

FORMULATION AND EVALUATION ETHOSOME BASED GEL FOR ATOPIC DERMATITIS

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Abstract:

Background: Atopic dermatitis is a chronic inflammatory skin disorder in which impaired barrier function and microbial involvement can complicate topical management. Curcumin and Nimbidin possess complementary pharmacological properties, but their effective topical delivery remains challenging. Therefore, the present study aimed to develop a Curcumin–Nimbidin-loaded ethosomal gel as a potential topical delivery system for atopic dermatitis.

Methods: Curcumin and Nimbidin-loaded ethosomes were prepared by the hot method using soya lecithin, ethanol, and propylene glycol. Five formulations (CN1–CN5) were developed by varying the drug-to-lecithin ratio. The formulations were characterized for vesicle morphology, vesicle size, entrapment efficiency, pH, viscosity, spreadability, and in-vitro drug release. The optimized ethosomal dispersion was incorporated into a Carbopol 940 gel base for topical evaluation.

Results: The prepared ethosomes exhibited predominantly spherical to near-spherical morphology, with vesicle sizes ranging from 178.5 ± 3.7 to 245.6 ± 4.8 nm. Entrapment efficiency ranged from $75.5 \pm 0.33\%$ to $82.6 \pm 0.25\%$, with CN4 showing the highest entrapment. The ethosomal gels demonstrated satisfactory physical characteristics, including acceptable pH, viscosity, and spreadability. In-vitro release studies revealed a gradual release of Curcumin over 240 min, whereas Nimbidin showed a comparatively faster release profile over 120 min. CN4 demonstrated the most favourable overall formulation characteristics.

Conclusion: The developed Curcumin–Nimbidin ethosomal gel, particularly CN4, demonstrated promising physicochemical and release characteristics for topical delivery. The formulation may provide a suitable nanovesicular approach for delivering herbal bioactives in atopic dermatitis; however, further ex vivo, stability, irritation, and in-vivo investigations are required to substantiate its therapeutic potential.

Keywords: Atopic dermatitis; Curcumin; Nimbidin; Ethosomes; Ethosomal gel; Topical drug delivery; Entrapment efficiency; In-vitro drug release.

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INTRODUCTION

Atopic Dermatitis is a long-term, relapsing inflammatory skin condition that typically begins in early childhood and is often linked with other atopic disorders such as asthma, allergic rhinitis, and food allergies [1]. Nearly 60% of cases appear within the first year of life, most commonly between 3 and 6 months of age. It is clinically identified by intense itching, dry skin, and eczematous lesions that tend to recur over time [2]. AD significantly affects patients' quality of life and also creates a notable economic burden on healthcare systems.

The development of AD is complex and results from the interaction of multiple factors, including genetic predisposition, impaired skin barrier function, immune system imbalance, environmental triggers, and changes in skin microbiota [3]. Damage to the skin barrier increases water loss and allows easier entry of allergens and microorganisms. Moreover,

Staphylococcus aureus colonization is commonly found in affected skin and can worsen inflammation and disease severity [4]. Together, these factors lead to persistent inflammation, itching, dryness, and repeated flare-ups, indicating the need for treatment strategies that address multiple disease mechanisms [5].

Current management of AD focuses on restoring the skin barrier, controlling inflammation, preventing relapses, and managing secondary infections. Standard therapies include emollients, topical corticosteroids, calcineurin inhibitors, immunomodulators, and systemic drugs in severe cases [6]. Although these treatments are effective in controlling symptoms, long-term use may be limited by frequent application requirements, poor skin penetration, irritation, and potential side effects [7]. As a result, there is growing interest in advanced

topical drug delivery systems that can enhance drug penetration and maintain therapeutic activity at the site of application.

In recent years, natural bioactive compounds have gained attention as alternative or supportive options for inflammatory skin diseases. **Curcumin**, a polyphenolic compound derived from the rhizomes of *Curcuma longa* (family Zingiberaceae), exhibits strong anti-inflammatory and antioxidant activities. It also shows antibacterial and antifungal effects [8]. These properties make curcumin a promising candidate for treating inflammatory skin conditions. However, its poor water solubility, lipophilic nature, and low bioavailability limit its effectiveness in conventional formulations, necessitating an efficient delivery system to improve its skin absorption and therapeutic action [9].

