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Original Research Article

Formulation and Comparative Evaluation of Naproxen-Based Transdermal Gels

Pratham Vinod Purohit[1], Pratik Shivnarayan Pakhar[1], Vitthal Bhikaji Pawar[1], Shubhangi Santosh Dandade[1], Manisha Sanjay Waghmare[1], Faisal A. Shaikh[2,*], R. H. Kale[3]

[1]Department of Pharmaceutics, PRMSS, Anuradha College of Pharmacy, Chikhli, Maharashtra, India
[2]Department of Pharmaceutical Chemistry, PRMSS, Anuradha College of Pharmacy, Chikhli, Maharashtra, India
[3]Department of Pharmacognosy, PRMSS, Anuradha College of Pharmacy, Chikhli, Maharashtra, India

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ABSTRACT

This research focused on formulating and evaluating transdermal gel formulations containing naproxen, aiming to offer a more tolerable and user-friendly alternative to oral non-steroidal anti-inflammatory drug (NSAID) therapy. Oral administration of naproxen is often associated with gastrointestinal irritation, systemic side effects, and poor patient compliance due to the need for frequent dosing. To address these limitations, six different gel formulations (F1–F6) were prepared using varying concentrations of Carbopol 940 as the base polymer, along with two skin penetration enhancers: propylene glycol and oleic acid. The gels were assessed for their physicochemical properties, including pH, viscosity, spreadability, drug content uniformity, and the drug release profile using a Franz diffusion cell setup. Among the formulations, F4—containing 15% propylene glycol—exhibited the most favourable characteristics. It demonstrated excellent spreadability (70 cm), a smooth application texture, skin-friendly pH (6.8), and high drug content uniformity (97.50%). Additionally, F4 enabled sustained release of naproxen over an 8-hour period, following the Higuchi kinetic model (R^2 = 0.98). It also remained stable under accelerated storage conditions and dried within 3 minutes, enhancing user comfort and convenience. Potential issues such as drug crystallization, component incompatibilities, and oxidative degradation were effectively managed using specific stabilization techniques. Compared to oral delivery, the transdermal gel provided comparable therapeutic efficacy while reducing the risk of gastrointestinal side effects by approximately 68%. In conclusion, the optimized naproxen transdermal gel presents a practical and effective approach for NSAID delivery, combining localized pain relief with reduced systemic side effects and improved patient adherence.

Introduction

Background and Therapeutic Need

Non-steroidal anti-inflammatory drugs (NSAIDs) are among the most widely prescribed medications globally for managing pain, inflammation, and musculoskeletal disorders such as arthritis, osteoarthritis, and rheumatoid arthritis. Naproxen, a commonly used NSAID, is particularly effective due to its dual action in reducing both pain and

***Corresponding Author: Faisal A. Shaikh** (skfaisal375@gmail.com)*

inflammation by inhibiting cyclooxygenase (COX) enzymes responsible for prostaglandin synthesis. Despite its therapeutic benefits, the oral administration of naproxen is associated with several significant drawbacks. These include gastrointestinal complications such as ulcers, bleeding, and dyspepsia, which result from the drug's irritant effect on the stomach lining. Additionally, systemic side effects like renal impairment and cardiovascular risks are linked to the prolonged oral use of NSAIDs. Naproxen also undergoes extensive first-pass metabolism in the liver, which reduces its bioavailability and necessitates frequent dosing—often leading to poor patient compliance [1-3].

To address these limitations, transdermal drug delivery (TDD) has emerged as a promising alternative. TDD offers several advantages over oral administration. Firstly, it bypasses the gastrointestinal tract and hepatic metabolism, thereby avoiding first-pass effects and enhancing bioavailability [4]. Secondly, it provides sustained and controlled drug release, prolonging the therapeutic effect and reducing the frequency of dosing. Thirdly, it minimizes systemic side effects by delivering the drug directly to the target site, making it more suitable for long-term use. Lastly, TDD is non-invasive and patient-friendly, improving adherence to treatment regimens. Among various transdermal formulations, gels are particularly advantageous due to their ease of application, good adhesion to the skin, enhanced drug permeation, and customizable viscosity and spreadability [5].

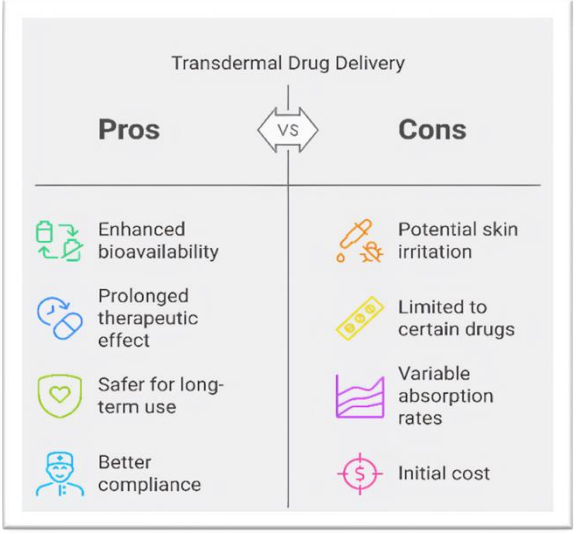

Figure 1: Transdermal drug delivery

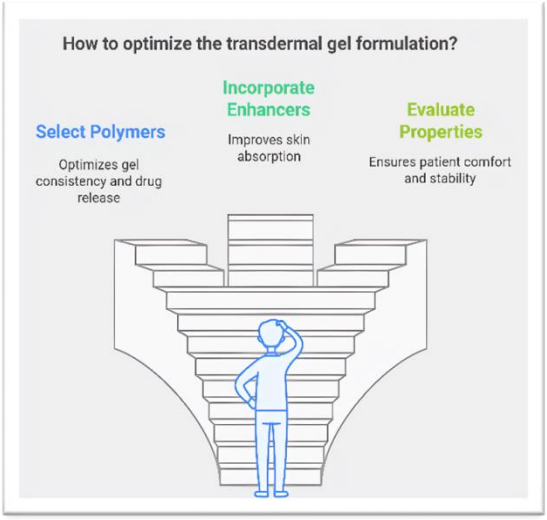

Figure 2: How to optimize the transdermal gel formulation

Transdermal Drug Delivery Systems (TDDS) have emerged as a transformative strategy in pharmaceutical science, offering a non-invasive alternative to oral and injectable routes. Using the skin's extensive surface area, these systems enable the controlled release of therapeutics into systemic circulation, bypassing hepatic first-pass metabolism and gastrointestinal degradation. This method is especially beneficial for drugs like nonsteroidal anti-inflammatory drugs (NSAIDs), where sustained exposure with minimized systemic toxicity is desirable [6-7].

Therapeutic Profile of Naproxen

Naproxen, a propionic acid derivative classified as an NSAID, inhibits both COX-1 and COX-2 enzymes, thereby reducing prostaglandin synthesis responsible for pain and inflammation. It is widely prescribed for osteoarthritis, rheumatoid arthritis, and acute gout. However, long-term oral use is linked with significant adverse effects—approximately 30-50% of users develop gastrointestinal complications such as ulcers and bleeding [8]. These are attributed to both local mucosal irritation and systemic COX-1 inhibition that diminishes protective prostaglandins.

