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Acitretin-Loaded Glycerosomal Cream: Physicochemical Characterization and Antibacterial Evaluation

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Abstract: The present study was undertaken with the aim of developing and evaluating a glycerosomal cream formulation containing Acitretin for topical drug delivery. Acitretin is a second-generation retinoid used in the treatment of psoriasis and other keratinization disorders. Due to its poor aqueous solubility and lipophilic nature, glycerosomal vesicular technology was explored to improve its topical delivery. Initially, preformulation studies of Acitretin were carried out to determine its physicochemical properties. Acitretin was found to be a yellow to pale yellow, odorless crystalline powder, freely soluble in ethanol, methanol and DMSO, with a pH of 5.7 and melting point of 228°C. The maximum absorption wavelength was found to be 343 nm, and the calibration curve showed good linearity in the concentration range of 5–25 µg/mL with R^2 = 0.9978. Acitretin-loaded glycerosomes were prepared by the thin-film hydration method using different concentrations of phospholipid. Five formulations (GF1–GF5) were prepared and evaluated for particle size, zeta potential, entrapment efficiency and surface morphology. GF3 was selected as the optimized formulation, exhibiting a particle size of 156.5 nm, zeta potential of −30.3 mV and entrapment efficiency of 92.55%. The optimized glycerosomes were incorporated into a cream base and evaluated for physical properties, pH, viscosity and spreadability. The formulation showed a pH of 6.3, viscosity of 4286 ± 12.5 cps and spreadability of 11.3 g·cm/s. In-vitro drug release showed 98.95% cumulative drug release after 14 h. The formulation also exhibited concentration-dependent antibacterial activity against *E. coli* and *S. aureus*. Overall, the developed Acitretin-loaded glycerosomal cream demonstrated promising characteristics for topical drug delivery.

Keywords: *Acitretin; Glycerosomes; Topical Drug Delivery; Vesicular Drug Delivery; Glycerosomal Cream; Phospholipid; Entrapment Efficiency; In-Vitro Drug Release.*

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I. INTRODUCTION

Topical drug delivery systems serve as a vital pathway for administering therapeutic agents directly to the target site on the skin, offering localized treatment while minimizing systemic side effects. Despite their utility, conventional topical formulations often encounter significant drawbacks, including poor drug solubility, limited skin retention, and insufficient permeation across the formidable stratum corneum barrier. The outer layer of the skin acts as an impermeable shield to many large or hydrophilic molecules, severely restricting the therapeutic efficacy of conventional creams and ointments. To overcome these limitations, advanced vesicular drug delivery systems have gained widespread interest for enhancing the therapeutic performance of topically applied agents. These lipid-based vesicular carriers efficiently encapsulate active pharmaceutical ingredients, promoting targeted drug localization, membrane flexibility, and sustained release profiles.

Acitretin, a well-known second-generation retinoid, plays a critical role in treating severe psoriasis and various keratinization disorders. Pharmacologically, Acitretin acts by binding to specific nuclear retinoid receptors—such as retinoic acid receptors (RAR) and retinoid X receptors (RXR)—thereby normalizing epidermal cell proliferation, reducing cellular differentiation abnormalities, and inhibiting the excessive scaling and plaque formation characteristic of psoriatic lesions. Nevertheless, its inherent lipophilicity and extremely low aqueous solubility present major challenges during both formulation development and effective skin permeation. When administered orally, Acitretin undergoes extensive systemic exposure, which can lead to well-

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documented adverse effects. Consequently, localized topical delivery provides a safer and more targeted therapeutic alternative. These physicochemical hurdles create a strong scientific rationale for employing a specialized carrier system capable of improving drug entrapment, protecting the drug from degradation, and ensuring prolonged, controlled release directly at the site of application.

In recent years, lipid-based nanocarriers have emerged as superior alternatives to conventional topical vehicles. Among these, glycerosomes represent a specialized class of soft vesicular carriers characterized by the inclusion of high amounts of glycerol (ranging from 10% to 50% v/v) as an essential structural component of the aqueous phase. While conventional liposomes rely purely on phospholipid bilayers, the incorporation of glycerol in glycerosomes modifies membrane fluidity and deformability. Glycerol acts as an effective edge activator, humectant, and membrane plasticizer, which significantly improves the functional properties of the vesicular carriers. The presence of glycerol molecules interacts directly with the polar head groups of the phospholipids, altering bilayer packing and reducing the natural barrier resistance of the stratum corneum. This unique mechanism allows glycerosomal vesicles to squeeze through narrow intercellular pathways of the skin, facilitating deeper dermal penetration and enhanced localized drug accumulation. Furthermore, glycerosomes exhibit superior physical stability compared to traditional liposomes, which are often prone to aggregation and particle size growth over time. The structural stability and negative zeta potential typically observed in glycerosomal systems prevent particle agglomeration, ensuring long-term shelf stability. These attributes make glycerosomes exceptionally well-suited for dermatological applications involving poorly soluble therapeutic agents.