Nimbidin, an active compound extracted from the seeds of *Azadirachta indica* (neem), is also known for its anti-inflammatory, antimicrobial, and wound-healing properties. It helps reduce symptoms such as redness, swelling, and irritation while also inhibiting microbial growth. Since AD is often associated with skin barrier disruption and microbial colonization, nimbidin's combined anti-inflammatory and antimicrobial effects make it a valuable candidate for AD management [10].

Using curcumin and nimbidin together may offer a synergistic therapeutic effect by simultaneously targeting inflammation and microbial infection in AD. However, delivering these compounds effectively through the skin remains challenging [11]. Conventional topical formulations such as creams and gels often fail to provide adequate penetration, stability, or sustained release of active herbal agents. Therefore, an advanced delivery system is required to enhance their therapeutic performance [12].

Among various vesicular systems, **ethosomes** are lipid-based carriers composed of phospholipids, ethanol, and water. The high ethanol content increases vesicle flexibility and improves interaction with the lipids of the stratum corneum, thereby enhancing skin penetration of loaded drugs. Ethosomes are widely studied for topical and transdermal delivery due to their ability to improve drug transport into deeper skin layers [13]. When incorporated into a gel base, they offer additional advantages such as ease of application, better skin contact time, improved spreadability, and higher patient compliance [14].

Despite increasing research on herbal drugs and vesicular systems in dermatology, very few studies have investigated the combined delivery of curcumin and nimbidin using an ethosomal gel for the treatment of atopic dermatitis. Most available studies focus on single herbal agents or different delivery systems, with limited exploration of dual-herbal ethosomal formulations that combine the anti-inflammatory and antioxidant effects of

curcumin with the antimicrobial and anti-inflammatory properties of Nimbidin [15].

Therefore, the present investigation was carried out to develop and evaluate a Curcumin- and Nimbidin-loaded ethosomal gel for topical delivery in atopic dermatitis (AD). The prepared formulation was characterized for various parameters including physicochemical properties, entrapment efficiency of the drug, vesicle size, topical performance, and in vitro drug release behaviour [16]. The ethosomal gel system was intended to enhance the dermal delivery of both herbal constituents and demonstrated potential in improving their therapeutic application in the treatment of atopic dermatitis [17].



Fig: 1 Atopic dermatitis on Different areas of human body

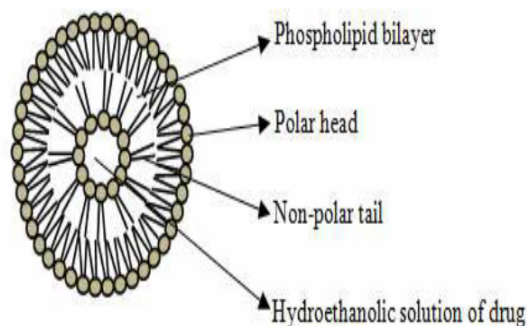


Fig: 2 Structure of Ethosome (Singh and Kumar)[18]

MATERIALS AND METHODOLOGY

Material – Curcumin and Nimbidin served as the active constituents of the developed formulation. Soya lecithin was selected as the primary phospholipid for vesicle formation, whereas ethanol and propylene glycol were incorporated as co-solvent and penetration-enhancing agents. Carbopol 940 was utilized to provide the desired gel structure, with distilled water serving as the aqueous medium [19-20]. Ethanol was purchased from Sisco Research Laboratories, while the remaining materials were sourced from their respective suppliers and used without further purification.