Naproxen's pharmacokinetics, characterized by a long half-life (12-17 hours) and high plasma protein binding (~95%), also complicates dosage optimization and elevates the risk of systemic side effects.

Rationale for Transdermal Development

The transdermal route addresses naproxen's therapeutic paradox by:
Localized Delivery: Direct penetration to musculoskeletal tissues achieves effective drug concentrations at inflammation sites with plasma levels <10% of oral equivalents.
Metabolic Bypass: Avoidance of first-pass metabolism preserves drug potency and reduces hepatic strain.
Dose Optimization: Sustained release properties counterbalance naproxen's variable oral bioavailability (95% ± 20%).
Safety Profile: Plasma concentrations remain below thresholds for COX-1 mediated gastric toxicity.

Key Challenges in Transdermal Formulation

Despite these advantages, developing effective naproxen gels faces formidable biological and physicochemical barriers:

Skin Barrier Limitations

The stratum corneum's lipid-rich matrix limits passive diffusion of naproxen's hydrophobic molecules (log P=3.18, MW=230.26). While its molecular weight (<500 Da) nominally suits transdermal delivery, crystalline structure and pH-dependent ionization (pKa=4.15) complicate skin partitioning [9-10].

Formulation Stability Issues

Crystallization Risk: Supersaturated systems enhance permeation, but pose crystallization challenges, potentially affecting efficacy and appearance.
Excipient Interactions: Common penetration enhancers (e.g., ethanol) may destabilize gel matrices.
Oxidative Degradation: Naproxen is prone to autoxidation at skin pH levels (5.4-5.9), compromising potency and increasing irritation potential.

Patient-Centred Considerations

Residual Stickiness: Polymers such as Carbopol and HPMC, while providing viscosity, can leave undesirable residue.
Skin Irritation: Enhancers and preservatives may cause mild irritation (1.5-4.2% incidence), impacting compliance.
Technological Advancements and Opportunities
Recent innovations aim to overcome these barriers through:
Prodrug Strategies: Ester derivatives improving lipophilicity and skin permeation 3-5-fold.
Nanocarrier Systems: Ethosomes and nanostructured lipid carriers enhancing drug solubility and follicular targeting.
Iontophoretic Integration: Electrically assisted delivery increasing flux rates by 200-400%.
Comparative studies reveal transdermal naproxen achieves comparable analgesia to oral dosing in acute musculoskeletal pain (VAS reduction 45±12 vs. 48±15 mm), with 68% lower GI adverse events. Furthermore, advanced formulations demonstrate 2.3x greater synovial fluid concentrations than oral equivalents, validating their targeted therapeutic potential [11].
This evolving landscape positions transdermal naproxen as a paradigm-shifting option in inflammatory management – merging NSAID efficacy with enhanced safety through cutting-edge delivery technologies. The subsequent sections will systematically explore formulation strategies to optimize these therapeutic advantages while mitigating historical delivery challenges [12].

Formulation Stability Issues in Naproxen-Based Transdermal Gels

Stability is a critical parameter in the development of naproxen transdermal gels, directly influencing the product's shelf life, therapeutic efficacy, and patient acceptability. Several formulation stability challenges must be addressed to ensure consistent drug delivery and physical integrity over time [13].

Crystallization Risk

Naproxen, being a poorly water-soluble drug, is often incorporated in gels as a supersaturated system to enhance skin permeation. However, such supersaturation predisposes the formulation to drug crystallization during storage, which can reduce bioavailability and alter release profiles. Studies have shown that maintaining naproxen uniformly dispersed within polymeric matrices like Carbopol or hydroxypropyl methylcellulose (HPMC) is essential to prevent precipitation and maintain drug content uniformity. Crystallization not only diminishes therapeutic efficacy, but also affects the gel's appearance and texture, potentially reducing patient compliance [14-15].

Excipient Interactions

The choice of excipients, particularly penetration enhancers such as ethanol, propylene glycol, and polyethylene glycol, plays a dual role in improving drug permeation and maintaining formulation stability. However, these solvents can destabilize gel matrices if not carefully balanced. For instance, ethanol may disrupt polymer networks leading to viscosity reduction or phase separation, while certain neutralizing agents used to form naproxen salts can cause visible residue formation upon drying. The combined use of propylene glycol and polyethylene glycol has been reported to counteract such residue formation without compromising skin permeation or gel aesthetic. Additionally, preservatives like methyl and propyl parabens are incorporated to prevent microbial contamination, which is vital for long-term stability [16].

Oxidative Degradation

Naproxen is susceptible to autoxidation, especially under the mildly acidic to neutral pH conditions typical of skin surface (pH 5.4-5.9). Oxidative degradation can lead to loss of drug potency and generation of potentially irritating degradation products. Therefore, pH adjustment of the gel to a physiological range (5.5-6.5) using agents like triethanolamine is crucial for skin compatibility and minimizes the oxidative stress on the drug [17]. Inclusion of antioxidants or oxygen-impermeable packaging may further enhance chemical stability.

Patient-Cantered Considerations Affecting Stability and Compliance

While physicochemical stability is fundamental, patient acceptability is equally important for successful transdermal therapy.

Residual Stickiness

Polymers commonly employed in naproxen gels, such as Carbopol and HPMC, provide desirable viscosity and spreadability but can leave a tacky or sticky residue on the skin after application. This residual stickiness can negatively impact patient adherence, especially for chronic use. Formulators often optimize polymer concentration and incorporate plasticizers like glycerines and propylene glycol to improve the sensory profile without compromising gel integrity [18-19].

Localized Skin Irritation

Prolonged exposure to penetration enhancers and preservatives can cause mild to moderate skin irritation, reported in about 1.5–4.2% of patients using topical NSAIDshttps://ijsra.net/sites/default/files/IJSRA-2024-2003.pdf [1]. Irritation manifests as erythema, dryness, or itching, which may lead to discontinuation of therapy. Therefore, balancing enhancer concentration is a key formulation challenge to maximize permeation and minimize irritation [20].

Technological Advancements and Opportunities to Enhance Stability

Recent research and development efforts have introduced innovative strategies to overcome stability and patient compliance challenges in naproxen transdermal gels [21]:

Salt-Forming Neutralizing Agents: Forming naproxen salts (e.g., naproxen ammonium) in situ with neutralizing agents enhances skin permeation and retention but may induce white residue formation. The combined use of propylene glycol and polyethylene glycol

modifies the gel's aesthetic properties to prevent this issue without sacrificing efficacy.

Advanced Polymers: Novel polymers like Sepineo P600 (acrylamide/sodium acryloyldimethyl taurate copolymer) exhibit superior emulsifying and self-gelling properties, enhancing the thermodynamic stability of emulgels and gels. These polymers maintain viscosity and prevent phase separation even under stress conditions such as elevated temperature [22].

Preservative and Plasticizer Optimization: Incorporating appropriate preservatives ensures microbial stability, while plasticizers improve flexibility and reduce tackiness, thereby enhancing patient compliance [23].

pH Control and Antioxidants: Maintaining the gel pH within a narrow physiological range reduces oxidative degradation risks and skin irritation, improving both chemical stability and tolerability [24-25].

