosphate buffered saline containing varying concentrations of glycerol, followed by rotation and manual stirring to form vesicles. The resulting glycerosomal dispersion was collected and stored for further evaluation.

Table 1: Composition of Glycerosomes formulation

Formulation Code	Terbinafine (%)	Soy Lecithin (mg)	Cholesterol (mg)	Glycerol (%)	PBS (mL)	Chloroform (mL)	Stirring Time (min)
GF 1	1.0	100	20	10	q.s. to 10 mL	5.0	30
GF 2	1.0	150	30	20	q.s. to 10 mL	5.0	30
GF 3	1.0	200	40	30	q.s. to 10 mL	5.0	30
GF 4	1.0	250	50	40	q.s. to 10 mL	5.0	30
GF 5	1.0	300	60	50	q.s. to 10 mL	5.0	30

2.4 Characterization parameter

2.4.1 Physical Appearance

The prepared terbinafine-loaded glycerosomal formulations (GF1–GF5) were visually evaluated to assess their physical characteristics, including color, clarity, and overall uniformity **(Hetrick *et al.,* 2013).**

2.4.2 Vesicle Size and Distribution

In the case of terbinafine-loaded glycerosomes, the average vesicle size and size distribution were determined using dynamic light scattering (DLS) with a Zetasizer Nano ZS (Malvern Instruments) **(Blott and Pye 2012).**

2.4.3 Zeta potential

The surface charge of terbinafine-loaded glycerosomal vesicles was determined by measuring the zeta potential, which is a key indicator of colloidal stability. The analysis was carried out using a Zetasizer Nano ZS (Malvern Instruments, UK) based on the principle of electrophoretic mobility **(Wang *et al.,* 2013).**

2.4.4 Scanning Electron Microscopy

The surface morphology and structural characteristics of the terbinafine-loaded glycerosomal vesicles were examined using scanning electron microscopy (SEM). This technique provides detailed information regarding the shape, surface texture, and physical integrity of the vesicles **(Mohammed and Abdullah 2018).**

2.4.5 Entrapment Efficiency

Entrapment efficiency of Terbinafine in glycerosomes was determined to assess drug loading capacity. The vesicular dispersion was centrifuged at 15,000 rpm for 30 minutes at 4 °C to separate free drug from entrapped drug. The supernatant containing unencapsulated drug was analyzed using

UV–Visible spectrophotometry at the predetermined λmax.
The drug entrapment efficiency (%EE) was calculated using the following formula:

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

2.5 Preparation of Drug loaded glycerosomal gel

The terbinafine-loaded glycerosomal gel was formulated to facilitate topical application and enhance drug delivery. The gel base was prepared by dispersing Carbopol 940 (1.0 g) and carboxymethyl cellulose (CMC, 1.10 g) in distilled water (up to 100 mL) with continuous stirring, allowing complete polymer hydration and uniform swelling. Propylene glycol (1.0 mL) was added as a plasticizer and humectant to improve the gel's Spreadability and moisturizing properties, while methylparaben (0.3 g) was incorporated as a preservative to prevent microbial growth. Subsequently, 10 ml of terbinafine-loaded glycerosomes (prepared via thin-film hydration) were gradually dispersed into the gel base under gentle stirring to achieve a homogeneous mixture. Triethanolamine was added dropwise to neutralize the Carbopol, facilitating gel formation and adjusting the pH to a skin-compatible range. The final gel was thoroughly mixed to ensure uniform consistency and stored in airtight containers at 4 °C until further evaluation **(Salem *et al.,* 2022).**

Table 2: Composition of glycerosomal gel formulation

Component	Concentration / Amount	Function
Carbopol 940	1.0 g	Gelling agent / viscosity enhancer
Carboxymethyl cellulose (CMC)	1.10 g	Viscosity modifier / stabilizer
Propylene glycol	1.0 mL	Plasticizer / humectant
Methylparaben	0.3 g	Preservative
Terbinafine-loaded glycerosomes	10 ml	Active drug carrier
Triethanolamine	q.s. to neutralize pH	pH adjuster / gel formation
Distilled water	Up to 100 mL	Vehicle / solvent

2.6 Characterization parameters of Terbinafine-loaded glycerosomal gel

2.6.1 pH determination

The pH of the prepared terbinafine-loaded glycerosomal gel was measured to ensure skin compatibility and stability of the formulation **(Wang *et al.,* 2017).**