METHODOLOGY

Pre-Formulation Studies

Curcumin and nimbidin were first characterized for their physical appearance, solubility behavior, melting point, UV absorption profile, partition coefficient, and compatibility with excipients. Solubility testing was performed in selected aqueous and non-aqueous solvents to identify a suitable medium for formulation work. The maximum absorption wavelengths of both drugs were determined using UV-Visible spectrophotometry by scanning solutions in the range of 200–800 nm [22]. The partition coefficient was evaluated using the shake-flask technique with chloroform and water as the two phases. Compatibility between drugs and excipients was investigated through FTIR spectroscopy by comparing the spectra of curcumin, nimbidin, soya lecithin, and their physical mixtures over the range of 4000–400 cm^{-1} . Standard calibration curves of both active compounds were also developed using UV-Visible spectrophotometry for their quantitative analysis during formulation and evaluation [23-24].

Preparation of Curcumin and Nimbidin Loaded Ethosomal

Ethosomal vesicles containing curcumin and nimbidin were prepared by the hot method. Measured amounts of curcumin, nimbidin, and soya lecithin were dissolved in a hydroalcoholic mixture of ethanol and propylene glycol. This solution was kept at $40 \pm 2^\circ\text{C}$ with continuous stirring [25]. In a separate vessel, distilled water was heated to the same temperature and slowly introduced into the ethanolic phase under constant stirring to promote vesicle formation. The resulting dispersion was further stirred at 700 rpm and then sonicated in three cycles of 5 minutes each, with 5-minute cooling intervals between cycles, to achieve reduced particle size and uniform distribution [26]. A total of five formulations (CN1–CN5) were developed by altering the ratio of drug to soya lecithin.

Preparation of Ethosomal Gel

The optimized ethosomal dispersion was incorporated into a Carbopol 940-based gel system. Carbopol 940 (0.75 g) was first dispersed in 100 mL of distilled water and allowed to hydrate completely to form a uniform gel base [27]. After hydration, 20 mL of the prepared ethosomal dispersion was slowly added under continuous stirring. The mixture was maintained at $30 \pm 2^\circ\text{C}$ and stirred at 700 rpm until a smooth and homogeneous gel was obtained. The final gel was then adjusted to the desired pH and stored in airtight containers for further studies [28].

Evaluation of Ethosomal Gel

The prepared formulations were assessed for key physicochemical and performance characteristics such as pH, viscosity, spreadability, entrapment efficiency, vesicle properties, and drug permeation behaviour [29-30]. The pH was determined using a calibrated digital pH meter. Viscosity measurements were carried out using a Brookfield viscometer, while spreadability was evaluated by the glass-slide method. Entrapment efficiency and vesicle characteristics were analyzed using suitable analytical and microscopic techniques [31].

In Vitro Drug Permeation Study

Drug permeation in vitro was studied using a Franz diffusion cell equipped with a hydrated dialysis membrane. The effective diffusion area was 2.4 cm^2 , and phosphate buffer (pH 7.4) served as the receptor medium [32]. The receptor compartment was maintained at $37 \pm 0.5^\circ\text{C}$ with continuous stirring throughout the experiment. At predetermined time intervals, samples were withdrawn and immediately replaced with fresh buffer to maintain constant volume conditions [33-34]. The collected samples were analyzed using UV-Visible spectrophotometry, and cumulative drug permeation was calculated accordingly [35].

Results

Preformulation Studies Curcumin & Nimbidin

Preformulation evaluation of Curcumin and Nimbidin was carried out to assess their organoleptic characteristics, solubility behavior, and melting point.

Organoleptic properties

Curcumin was observed as a bright yellow, crystalline powder with a mild characteristic odour, whereas Nimbidin appeared brownish-yellow to dark brown with a slight pungent smell.

Solubility

Curcumin showed poor solubility in water but dissolved better in hot ethanol, methanol, and acetone. Nimbidin was also insoluble in water; however, it exhibited solubility in ethanol, methanol, acetone, and was freely soluble in hexane. Based on these findings, ethanol was selected as the solvent for formulation development.

Melting point

The melting point of Curcumin was found to be $183 \pm 3.0^\circ\text{C}$. The melting point of Nimbidin was not evaluated.

Absorption maxima

UV-Visible spectrophotometric analysis showed maximum absorbance at **419 nm for Curcumin** and **215 nm for Nimbidin**, which were considered their respective λ_{max} values.

