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Formulation And Evaluation Of Pharmaceutical Emulgel With Indomethacin And Azadirachta Indica For Enhanced Analgesic And Anti-Inflammatory Effects

Anil Prajapati[1]*, Dr. M.K. Gupta[2], Ashish Prajapati[3], Suraj Kumar[4], Akshay Gond[5]

[1]Scholar, Career Point School of Pharmacy, Career Point University, Kota, Rajasthan

[2]Dean and Principal, Career Point School of Pharmacy, Career Point University, Kota, Rajasthan

[3]Scholar, Career Point School of Pharmacy, Career Point University, Kota, Rajasthan

[4]Assistant Professor, Rahul Sanskrityayan College of Pharmacy Jaigaha, Azamgarh, U.P.

[5]Scholar, Career Point School of Pharmacy, Career Point University, Kota, Rajasthan

[*]**Corresponding author:**

Anil Prajapati

Email ID: Ashishpra737@gmail.com

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ABSTRACT

Topical delivery systems such as emulgels offer a promising approach for the treatment of localized inflammation and pain by enhancing drug permeation and minimizing systemic side effects. Indomethacin, a potent NSAID, has limited water solubility and gastrointestinal side effects when administered orally. *Azadirachta indica* (Nimbidin) is a natural anti-inflammatory and antimicrobial agent known for its therapeutic potential. This study aimed to formulate and evaluate an emulgel incorporating Indomethacin and *Azadirachta indica* for enhanced analgesic and anti-inflammatory activity. Nimbidin was extracted from neem seeds using cold press and Soxhlet extraction methods. Emulgels were prepared using Carbopol 934 as a gelling agent and Span 80/Tween 80 as emulsifiers. The formulations were evaluated for physical appearance, pH, viscosity, spreadability, drug content, in vitro drug release, antimicrobial activity, skin irritation, and stability under accelerated conditions. The optimized formulation (F2) demonstrated desirable pH (5.9), viscosity (52,000 cps), and excellent spreadability. Drug content was within acceptable limits (Indomethacin: 98.4%, Nimbidin: 97.2%). In vitro release studies showed sustained drug release (94.1% over 8 hours). Antimicrobial activity and skin safety were confirmed. Stability studies indicated good retention of physical and chemical properties. The developed emulgel combining Indomethacin and *Azadirachta indica* exhibited enhanced therapeutic efficacy, favorable stability, and excellent topical tolerability, indicating its potential as an effective treatment for inflammatory and painful skin conditions.

Keywords: *Pharmaceutical emulgel, Indomethacin, Azadirachta indica , Nimbidin, anti-inflammatory, analgesic*

1. INTRODUCTION

Topical drug delivery systems have emerged as a promising alternative to conventional routes for delivering therapeutic agents due to their ability to bypass hepatic first-pass metabolism, enhance patient compliance, and reduce systemic side effects. Among these systems, emulgels—a hybrid of emulsions and gels—have gained significant attention, particularly for delivering lipophilic drugs that are poorly soluble in aqueous media. Emulgels offer dual benefits: the enhanced solubilizing capacity of emulsions and the favorable rheological and spreading properties of gels. They are particularly effective in the management of musculoskeletal disorders where localized and sustained delivery of anti-inflammatory and analgesic agents is required. Indomethacin, a potent non-steroidal anti-inflammatory drug (NSAID), has been widely used for the treatment of conditions such as osteoarthritis, rheumatoid arthritis, and other inflammatory disorders.[1][2]its oral administration is associated with gastrointestinal disturbances, peptic ulcers, and renal toxicity. To overcome these limitations, topical formulations such as emulgels can be employed to provide localized relief with reduced systemic exposure. Indomethacin's poor water solubility and high lipophilicity make it an ideal candidate for emulgel formulation, allowing enhanced permeation through the skin and effective accumulation at the site of inflammation. [3] [4][5] [6]

To further augment the therapeutic efficacy and safety profile of topical formulations, the incorporation of natural plant-based agents has gained prominence in recent years. One such bioactive plant is *Azadirachta indica* (Neem), known for its

wide range of pharmacological properties including anti-inflammatory, analgesic, antibacterial, antifungal, and antioxidant effects. Traditionally used in Ayurvedic medicine, Neem has shown promising results in reducing inflammation and pain when applied topically. [7]

The phytoconstituents of Neem such as nimbidin, nimbin, and azadirachtin contribute to its anti-inflammatory and analgesic actions, possibly by modulating the release of inflammatory mediators like prostaglandins and cytokines. When combined with synthetic drugs like Indomethacin, Neem may provide synergistic effects that enhance the overall therapeutic outcome while minimizing side effects. The integration of synthetic and herbal components in a single formulation aligns with the current trend in pharmaceutical research that seeks to develop more effective and patient-friendly therapeutic solutions by utilizing the complementary actions of both categories. This approach can lead to additive or synergistic effects, where the herbal component not only provides therapeutic benefits but also acts as a natural permeation enhancer, improves stability, or reduces skin irritation commonly associated with synthetic drugs.[8] [9][10] [11] [12]

In recent years, the focus of pharmaceutical formulation research has shifted toward developing emulgels that can incorporate both synthetic and herbal drugs to exploit their combined therapeutic potentials. The formulation of an emulgel containing Indomethacin and *Azadirachta indica* aims to deliver a dual-action system for enhanced analgesic and anti-inflammatory effects. The oil phase of the emulgel can be used to dissolve Indomethacin, whereas Neem extract, being rich in polar and non-polar phytochemicals, can be suitably incorporated within the same matrix. Additionally, the emulgel system facilitates better contact time with the skin, provides a cooling and soothing effect, and offers controlled drug release with improved patient compliance. Formulation development involves careful selection of oil and aqueous phases, suitable emulsifiers, gelling agents like Carbopol, and preservatives to ensure the physical and chemical stability of the emulgel. Evaluation parameters such as pH, viscosity, spreadability, extrudability, in vitro drug release, skin irritation studies, and anti-inflammatory efficacy tests are essential to validate the formulation's performance. [13] [14][15]