2.6.2 Spreadability of glycerosomal gel

The Spreadability of the terbinafine-loaded glycerosomal gel was evaluated to determine its ease of application and uniform coverage on the skin. This parameter is important for topical formulations, as it affects patient compliance and drug release.For the assessment, a fixed quantity of gel (approximately 1 g) was placed between two glass slides. A standard weight (e.g., 500 g) was applied on the top slide for a defined period (typically 1–2 minutes) to allow the gel to spread. The spread diameter of the gel was then measured in centimetres(**Gaber *et al.,* 2023).**

The Spreadability (S) was calculated using the formula:

$$S = \frac{M \times L}{T}$$

2.6.3 Viscosity

The viscosity of Terbinafine-loaded glycerosomal gels (GF1–GF5) was measured to evaluate their rheological properties, which affect spreadability, application, and drug release. The measurement was performed using a rotational viscometer (e.g., Brookfield viscometer) **(Patil *et al.,* 2019).**

2.7 *In Vitro* Drug Release and Kinetic Study

In vitro drug release of Terbinafine from glycerosomal gel was studied using a Franz diffusion cell with a pre-soaked semi-permeable membrane and phosphate buffer (pH 7.4) as the receptor medium. The system was maintained at 37 ± 2 °C with continuous stirring. Samples were withdrawn at predetermined intervals, replaced with fresh buffer, and analyzed using UV–Visible spectrophotometry at λmax. The cumulative drug release was calculated and plotted against time. Release data were fitted to kinetic models **(Bohrey*et al.,* 2016).**

To evaluate the drug release mechanism, the release data were fitted into different kinetic models:

- **Zero-order kinetics:** Cumulative percentage drug release versus time was plotted to determine constant drug release behavior.

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- **First-order kinetics:** Log cumulative percentage drug remaining versus time was plotted to evaluate concentration-dependent release.
- **Higuchi model:** Cumulative percentage drug release versus square root of time was plotted to assess diffusion-controlled release.
- **Korsmeyer–Peppas model:** Log cumulative percentage drug release versus log time was plotted to determine the release exponent (n), indicating the mechanism of drug release such as Fickian diffusion or non-Fickian transport.

2.8 Stability Studies

Stability studies of the optimized Terbinafineglycerosomal gel were conducted at 25 ± 2°C / 60 ± 5% RH and 40 ± 2°C / 75 ± 5% RH for 3 months. The formulation was evaluated at regular intervals for appearance, pH, and viscosity. No significant changes were observed in color, homogeneity, or phase separation. The pH and viscosity remained within acceptable limits, indicating good stability. Overall, the formulation was found to be stable and suitable for storage.

III.RESULT AND DISCUSSION

3.1 Pre-formulation study of Terbinafine

3.1.1 Organoleptic properties

Table 3: Organoleptic properties of Terbinafine

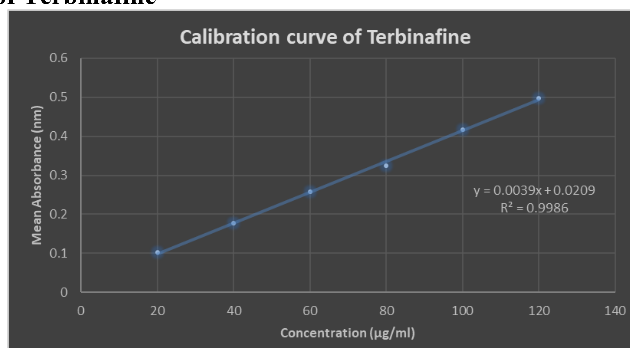
Parameter	Observation
Color	White to off-white
Odor	Odorless or faint odor
Appearance	Crystalline powder
State	Solid

3.1.2 pH and Melting point Determination

Table 4: pH and Melting point of Terbinafine

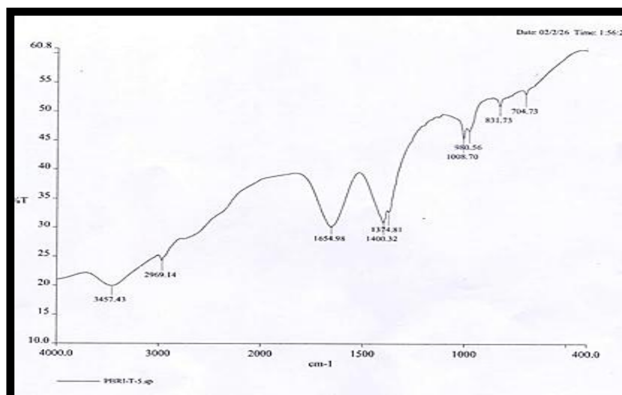
Drugs	pH (Observed)	pH (Reference)	Melting point (Observed)	Melting point (Reference)
Terbinafine	4.81	4.0-5.0	197.09 °C	195°C to 198°C.