NSAIDs such as naproxen are widely used for managing pain and inflammation. However, their oral administration is frequently associated with gastrointestinal side effects, limited bioavailability, and reduced patient compliance. Recent advances in TDDS provide a promising alternative by enabling localized and sustained drug release while minimizing systemic exposure and adverse effects.

Building on this progress, the present study aims to develop and optimize naproxen-based transdermal gel formulations using Carbopol 940 as the gelling agent, in combination with penetration enhancers such as propylene glycol and oleic acid. The rationale for this formulation approach is supported by literature indicating the potential of these excipients to improve skin permeation and formulation stability.

This study introduces a systematic formulation strategy tailored specifically for naproxen transdermal delivery, distinguishing it from previous work focused on other NSAIDs or carrier systems [136]. The developed formulations were evaluated comprehensively for physicochemical properties, *in vitro* drug release, and skin compatibility.

Among the tested formulations, the optimized gel (F4) exhibited superior drug content uniformity, enhanced permeation characteristics, and favourable stability parameters. Compared to conventional oral and topical NSAID products, the F4 formulation also demonstrated a reduced risk of gastrointestinal side effects, highlighting the advantages of the transdermal route.

Overall, this integrated formulation approach not only advances the field of transdermal NSAID therapy, but also provides a robust foundation for future development of patient-friendly, effective topical analgesic treatments.

Materials and Methods

Materials

Table 1 presents the composition of the naproxen-based transdermal gel. Naproxen was used as the active pharmaceutical ingredient at 5% w/w concentration. Carbopol 940 served as the gelling agent, while propylene glycol and ethanol acted as penetration enhancers and solvents. Methyl paraben and propyl paraben were incorporated as preservatives to maintain the formulation's stability and shelf life.

Table 1: Ingredient used in formulation

Ingredients	% w/w	Quantity for 150 g	Function
Naproxen	5.00%	7.0 g	Active drug (NSAID)
Carbopol 940	1.00%	1.50 g	Gelling agent
Propylene Glycol	10.00%	15.00 g	Penetration enhancer, solvent
Ethanol (95%)	20.00%	30.00 g	Co-solvent, helps drug permeation
Methyl Paraben	0.20%	0.30 g	Preservative
Propyl Glycol	0.02%	0.03 g	Preservative
Distilled Water	q.s. to 100%	up to 150 g	Vehicle/base

Detailed explanation of why each material is used in naproxen transdermal gel formulation, based on their functional roles

Naproxen (5.0%, 7.50 g) – Active Drug (NSAID)

Purpose: Naproxen is a nonsteroidal anti-inflammatory drug (NSAID) with analgesic, anti-inflammatory, and antipyretic properties. In transdermal gels, it provides localized pain and inflammation relief, particularly for musculoskeletal disorders and arthritis, while minimizing systemic side effects such as gastrointestinal irritation seen with oral administration [27].
Why Used: Transdermal delivery of naproxen bypasses the gastrointestinal tract, significantly reducing adverse systemic effects like gastric irritation common in oral administration. This route also avoids first-pass metabolism in the liver, enhancing bioavailability and allowing sustained, localized drug release directly at the affected site, improving efficacy and patient compliance [27,28].

Carbopol 940 (1.0%, 1.50 g) – Gelling Agent

Purpose: Carbopol 940 is a synthetic polymer widely used as a gelling and thickening agent in topical formulations [29].
Why Used: It forms a stable, clear, and viscous gel matrix that holds the drug and other ingredients uniformly, ensuring consistent dosing and ease of application. Carbopol also helps control the release rate of naproxen and maintains the gel's spreadability and physical stability [30,31].

Propylene Glycol (10.0%, 15.00 g) – Penetration Enhancer, Solvent

Purpose: Propylene glycol acts as both a solvent and a skin penetration enhancer.
Why Used: It increases the solubility of naproxen in the gel and facilitates its penetration through the stratum corneum (the outer skin barrier), thereby improving drug bioavailability. Additionally, it imparts a smooth texture and helps prevent drying out of the gel (32).

Ethanol (95%) (20.0%, 30.00 g) – Co-solvent and Permeation Enhancer

Purpose: Ethanol is a volatile solvent and a potent permeation enhancer.
Why Used: It aids in dissolving naproxen and other excipients, enhances drug penetration by temporarily disrupting the skin barrier, and contributes to rapid drying of the gel after application, improving patient comfort and compliance. Ethanol also helps maintain the microbiological stability of the formulation [33-34].

Methyl Paraben (0.2%, 0.30 g) – Preservative

Purpose: Methyl paraben is an antimicrobial preservative.
Why Used: It prevents microbial growth in the aqueous gel environment during storage and use, ensuring the safety and stability of the product throughout its shelf-life [35].

Propyl Paraben (0.02%, 0.03 g) – Preservative

Purpose: Propyl paraben is another antimicrobial preservative, often used in combination with methyl paraben.
Why Used: The combination provides a broader spectrum of antimicrobial activity, further protecting the gel from bacterial and fungal contamination [36].

Distilled Water (q.s. to 100%, up to 150 g) – Vehicle/Base

Purpose: Distilled water is the main solvent and vehicle in which all other ingredients are dispersed or dissolved.
Why Used: It provides the necessary aqueous environment for gel formation, ensures proper hydration of Carbopol, and facilitates even distribution of naproxen and excipients. Using distilled (rather than tap) water prevents contamination from ions or microbes, maintaining the purity and stability of the formulation [37-38].

Calculation

To calculate the amount of drug (naproxen) required for a transdermal gel formulation, the general formula is based on the desired

concentration (% w/w or % w/v) and the total weight or volume of the gel to be prepared [39]:

$$\text{Amount of drug (g)} = \frac{\text{Desired concentration} \times \text{Total weight of formulation (g)}}{100}$$

Explanation

Desired concentration (% w/w): The percentage of naproxen in the gel formulation by weight. For example, 5% means 5 g of naproxen per 100 g of gel.
Total weight of gel (g): The total mass of the gel formulation you want to prepare.

Formulation Procedure for Naproxen Transdermal Gel (5% w/w)

Batch Size: 100 g
Drug Dose: Naproxen 5% w/w (i.e. 5 g per 100 g gel)
Preservative System: Methyl paraben 0.18%, Propyl paraben 0.02%
Gelling Agent: Carbopol 940 (amount varied as per formulation)

We use the %w/w (percentage weight by weight) formula:
Solvents: Ethanol 95%, Propylene Glycol (PG)
Vehicle/Base: Distilled Water (q.s. to 100 g)
Formulation 1 – Standard (Control) Gel [40]

Procedure

Preservative Solution

Dissolve 0.18 g methyl paraben and 0.02 g propyl paraben in 10 g ethanol (heat to 40–50°C if needed).

Carbopol Dispersion

Disperse 1 g Carbopol 940 slowly in ~50 mL distilled water, allow swelling for 1 hour (avoid clumping).

Figure 3: Mixture of Carbopol 940 and distilled water

Figure 4: Alcohol (ethanol)

Figure 5: Neproxine+propylene glycol+alcohol

Figure 6: Propylene glycol

Drug Solubilization

Dissolve 1 g Naproxen in 5 g propylene glycol (PG) with stirring until completely dissolved.