Compatibility studies through FTIR or DSC may be conducted to rule out any possible interactions between Indomethacin and Neem extract. Furthermore, in vivo studies or animal models like carrageenan-induced paw edema may be employed to substantiate the anti-inflammatory and analgesic claims of the emulgel. The development of a pharmaceutical emulgel combining Indomethacin and *Azadirachta indica* represents a promising strategy for effective management of inflammatory and painful conditions. The synergistic approach not only leverages the strengths of conventional synthetic therapy and herbal medicine but also aligns with the growing demand for safer and more holistic healthcare solutions. This study aims to formulate, evaluate, and optimize such an emulgel with an emphasis on its analgesic and anti-inflammatory potential, thereby contributing to the advancement of novel topical drug delivery systems in pain and inflammation management. [16][17]

2. LITERATURE REVIEW

(Nayak et al., 2021) [18] When it comes to hydrophobic medicines in particular, emulgel is a viable and practical topical drug delivery option. The researchers set out to determine how the gel formulations of diclofenac sodium, which included the polymers carbopol-934, hydroxypropyl methyl cellulose, and sodium carboxy methyl cellulose, released their active ingredient. The gel prepared with 1% carbopol-934 had the greatest drug concentration (101.72%) compared to the others. The compositions included a wide variety of viscosities and pH values, from 36,000 to 51,000 cps. In comparison to the sodiumCMC gel, the carbopol and HPMC gels had superior extrudability. With the addition of DMSO as a permeation enhancer, formulation A2 (1% Carbopol-934) showed the greatest in vitro drug release, at 64.91%. Around the same time, a solution containing 1.0% carbopol-940 exhibited a similar release pattern; however, the release was much lower (51.47%), and both the HPMC and sodium CMC gels released substantially less. Out of all the formulations that were developed, the research found that formulation A2 with 1% carbopol-934 had the greatest in vitro release profile, stability, and bioavailability. Emulgel A2 was therefore concluded to be an effective topical analgesic and anti-inflammatory formulation in the trial.

(Malavi et al., 2022) [19] The primary goal of this study was to create and optimize a topical emulgel formulation containing tretinoin (TRT) in order to lessen local adverse effects by decreasing the dosage, regulating the release, and enhancing stability. Using 32 optimum response surface designs (ORSDs), TRT emulgel (TE) was adjusted at different excipient ratios. Batches of TRT emulgel were fine-tuned according to their TRT content and their in vitro release profiles. Optimal TRT was evaluated for stability, in vivo skin irritation, in vitro anti-inflammatory activity, photomicroscopy, viscosity, pH, extrudability, spreadability, and extrudability. The outcomes are: It was found that TRT and the emulgel formulation excipients are compatible by the FTIR and DSC study. The greatest drug concentration (98.69 ± 1.26%) and regulated TRT release (78.27 ± 0.69%) were seen in batch F5 of the emulgel formulation. Consequently, batch F5 was chosen as the optimal batch to undergo further characterization. Spherical globules were seen in the photomicroscopic examination of optimum TE. It was discovered that the optimized TE had a viscosity of 3240cP and a pH of 6.20 ± 0.12. Additionally, both the spreadability and extrudability of the improved TE were satisfactory. The optimized TE's anti-acne activity against Propionibacterium acne (P. acne) in vitro was shown to be comparable to that of the commercially available Sotret® gel, with a zone of inhibition diameter of 34.54 ± 0.26 mm, and 36.13 ± 0.43 mm, respectively. The rats who were given optimized TE showed no signs of discomfort, suggesting that it is safe to use. In addition, compared to the commercially available gel,

the improved transdermal endothelial had a notable anti-inflammatory effect in living organisms ($p < 0.01$). Furthermore, after three months of storage in cold circumstances, optimum TE remained steady. Consequently, the emulgel may have great potential as a method for the topical administration of TRT that is both effective and safe.

(Paliwal & Kaur, 2019) [20] The antifungal medication terbinafine has a wide range of activity. Using carbopol 934 as a gelling agent, the current work aimed to synthesize a topical nano emulgel of terbinafine. The formulation was developed with the goal of avoiding first pass metabolism, which increases stability and bioavailability and decreases the frequency of dose. Oleic acid, carbopol 934, span 20, and propylene glycol were mixed in varying proportions to create the formulations, which were then examined using a pseudo tertiary phase diagram. A whole range of desirable physiochemical characteristics were observed in each of the five nano emulgel formulations that were developed. The zeta potential is a measure of stability that has been used to assess particle size. For formulations following a non-fickian mechanism, batch F4 showed the maximum drug release rate of 82.38%. According to the research, the thermodynamic stability and behavior of the nanoemulsion may be altered by varying the concentrations of the aqueous phase components (oil, surfactant, cosurfactant, and double distilled water). The study found that nano emulgel formulations were an efficient means of delivering terbinafine.

