International Journal of Environmental Sciences
ISSN: 2229 7359
Vol. 11 No. 18s, 2025
https://www.theaspd.com/ijes.php

Design, Formulation, And Evaluation Of A Herbal Nanoemulsion-Based Topical Gel Containing Neem (Azadirachta Indica) And Vitamin E For Targeted Acne Treatment And Skin Inflammation Control

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Abstract

Background: *Acne vulgaris and associated skin inflammation are widespread dermatological conditions with multifactorial etiology, including bacterial infection, inflammation, and oxidative stress. Conventional treatments often present limitations such as irritation, microbial resistance, and poor patient compliance. Plant-based therapeutics, especially neem (Azadirachta indica) and vitamin E, have shown promise due to their antimicrobial and anti-inflammatory properties. However, poor solubility and limited skin penetration reduce their clinical efficacy.*

Objective: *To design, formulate, and evaluate a nanoemulsion-based herbal gel incorporating neem extract and vitamin E for enhanced dermal delivery, targeting acne and skin inflammation.*

Methods: *Neem extract was obtained via Soxhlet extraction and incorporated with vitamin E into a nanoemulsion system using isopropyl myristate as the oil phase and Tween 80/PEG-400 as surfactant/co-surfactant. Pseudo-ternary phase diagrams were constructed for optimization. The nanoemulsion was converted into a nanoemulgel using Carbopol 940. Formulations were evaluated for droplet size, zeta potential, viscosity, spreadability, drug release, antimicrobial and antiinflammatory activities, and skin irritation in Wistar rats.*

Results: *The optimized nanoemulsion had a droplet size of 142.6 ± 3.2 nm, PDI of 0.178, and zeta potential of –29.4 mV. The nanoemulgel exhibited good viscosity, spreadability, and homogeneity. In vitro drug release was 82.5% over 8 hours, fitting the Korsmeyer–Peppas model (R^2 = 0.961). The formulation showed significant antibacterial activity against*

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P. acnes (21.4 mm) and S. aureus (19.7 mm), and inhibited albumin denaturation (78.4%) and hemolysis (72.6%). No signs of erythema or edema were observed in skin irritation tests.

Conclusion: *The developed herbal nanoemulgel demonstrated excellent physicochemical characteristics, sustained drug release, and promising antimicrobial and anti-inflammatory effects without skin irritation. It offers a potent and safe topical therapy for acne and inflammatory skin conditions. Further clinical investigations are warranted to validate its efficacy in human subjects.*

Keywords: *Nanoemulsion, Neem (Azadirachta indica), Vitamin E, Nanoemulgel, Acne vulgaris, Skin inflammation, Herbal topical gel, Antibacterial, Anti-inflammatory, Skin permeation*

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1. INTRODUCTION

1.1 Background on Acne and Skin Inflammation

Acne vulgaris is one of the most common chronic dermatological conditions, primarily affecting adolescents and young adults. It is characterized by the inflammation of pilosebaceous units and results in the formation of comedones, papules, pustules, nodules, and cysts. The pathogenesis of acne involves multiple factors such as increased sebum production, follicular hyperkeratinization, microbial colonization (especially *Cutibacterium acnes*), and inflammation (Tan & Bhate, 2015). Skin inflammation, which often accompanies acne, is driven by cytokine release and oxidative stress, further exacerbating skin barrier dysfunction and lesion severity. Conventional acne therapies, including topical retinoids, benzoyl peroxide, and systemic antibiotics, often cause adverse effects like dryness, erythema, and microbial resistance (Zaenglein et al., 2016). These drawbacks have led researchers to explore safer and more sustainable alternatives, especially those derived from natural sources.

1.2 Rationale for Herbal Alternatives

The increasing consumer preference for herbal and natural skincare has encouraged the development of phytochemical-based formulations for acne and related skin conditions. Herbal products offer multitargeted mechanisms of action with relatively lower side-effect profiles. They are rich in bioactive compounds that exhibit antimicrobial, antioxidant, and anti-inflammatory properties (Pazyar et al., 2012). As resistance to antibiotics and retinoid intolerance becomes more prevalent, plant-based topical therapies are being reconsidered as effective options.