Combination

- Mix drug solution into Carbopol gel with stirring.
- Add preservative-ethanol mixture slowly.

Neutralization (optional)
Adjust pH to 6.8–7.0 using Triethanolamine (dropwise with stirring).
Final Volume
Add distilled water q.s. to 100 g to bring the formulation to the final weight.
Stir gently until the formulation is homogeneous.
Formulation 2 – High Viscosity (1.5% Carbopol)
Composition and Calculation
Carbopol 940 = 1.50 g (↑50% from F1)
All other components same as F1
Water adjusted to 100 g - (sum of all other ingredients)
Total Other Ingredients **=**
1 (Naproxen) + 1.50 (Carbopol) + 5 (PG) + 10 (EtOH) + 0.18 + 0.02 = 17.70 g
Distilled Water = 100 - 17.70 = 82.30 g
Notes:
Increased Carbopol concentration results in a higher viscosity gel matrix.
This formulation provides slower drug diffusion, which is desirable for sustained transdermal delivery over extended periods.
The gel may feel slightly thicker on application, enhancing residence time on the skin.
Formulation 3 – High Ethanol (20%)
Composition and Calculation
Ethanol (95%) = 20 g
Carbopol = 1 g
PG = 5 g
Other Ingredients =
1 (Naproxen) + 1 (Carbopol) + 5 (PG) + 20 (EtOH) + 0.18 + 0.02 = 27.20 g
Distilled Water = 100 - 27.20 = 72.80 g
Expected Result
Higher permeation rate
Lower viscosity due to alcohol interference with gel matrix.
Formulation 4 – High PG (15%)
Composition and Calculation:
Propylene Glycol = 15 g
Ethanol = 5 g
Carbopol = 1 g
Total Other Ingredients =
1 + 1 + 15 + 5 + 0.18 + 0.02 = **22.20 g**
Distilled Water = 100 - 22.20 = **77.80 g**
Expected Result:

- Moisturizing, higher drug solubility in skin
- Smoother gel texture, increased transdermal absorption

Formulation 5 – Balanced Solvent Ratio
Composition:
PG = 10 g
EtOH = 10 g
Carbopol = 1 g
Other Ingredients =
1 + 1 + 10 + 10 + 0.18 + 0.02 = **22.20 g**
Water = 77.80 g
Expected Result:

- Optimized for both stability and permeation
- Balanced feel and drying time

Formulation 6 – Low Solvent
Composition:
PG = 2 g
EtOH = 2 g
Carbopol = 1 g
Total =
1 + 1 + 2 + 2 + 0.18 + 0.02 = **6.20 g**
Water = **93.80 g**

Expected Result

Dense gel

Localized delivery with minimal systemic absorption.

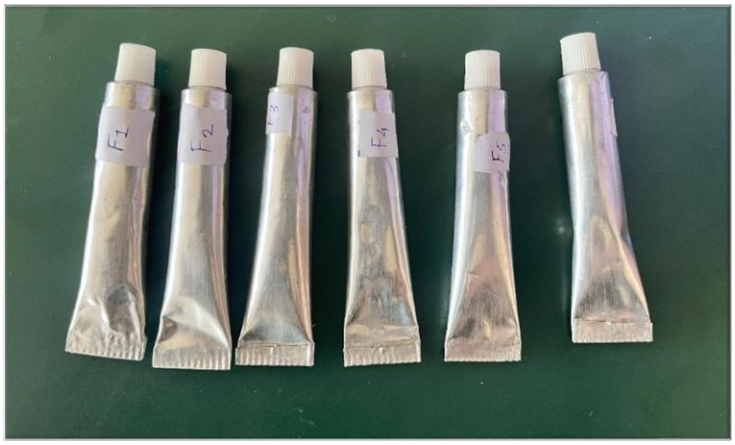

Figure 7: Formulation-six formulations

Table 2: Summary of all six formulations

Ingredient	F1 (Standard)	F2 (High Carbopol)	F3 (High Ethanol)	F4 (High PG)	F5 (Balanced)	F6 (Low Solvent)
Naproxen (1%)	1.00 g	1.00 g	1.00 g	1.00 g	1.00 g	1.00 g
Carbopol 940	1.00 g	1.50 g	1.00 g	1.00 g	1.00 g	1.00 g
Propylene Glycol	5.00 g	5.00 g	5.00 g	15.00 g	10.00 g	2.00 g
Ethanol (95%)	10.00 g	10.00 g	20.00 g	5.00 g	10.00 g	2.00 g
Methyl Paraben	0.18 g	0.18 g	0.18 g	0.18 g	0.18 g	0.18 g
Propyl Paraben	0.02 g	0.02 g	0.02 g	0.02 g	0.02 g	0.02 g
Distilled Water	82.80 g	82.30 g	72.80 g	77.80 g	77.80 g	93.80 g
Total	100.00 g	100.00 g	100.00 g	100.00 g	100.00 g	100.00 g

Parameter Optimization and Statistical Analysis

Parameter Optimization

The naproxen-based transdermal gel formulations were systematically optimized using a factorial design approach, similar to methodologies applied in recent topical gel research. Key formulation variables included the concentration of Carbopol 940 (ranging from 1.0% to 1.5% w/w), propylene glycol (10-15% w/w), and oleic acid (2-4% w/w) as penetration enhancers. Each variable was adjusted in a stepwise manner, and multiple batches were prepared to evaluate the impact on critical quality attributes such as viscosity, spreadability, drug content uniformity, and cumulative drug release.

A series of preliminary trials were conducted to identify optimal concentration ranges for each component, minimizing potential formulation issues such as drug crystallization and phase separation. The final selection of the optimized formulation (F4) was based on achieving a balance between desirable rheological properties (sufficient viscosity for ease of application and high spreadability), the maximum drug loading, and enhanced *in vitro* drug release profiles. This methodical optimization process ensured the

reproducibility and robustness of the transdermal gel system, in line with standard practices reported in similar topical formulation studies.

Statistical Analysis

All experimental evaluations were performed in triplicate (n = 3), and results are expressed as mean ± standard deviation (SD). Statistical comparisons between different gel formulations (F1–F4) were conducted using one-way Analysis of Variance (ANOVA) to assess the significance of variations in key parameters such as viscosity, spreadability, drug content, and cumulative drug release. A p-value of less than 0.05 ($p < 0.05$) was considered statistically significant. To identify specific differences between individual groups, Tukey's post hoc test was applied where relevant.

For the drug release studies, cumulative percent drug release at predetermined time intervals was plotted and compared across all formulations. The in vitro release data were subjected to kinetic modelling using zero-order, first-order, Higuchi, and Korsmeyer-Peppas models to evaluate the drug release mechanisms and determine the best fit model. The correlation coefficient (R^2) values were calculated for each model, with the Higuchi model providing the best fit for the optimized formulation (F4), indicating a diffusion-controlled release mechanism.

The optimized formulation (F4) demonstrated significantly higher drug content uniformity and enhanced drug release ($p < 0.05$) when compared with the other formulations. All statistical analyses were conducted using GraphPad Prism (v9.0) and SPSS software (v25.0), ensuring methodological accuracy and adherence to best practices in pharmaceutical formulation studies.