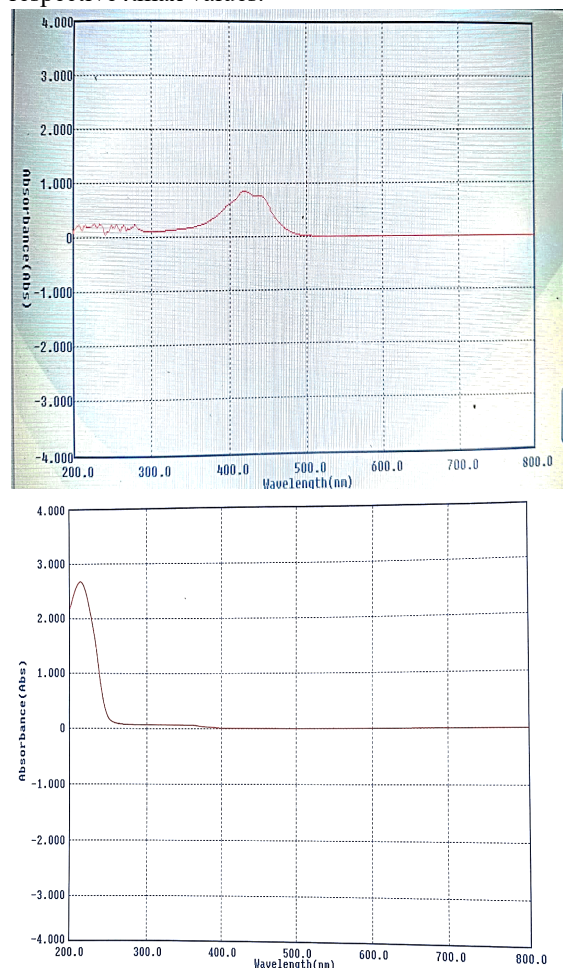


Fig: 3,4 Determination of Absorption Maxima of Curcumin & Nimbidin

Partition Coefficient (Log P)

The partition coefficient (Log P) of Curcumin and Nimbidin was found to be 1.16 ± 0.02 and 2.66 ± 0.02 , respectively. The values indicated the lipophilic nature of both compounds, supporting their suitability for incorporation into ethosomal vesicles and topical drug delivery.

Using Fourier Transform Infrared Spectroscopy (FTIR) Analysis

FTIR spectra exhibited the characteristic functional group bands of Curcumin and Nimbidin, confirming their presence. These characteristic bands remained unchanged in the Curcumin-Nimbidin-Lecithin formulation, without any notable new peaks or shifts, suggesting good compatibility and no significant chemical interaction between the formulation components.