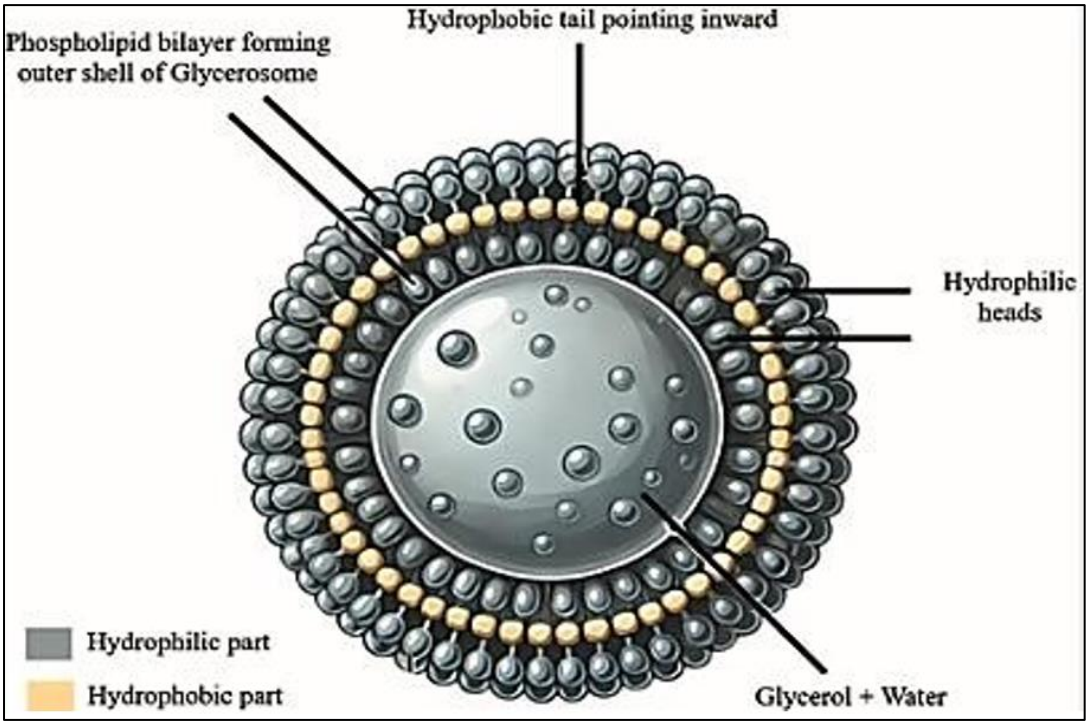

Fig 1 Glycerosomes

➢ *Applications and Functional Versatility of Glycerosomes*

Beyond conventional dermatological applications, glycerosomal vesicular technology has demonstrated immense versatility and robust performance across multiple administration routes and therapeutic categories:

- *Inhaled Drug Delivery:*

Research has explored the incorporation of active compounds (such as curcumin) into polymer-coated glycerosomes for pulmonary delivery. Studies reveal that such vesicular systems form unilamellar structures ranging from 65 to 112 nm, facilitating effective drug accumulation in the lungs with excellent biocompatibility and stability governed by hydrophilic polymer networks (Manca et al., 2016).

- *Oral Cavity Administration:*

Glycerosomes and PEGylated penetration-enhancing vesicles have been successfully formulated to deliver plant extracts (such as citrus lemon extract) to the oral cavity, offering significantly higher penetration and therapeutic efficacy for oral mucosal conditions compared to conventional systems (Manconi et al., 2018).

- *Topical and Transdermal Drug Delivery:*

Glycerosomes are highly effective in transporting NSAIDs (such as Diclofenac Sodium, Celecoxib, and Cupferron) across the skin barrier. Formulations containing 10–30% glycerol show superior flux, cumulative permeation, and reduced rat paw edema due to the extreme deformability imparted by glycerol and surfactants like Tween 80 (Wang et al., 2010; Salem et al., 2018).

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- *Enhancement of Antioxidants and Polyphenols:*

Potent antioxidants like Quercetin, Resveratrol, and Gallic Acid suffer from poor skin permeability. Encapsulating them in glycerosomes enables targeted accumulation within the stratum corneum and epidermis, maintaining high radical scavenging activity (~95%) and boosting keratinocyte cell viability under oxidative stress from 26% to 70% (Manca et al., 2014).

- *Treatment of Skin Infections and Disorders:*

The elastic nature of glycerosomes allows them to treat localized skin disorders and infections more efficiently than standard creams. For instance, Sertaconazole Nitrate-loaded glycerosomes show superior antifungal activity by squeezing into deeper skin layers, while Minoxidil glycerosomes optimize drug release profiles over extended periods for hair growth management (Manca et al., 2016).