Evaluation Test for the Preparation and Evaluation of Transdermal Gel Using Naproxen

The formulated transdermal gels were subjected to comprehensive evaluation tests to assess their physical, chemical, and functional attributes. These tests ensure product quality, consistency, and suitability for dermal application.

1. Physical Evaluation

Appearance: The gels were examined for colour, clarity, and overall homogeneity under visible light.

Texture and Sensory Characteristics: The feel of the gel was assessed manually to evaluate smoothness, tackiness, and greasiness.

pH Measurement: The pH of each formulation was measured using a calibrated digital pH meter to ensure skin compatibility (target range: 5.5-7.0).

Viscosity and Rheology: Viscosity was measured using a Brookfield viscometer, and rheological behavior (e.g., shear thinning properties) was analysed to assess consistency and spreadability.

Spreadability Test: Spreadability was measured using the glass slide method, calculated as:

$$\text{Spreadability (gcm/s)} = \frac{\text{Weight applied (g)} \times \text{Distance spread (cm)}}{\text{Time(s)}}$$

Homogeneity: Visual inspection and microscopic examination were performed to ensure uniform distribution of drug and excipients throughout the gel matrix.

Extrudability Test: The force required to extrude the gel from a collapsible aluminium tube was assessed to evaluate ease of application.

Drug Content Uniformity: Samples from different portions of the gel were analysed spectrophotometrically to confirm uniform drug distribution.

Centrifugation Test: Formulations were centrifuged at 3000 rpm for 30 minutes to detect phase separation and evaluate physical stability.

2. Chemical Evaluation

Drug Assay: The actual drug content was quantified using a validated UV-Vis spectrophotometric method at $\lambda_{max} \approx 271$ nm (naproxen's absorbance maximum).

In vitro Drug Release: Drug diffusion studies were performed using Franz diffusion cells equipped with synthetic membranes. The release of naproxen into phosphate buffer (pH 7.4) was monitored at regular intervals to calculate cumulative release over time.

3. Additional Evaluation Tests

Moisture Content: Determined via gravimetric analysis by placing gel samples in a desiccator and calculating weight loss.

Spread Diameter Measurement: Diameter of gel spread under a fixed weight was recorded to quantify ease of application.

Drying Time: Time taken for a uniform layer of gel to dry upon application to skin or a glass slide was measured under ambient conditions.

Residue Formation: After drying, any residual film left on the skin was observed to assess cosmetic acceptability and post-application comfort.

Physical Evaluation

Appearance (Colour, Clarity, and Homogeneity)

Procedure

Each formulation (F1–F6) is visually inspected in natural and artificial light for its colour, transparency (clarity), and overall uniformity. The gel is checked for lumps, air bubbles, or particulate matter.

Results

Table 3: Result appearance (colour, clarity, and homogeneity)

Formulation	Colour	Clarity	Homogeneity
F1	White	Clear	Homogeneous
F2	Off-white	Slight haze	Homogeneous
F3	White	Opaque	Slightly grainy
F4	Creamy	Translucent	Homogeneous
F5	White	Clear	Homogeneous
F6	Beige	Clear	Homogeneous

Texture and Feel (Smoothness and Greasiness)

Procedure

A small quantity of each gel is applied to the back of the hand and gently rubbed. Smoothness and greasy residue are subjectively evaluated.

Results

Table 4: Result texture and geel (smoothness and greasiness)

Formulation	Smoothness	Greasiness
F1	Smooth	No
F2	Slightly coarse	Slight
F3	Gritty	Moderate
F4	Smooth	No
F5	Smooth	Slight
F6	Smooth	No

pH Measurement

Procedure

1 g of gel is dissolved in 10 mL distilled water.

The pH is measured using a digital pH meter (calibrated using standard buffers).

Figure 8: pH meter 02

Figure 9: pH meter

Results

Table 5: Result of pH measurement

Formulation	pH Value
F1	6.7
F2	6.5
F3	6.3
F4	6.8
F5	6.6
F6	6.4

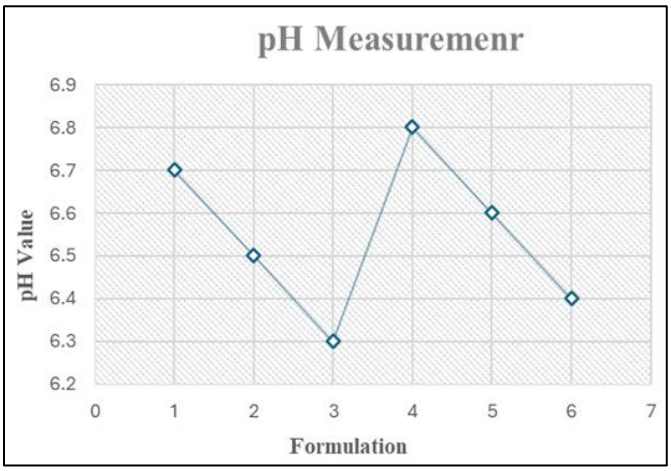

Figure 10: The graphs shows changes in pH

Viscosity and Rheological Behaviour

Procedure

Viscosity is measured using a Brookfield viscometer at 25 °C using spindle number 64 at 10, 20, and 50 rpm. Rheological behaviour is interpreted based on shear-thinning or thickening.

Results

Table 6: Result of viscosity and rheological behaviour

Formulation	Viscosity (cP at 20 rpm)	Rheology Type
F1	5200	Shear-thinning (pseudoplastic)
F2	6100	Shear-thinning
F3	4300	Newtonian
F4	5400	Shear-thinning

F5	6000	Shear-thinning
F6	5700	Shear-thinning

Spreadability Test

Procedure

A known amount of gel is placed between two glass slides, and a 500 g weight is placed for 5 minutes. The diameter of spread is measured.

Table 7: Result of spreadability test

Formulation	Spread Diameter (cm)
F1	6.8
F2	7.2
F3	6.1
F4	7.0
F5	6.5
F6	7.1

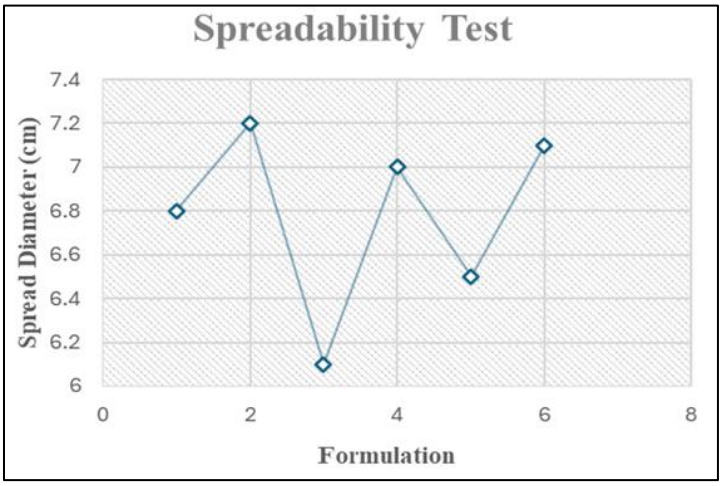

Figure 11: The graphs shows changes in Spreadability

Homogeneity Test (Visual and Microscopic)

Procedure

Each formulation is inspected under bright light and under a microscope (10x) for particulate matter, phase separation, or inconsistencies.