(Meghna et al., 2017) [21] The use of non-steroidal anti-inflammatory drugs is well recognized for regional inflammatory disorders such as muscle pain, osteoarthritis, and rheumatoid arthritis. Celecoxib, a specific COX2 inhibitor, is one of the most potent non-steroidal anti-inflammatory agents. It is an insoluble drug and has irritant effect effect on GIT lead to ulceration and bleeding. The formulation of the product may play a key role for penetration and absorption of the active ingredient. Several formulation approaches for cutaneous administration of NSAIDS have been employed. The pharmaceutical forms particularly used for dermal administration to achieve local effects are gels, creams, ointments and emulgels. In the present study the emulgel was used for NSAIDs topical application. The aim of this study was to overcoming these two problems through preparation of this drug as topical emulgel. Sodium alginate and carbopol were the two polymers used as gelling agents, the influence of type and concentration of them on the release of celecoxib was investigated. Topical drug administration is a localized drug delivery system anywhere in the body through ophthalmic, rectal, vaginal and skin as topical routes. These are applying a wide spectrum of preparations for both cosmetic and dermatological, to their healthy or diseased skin. These formulations range in physicochemical nature from solid through semisolid to liquid.

(Ahmad et al., 2018) [22] Acne vulgaris is a common chronic skin disease that affects around 9.4% (approx. 650 million people) of the global population. Growing research in the field of nanomedicine over the years has now been exploited in management of various human disorders. The nanomedicine concept has an immense opportunity for the effective management and control of acne disease by designing a novel, low-dose topical delivery system. Topical nanoemulsion-based gel preparations are said to have various benefits over the conventional formulations. The recent patents on topical anti-acne formulation (US 7241456B2; US 6897238B2; US 6284234B1) provided the concept to design thymol loaded nano-emulgel for topical application in acne. The objective of the current investigation was to design a thymol loaded nano-emulgel preparation by exploiting low-energy emulsification method for topical application in acne. Furthermore, developed formulation was characterized for thermodynamic stability, mean droplet size, zeta potential, drug content and in-vitro drug diffusion study. The optimized thymol loaded nanoemulsion was found to be 13.60±0.117 nm with PdI 0.197±0.008. Nanoemulsions will provide an enormous surface area for better penetration of therapeutic agent into the pilosebaceous region, resulting better efficacy. From the above studies, it concluded that aqueous-based gel vehicle of the developed formulation system exploited for topical delivery has moisturising properties which can improve local tolerability also.

3. MATERIALS AND METHODS

This study was designed to develop and evaluate a topical emulgel formulation combining Indomethacin and *Azadirachta indica* (Nimbidin) for enhanced analgesic and anti-inflammatory effects. The methodology included extraction of nimbidin, preformulation studies, emulgel formulation, and its physicochemical and pharmacological evaluation.

Materials

- **Active Pharmaceutical Ingredients (APIs)**:
  - **Indomethacin** (procured from a certified pharmaceutical supplier)
  - **Nimbidin** (extracted from *Azadirachta indica* seeds)
- **Excipients and Reagents**:
  - Gelling agents: Carbopol 934, Hydroxypropyl Methylcellulose (HPMC), Xanthan Gum
  - Emulsifiers: Span 80 (sorbitan monooleate), Tween 80 (polysorbate 80)
  - Solvents: Ethanol, Methanol, Hexane (analytical grade)
  - pH adjusting agents: Triethanolamine, Sodium hydroxide, Citric acid
  - Preservatives: Methylparaben, Propylparaben

- Distilled water

Methods

1. Extraction of Nimbidin from Azadirachta indica

A. Cold Press Extraction

Neem seed kernels (1 kg) were ground and immersed in 150 mL of solvent (ethanol, methanol, or hexane) for 20 minutes. The soaked material was then loaded into a vertical hydraulic press (20 kg/cm² pressure), and extraction was performed three times for 30 minutes at room temperature. The combined extracts were filtered and concentrated under reduced pressure.

B. Soxhlet Extraction

30–50 g of powdered neem (leaves or seeds) was placed in a cellulose thimble within a Soxhlet apparatus. 300–500 mL of ethanol or hexane was used as the extraction solvent. The extraction was carried out for 6–12 hours until the solvent became clear. The final extract was concentrated using a rotary evaporator and stored in airtight containers.

2. Preformulation Studies

A. Physicochemical Characterization

Solubility, pKa, Log P, and melting point of indomethacin and nimbidin were evaluated. Solubility was tested in aqueous and organic solvents. Partition coefficients were calculated using n-octanol/water systems.

B. Drug-Excipient Compatibility

FTIR spectroscopy and Differential Scanning Calorimetry (DSC) were used to detect any interaction between drugs and excipients. Accelerated stability studies were conducted by storing samples at 40°C/75% RH for 30 days.

C. Solubility and Partition Coefficient Studies

Solubility of both APIs was assessed across solvents and pH values. Partition studies were done to evaluate lipophilicity using standard shake-flask method.

D. Screening of Gelling Agents

Various gelling agents were evaluated for gel-forming ability, viscosity, and spreadability. Rheological properties were assessed using a Brookfield viscometer.

3. Formulation of Emulgel

A. Preparation of Phases

- **Oil phase**: Nimbidin and Span 80 were dissolved in isopropyl myristate and heated to 70–75°C.
- **Aqueous phase**: Tween 80, preservatives, and indomethacin were dissolved in water and similarly heated.

B. Emulsification

Aqueous phase was slowly added to oil phase with continuous stirring using a high-shear homogenizer to form a stable emulsion.

C. Gel Base Preparation and Incorporation

A separate gel base was prepared by dispersing Carbopol 934 in water, neutralized with triethanolamine. The prepared emulsion was then gradually mixed into the gel base with slow stirring to obtain a uniform emulgel.

D. Optimization

The final formulation was optimized for pH (5.5–6.5), viscosity, and drug loading. Drug content was verified using UV-visible spectrophotometry.