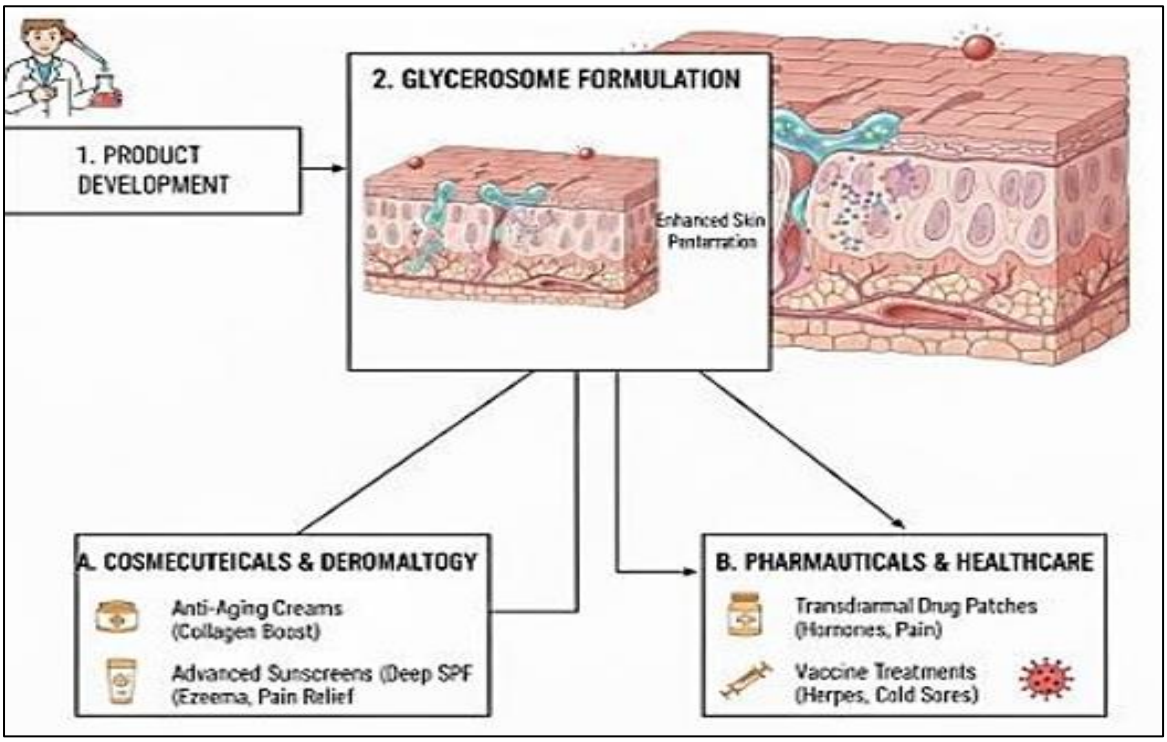

Fig 2 Applications of Glycerosomes

➢ *Key Functional Benefits and Mechanisms*

The superior performance of glycerosomes over traditional vesicular systems is governed by several core mechanisms (Abdellatif et al., 2017):

- *Edge Activation:*

At concentrations exceeding 10%, glycerol functions as an edge activator, significantly increasing the vesicle's deformability index and bilayer fluidity.

- *Vesicular Stabilization:*

Unlike standard liposomes that tend to aggregate within 30 days, glycerosomes maintain structural size stability for up to 90 days.

- *Skin Barrier Modification:*

Glycerol interacts directly with phospholipid polar head groups, modifying bilayer packing to lower natural skin resistance.

- *Cellular Uptake:*

Endocytosis serves as the primary mechanism through which these soft vesicles transfer encapsulated drugs and phospholipids directly into skincells, such as keratinocytes.

II. MATERIALS AND METHODS

➢ *Materials*

Acitretin was used as the active pharmaceutical ingredient. Soya lecithin served as the vesicle-forming phospholipid, while cholesterol and glycerol were utilized as stabilizing and glycerosomal components. Methanol and chloroform were used as organic solvents for lipid film preparation. Beeswax, liquid paraffin, borax, methyl paraben, and lavender oil were used to formulate the topical cream base. Phosphate-buffered saline (PBS) and phosphate buffer (pH 7.4) served as hydration and in-vitro diffusion media, respectively. Nutrient agar and Mueller-Hinton agar were used for microbiological assays.

➢ *Preformulation Studies of Acitretin*

Preformulation tests were conducted to evaluate the physicochemical properties of Acitretin. Organoleptic characteristics (color, odor, state) were visually inspected. Solubility was tested across various solvents including water, ethanol, methanol, chloroform, DMSO, and acetone. Melting point and pH values were measured using standard analytical equipment. For spectrophotometric analysis, a standard stock solution of Acitretin (100 µg/mL) was prepared in DMSO, and serial dilutions (5–25 µg/mL) were scanned using a UV-visible spectrophotometer to determine the maximum

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absorption wavelength (λ_{max}) at 343 nm and establish the calibration curve. Fourier Transform Infrared (FTIR) spectroscopy was performed using the KBr pellet method over the range of 4000–400 cm^{-1} to identify characteristic functional groups.

➢ *Preparation of Acitretin-Loaded Glycerosomes*

Acitretin-loaded glycerosomes were fabricated via the conventional thin-film hydration method. Accurately weighed quantities of Acitretin (0.1% w/w), cholesterol (40 mg), and varying concentrations of Soya lecithin phospholipid (10–50 mg) were dissolved in a methanol-chloroform mixture (10:10 mL). The organic solvent was removed under reduced pressure using a rotary evaporator at 40°C to deposit a uniform thin lipid film, which was kept under vacuum overnight. The dried lipid film was hydrated with 15 mL of phosphate-buffered saline (PBS, pH 6.8) containing 10% v/v glycerol at 40°C with continuous mechanical stirring for 1 hour. The resulting vesicular suspension was probe-sonicated to reduce vesicle size, and unentrapped drug was removed by centrifugation at 1500 rpm for 10 min at 4°C. Five distinct formulations (GF1–GF5) were prepared by varying the phospholipid concentration.

➢ *Characterization of Glycerosomes*

- *Physical Appearance:*

Evaluated for color, clarity, homogeneity, and absence of phase separation or sedimentation.

- *Particle Size and Zeta Potential:*

Determined using a Malvern Zetasizer based on dynamic light scattering (DLS) and electrophoretic mobility after appropriate dilution.

- *Entrapment Efficiency (% EE):*

Quantified by separating unentrapped drug via centrifugation and analyzing the supernatant spectrophotometrically at 247 nm using the standard entrapment formula.

- *Surface Morphology:*

Examined using Scanning Electron Microscopy (SEM) to determine vesicular shape and surface uniformity.

➢ *Preparation of Glycerosomal Cream*

The optimized glycerosomal formulation (GF3) was incorporated into a semi-solid cream base. Liquid paraffin and beeswax were heated to 75°C (oil phase), while borax and methyl paraben were dissolved in distilled water at 75°C (aqueous phase). The aqueous phase was slowly blended into the oil phase under continuous stirring. The optimized glycerosomes (10 mL) along with lavender oil (3–4 drops) were incorporated into the cooled base to yield the final formulation containing beeswax (4.0 g), liquid paraffin (15 mL), borax (0.4 g), and methyl paraben (0.03%).

➢ *Evaluation of Glycerosomal Cream*

- *Physical Properties & pH:*

Checked for visual appearance, homogeneity, and skin-compatible pH using a calibrated digital pH meter.

- *Viscosity:*

Measured using a Brookfield DV-III programmable viscometer with spindle S-6 at 37°C and 100 rpm.

- *Spreadability:*

Evaluated by the horizontal slide method using 1 g of cream and a 125 g weight.