3.1.3 Calibration curve of Terbinafine



Graph 1: Calibration curve of Terbinafine

3.1.4 Fourier transmission Infra-Red Spectroscopy of Terbinafine drug



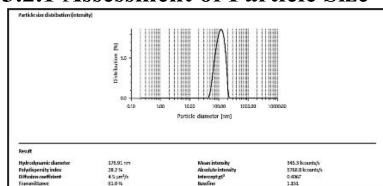
Graph 2: FTIR study of Terbinafine

3.2 Formulation of drug loaded glycerosomes formulation

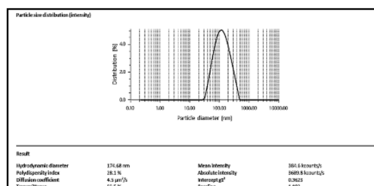
Table 5: Composition of Glycerosomes formulation

Formulation Code	Phospholipid (mg)	Cholesterol (mg)	Glycerol (% v/v)	Terbinafine (% w/w)	Methanol (mL)	Chloroform (mL)	PBS (mL)	Stirring Time (min)
GF1	100	20	10	1.0%	5.0	5.0	10	30
GF2	150	30	20	1.0%	5.0	5.0	10	30
GF3	200	40	30	1.0%	5.0	5.0	10	30
GF4	250	50	40	1.0%	5.0	5.0	10	30
GF5	300	60	50	1.0%	5.0	5.0	10	30

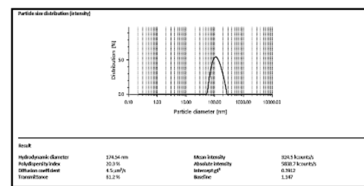
3.2.1 Assessment of Particle Size



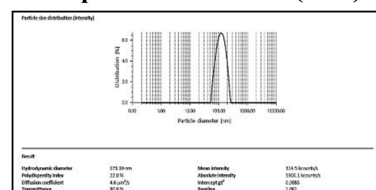
Graph 4: Particle Size (GF1)



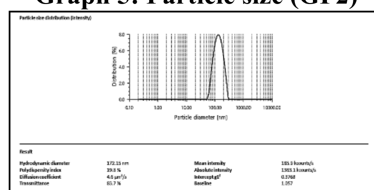
Graph 5: Particle size (GF2)



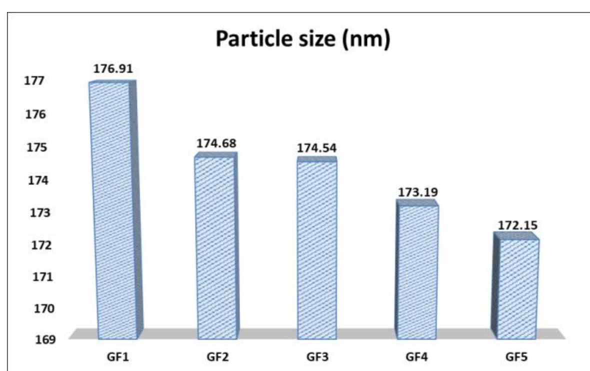
Graph 6: Particle size (GF3)



Graph 7: Particle size (GF4)

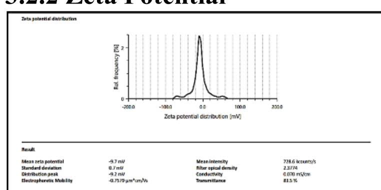


Graph 8: Particle size (GF5)

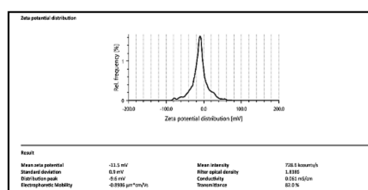


Graph 9: Graphical representation of Particle size determination

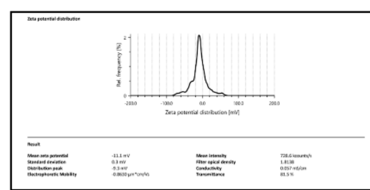
3.2.2 Zeta Potential



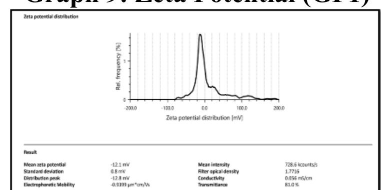
Graph 9: Zeta Potential (GF1)