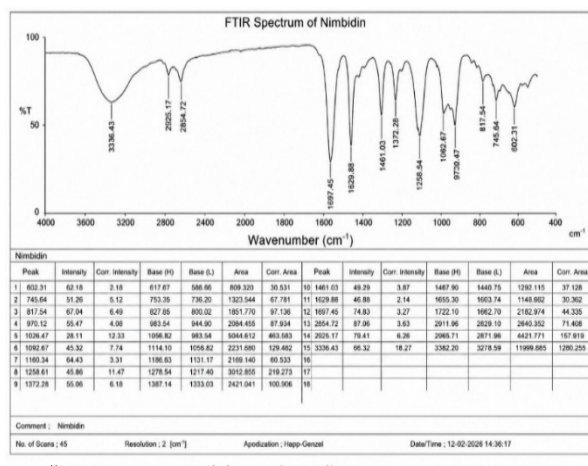


Fig 5 FTIR of Curcumin

6 FTIR of Nimbidin

Fig

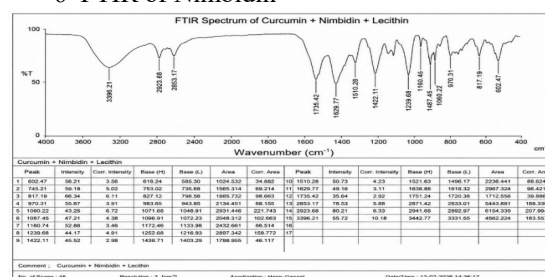
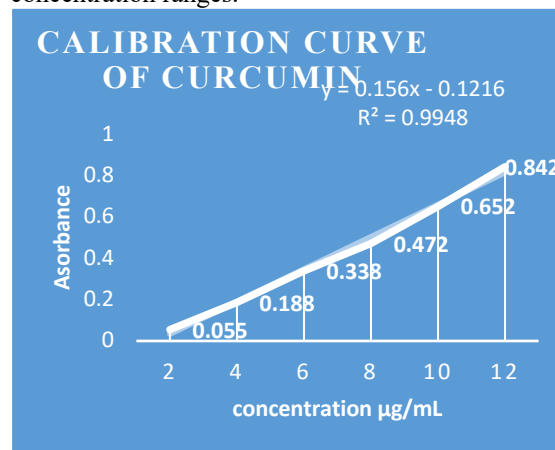


Fig 7 FTIR of Curcumin+Nimbidin+lecithin

Preparation of Standard Calibration Curves of Curcumin and Nimbidin

Standard calibration curves of Curcumin and Nimbidin were prepared using UV-Visible spectrophotometry by plotting absorbance against the respective drug concentrations. Both drugs showed good linearity over the selected concentration ranges.



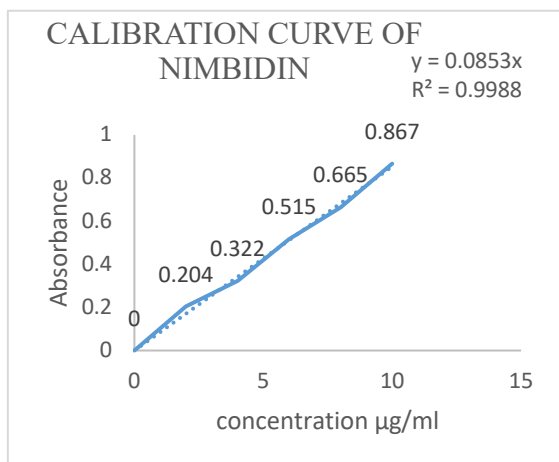


Fig 8 Calibration Curve of Curcumin
Fig 9 Calibration curve of Nimbidin

Drug	Slope(m)	Intercept (c)	Correlation coefficient (R ²)
Curcumin	0.0156	0.1216	0.9948
Nimbidin	0.0853	0	0.996

For Curcumin, the slope was **0.0156**, intercept **0.1216**, and R² **0.9948**. For Nimbidin, the slope was **0.0853**, intercept **0.0000**, and R² **0.9960**. The high R² values confirmed the good linearity and suitability of the method for quantitative estimation of both drugs.

Optical microscopy of ethosomal formulation (CN1-CN5)

Optical microscopy of formulations CN1–CN5 showed clearly formed vesicular structures, mainly spherical to almost spherical in morphology. The vesicles were evenly dispersed, although minor differences in size and spatial distribution were observed between the different formulations. These findings verify the successful development of Curcumin–Nimbidin-loaded ethosomes and indicate their potential applicability for topical drug delivery.

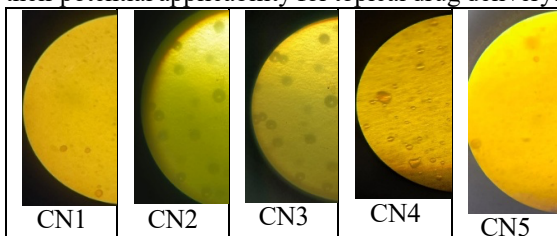


Fig: 10 Optical microscopy of ethosomal formulation (CN1-CN5)

Evaluation of Ethosomal Gel

Physical Description

The color, odor, homogeneity, and physical appearance of the Curcumin–Nimbidin ethosomal gel were assessed. There was no discernible phase separation or grittiness, and the formulation had a

smooth, uniform texture with a bright yellow color, indicating adequate physical stability.

pH Determination

The pH of the prepared ethosomal gel formulations was determined using a calibrated digital pH meter.