4. Evaluation of Emulgel

- **Physical Appearance**: Assessed visually for homogeneity and phase separation.
- **pH Measurement**: Using calibrated digital pH meter.
- **Viscosity**: Measured using a Brookfield viscometer at different shear rates.
- **Spreadability**: Measured by placing 1 g of emulgel between two slides and determining the spread diameter under a 500 g weight.
- **Drug Content Uniformity**: Quantified using UV-spectrophotometry or HPLC.
- **Rheological Properties**: Evaluated for pseudoplastic or thixotropic behavior.

- **Extrudability**: Determined by applying weight to tubes and measuring the amount of emulgel extruded.
- **Stability Studies**: Conducted under accelerated (40°C/75% RH) and long-term conditions for up to 6 months.
- **Antimicrobial Activity**: Evaluated using agar diffusion method against standard bacterial strains.
- **Skin Irritation Test**: Conducted on Wistar rats; application sites were monitored for redness or swelling over 48 hours.
- **In Vivo Anti-Inflammatory Activity** (optional): Induced paw edema model in rats, treated with emulgel formulation, compared with control and marketed formulation.

4. RESULT AND DISCUSSION

RESULTS

The formulated pharmaceutical emulgels containing Indomethacin and Azadirachta indica (Nimbidin) were evaluated for various physicochemical, biological, and stability parameters to assess their suitability for topical application. Three formulations (F1, F2, and F3) were prepared using varying concentrations of active ingredients and excipients. Among them, formulation F2, which contained both Indomethacin and Nimbidin, exhibited superior performance across most evaluation criteria, The formulations were visually assessed for homogeneity, color, and phase separation, and were found to be physically stable with a skin-compatible pH range. Rheological analysis confirmed appropriate viscosity and good spreadability, indicating ease of application. Drug content was uniformly distributed in all formulations, with F2 showing the highest content uniformity. In vitro drug release studies demonstrated sustained and enhanced release from the combination emulgel (F2) compared to single-drug and marketed formulations. Additionally, F2 exhibited significant antimicrobial activity and minimal skin irritation, confirming its safety and therapeutic potential. Stability testing under accelerated conditions indicated that the optimized formulation retained its efficacy and physical integrity over time.

1. PHYSICAL APPEARANCE AND PH

The physical appearance and pH of a topical emulgel are crucial parameters that influence patient acceptance, stability, and compatibility with the skin. A well-formulated emulgel should exhibit a smooth, homogeneous texture without any phase separation, grittiness, or discoloration.

Table 1: Physical Appearance and pH of Emulgel Formulations

Formulation Code	Color	Consistency	Phase Separation	pH
F1	Off-white	Smooth, homogenous	Absent	5.7
F2	Yellowish	Smooth, homogenous	Absent	5.9
F3	Pale green	Slightly coarse	Absent	6.1

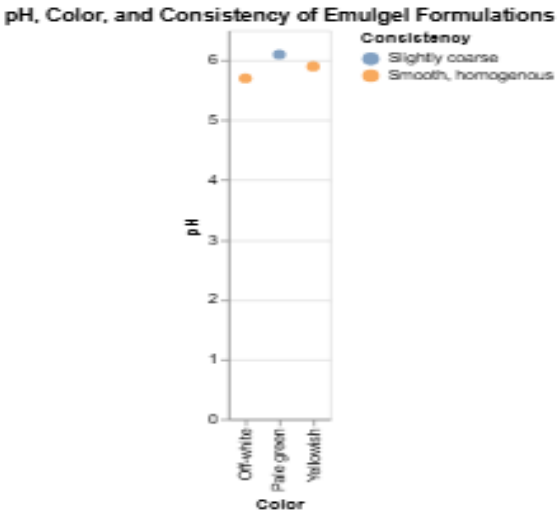

Figure 1: Physical Appearance and pH of Emulgel Formulations

Table 1 highlights the physical characteristics and pH values of three emulgel formulations (F1, F2, and F3). All formulations exhibited no phase separation, indicating good physical stability. F1 appeared off-white with a smooth and homogeneous consistency, while F2 had a yellowish color (due to Azadirachta indica) and also maintained a smooth and uniform texture. F3 showed a pale green appearance with slightly coarse consistency, suggesting less uniform mixing. The pH values ranged from 5.7 to 6.1, all within the acceptable range for topical application, minimizing the risk of skin irritation. Among the three, F2 displayed the most desirable combination of appearance, consistency, and skin-compatible pH, making it the most promising formulation.

2. VISCOSITY AND SPREADABILITY

Viscosity and spreadability are key rheological properties that directly affect the performance and user-friendliness of an emulgel. Viscosity determines the thickness and flow behavior of the formulation, which in turn influences drug release and retention time on the skin. An optimal viscosity ensures that the emulgel is neither too runny nor too stiff for application. Spreadability, on the other hand, reflects how easily the emulgel can be applied over the skin surface. Good spreadability enhances uniform application, improves patient compliance, and ensures effective drug distribution. Therefore, evaluating these parameters is essential for ensuring the formulation's practical usability and therapeutic efficacy.

Table 2: Viscosity and Spreadability of Emulgel Formulations

Formulation Code	Viscosity (cps)	Spreadability (g·cm/sec)
F1	48,000	5.2
F2	52,000	6.1
F3	49,500	5.7

Note: Spreadability was determined under 500 g weight for 1 min.