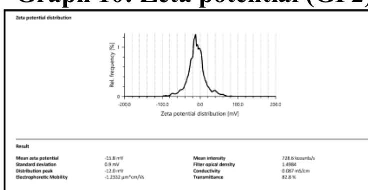
Graph 10: Zeta potential (GF2)



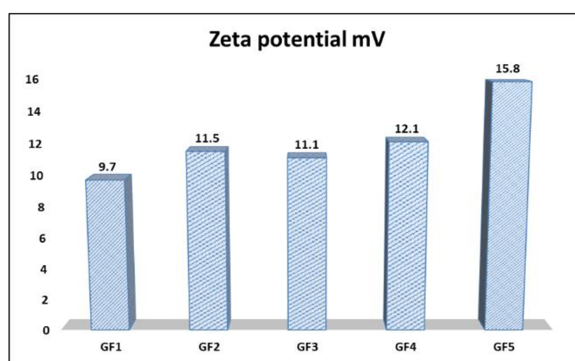
Graph 11: Zeta potential (GF3)



Graph 12: Zeta potential (GF4)



Graph 13: Zeta potential (GF5)

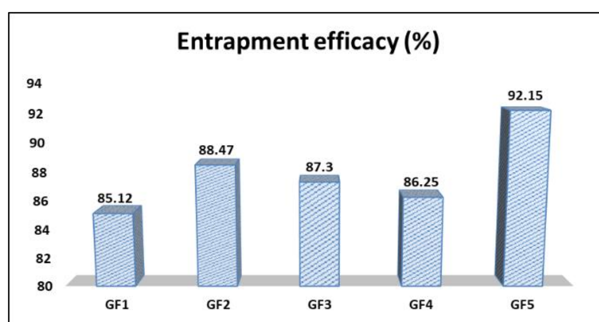


Graph 14: Graphical representation of Zeta potential determination

3.2.3 Entrapment efficacy determination

Table 6: Entrapment efficacy

Formulations (GF1-GF5)	Entrapment efficacy (%)
GF1	85.12
GF2	88.47
GF3	87.30
GF4	86.25
GF5	**92.15**



Graph 15: Graphical representation of Entrapment efficacy (%)

3.2.4 Scanning electron microscope (SEM)

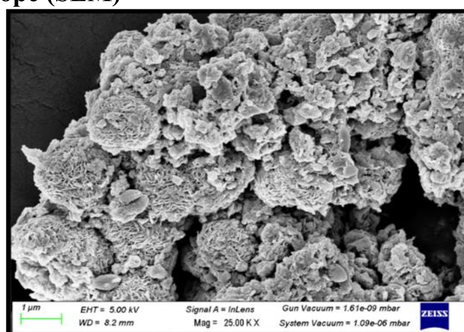


Figure 1: Scanning electron microscope (SEM)

3.3 Evaluation parameter of drug loaded Glycerosomal gel formulation

Table 7: Viscosity, pH and Spreadibility determination of Glycerosomal gel

Formulation	Viscosity (Cps)	pH	Spreadability (g.cm/s)
Glycerosomal gel	4119±0.31 cps	6.70	11.50 g-cm/sec

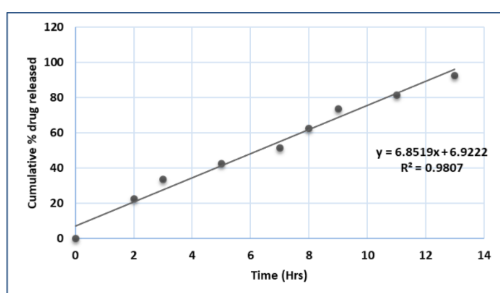
3.4*In Vitro* Drug Release Study of glycerosomal Gel

Table 8: *In-vitro* drug release studies

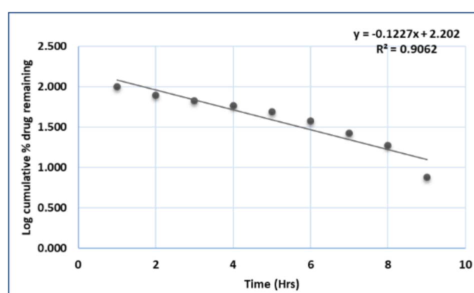
Time (Hr)	cumulative % drug released	% drug remaining	Square root time	log Cumu % drug remaining	log time	log Cumu % drug released
0	0	100	0.000	2.000	0.000	0.000
2	22.41	77.59	1.414	1.890	0.301	1.350
3	33.39	66.61	1.732	1.824	0.477	1.524
5	42.42	57.58	2.236	1.760	0.699	1.628
7	51.46	48.54	2.646	1.686	0.845	1.711
8	62.5	37.5	2.828	1.574	0.903	1.796
9	73.51	26.49	3.000	1.423	0.954	1.866
11	81.49	18.51	3.317	1.267	1.041	1.911
13	92.53	7.47	3.606	0.873	1.114	1.966