S.No	Formulations	Mean pH
1	CN1	6.03 ± 0.02
2	CN2	5.96 ± 0.04
3	CN3	6.23 ± 0.03
4	CN4	5.20 ± 0.03
5	CN5	6.53 ± 0.05

Table 1 pH of Ethosomal Gel

Viscosity

The flow characteristics of the Curcumin–Nimbidin ethosomal gels were assessed by measuring their viscosity with a Brookfield digital viscometer.

Table 2 Viscosity of ethosomal gel

S.No	Formulation	Viscosity (cps)
1.	CN1	1564.4 ± ± 12.4
2.	CN2	1355.6 ± ± 10.8
3.	CN3	1589.9 ± 13.1
4.	CN4	1646.9 ± 11.6
5.	CN5	1532.9 ± 12.0

Spreadability

The spreading ability of the formulated Curcumin–Nimbidin ethosomal gels was assessed using the slip-and-drag technique.

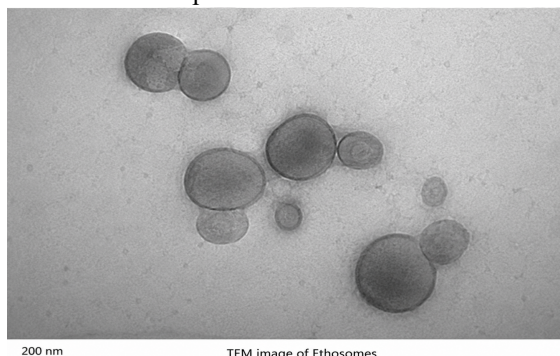
Table 3 Spreadability of ethosomal gel

S.No	Formulation	Spreadability(g.cm/sec)
1	CN1	15.8 ± 0.14
2	CN2	17.5 ± 0.16
3	CN3	16.7 ± 0.15
4	CN4	18.3 ± 0.13
5	CN5	15 ± 0.14

TEM of Ethosome

TEM characterization indicated the formation of predominantly spherical to nearly spherical vesicles, with particle dimensions in the range of

approximately 100–300 nm, supporting successful ethosomal development.



Vesicle size

The vesicle size of the formulations ranged from 178.5 ± 3.7 to 245.6 ± 4.8 nm, with CN4 showing the largest vesicle size.

Table 4 vesicle size

Formulation	Vesicle size (nm)
CN1	192.3 ± 3.9
CN2	228.4 ± 5.2
CN3	210.7 ± 4.6
CN4	245.6 ± 4.8
CN5	178.5 ± 3.7

Drug (%) Entrapment Efficiency

The entrapment efficiency of the prepared formulations was assessed using a UV–Visible spectrophotometer (Shimadzu UV-1800), and the values were compared across the respective batches.

Table 5 Drug Entrapment Efficiency (%) of Trial Batches

Serial number	Ethosome	
	Trial No.	% Drug Entrapment Efficiency
1	CN1	77.9 ± 0.28
2	CN2	79.8 ± 0.31
3	CN3	81.4 ± 0.27
4	CN4	82.6 ± 0.25
5	CN5	75.5 ± 0.33

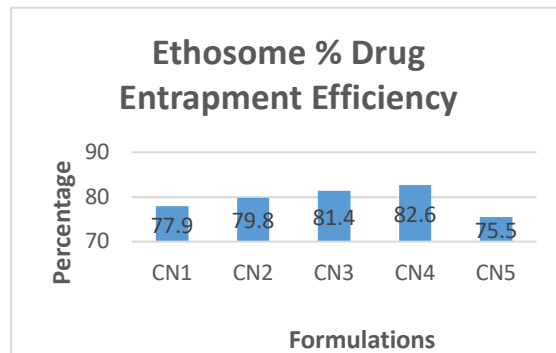


Fig: 11 Drug Entrapment Efficiency (%) of Ethosomal gel (CN1-CN5)

In Vitro Permeation Study of Curcumin and Nimbidin Loaded Ethosomal Gel

The in-vitro release profile of the Curcumin–Nimbidin-loaded ethosomal gel was studied using a locally fabricated Franz diffusion cell. Samples collected at specified time intervals were analyzed by UV–Visible spectrophotometry to determine drug release.