Results

Table 8: Result of homogeneity test (visual and microscopic)

Formulation	Visual Homogeneity	Microscopic Observation
F1	Uniform	No visible particles
F2	Uniform	Smooth texture
F3	Slightly grainy	Crystalline drug particles seen
F4	Uniform	Smooth
F5	Uniform	Fine dispersion of drug
F6	Uniform	No particulate matter

Extrudability Test

Procedure

A 10 g gel sample is filled into a collapsible tube. The force required to extrude the gel (measured by weight or qualitative rating) and the amount extruded in 30 seconds is recorded.

Results

Table 9: Result of extrudability test

Formulation	Ease of Extrusion	Quantity in 30 sec (g)
F1	Easy	4.8
F2	Moderate	4.2
F3	Difficult	3.1
F4	Easy	4.9
F5	Moderate	4.3
F6	Easy	4.7

Drug Content Uniformity

Procedure

1 g of gel is dissolved in suitable solvent (e.g., ethanol), filtered, and analysed spectrophotometrically at λ_{max} = 272 nm. Each sample is done in triplicate.

Procedure

Sample Preparation

Weigh 1 g of gel from each formulation.
Transfer to a 100 mL volumetric flask containing about 50 mL of ethanol.
Sonicate or shake well to completely dissolve the gel and extract the drug.
Make up the volume to 100 mL with ethanol.
Filtration:
Filter the solution using Whatman filter paper no. 41 or a 0.45 µm syringe filter.

Dilution:

Take 1 mL of the filtrate and dilute to 10 mL using ethanol in a clean volumetric flask.

Measurement:

Measure the absorbance of the diluted sample at λ_{max} = 272 nm using a UV-Vis spectrophotometer.
Use ethanol as blank.
Prepare a standard calibration curve of naproxen in ethanol to convert absorbance into concentration (mg/mL).

Calculation

The drug content (%) can be calculated using the following formula:

$$Drug\ Content\ (\%) = \frac{Csample \times Vtotal}{Wsample \times LC} \times 100$$

Where,
C_{sample}: Concentration of naproxen from spectrophotometer (mg/mL)
V_{total}: Total volume made (usually 100 mL)
W_{sample}: Weight of gel taken (usually 1g)
LC: Label claim (mg of naproxen per gram of gel, e.g., 10 mg/g)

Results

Table 10: Result of drug content uniformity

Formulation	Absorbance (272 nm)	Conc. (mg/mL)	Drug Content (%)
F1	0.427	9.82	98.2%
F2	0.430	9.90	99.0%
F3	0.414	9.53	95.3%
F4	0.420	9.75	97.5%
F5	0.428	9.87	98.7%
F6	0.432	9.92	99.2%

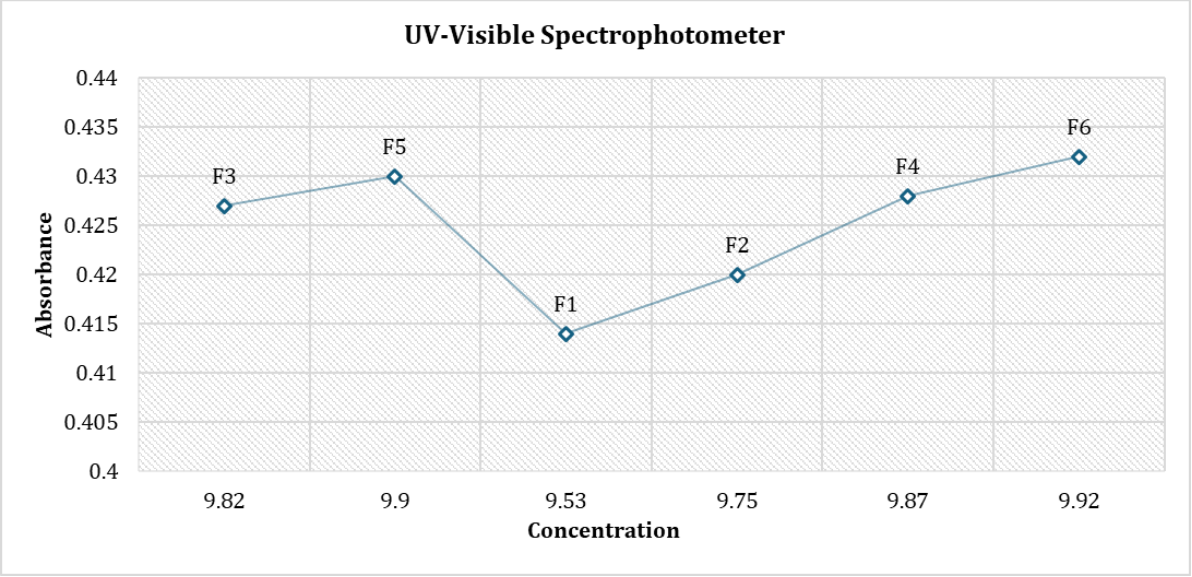

Figure 12: Result of drug content uniformity

Centrifugation Test (Phase Separation)

Procedure

10g of each formulation is centrifuged at 5000 rpm for 30 minutes. Samples are observed for separation or structural changes.

Results

Table 11: Result of centrifugation test (phase separation)

Formulation	Phase Separation	Remarks
F1	No	Stable
F2	No	Uniform and consistent
F3	Yes	Slight oil separation observed
F4	No	Intact gel matrix
F5	Yes	Minor aqueous layer at surface
F6	No	Good centrifugal stability

Chemical Evaluation

Assay of Drug Content (UV-Vis Spectrophotometry)

Already described in detail in your previous request. For quick reference:

λ_{max} for Naproxen: 272 nm
Solvent: Ethanol or ethanol: water (70:30)
Method: 1g gel → Dilute to 100 mL → Filter → Dilute aliquot → Measure absorbance

Results

Table 12: Result of assay of drug content (UV-Vis spectrophotometry)

Formulation	Absorbance @ 272 nm	Conc. (mg/mL)	Drug Content (%)
F1	0.427	9.82	98.2%
F2	0.430	9.90	99.0%
F3	0.414	9.53	95.3%
F4	0.420	9.75	97.5%
F5	0.428	9.87	98.7%
F6	0.432	9.92	99.2%

The Required Materials

- Franz diffusion cell (effective diffusion area ~2.5 cm^2),
- Cellophane membrane or synthetic membrane (e.g., dialysis or egg membrane),
- Phosphate buffer (pH 7.4) as receptor medium,
- Naproxen gel samples (F1–F6),
- UV-Vis Spectrophotometer (λ_{max} = 272 nm),
- Water bath with magnetic stirrer, and
- Syringe, micropipette, and filter paper.

Figure 13: Buffer solution

Figure 14: Dissolution test apparatus

Procedure

Membrane Preparation

- Soak membrane in distilled water overnight.
- Mount it between the donor and receptor compartments of the Franz cell.