➢ *In-Vitro Drug Release Study:*

The release profile of Acitretin from the glycerosomal cream was assessed using the dialysis bag diffusion method. A measured amount of cream was placed inside a dialysis membrane immersed in 100 mL of phosphate buffer (pH 7.4) maintained at 37 ± 2°C with continuous stirring at 100 rpm. Aliquots were withdrawn at predetermined time intervals for up to 14 hours, replaced with fresh buffer, and analyzed spectrophotometrically at 301 nm. Release data were fitted into zero-order, first-order, Higuchi, and Korsmeyer-Peppas kinetic models.

➢ *Antimicrobial Activity :*

The antimicrobial efficacy of the glycerosomal cream was evaluated against Escherichia coli and Staphylococcus aureus using the agar well diffusion method. Nutrient agar plates were inoculated with bacterial suspensions, wells were created, and different concentrations of the formulation (control C1, along with 2, 4, and 8 mg/mL designated as C2, C3, and C4) were introduced. The zones of inhibition were measured after 24 hours of incubation at 37°C.

III. RESEARCH & DISCUSSION

➢ *Pre-formulation Studies of Acitretin*

- *Organoleptic Properties*

The organoleptic evaluation confirmed that Acitretin is a solid, odorless, crystalline powder with a yellow to pale yellow appearance, indicating good purity and stability.

Table 1 Organoleptic Properties of Acitretin

S. No.	Parameter	Result
1	Color	Yellow to pale yellow
2	Odor	Odorless
3	Appearance	Crystalline powder
4	State	Solid

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- *Solubility Study*

Solubility studies revealed that the drug is freely soluble in ethanol, methanol, and DMSO, moderately soluble in acetone, sparingly soluble in chloroform, and slightly soluble in water, confirming its lipophilic nature.

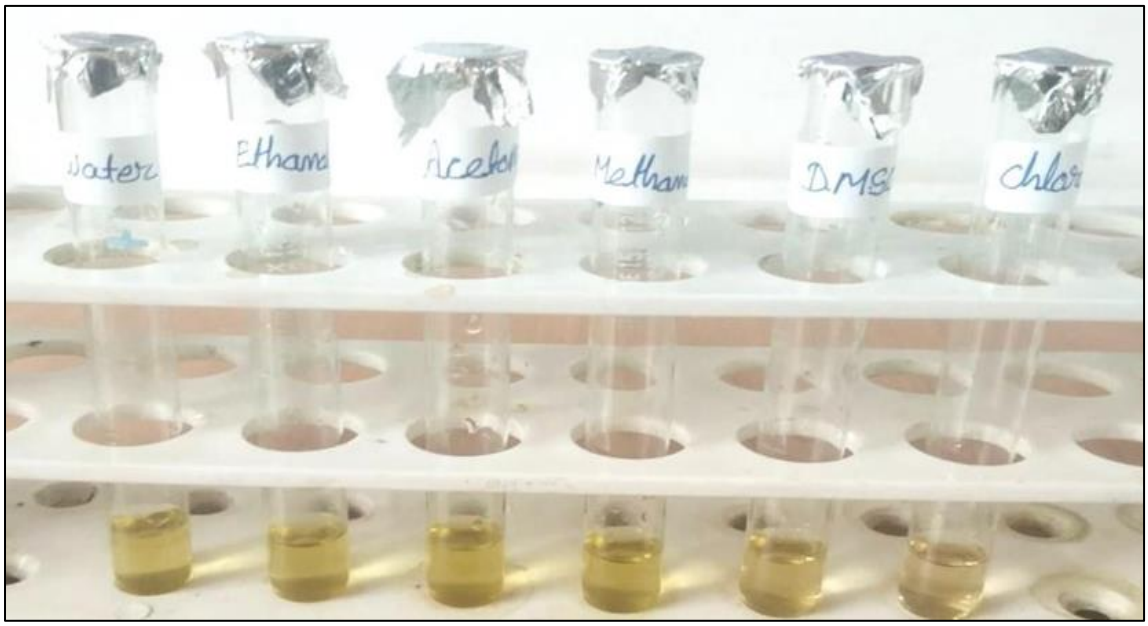

Fig 3 Solubility Study of Acitretin

- *pH Determination*

The pH of Acitretin was observed to be 5.7, lying well within the reference range of 5.0–6.5.

Fig 4 pH of Acitretin

- *Thermal Characterization: Melting Point analysis*

The melting point was determined to be 228°C, which complies with the standard reference range of 223°C to 230°C.

- *Lambda Max Determination of Acitretin*

UV-visible spectral analysis identified the maximum absorption wavelength (λ max) at 343.0 nm.

Table 2 Lambda Max of Acitretin

S. No.	Drug	UV absorption maxima (Lambda max)
1.	Acitretin	343.0 nm

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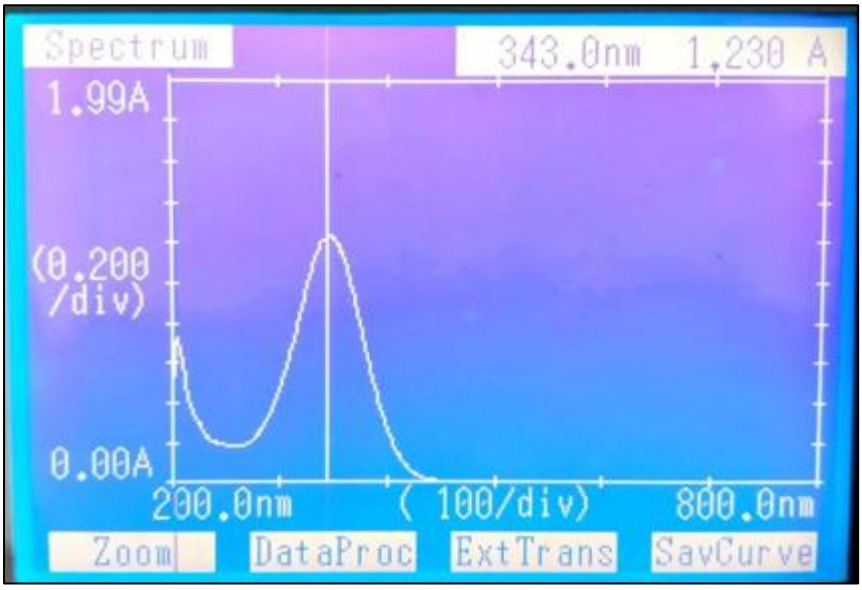