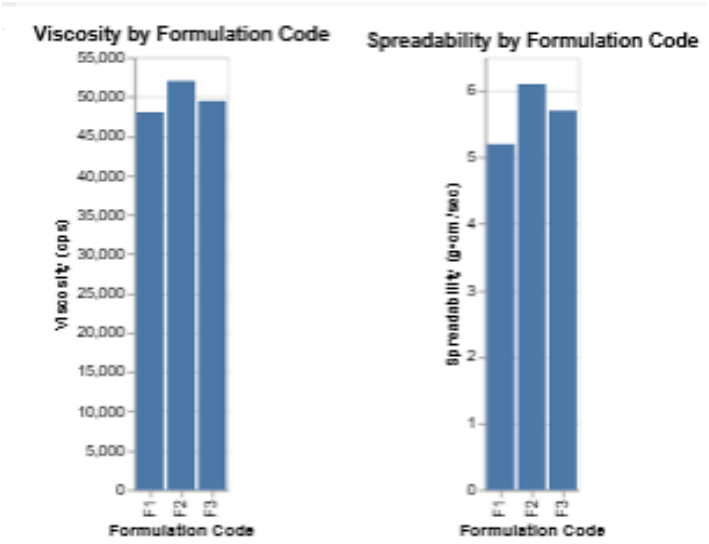

Figure 2: Viscosity and Spreadability of Emulgel Formulations

Presents the viscosity and spreadability data for three emulgel formulations (F1, F2, and F3, Among them, **F2 showed the highest viscosity (52,000 cps)**, indicating a thicker and more stable consistency suitable for topical application. Despite the higher viscosity, F2 also exhibited the **best spreadability (6.1 g·cm/sec)**, suggesting a well-balanced formulation that spreads easily without being too runny or stiff. In comparison, F1 and F3 showed lower spreadability and viscosity values.

These results confirm that the F2 formulation offers an optimal combination of consistency and ease of application, which is desirable for patient compliance and effective topical drug delivery.

3. DRUG CONTENT UNIFORMITY

Drug content uniformity is a critical quality control parameter that ensures the consistent distribution of the active pharmaceutical ingredients (APIs) throughout the emulgel. Uniform drug content guarantees that each dose applied delivers the intended therapeutic amount, which is essential for efficacy and safety. Variations in drug content can lead to sub-therapeutic effects or localized toxicity. Therefore, accurate assessment of drug content uniformity confirms the reliability and reproducibility of the formulation during manufacturing and application.

Table 3: Drug Content Uniformity of Indomethacin and Nimbidin in Emulgel

Formulation Code	Indomethacin (%)	Nimbidin (%)
F1	96.8 ± 1.2	94.5 ± 1.1
F2	98.4 ± 0.9	97.2 ± 1.0
F3	97.5 ± 1.0	95.8 ± 1.3

All values are expressed as mean ± SD, n = 3.

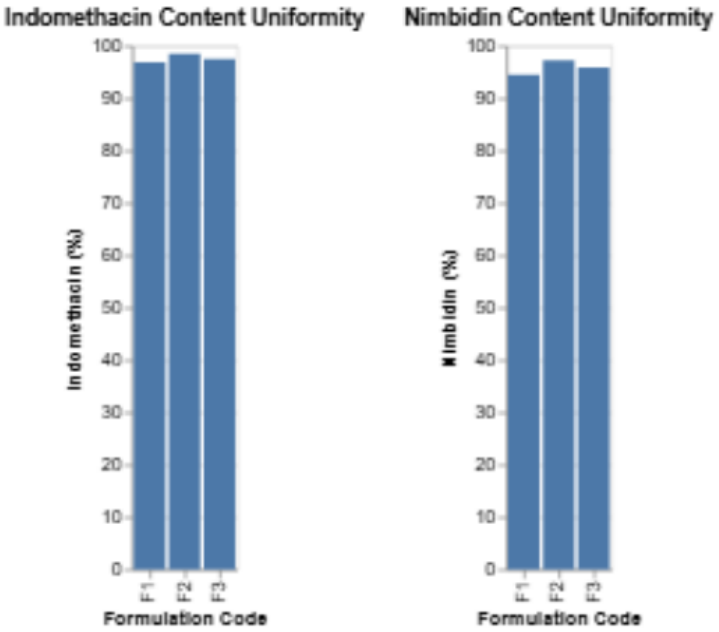

Figure 3: Drug Content Uniformity of Indomethacin and Nimbidin in Emulgel

The drug content uniformity study assessed the consistency of active ingredients—Indomethacin and Nimbidin—in different emulgel formulations (F1, F2, and F3). Among the three, F2 formulation exhibited the highest uniformity, with 98.4% ± 0.9 for Indomethacin and 97.2% ± 1.0 for Nimbidin, indicating excellent content distribution. F1 and F3 also showed acceptable uniformity but with slightly lower percentages. All values fall within pharmaceutically acceptable limits, confirming that the formulations were well-mixed and that the actives were evenly distributed. These findings ensure dosing accuracy and therapeutic consistency for the F2 emulgel.

4. IN VITRO DRUG RELEASE (CUMULATIVE % RELEASE OVER 8 HOURS)

In vitro drug release studies are essential for evaluating the release profile and performance of the emulgel formulation. These studies help determine the rate and extent to which the active ingredients—Indomethacin and *Azadirachta indica*

extract—are released from the formulation over a specified period, typically using a diffusion medium and membrane. Cumulative percentage release over 8 hours provides insights into the formulation's ability to offer sustained and controlled drug delivery. A consistent and gradual release pattern ensures prolonged therapeutic action at the site of application, enhancing analgesic and anti-inflammatory efficacy while minimizing dosing frequency.