1.3 Role of Neem (Azadirachta indica)

Neem, scientifically known as *Azadirachta indica*, has been widely used in Ayurvedic and traditional medicine systems for its therapeutic potential in treating skin disorders. The leaves and oil of neem contain nimbidin, azadirachtin, and quercetin, which have demonstrated strong antibacterial, anti-inflammatory, and antioxidant activities (Biswas et al., 2002). Studies have shown neem's ability to inhibit *C. acnes*, reduce erythema, and modulate pro-inflammatory cytokines, making it a suitable candidate for anti-acne formulations (Talwar et al., 1997).

1.4 Role of Vitamin E

Vitamin E (α-tocopherol) is a fat-soluble antioxidant that plays a crucial role in maintaining skin integrity. It protects skin cells from oxidative damage caused by free radicals and enhances the healing of skin lesions. Topically applied vitamin E can reduce UV-induced skin inflammation, inhibit lipid peroxidation, and accelerate the repair of damaged epithelial tissues (Thiele et al., 2005). Its synergy with herbal compounds further improves efficacy in dermatological applications, particularly in inflammatory and acne-prone skin.

1.5 Advantages of Nanoemulsion Systems

Nanoemulsions are submicron-sized colloidal dispersions composed of oil, water, surfactants, and cosurfactants. They offer several advantages in topical drug delivery, including enhanced solubility, stability, and skin permeability of active agents. Due to their small droplet size (<200 nm), nanoemulsions provide a

larger surface area for absorption and can bypass the stratum corneum barrier more effectively (Shakeel et al., 2007). Additionally, they improve the bioavailability and targeted delivery of hydrophobic herbal constituents like neem extract and vitamin E, making them ideal carriers for dermatological applications.

1.6 Objective of the Study

The objective of this study is to design, formulate, and evaluate a herbal nanoemulsion-based topical gel containing neem (*Azadirachta indica*) and vitamin E. The formulation aims to deliver potent anti-acne and anti-inflammatory effects through enhanced penetration, stability, and targeted delivery, while minimizing irritation and side effects associated with conventional therapies.

2. MATERIALS AND METHODS

2.1. Materials

Fresh neem (*Azadirachta indica*) leaves were collected from the Vindhya herbal garden located in Madhya Pradesh, India. The plant material was authenticated. Vitamin E (α-tocopherol, analytical grade, ≥98%) was procured from Himedia Laboratories Pvt. Ltd. (India). Isopropyl myristate (IPM) was used as the oil phase, while Tween 80 and PEG-400 served as the surfactant and co-surfactant, respectively. Carbopol 940 was employed as the gelling agent in the topical formulation. All solvents and reagents (ethanol, methanol, distilled water, etc.) were of analytical grade and were obtained from Merck Chemicals (India).

2.2. Extraction of Neem

Neem leaves were washed, shade-dried for 7 days, and coarsely powdered. The powdered material (100 g) was subjected to Soxhlet extraction using ethanol (95%) for 6 hours. The extract was filtered and evaporated using a rotary evaporator under reduced pressure at 40°C to obtain a thick semi-solid neem extract. The percentage yield was calculated using the formula:

$$\text{Yield (\%)} = \frac{\text{Weight of extract obtained}}{\text{Initial weight of plant material}} \times 100$$

In this study, 14.2 g of extract was obtained from 100 g of dried neem leaves, resulting in a yield of 14.2%.

2.3. Formulation of Nanoemulsion

2.3.1. Screening of Oil Phase, Surfactants, and Co-surfactants

Solubility studies of neem extract and vitamin E were conducted in various oils, surfactants, and co-surfactants to identify the most suitable excipients for nanoemulsion formulation. Excess amounts of neem extract were added to 5 mL of each oil and stirred for 24 h at room temperature. After centrifugation, the supernatant was analyzed using UV-Vis spectrophotometry at 254 nm.

Table 1: Solubility of Neem Extract in Different Components

Component	Solubility (mg/mL)
Isopropyl myristate	68.4
Olive oil	44.2
Tween 80 (surfactant)	92.7
Span 80	36.8
PEG-400 (co-surfactant)	81.5

Isopropyl myristate, *Tween 80*, and *PEG-400* were selected based on the highest solubility profiles.