Fig 5 Lambda max of Acitretin (343.0 nm)

- *Lambda Max Determination of Acitretin*

The calibration curve demonstrated excellent linearity within the concentration range of 5–25 µg/mL with a regression equation of y=0.0196x+0.0523 and a correlation coefficient (R2) of 0.9978.

Table 3 Calibrationcurve of Acitretin

S. No.	Concentration (µg/ml)	Mean Absorbance
1	5	0.142
2	10	0.254
3	15	0.351
4	20	0.449
5	25	0.534
Mean		**0.346**
SD		**0.15496**

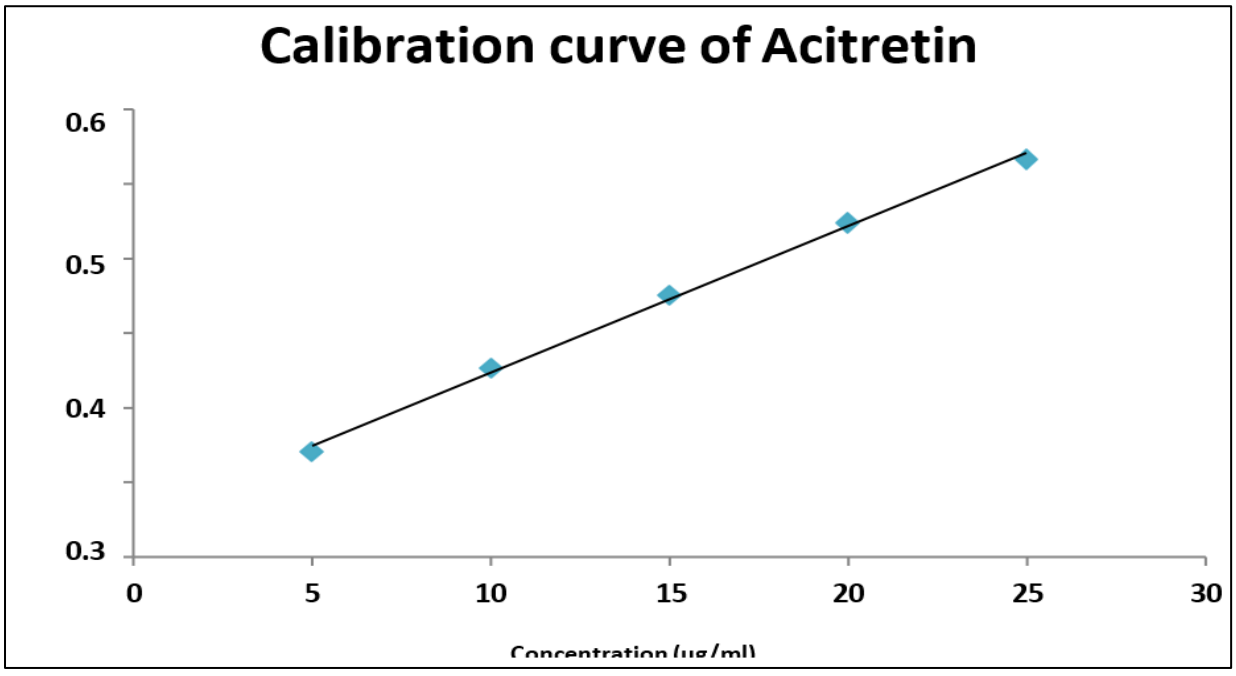

Fig 6 Calibration Curve of Acitretin

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- *Fourier Transmission Infra-Red Spectroscopy of Acitretin Drug*

FTIR spectral analysis confirmed the structural integrity of the drug by identifying characteristic peaks for O–H stretching (3754.29 cm^{-1}), N–H stretching (3457.71 cm^{-1}), C–H alkane stretching (2850.02 cm^{-1}), and conjugated acid C=O stretching (1703.69 cm^{-1}).