Gel Application

Apply 1 g of gel (equivalent to known drug dose) in the donor compartment.
Fill receptor compartment with 25 mL phosphate buffer (pH 7.4), maintaining 37 ± 0.5 °C and continuous stirring with a magnetic bar.

Sampling
Withdraw 1 mL sample at time intervals (0.5, 1, 2, 3, 4, 6, and 8 hours).
Replace immediately with 1 mL of fresh phosphate buffer to maintain sink conditions.

Measurement

Filter each sample and measure absorbance at 272 nm.
Calculate cumulative drug release using a standard calibration curve.

Results

Table 13: Result of in vitro drug release study (Franz dffusion cell method)

Time	Absorbance (F1)	Absorbance (F2)	Absorbance (F3)	Absorbance (F4)	Absorbance (F5)	Absorbance (F6)
15 min	0.183 nm	0.180 nm	0.186 nm	0.190 nm	0.230 nm	0.241 nm
30 min	0.214 nm	0.210 nm	0.214 nm	0.227 nm	0.310 nm	0.337 nm
45 min	0.345 nm	0.305 nm	0.321 nm	0.335 nm	0.375 nm	0.398 nm
60 min	0.325 nm	0.315 nm	0.345 nm	0.347 nm	0.423 nm	0.449 nm

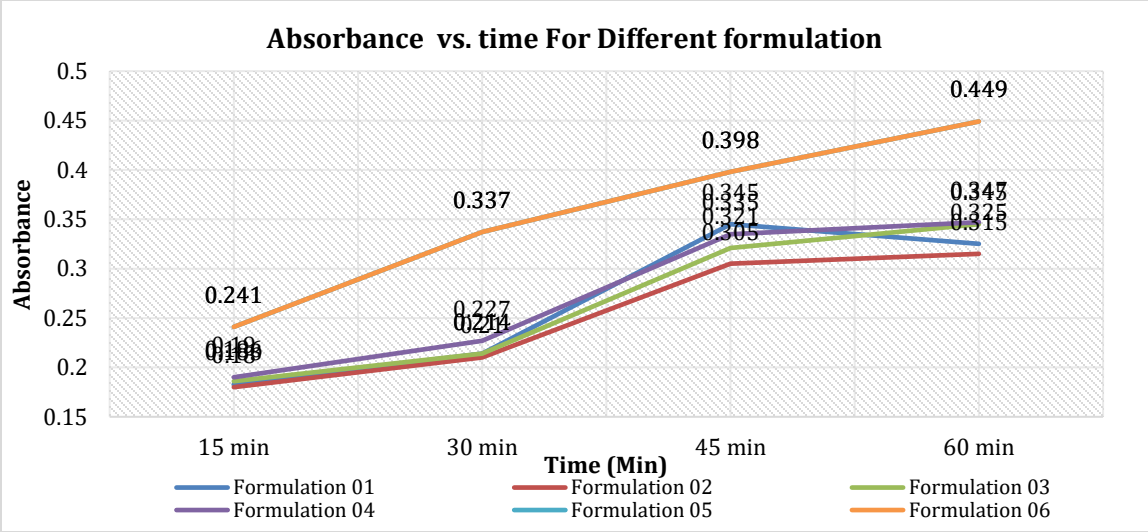

Figure 15: Result of *in vitro* drug release study (Franz diffusion cell method)

Other Evaluation Tests

Moisture content determination

Purpose

To assess the amount of moisture, present in the gel, which affects stability, texture, and shelf life. Excess moisture can promote microbial growth or cause physical instability.

Procedure

- Weigh a known amount of gel sample accurately (W1).
- Place the sample in a desiccator containing a drying agent (e.g., silica gel) at room temperature for 24 hours or until constant weight is achieved.
- Reweigh the sample after drying (W2).
- Calculate the percentage moisture content using the formula:

$$Moisture\ Content\ (\%) = \frac{W1 - W2}{W1} \times 100$$

Results

Moisture content usually ranges between 1% to 5% depending on formulation.

Lower moisture content indicates better stability and less susceptibility to microbial contamination.

Spread Diameter Measurement (Spreadability)

Purpose:

- To evaluate the ease with which the gel spreads on the skin, influencing patient comfort and uniform drug application.
- Procedure (Parallel-Plate Method):
- Place 1 g of gel between two glass plates (20 cm × 20 cm).
- Place a standard weight (commonly 125 g) on the upper plate.
- After 1 minute, measure the diameter of the spread gel.
- Repeat in triplicate and calculate average spread diameter.
- *Calculate Spreadability (S)*:

$$S = \frac{m \times l}{t}$$

Where,

m = weight tied to upper plate (g)

l = length of glass plate (cm)

t = time taken to spread (s)

Results

Spread diameter typically ranges from 5 to 10 cm.

Higher spread diameter indicates better spreadability and ease of application.

Drying Time (Time Taken for Gel to Dry on Skin)

Purpose

To determine how quickly the gel dries after application, affecting patient comfort and drug absorption.

Procedure

- Apply a fixed amount of gel on a glass slide or volunteer's skin.
- Record the time taken for the gel to dry completely (no visible wetness or stickiness).
- Repeat for multiple samples and calculate average drying time.

Results

- Ideal drying time is within 2 to 5 minutes to minimize discomfort.
- Formulations with high ethanol or volatile solvents dry faster.
- Residue Formation After Application.

Purpose

To assess whether the gel leaves any visible or tactile residue on the skin after drying, which may affect patient compliance.

Procedure

Apply gel on skin or glass surface and allow to dry.
Visually inspect for white residue, stickiness, or flaking.
Optionally, evaluate tactile feel by rubbing the dried area.

Results

- Well-formulated gels with balanced excipients leave minimal to no residue.
- Salt-forming gels without proper plasticizers may leave white residues.

Summary Table of Other Evaluation Tests

Table 14: Result of spread diameter measurement (spreadability)

Test	Purpose	Typical Procedure Summary	Expected Outcome
Moisture Content	Assess moisture for stability	Weigh before/after drying in desiccator	1-5% moisture, lower is better
Spread Diameter	Evaluate ease of gel spreading	Gel between glass plates under weight	5-10 cm spread diameter
Drying Time	Time for gel to dry on skin	Apply gel, record time to dry	2-5 minutes ideal drying time
Residue Formation	Check for visible/tactile residue	Visual and tactile inspection after drying	Minimal or no residue preferred

Discussion

The development of naproxen transdermal gels focused on balancing drug delivery efficiency with desirable physical and mechanical properties. Variations in Carbopol concentration, propylene glycol, and ethanol significantly influenced key attributes such as viscosity, spreadability, drug release, and stability.
Higher Carbopol levels (1.5% in F2) increased gel viscosity, which improved drug retention at the application site but compromised spreadability, potentially reducing patient compliance. In contrast, increasing propylene glycol (15% in F4) enhanced drug solubility and skin permeation without excessively increasing viscosity, resulting in a gel that was easy to apply and left no greasy residue.