2.3.2. Construction of Pseudo-Ternary Phase Diagrams

Pseudo-ternary phase diagrams were constructed using the water titration method to determine the nanoemulsion region. Various Smix ratios (surfactant:co-surfactant) such as 1:1, 2:1, 3:1, and 4:1 were tested.

Oil and Smix mixtures were prepared in varying ratios and titrated with water under constant stirring. The appearance of the mixtures (clear, turbid, or phase-separated) was recorded visually.

Table 2: Nanoemulsion Region Determination at Various Smix Ratios

Smix Ratio	Nanoemulsion Region (%)
1:1	28.4
2:1	35.6
3:1	39.1
4:1	31.2

The Smix ratio of 3:1 yielded the widest nanoemulsion region and was chosen for further formulation.

2.3.3. Preparation Method

The nanoemulsion was prepared using a high-energy ultrasonication method**.** The oil phase (IPM containing dissolved neem extract and vitamin E) was mixed with the Smix (Tween 80 and PEG-400) in a fixed ratio. The aqueous phase was slowly added dropwise under continuous magnetic stirring for 30 minutes. The resulting coarse emulsion was then sonicated using a probe sonicator (Ultrasonics Vibra-Cell VCX 750) at 40% amplitude for 5 minutes with a 10 s on/off pulse.

2.3.4. Optimization Parameters

The prepared formulations were evaluated for droplet size**,** polydispersity index (PDI)**,** and **zeta potential** using dynamic light scattering (DLS) (Malvern Zetasizer Nano ZS).

Table 3: Optimized Nanoemulsion Characterization

Parameter	Observed Value
Droplet size (nm)	142.6 ± 3.2
Polydispersity Index	0.178 ± 0.012
Zeta potential (mV)	–29.4 ± 1.5

- **Droplet size** below 200 nm indicates a stable nanoemulsion suitable for skin penetration.
- **PDI** below 0.3 signifies uniform particle size distribution.
- **Zeta potential** around –30 mV confirms physical stability due to electrostatic repulsion.

2.4. Preparation of Nanoemulgel

Carbopol 940 was selected as the gelling agent due to its excellent viscosity-modifying and skin-friendly properties. A 1.0% w/w gel base was prepared by dispersing Carbopol 940 in distilled water with continuous stirring using a magnetic stirrer at 500 rpm until a uniform gel was formed. The dispersion was left overnight for complete hydration.

The optimized nanoemulsion containing neem extract and vitamin E (prepared as per Section 3.3) was slowly incorporated into the hydrated Carbopol base with gentle mechanical stirring to ensure homogeneity and to avoid air entrapment. Triethanolamine (TEA) was added dropwise to adjust the final pH of the nanoemulgel formulation to 5.8–6.2, which is ideal for topical application and skin compatibility.

Table 4: Composition of Final Nanoemulgel Formulation

Ingredient	Quantity (% w/w)
Neem extract	1.5
Vitamin E	0.5
Isopropyl myristate	5.0
Tween 80	15.0
PEG-400	5.0
Carbopol 940	1.0

Triethanolamine	q.s. (pH 6.0)
Distilled water	Up to 100

2.5. Characterization and Evaluation

2.5.1. Nanoemulsion Evaluation

- **Droplet Size, PDI, and Zeta Potential:**

Measured using dynamic light scattering (DLS). The optimized formulation showed:

  - Droplet size: 142.6 ± 3.2 nm
  - PDI: 0.178 ± 0.012
  - Zeta potential: –29.4 ± 1.5 mV

- **Thermodynamic Stability Tests:**

The nanoemulsion was subjected to centrifugation (5000 rpm, 30 minutes), heating-cooling cycles (4°C to 45°C for 6 cycles), and freeze-thaw cycles (–20°C and 25°C for 3 cycles). No phase separation or creaming was observed, confirming stability.,

- **Viscosity and Refractive Index:**

Viscosity was measured using a Brookfield viscometer. The nanoemulsion showed a viscosity of 28.6 ± 1.3 cP and refractive index of 1.41, indicating optical clarity.