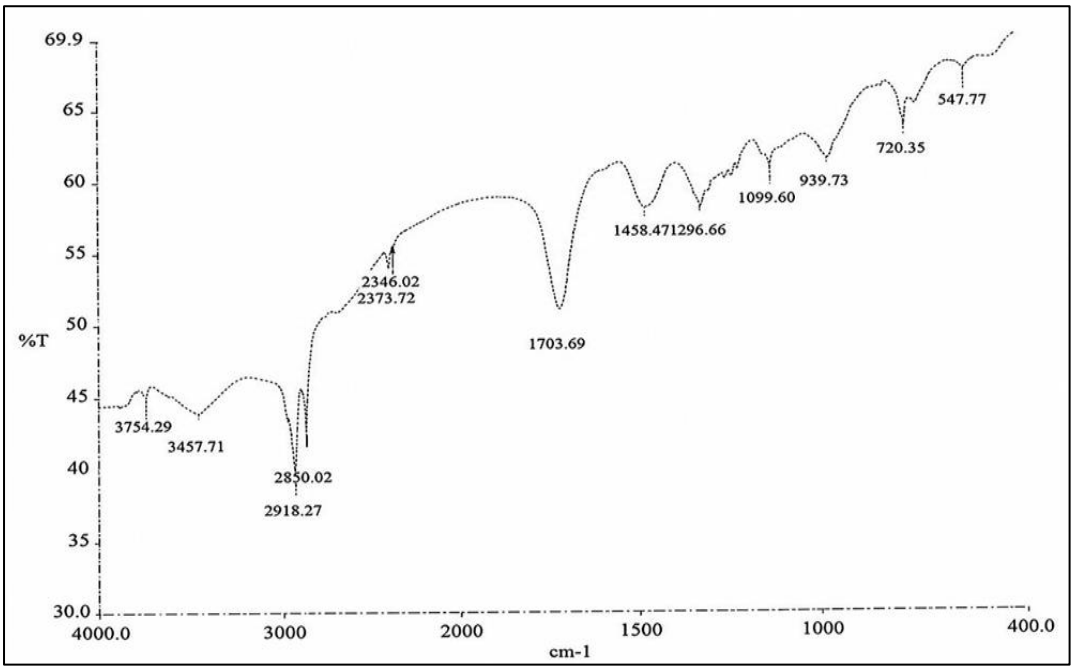

Fig 7 FTIR study of Acitretin

➢ *Characterization of Acitretin-Loaded Glycerosomes (GF1–GF5)*

Five formulations (GF1–GF5) were successfully prepared by varying phospholipid concentrations while keeping other components constant.

- *Physical Appearance:*

Formulations GS1, GS2, and GS3 showed pale yellow color, clear to translucent appearance, and uniform homogeneity without phase separation or sedimentation, while GS4 and GS5 exhibited minor sedimentation and phase separation upon storage.

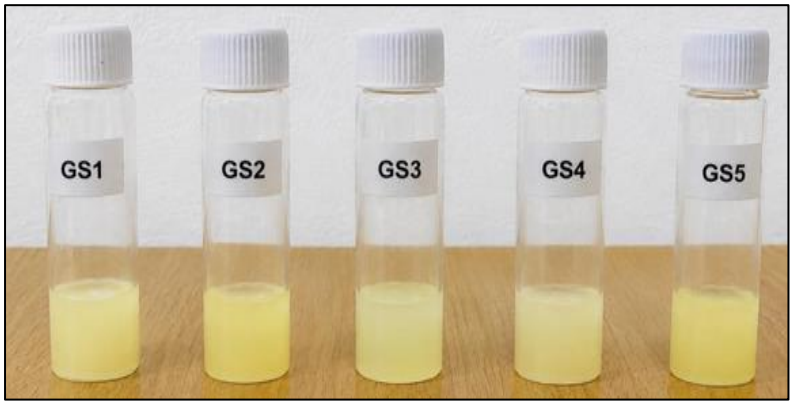

Fig 8 Glycerosome Formulation

- *Particle Size:*

The vesicle size varied from 156.5 nm to 255.6 nm. Formulation GF3 exhibited the smallest and most favorable particle size of 156.5 nm, whereas GF5 showed the largest size of 255.6 nm.

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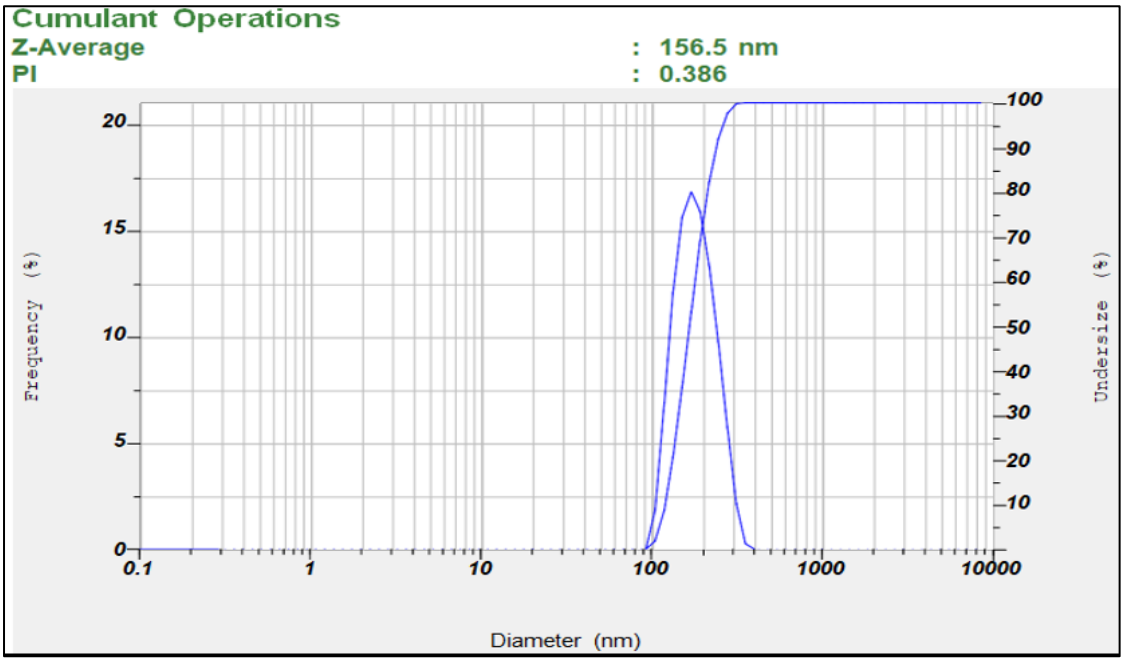

Fig 9 Particle Size (GF3)

- *Zeta Potential:*

Zeta potential values ranged from −11.8 mV to −30.3 mV. Formulation GF3 showed the highest negative zeta potential of −30.3 mV, indicating strong electrostatic repulsion and excellent colloidal stability.