Fig: 12 Franz diffusion cell assembly utilized for monitoring the in-vitro drug release profile

Table 6 Percentage Drug Release Different Formulations of Curcumin

Time (min)	CN1	CN2	CN3	CN4	CN5
0	0	0	0	0	0
30	10.8	9.4	11.2	13.8	10.1
60	15.2	12.1	14	18.9	16
90	18	14.2	16.1	23.7	19.6
120	21.4	16.8	18.2	28.1	23
150	23.7	19	20.1	32.4	26
180	26.1	21.3	22	34.8	28.8
210	29	23.8	24.3	39.2	31.7
240	33.5	27.8	28.1	42.5	35.4

Table 7 Percentage Drug Release Different Formulations of Nimbidin

Time (min)	CN1	CN2	CN3	CN4	CN5
0	0	0	0	0	0
30	20.39 %	26.94 %	27.73 %	28.51 %	12.06 %
60	35.45 %	67.14 %	58.96 %	46.63 %	28.14 %
90	72.16 %	87.84 %	90.59 %	86.41 %	59.53 %
120	92.59 %	92.61 %	93.75 %	96.98 %	83.18 %

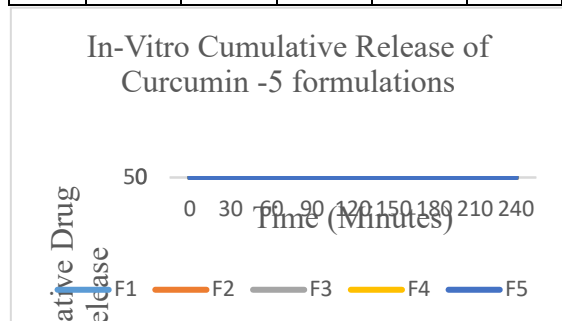


Fig: 13 In Vitro cumulative release of Curcumin

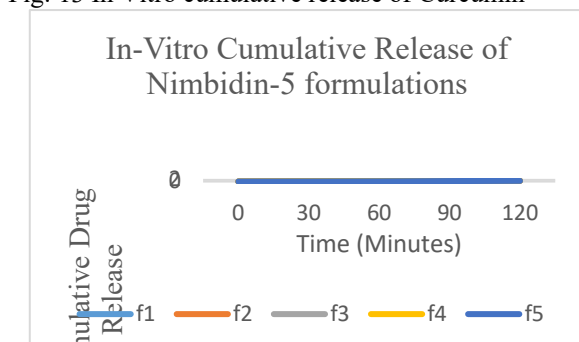


Fig: 14 In Vitro cumulative release of Nimbidin

Conclusion

The present investigation demonstrated the successful formulation of a Curcumin- and Nimbidin-loaded ethosomal gel intended for topical delivery in atopic dermatitis. The prepared ethosomes exhibited satisfactory vesicular characteristics, with particle sizes of 178.5 ± 3.7 – 245.6 ± 4.8 nm and entrapment efficiencies ranging from $75.5 \pm 0.33\%$ to $82.6 \pm 0.25\%$. TEM observations revealed predominantly spherical or nearly spherical vesicles, confirming effective vesicle formation.

The optimized ethosomal dispersion was successfully incorporated into a Carbopol 940 gel,

resulting in formulations with satisfactory physical appearance, pH, viscosity, and spreadability. Among all batches, CN4 was identified as the optimized formulation, showing the highest entrapment efficiency ($82.6 \pm 0.25\%$) and favourable topical characteristics. The in-vitro release study showed comparatively sustained release of Curcumin, with 85.73% drug release from CN4 at 240 min, while Nimbidin exhibited faster release, reaching 99.98% at 120 min.

Thus, the developed Curcumin–Nimbidin ethosomal gel, particularly CN4, demonstrated promising characteristics for topical drug delivery and may provide an effective approach for delivering herbal bioactive compounds in atopic dermatitis. Further ex vivo permeation, stability, irritation, and in-vivo studies are necessary to establish its therapeutic efficacy and long-term suitability.

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