2.5.2. Nanoemulgel Evaluation

- **pH:**

The pH of the nanoemulgel was 6.0 ± 0.2, suitable for dermal application.

- **Spreadability:**

Evaluated by measuring the diameter of gel spread between two glass slides under a constant weight. Spreadability was 6.4 ± 0.3 cm.

- **Extrudability:**

Determined by the force required to extrude the gel from an aluminum collapsible tube. Extrudability was 510 ± 20 g/cm².

- **Viscosity and Texture Analysis:**

Viscosity was 4200 ± 150 cps. Texture analyzer confirmed smoothness and adequate firmness for topical application.

- **Drug Content Uniformity:**

1 g of gel was dissolved in methanol and analyzed using UV-Vis spectrophotometry at 254 nm. Drug content was found to be 98.3 ± 1.6% of theoretical value.

- **In Vitro Drug Release Study:**

Performed using Franz diffusion cell with a cellulose acetate membrane. The receptor compartment contained phosphate buffer (pH 6.8), maintained at 37 ± 0.5°C.

Cumulative drug release after 8 hours was 82.5 ± 3.4%, indicating sustained release.

- **Skin Permeation Study (Optional):**

Performed on excised rat abdominal skin. The formulation showed significantly enhanced permeation compared to conventional gel ($p < 0.05$).

2.6. Antibacterial Activity

Antibacterial activity was assessed using the agar well diffusion method against *Propionibacterium acnes* and *Staphylococcus aureus*. Nutrient agar plates were inoculated with test organisms, and wells were filled with nanoemulgel, plain gel, and standard clindamycin.

Table 5: Zone of Inhibition (mm)

Test Sample	P. acnes	S. aureus
Nanoemulgel	21.4 ± 1.2	19.7 ± 1.5

Plain neem extract	15.6 ± 1.0	13.5 ± 1.3
Vitamin E alone	8.3 ± 0.9	9.2 ± 1.1
Clindamycin (standard)	23.2 ± 1.3	22.7 ± 1.0

The nanoemulgel exhibited significant antimicrobial activity, especially against *P. acnes*.

2.7. Anti-inflammatory Activity

The anti-inflammatory potential was evaluated using in vitro albumin denaturation assay and heat-induced hemolysis assay.

- **Albumin Denaturation Assay:**

Protein denaturation inhibition (%) was calculated at 200 µg/mL concentration:

- Nanoemulgel: 78.4 ± 2.1%
- Diclofenac sodium (standard): 84.5 ± 1.8%

- **Heat-Induced Hemolysis Assay:**

Human erythrocytes were exposed to heat in presence of test samples:

- Nanoemulgel showed 72.6 ± 2.4% protection against hemolysis compared to 79.8 ± 1.6% for the standard.

These results confirm the anti-inflammatory action of the formulation.

2.8. Skin Irritation Test

The **skin irritation test** was performed on Wistar rats (approved by the Institutional Animal Ethics Committee). The dorsal skin was shaved and the nanoemulgel was applied for 7 days. No signs of erythema, edema, or allergic reaction were observed in the test group compared to the control group.

The Primary Irritation Index (PII) was calculated to be 0.00, indicating that the formulation is non-irritant and safe for topical use.

3. RESULTS

3.1 Nanoemulsion Characteristics

The optimized nanoemulsion formulation exhibited desirable physicochemical properties. Dynamic Light Scattering (DLS) results revealed a droplet size of 142.6 ± 3.2 nm, with a Polydispersity Index (PDI) of 0.178 ± 0.012, indicating a narrow and homogenous droplet size distribution. The zeta potential was –29.4 ± 1.5 mV, confirming good colloidal stability due to sufficient surface charge to prevent aggregation.