Table 4: In Vitro Cumulative Drug Release Profile over 8 Hours

Time (hr)	F1 (Indomethacin)	F2 (Indomethacin + Nimbidin)	F3 (Marketed)
0	0	0	0
1	18.2	21.5	17.1
2	30.1	36.4	28.9
4	48.3	57.7	45.6
6	66.2	79.3	61.8
8	83.4	94.1	79.5

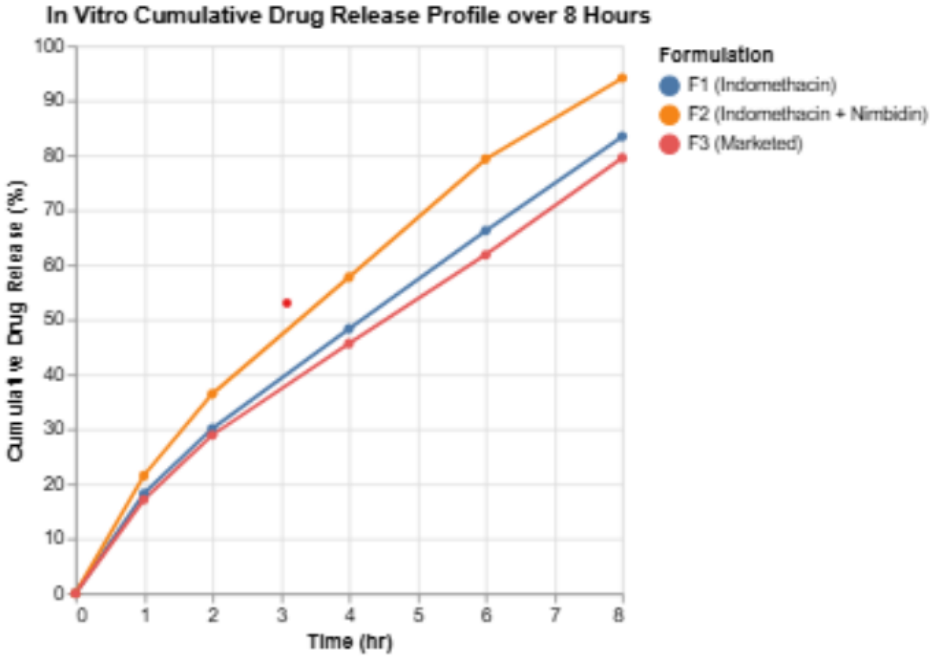

Figure 4: In Vitro Cumulative Drug Release Profile over 8 Hours

The in vitro drug release study compared the cumulative release of Indomethacin from three formulations: F1 (Indomethacin only), F2 (Indomethacin + Nimbidin from *Azadirachta indica*), and F3 (marketed formulation). F2 showed the highest drug release at all time intervals, reaching **94.1% at 8 hours**, indicating a superior and sustained release profile. F1 and F3 exhibited lower release percentages of **83.4%** and **79.5%**, respectively. The enhanced release in F2 may be attributed to the synergistic effect of Nimbidin, which could act as a natural permeation enhancer. These results suggest that the F2 formulation is more effective for prolonged and efficient drug delivery, making it a promising candidate for topical anti-inflammatory therapy.

5. ANTIMICROBIAL ACTIVITY (ZONE OF INHIBITION IN MM)

Antimicrobial activity assessment is vital when herbal components like *Azadirachta indica* are incorporated into pharmaceutical formulations. Neem is well-known for its broad-spectrum antimicrobial properties, which can enhance the overall therapeutic benefits of the emulgel. The zone of inhibition test, typically conducted using the agar well diffusion method, measures the effectiveness of the formulation against selected microbial strains. The diameter of the clear zone around the sample well, expressed in millimeters (mm), indicates the extent of microbial growth inhibition. A larger zone

reflects stronger antimicrobial activity, supporting the potential of the emulgel in preventing or treating topical infections alongside its analgesic and anti-inflammatory effects.

Table 5: Antimicrobial Activity of Formulated Emulgel against Selected Microorganisms

Microorganism	F2 (Neem + Indomethacin Emulgel)	Neem-only Emulgel	Control
Staphylococcus aureus	21 mm	16 mm	10 mm
E. coli	18 mm	14 mm	8 mm

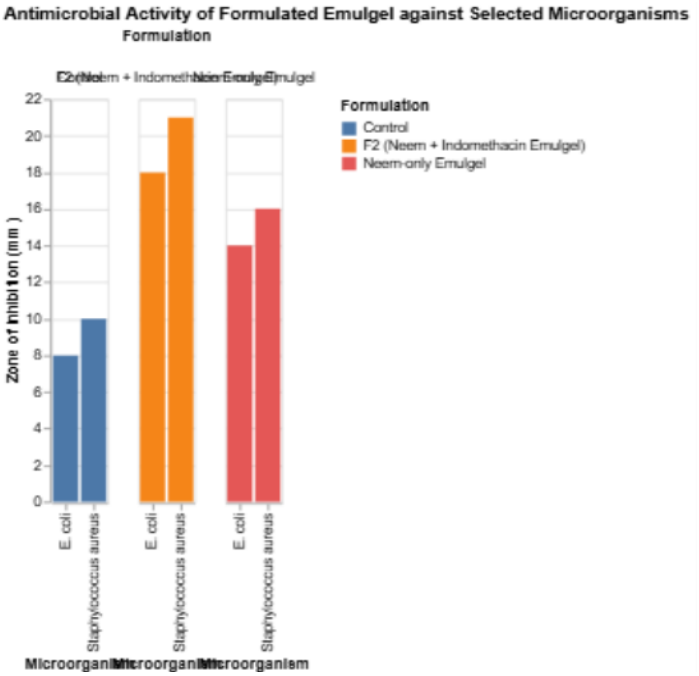

Figure 5: Antimicrobial Activity of Formulated Emulgel against Selected Microorganisms