Table 9: Correlation value (R^2 value)

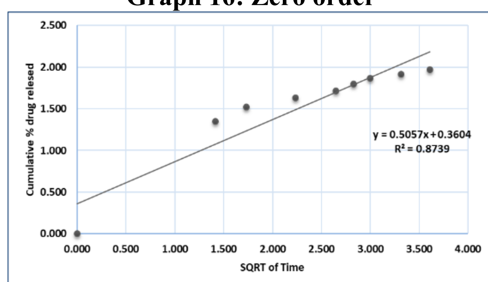
Formulation	Model	Kinetic parameter values
Glycerosomal Gel Formulation	Zero Order	$R^2 = 0.980$
	First Order	$R^2 = 0.906$
	Higuchi	$R^2 = 0.873$
	Korsmeyerpeppas	$R^2 = 0.803$



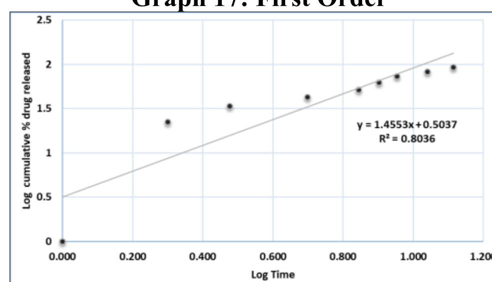
Graph 16: Zero order



Graph 17: First Order



Graph 18: Higuchi



Graph 19: Korsmeyerpeppas

3.5 Stability study

Table 10: Stability Study of Gelformulation

Time (Days)	25 °C ±2 °C and 60 ± 5% RH			40 °C ±2 °C and 70 ±5% RH		
	pH	Viscosity (Cps)	Colour	pH	Viscosity (Cps)	Colour
0	6.70	4119	Transparent light yellow	6.70	4119	Transparent light yellow
30	6.68	4105	Transparent light yellow	6.69	4107	Transparent light yellow
45	6.67	4100	Transparent light yellow	6.68	4102	Transparent light yellow
60	6.66	4095	Slightly pale yellow	6.67	4098	Slightly pale yellow
90	6.65	4090	Slightly pale yellow	6.66	4092	Slightly pale yellow

IV. Discussion

Preformulation studies confirmed that Terbinafine is a white to off-white crystalline, lipophilic drug with good solubility in organic solvents and acceptable pH and melting point, indicating its purity and suitability for formulation. The λmax was found at 283 nm, and the calibration curve showed good linearity, validating the analytical method. The prepared glycerosomal formulations (GF1–GF5) were homogeneous and stable, with nanosized vesicles (172–176 nm). Among them, GF5 showed the smallest particle size, highest zeta potential (−15.8 mV), and maximum entrapment efficiency (92.15%), indicating superior stability and drug-loading capacity. SEM analysis confirmed spherical vesicles with uniform distribution, supporting successful formulation.

The glycerosomal gel exhibited desirable physical properties, including suitable viscosity, pH close to skin, and good spreadability, ensuring effective topical application. In vitro drug release studies demonstrated sustained release up to 92.53% over 13 hours, following zero-order kinetics, indicating controlled drug delivery. Stability studies showed no significant changes in appearance, pH, or viscosity over 90 days under different conditions, confirming formulation stability. Overall, GF5 was identified as the optimized formulation with enhanced stability, controlled release, and improved potential for topical antifungal therapy.

V.CONCLUSION

The study successfully developed a Terbinafine-loaded glycerosomal gel with improved physicochemical and therapeutic properties. The optimized formulation (GF5) showed ideal particle size, high entrapment efficiency, and good stability. The gel exhibited suitable pH, viscosity, and spreadability for topical application. In vitro studies confirmed sustained drug release following zero-order kinetics, while stability studies indicated good formulation stability. Overall, the glycerosomal gel demonstrated enhanced potential for effective and controlled topical antifungal delivery.

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