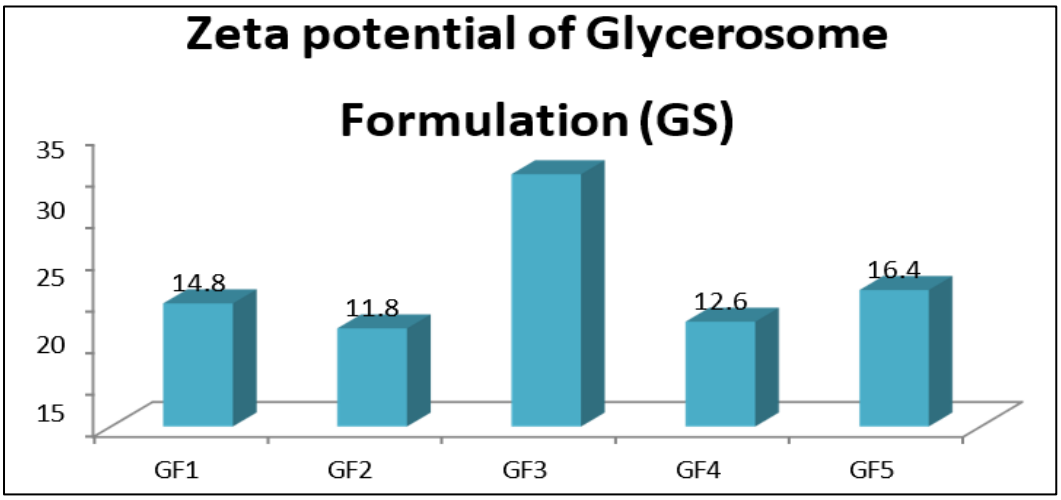

Fig 10 Zeta Potential of Glycerosomes Formulation

- *Entrapment Efficiency (% EE):*

The entrapment efficiency ranged between 79.51% and 92.55%. Formulation GF3 achieved the maximum entrapment efficiency of 92.55%.

Table 4 Entrapment efficacy

S. No.	Formulations (F1-F5)	Entrapment efficacy (%)
1.	GF1	85.23
2.	GF2	87.34
3.	**GF3**	**92.55**
4.	GF4	89.84
5.	GF5	79.51

- *Surface Morphology (SEM):*

Scanning electron microscopy confirmed that the optimized GF3 vesicles possessed a spherical to slightly irregular shape, smooth surface morphology, and uniform distribution with minimal aggregation.

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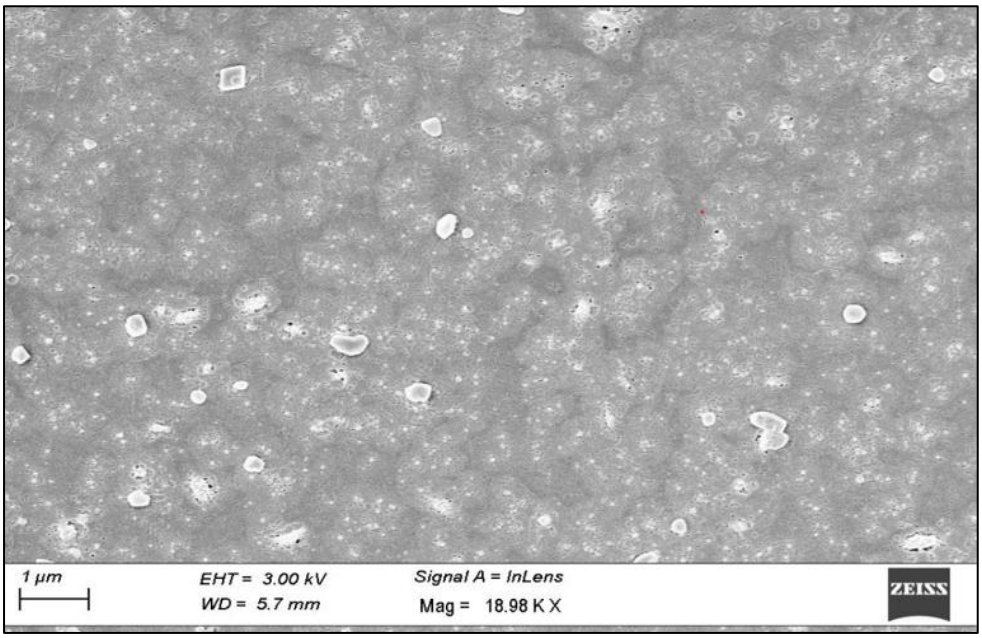

Fig 11 Scanning Electron Microscope (SEM)

➢ *Evaluation of Glycerosomal Cream*

The optimized glycerosomal formulation (GF3) was incorporated into a cream base containing beeswax, liquid paraffin, borax, methyl paraben, and lavender oil.

- *Physical Appearance*

The formulation exhibited a pale yellow colour with a characteristic odour, indicating acceptable organoleptic properties. It showed a smooth and creamy appearance, suggesting good consistency and suitability for topical application. The formulation was homogeneous, with no visible lumps or phase separation, indicating uniform distribution of ingredients. Overall, these observations suggest satisfactory physical characteristics and acceptable formulation quality.

- *pH and Viscosity:*

The pH of the cream was found to be 6.3, which is compatible with normal skin physiology. The viscosity was measured at 4286 ± 12.5 cps, reflecting good structural consistency and skin retention.

- *Spreadability:*

The spreadability was recorded at 11.3 g·cm/s, indicating smooth and uniform application over the skin surface without excessive resistance.

- *In-Vitro Drug Release and Release Kinetics*

The in-vitro release profile of Acitretin from the glycerosomal cream evaluated via the dialysis bag diffusion method showed a gradual and sustained release pattern over 14 hours. The cumulative percentage drug release reached 98.95% at the end of 14 hours. Mathematical modeling of the release data indicated that the release kinetics best fitted the Higuchi model (R2 =0.9911), confirming that drug release is primarily governed by a diffusion-controlled mechanism.