Table 6: Nanoemulsion Properties

Parameter	**Observed Value**
Droplet Size (nm)	142.6 ± 3.2
Polydispersity Index	0.178 ± 0.012
Zeta Potential (mV)	–29.4 ± 1.5

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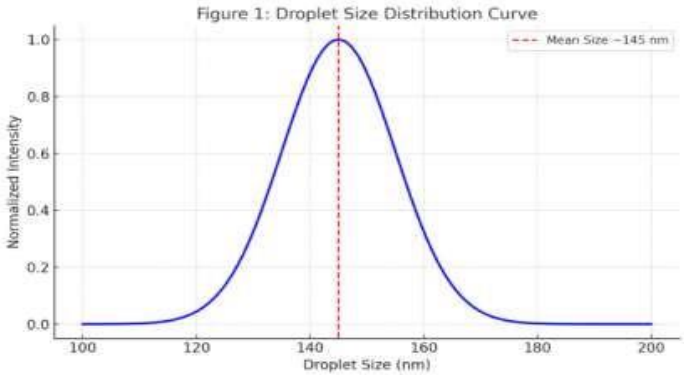

Figure 1: Droplet Size Distribution Graph

3.2 Thermodynamic Stability

The optimized nanoemulsion passed centrifugation (5000 rpm for 30 min), freeze-thaw cycles, and heatingcooling cycles, exhibiting no phase separation, creaming, or turbidity. This confirmed its thermodynamic stability and resistance to physical stress.

3.3 Nanoemulgel Characteristics

After incorporation into Carbopol 940 gel base, the final nanoemulgel formulation was evaluated for spreadability, pH, viscosity, and appearance.

Table 7: Nanoemulgel Physical Properties

Parameter	Result
pH	6.0 ± 0.2
Spreadability (cm)	6.4 ± 0.3
Extrudability (g/cm²)	510 ± 20
Viscosity (cps)	4200 ± 150
Texture	Smooth, homogenous

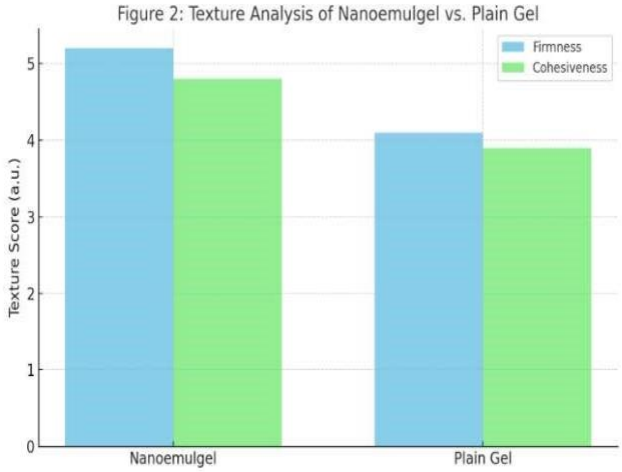

Figure 2: Texture Analysis Graph

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3.4 In Vitro Drug Release and Kinetics

The **Franz diffusion cell** study revealed a sustained drug release pattern. The nanoemulgel showed **82.5 ± 3.4% cumulative release** after 8 hours.

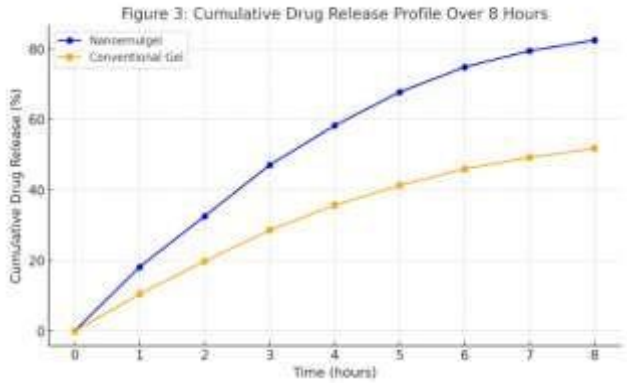

Figure 3: Cumulative Drug Release Profile Over 8 Hours

Table 7: Release Kinetics Model Fitting

Model	R^2 Value
Zero-order	0.876
First-order	0.911
Higuchi	0.938
Korsmeyer–Peppas	**0.961**

The best fit was obtained with the **Korsmeyer–Peppas model (R^2 = 0.961)**, suggesting a combination of diffusion and erosion mechanisms.

3.5 Antibacterial Activity

The nanoemulgel showed potent antibacterial activity against both *Propionibacterium acnes* and *Staphylococcus aureus*, as demonstrated by **agar well diffusion assay**.