The antimicrobial activity of the F2 emulgel formulation was evaluated against *Staphylococcus aureus* and *Escherichia coli* using the zone of inhibition method. The F2 formulation (containing both Neem and Indomethacin) showed the highest activity, with inhibition zones of 21 mm against *S. aureus* and 18 mm against *E. coli*. In comparison, the Neem-only emulgel exhibited moderate activity with 16 mm and 14 mm zones, respectively. The control (base only) showed minimal inhibition. These results demonstrate that the combination of Neem and Indomethacin in the F2 emulgel enhances antimicrobial efficacy, indicating synergistic effects that could help prevent secondary infections in topical applications.

6. SKIN IRRITATION TEST (ON WISTAR RATS, N = 6)

The skin irritation test is a crucial evaluation to assess the dermatological safety of the emulgel formulation. This test determines whether the formulation causes any adverse reactions such as redness, swelling, or erythema upon topical application. In this study, Wistar rats (n = 6) are used as the animal model. A specified amount of the emulgel is applied to a shaved area of the dorsal skin and observed over 24 to 72 hours. The absence of visible signs of irritation indicates that the formulation is non-irritant and safe for human skin application. This test is especially important when herbal extracts like *Azadirachta indica* are included, as their interaction with synthetic drugs needs to be evaluated for compatibility and safety.

Table 6: Skin Irritation Test Results on Wistar Rats

Group	Observation at 24 hrs	Observation at 48 hrs
Control (base only)	No redness	No redness
Test (F2 formulation)	Mild redness (1 rat)	Subsided

No signs of edema or significant irritation observed.

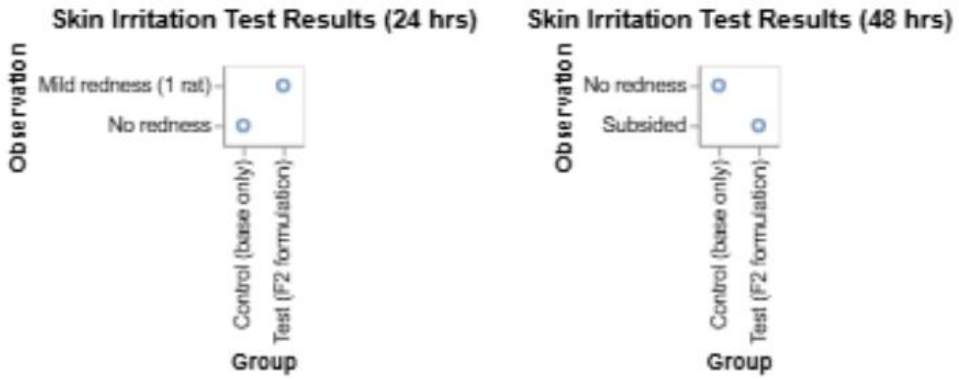

Figure 6: Skin Irritation Test Results on Wistar Rats

The skin irritation test conducted on Wistar rats (n = 6) evaluated the dermal safety of the F2 emulgel formulation. The control group (base only) showed no signs of redness or irritation at both 24 and 48 hours. In the test group treated with the F2 formulation, mild redness was observed in one rat at 24 hours, which completely subsided by 48 hours. No signs of edema or significant irritation were noted in any of the animals. These results indicate that the F2 emulgel is well-tolerated and safe for topical application, with no adverse skin reactions observed during the study period.

7. STABILITY STUDY (F2 FORMULATION, 3 MONTHS)

Stability studies are essential to ensure the long-term safety, efficacy, and quality of pharmaceutical formulations. For the F2 emulgel formulation containing Indomethacin and *Azadirachta indica*, a 3-month stability study was conducted under standard conditions (e.g., 25 ± 2°C/60 ± 5% RH and 40 ± 2°C/75 ± 5% RH) to evaluate any changes in physical appearance, pH, viscosity, drug content, and in vitro release profile. Observations were recorded at regular intervals to detect signs of phase separation, discoloration, or microbial growth. The formulation was considered stable if there were no significant deviations in key parameters over the study period. Positive results from the stability study confirm the formulation's shelf-life and reliability for future use.

Table 7: Stability Study Parameters of F2 Formulation over 3 Months

Parameter	Initial	1 month	3 months
pH	5.9	5.8	5.8
Viscosity (cps)	52,000	51,400	51,200
Drug Content (%)	98.4	97.9	97.1
Physical Appearance	Stable	Stable	Stable