Table 5 Drug Release Study

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
1	21.19	78.81	1.000	1.897	0.000	1.326
2	33.41	66.59	1.414	1.823	0.301	1.524
4	43.87	56.13	2.000	1.749	0.602	1.642
6	57.21	42.79	2.449	1.631	0.778	1.757
8	67.88	32.12	2.828	1.507	0.903	1.832
10	78.72	21.28	3.162	1.328	1.000	1.896
12	86.96	13.04	3.464	1.115	1.079	1.939
14	98.95	1.05	3.742	0.021	1.146	1.995

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➢ *Antimicrobial Activity*

- *Antimicrobial Activity of Glycerosome Cream Formulation*

Table 6 Antimicrobial activity of Glycerosome cream formulation (C1, C2, C3 and C4 Different Concentration) by *E. coli*

S. No.	Sample Name	Zone of Inhibition (mm)	Inference
1	C1 (Control)	0.0 mm	No antimicrobial activity was observed in the control formulation.
2	C2 (2 mg/ml)	7 mm	Moderate antibacterial activity was observed at lower concentration.
3	C3 (4 mg/ml)	10 mm	Increased zone of inhibition indicates enhanced antibacterial activity with increasing concentration.
4	C4 (8 mg/ml)	12 mm	Highest antibacterial activity was observed at 8 mg/ml concentration against *E. coli.*

The antimicrobial efficacy evaluated via the agar well diffusion method demonstrated concentration-dependent inhibition against both Escherichia coli and Staphylococcus aureus. The control formulation (C1) showed no inhibition zone (0.0 mm). For E. coli, the zones of inhibition were 7 mm (2 mg/mL), 10 mm (4 mg/mL), and 12 mm (8 mg/mL).

For S. aureus, the zones of inhibition were 9 mm (2 mg/mL), 13 mm (4 mg/mL), and 15 mm (8 mg/mL). The larger inhibition zones against S. aureus indicate that the formulation exhibits stronger antibacterial effectiveness against Gram-positive strains due to enhanced vesicular penetration.

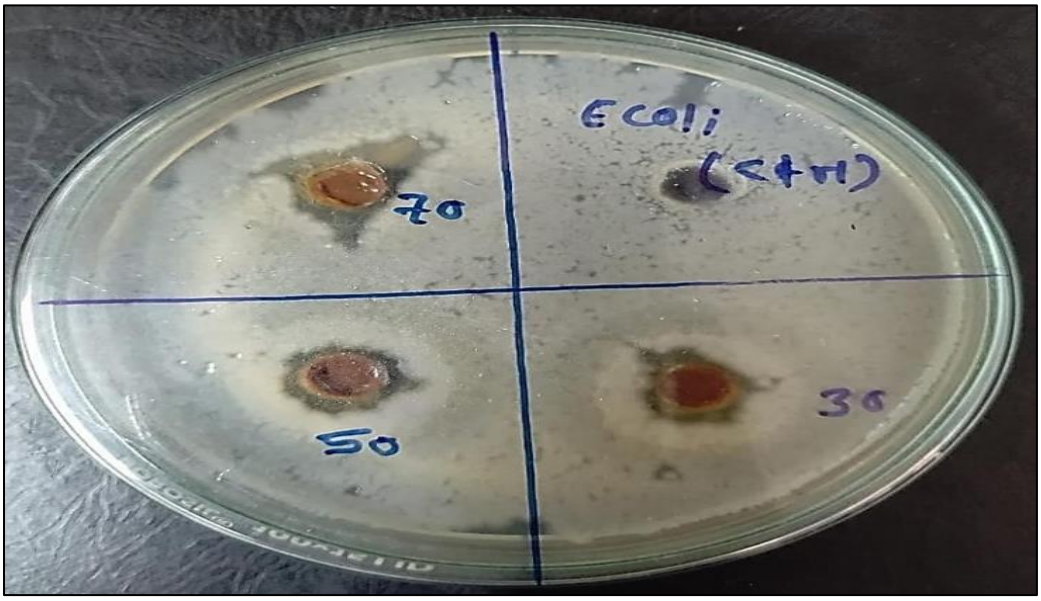

Fig 12 Antimicrobial activity by *E.coli*

IV. CONCLUSION

The present study successfully formulated and evaluated an Acitretin-loaded glycerosomal cream for topical drug delivery. Preformulation studies confirmed the purity, stability, and compatibility of Acitretin for formulation development. The prepared glycerosomal formulations exhibited satisfactory physicochemical properties, among which GF3 was identified as the optimized formulation based on its smaller particle size, higher zeta potential, superior entrapment efficiency, and better physical stability.

The optimized glycerosomal cream demonstrated desirable organoleptic properties, appropriate pH, suitable viscosity, and good spreadability, making it ideal for topical application. *In vitro* drug release studies confirmed sustained and controlled release of Acitretin over an extended period, which may enhance therapeutic efficacy and reduce dosing frequency. Furthermore, the formulation showed promising antimicrobial activity against both *Escherichia coli* and *Staphylococcus aureus*, indicating its additional potential in managing skin infections associated with dermatological disorders.

The incorporation of Acitretin into glycerosomal vesicles significantly improved formulation stability, drug entrapment, and release characteristics. The nanosized vesicular system may enhance skin penetration and localized drug delivery while minimizing systemic side effects commonly associated with conventional retinoid therapy.

Therefore, it can be concluded that the developed glycerosomal cream formulation containing Acitretin is a promising and effective topical drug delivery system with improved physicochemical properties, controlled drug release behavior, and enhanced antimicrobial activity. The

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formulation has potential for further clinical evaluation and future application in the treatment of psoriasis and other skin disorders.

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