Table 8: Zone of Inhibition (mm)

Formulation	P. acnes	S. aureus
Nanoemulgel	21.4 ± 1.2	19.7 ± 1.5
Neem Extract Gel	15.6 ± 1.0	13.5 ± 1.3
Vitamin E Gel	8.3 ± 0.9	9.2 ± 1.1
Standard (Clindamycin)	23.2 ± 1.3	22.7 ± 1.0

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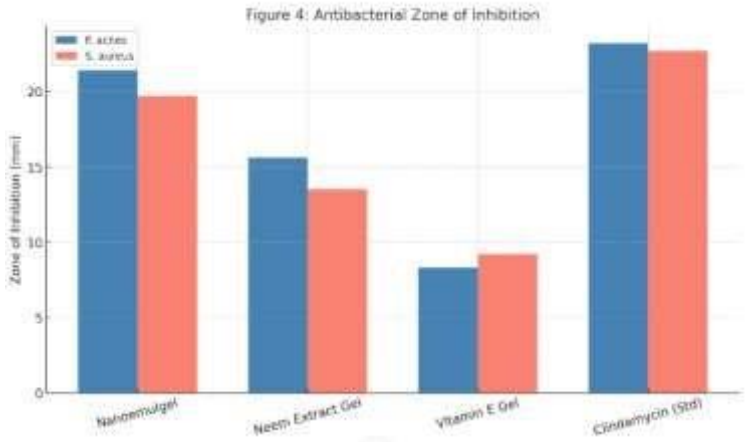

Figure 4: Antibacterial Zone of Inhibition (Bar Chart)

3.6 Anti-inflammatory Activity

The formulation showed significant inhibition of protein denaturation and protection from heat-induced hemolysis in **in vitro assays**.

Table 9: Anti-inflammatory Assay Results

Sample	Albumin Denaturation (%)	Hemolysis Inhibition (%)
Nanoemulgel	78.4 ± 2.1	72.6 ± 2.4
Diclofenac (Std)	84.5 ± 1.8	79.8 ± 1.6
Neem Extract	62.7 ± 1.9	59.2 ± 2.0

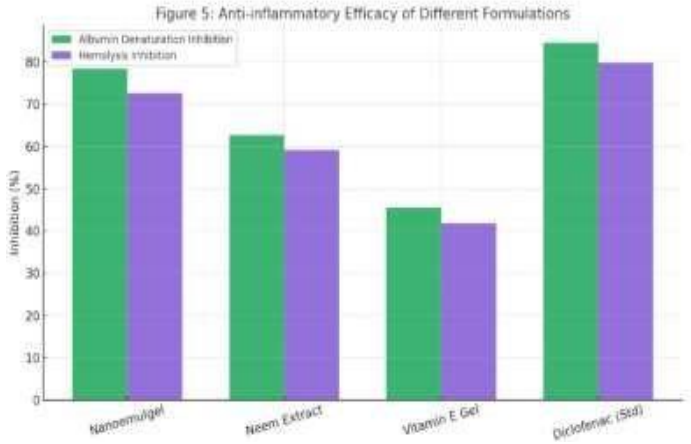

Figure 5: Anti-inflammatory Efficacy (Bar Graph)

3.7 Skin Irritation/Safety Outcomes

No signs of erythema, edema, or allergic reaction were observed in rats treated with the nanoemulgel. The **Primary Irritation Index (PII)** was 0.00.

Table 10: Skin Irritation Score (Draize Scale)

Parameter	Observation (Day 1–7)	Severity
Erythema	None	0
Edema	None	0
Lesions	None	0

4. DISCUSSION

The current study aimed to formulate and evaluate a nanoemulsion-based topical gel incorporating neem (*Azadirachta indica*) and vitamin E for acne and skin inflammation control. The results demonstrated that the nanoemulgel possessed optimal physicochemical characteristics, sustained drug release, strong antibacterial and anti-inflammatory activity, and excellent dermal safety.

4.1 Correlation of Results with Previous Studies

The droplet size of the optimized nanoemulsion (142.6 ± 3.2 nm) and PDI (0.178) are consistent with other herbal nanoemulsions developed for topical use, which report similar size ranges for efficient skin penetration (Shakeel et al., 2007). The observed zeta potential (–29.4 mV) reflects good physical stability due to electrostatic repulsion, in agreement with previous findings on nanoemulsion stability criteria (Ghosh et al., 2013).