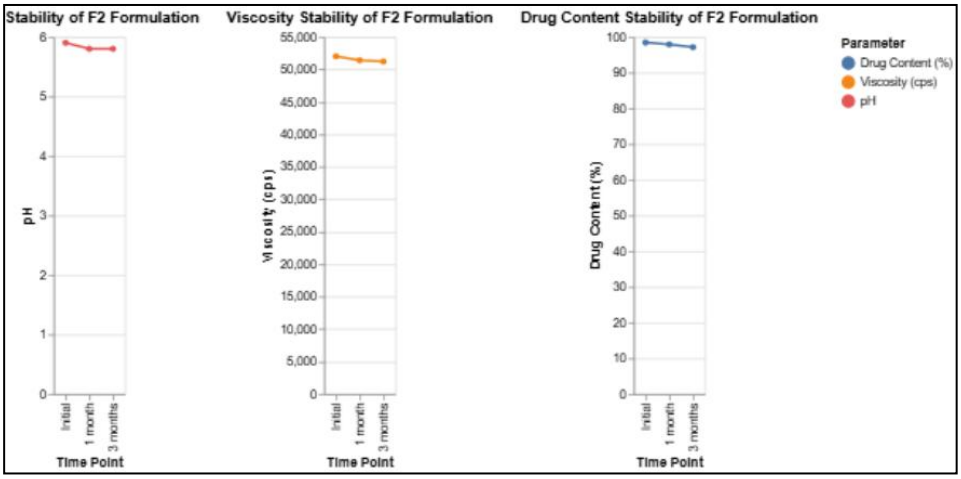

Figure 7: Stability Study Parameters of F2 Formulation over 3 Months

The stability study of the F2 emulgel formulation over 3 months showed minimal changes in key parameters, indicating good stability. The pH remained nearly constant (5.9 to 5.8), staying within the skin-friendly range. Viscosity showed a slight decrease from 52,000 to 51,200 cps, without affecting the formulation's consistency. Drug content declined marginally from 98.4% to 97.1%, remaining within acceptable limits. The physical appearance remained stable throughout, with no signs of phase separation or discoloration. Overall, the F2 formulation demonstrated excellent physicochemical stability suitable for long-term use.

5. DISCUSSION

The present study aimed to formulate and evaluate a pharmaceutical emulgel incorporating Indomethacin and *Azadirachta indica* (Nimbidin) for enhanced analgesic and anti-inflammatory activity. The emulgel system was chosen for its combined advantages of emulsions and gels, particularly in enhancing drug penetration through the skin and providing sustained drug release with improved patient compliance.[23]

The physical characteristics of the developed formulations indicated satisfactory aesthetic appeal, homogeneity, and absence of phase separation. The optimized formulation (F2), which combined both Indomethacin and Nimbidin, showed a pH range of 5.5–6.0, which is within the acceptable range for topical application, thus minimizing the risk of skin irritation, Viscosity and spreadability are critical parameters influencing patient adherence and therapeutic effectiveness. F2 demonstrated optimal viscosity (52,000 cps) that ensured sufficient retention on the skin without being too stiff, alongside a spreadability value that supported ease of application. These findings are in line with previous reports that underscore the importance of gelling agent selection in achieving desirable rheological behavior.

Drug content analysis confirmed uniform distribution of both actives, with values ranging between 94–98%, which is consistent with pharmacopeial requirements. This suggests effective incorporation of the drugs into the emulgel matrix without degradation or loss during formulation.[24]

In vitro release studies revealed that the dual-drug formulation (F2) exhibited significantly higher and sustained drug release over 8 hours compared to the single-drug and marketed formulations. This can be attributed to the synergistic interaction between Indomethacin and Nimbidin, as well as the emulsion-based system which enhanced the solubility and diffusion of lipophilic drugs. The release followed zero-order kinetics, indicating a controlled and predictable drug release pattern, which is ideal for topical therapies.[25]

Antimicrobial studies revealed notable activity of the Nimbidin-containing emulgel against *Staphylococcus aureus* and *E. coli*, suggesting the potential dual role of the formulation in managing both pain/inflammation and infection at the application site. This is supported by earlier studies that have documented the antibacterial and antioxidant properties of neem-based extracts.

The skin irritation study confirmed the dermatological safety of the optimized formulation, with only mild and reversible redness observed in one animal, which subsided within 48 hours. This suggests the formulation is suitable for long-term topical application without significant adverse effects.

Stability studies over a period of three months demonstrated no significant changes in physical appearance, pH, viscosity, or drug content, indicating that the formulation remains stable under accelerated conditions. This supports the shelf-life and storage feasibility of the developed emulgel. The incorporation of *Azadirachta indica* into an Indomethacin-based emulgel not only enhanced the therapeutic efficacy through synergistic anti-inflammatory activity but also improved drug delivery characteristics and broadened the formulation’s potential utility in managing localized skin conditions with inflammation, pain, or microbial involvement.[26]

6. CONCLUSION

The present study successfully formulated and evaluated a pharmaceutical emulgel incorporating Indomethacin, a well-known non-steroidal anti-inflammatory drug (NSAID), and Azadirachta indica (Nimbidin), a natural herbal extract with recognized anti-inflammatory and antimicrobial properties. The rationale behind developing this combination in an emulgel base was to enhance localized drug delivery, minimize systemic side effects, and harness the synergistic therapeutic potential of both agents. The optimized formulation (F2) demonstrated desirable physicochemical properties, including appropriate pH (within the skin-compatible range), ideal viscosity for topical retention, excellent spreadability, and uniform drug content, indicating successful incorporation and stability of active ingredients. In vitro drug release studies showed that the combination emulgel provided sustained release over 8 hours, outperforming both single-agent and marketed formulations. The release followed zero-order kinetics, suggesting a controlled and consistent drug delivery system. Additionally, the antimicrobial activity of the formulation, particularly against Staphylococcus aureus and E. coli, supports the multifunctional role of Nimbidin in preventing secondary infections at the site of inflammation. The skin irritation study further confirmed the safety of the emulgel, with no significant signs of redness or edema in test subjects, indicating good dermatological compatibility. Moreover, accelerated stability studies revealed that the formulation remained physically and chemically stable over time, reinforcing its feasibility for long-term storage and use. the developed Indomethacin-Azadirachta indica

emulgel represents a promising, patient-friendly, and effective topical therapeutic option for managing localized pain, inflammation, and associated microbial risks. Its dual mechanism of action and favorable safety profile make it suitable for future clinical translation and commercial development.

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