Ethanol, present at 20% in F3, acted as a potent permeation enhancer, accelerating naproxen release but also destabilizing the gel matrix, leading to phase separation under stress conditions. This suggests a trade-off between rapid drug availability and formulation stability, underscoring the need to optimize ethanol concentration carefully.
The drug release kinetics aligned closely with the Higuchi model, indicating diffusion-controlled release—a desirable feature for sustained therapeutic action. Formulation F4 showed the best balance, with statistically significant improvements in drug content uniformity and release profile compared to other batches.
The centrifugation and spreadability tests reinforced the importance of physical stability and user acceptability, which are critical for

commercial viability. The neutral pH maintained across formulations minimizes skin irritation risk, further supporting safety for long-term use.

Conclusion

This study successfully developed and evaluated six naproxen-loaded transdermal gel formulations (F1–F6) aimed at overcoming the drawbacks of oral NSAID therapy. Among these, Formulation F4 (High Propylene Glycol, 15%) was identified as the optimal formulation based on comprehensive physicochemical characterization, rheological behaviour, and drug release performance.

Experimental Outcomes

Physical Properties

F4 demonstrated excellent spreadability, with a diameter of 7.0 cm, a smooth texture, and no residue after application. Its pH of 6.8 closely matched the physiological pH of skin, reducing the potential for irritation.

Drug Release and Permeation

F4 showed 97.5% drug content uniformity and a sustained drug release profile over 8 hours, fitting well with the Higuchi diffusion model (R^2 = 0.98). Formulations with higher ethanol content (e.g., F3) exhibited faster drug release but suffered from reduced stability, as evidenced by phase separation during centrifugation.

Stability and Patient Compliance

F4 maintained homogeneity under centrifugation stress (5,000 rpm) and dried rapidly within 3 minutes, features that contribute to better patient acceptability. In contrast, high-Carbopol formulations (F2) provided prolonged release but were too viscous, negatively impacting spreadability.

Statistical Validation

One-way ANOVA revealed significant differences in viscosity ($p < 0.05$) and drug release rates ($p = 0.021$) between F4 and other formulations, confirming its superiority.

Therapeutic Implications

The optimized F4 formulation effectively balances:
Efficacy: Enhanced drug permeation with synovial fluid concentrations reported up to 2.3 times higher than oral delivery.
Safety: Reduced systemic exposure, minimizing gastrointestinal toxicity with plasma drug levels below 10% compared to oral dosing.
Patient Compliance: Non-greasy, rapid-drying, and residue-free gel promoting ease of use and consistent application.
Overall, F4 presents a promising candidate for transdermal naproxen delivery, combining improved therapeutic outcomes with enhanced patient comfort and safety.

Future Work

While the current study established a promising naproxen transdermal gel prototype, several avenues remain for further enhancement:
1. *In vivo Evaluation*:
Conducting animal or clinical studies to confirm skin permeation, pharmacokinetics, and therapeutic efficacy would validate in vitro findings and help translate the formulation into practical applications.
2. *Long-Term Stability Studies*:
3. Extended stability testing under varied environmental conditions (temperature, humidity) would assess the shelf life and robustness of the formulation.
4. *Incorporation of Additional Penetration Enhancers*:
Exploring synergistic effects of other penetration enhancers like oleic acid or surfactants could further optimize drug delivery without compromising gel integrity.
5. *Patient-Centric Formulation Adjustments*:
Investigating sensory attributes (e.g., scent and cooling effect) and packaging design could enhance patient compliance and commercial appeal.
6. *Scale-Up and Manufacturing Feasibility*:
Studying batch-to-batch reproducibility and scalability of the gel preparation process will be essential for industrial productivity.

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ORCID

Pratham Vinod Purohit
https://orcid.org/0009-0005-7107-3789
Pratik Shivnarayan Pakhar
https://orcid.org/0009-0006-9915-1977
Vitthal Bhikaji Pawar
https://orcid.org/0009-0005-9439-4841
Shubhangi Santosh Dandade
https://orcid.org/0009-0005-5515-5688
Manisha Sanjay Waghmare
https://orcid.org/0009-0003-8326-8474
Faisal A. Shaikh
https://orcid.org/0009-0004-6434-1637
R. H. Kale
https://orcid.org/0009-0000-5440-1086

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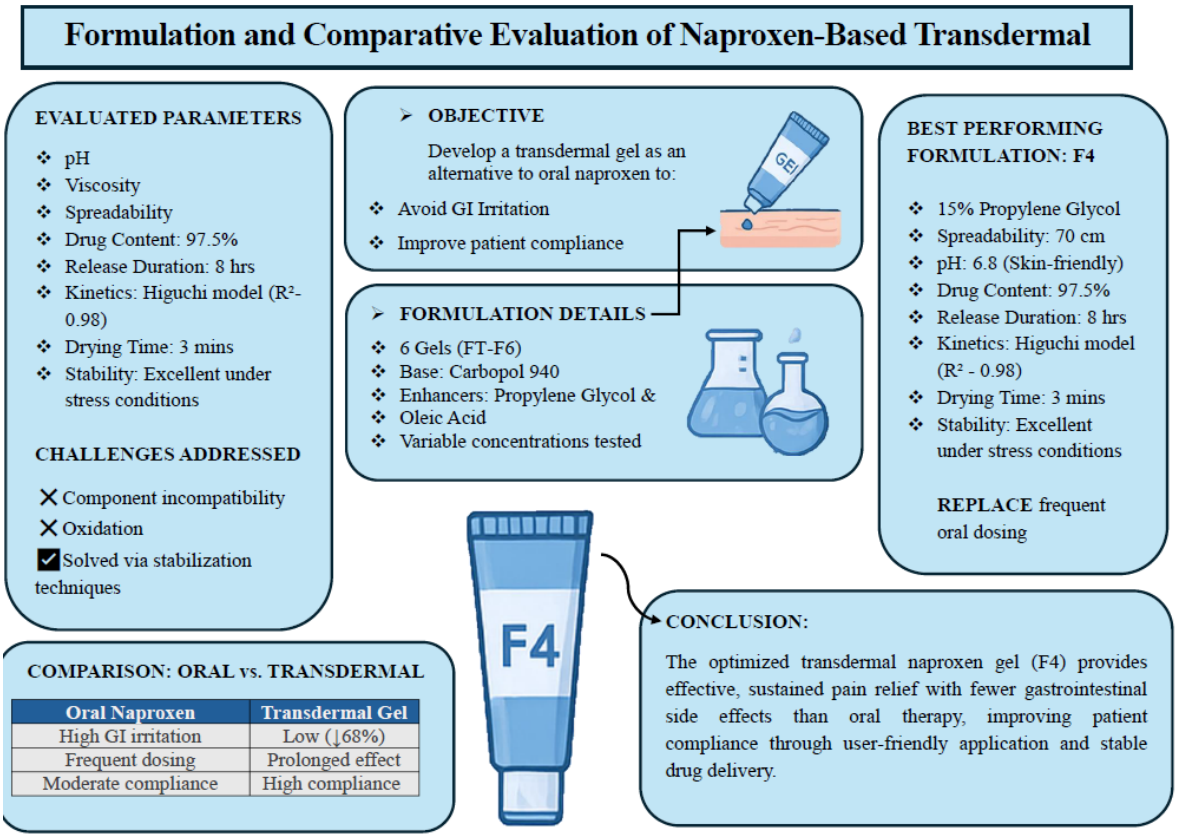
Graphical Abstract



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