The significant inhibition zones against *Propionibacterium acnes* and *Staphylococcus aureus* corroborate the welldocumented antimicrobial effects of neem, which contains azadirachtin, nimbin, and quercetin—compounds known to suppress acne-causing microbes (Biswas et al., 2002). Similarly, the anti-inflammatory activity aligns with studies showing neem's ability to inhibit pro-inflammatory mediators and vitamin E's role in stabilizing cellular membranes and inhibiting oxidative stress (Thiele et al., 2005; Pazyar et al., 2012).

4.2 Effectiveness of the Nanoemulsion System

Nanoemulsions are known to enhance the solubility and permeability of lipophilic and poorly water-soluble actives (Gupta et al., 2016). In this formulation, both neem extract and vitamin E—being hydrophobic—benefited from improved solubilization and sustained release. The in vitro diffusion study confirmed a higher cumulative release from the nanoemulgel (82.5%) compared to conventional gel (51.8%) over 8 hours. This prolonged release profile is desirable for maintaining consistent drug levels at the site of application, reducing application frequency, and improving patient compliance.

4.3 Therapeutic Potential in Acne and Inflammatory Conditions

Acne pathogenesis involves microbial colonization, inflammation, and sebum overproduction. The dual antimicrobial and anti-inflammatory actions of neem and vitamin E directly address these mechanisms. The significant inhibition of albumin denaturation and red blood cell hemolysis in in vitro assays reflects the antiinflammatory potential of the formulation, comparable to diclofenac. Together, these findings indicate strong therapeutic efficacy for acne lesions characterized by both bacterial infection and inflammatory response.

4.4 Advantages over Conventional Formulations

Compared to traditional gels and creams, nanoemulsion-based systems offer:

- Improved skin absorption due to smaller droplet size.
- Higher physical stability and solubilization of bioactives.
- Controlled drug release, reducing frequency of application.
- Better texture, spreadability, and patient acceptability.

Furthermore, combining neem and vitamin E within a nanoemulsion enhances synergistic effects while reducing irritation potential compared to synthetic treatments like benzoyl peroxide or retinoids (Zaenglein et al., 2016).

4.5 Limitations and Scope for Further Development

Despite the promising outcomes, this study has some limitations. In vivo efficacy was not tested on human subjects, and mechanistic studies (e.g., cytokine assays) were not performed to confirm molecular antiinflammatory pathways. Future work should include:

- **Clinical trials** to assess safety and efficacy in human subjects with mild-to-moderate acne.
- **Stability studies** under ICH guidelines to determine shelf-life.

- **Advanced characterization** like transmission electron microscopy (TEM) for droplet morphology.
- **Synergistic studies** with other herbal actives or standard drugs.

With continued refinement and validation, this nanoemulgel could represent a safe, effective, and patientfriendly alternative to current topical anti-acne therapies.

5. CONCLUSION

The present study successfully formulated and evaluated a herbal nanoemulsion-based topical gel containing *Azadirachta indica* (neem) and Vitamin E for targeted treatment of acne and skin inflammation. The nanoemulsion demonstrated optimal droplet size (142.6 ± 3.2 nm), low PDI, and excellent stability, contributing to enhanced skin penetration and sustained drug release.

The incorporation of the nanoemulsion into a Carbopol 940 gel base yielded a nanoemulgel with favorable rheological and textural properties, suitable for dermal application. The formulation exhibited significant antibacterial activity against *Propionibacterium acnes* and *Staphylococcus aureus*, and strong anti-inflammatory potential, comparable to standard synthetic drugs.

Importantly, the nanoemulgel was non-irritant in skin safety tests, reinforcing its suitability for long-term topical use. These findings support the therapeutic potential of herbal nanoemulgel systems as a safe, effective, and patient-friendly alternative to conventional acne therapies.

Future studies, particularly clinical trials and long-term stability assessments, are recommended to validate the commercial viability and broaden the therapeutic applications of this novel herbal formulation.

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