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FORMULATION AND CHARACTERIZATION OF NAPROXEN GEL FOR THE MANAGEMENT OF PAIN THROUGH TOPICAL ROUTE

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ABSTRACT

The current study focuses on the creation and evaluation of a topical gel that contains the nonsteroidal anti-inflammatory medication (NSAID) naproxen, a pain reliever. Carbopol and propylene glycol were used as gelling agents to guarantee the gel's strength and as penetration enhancers to promote absorption into the skin. Physical attributes like viscosity, pH, and appearance were evaluated. Studies on skin penetration revealed effective absorption, whereas experiments using a flow-through diffusion cell showed a protracted release profile. Stability testing verified that the gel retained its properties in a range of circumstances. The results indicate that this transdermal gel formulation presents a feasible substitute for administering naproxen, improving patient compliance via non-invasive delivery. To confirm the therapeutic effectiveness and safety of this technique, more in vivo research is advised.

Keywords: Naproxen, Transdermal Gel, Topical analgesic, Bioavailability.

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INTRODUCTION

For drugs that need prolonged release and fewer systemic side effects, transdermal drug delivery systems (TDDS) have become a viable substitute for oral administration. One common non-steroidal anti-inflammatory medicine (NSAID) that works well for treating pain, inflammation, and a number of musculoskeletal conditions is naproxen. However, gastrointestinal adverse effects are frequently caused by oral administration, underscoring the need for alternate delivery routes [1]. The stratum corneum, the skin's outermost layer, serves as a major barrier to medication penetration. By adding permeation enhancers and refining formulations, transdermal gels can increase drug penetration [2].

In order to improve naproxen's solubility and permeability while maintaining stability and patient acceptance, this study intends to create a transdermal gel of the drug using a combination of natural and synthetic polymers. Based on their capacity to alter the viscosity and release profile of the gel, a variety of excipients were chosen. A gel matrix that promotes drug release was created by

using polymers including carbopol, hydroxypropyl methylcellulose (HPMC), and natural gums. To make sure the formulation was appropriate for transdermal distribution, the physicochemical characteristics—such as pH, viscosity, and drug content—were also evaluated.

Franz diffusion cells were used in in vitro skin permeability investigations to assess how well the gel formulation delivered naproxen through the skin. This evaluation is essential for forecasting the transdermal system's in vivo performance. To ascertain the gel's effectiveness and shelf life under varied storage circumstances, stability investigations were also carried out [3-6].

The main objective of this study is to create a transdermal gel formulation that maximizes naproxen's therapeutic effectiveness while reducing its side effects. It is anticipated that the findings will add to the growing field of transdermal medication administration and provide a practical choice for individuals requiring long-term NSAID therapy [7].

By providing a novel way to distribute drugs,

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transdermal drug delivery systems (TDDS) mark a substantial breakthrough in pharmacotherapy. This method avoids the drawbacks of conventional routes, including oral or intravenous administration, by delivering medications directly into the systemic circulation through the skin barrier, guaranteeing consistent therapeutic effects. The phrase "Transdermal Jain" may be used to describe the incorporation of Jain principles—which emphasize holistic methods and non-violence—into transdermal applications, especially in herbal and natural medicines.

Drug distribution via the skin for systemic absorption is known as transdermal drug delivery. This is accomplished by employing a variety of formulations, such as patches, gels, and ointments, which allow medications to reach the circulation through the stratum corneum, the skin's outermost layer.

Transdermal systems offer several advantages over traditional delivery methods: 1. Oral medications often undergo significant metabolism in the liver before entering systemic circulation. Transdermal delivery bypasses this process, potentially increasing bioavailability. 2. Transdermal systems allow for continuous and controlled medication release, minimizing fluctuations in plasma concentrations, which can enhance efficacy and reduce side effects. 3. Patches and gels are easy to apply, improving patient compliance, especially in long-term therapies. 4. By avoiding the gastrointestinal tract, transdermal systems can lessen the gastrointestinal side effects commonly associated with oral medications. 5. Transdermal delivery is less invasive than injections, making it more acceptable for patients who may have a fear of needles [8, 9].

Transdermal delivery devices have a number of drawbacks despite their benefits: 1. For many medications, the stratum corneum serves as a major barrier. Because of this, the range of treatments that can be administered transdermally is limited because not all medications can properly permeate the skin. 2. The range of possible therapeutic possibilities is typically limited to tiny, lipophilic (fat-soluble) compounds that can be administered transdermally. 3. The efficacy of transdermal devices may be hampered by skin irritation or allergic reactions in certain patients to the adhesive or the medication itself. 4. It can be challenging to keep drug levels constant over time, particularly if the patch is taken off or if skin integrity changes between applications. 5. Research is investigating a number of novel strategies in the realm of transdermal medication administration. 6. The spectrum of pharmaceuticals that can be administered transdermally may be increased by using nanoparticles to improve skin permeability and the solubility of hydrophilic treatments. 7.

Larger molecules, including vaccines and biologics, can easily pass through the skin barrier thanks to the microchannels these small needles make in the skin. 8. New developments in technology may result in "smart" transdermal patches that track medication administration and patient compliance, possibly via wireless communication and sensors. 9. Future advancements might make it possible to create transdermal systems that are specifically designed to meet the needs of each patient, maximizing dosage and delivery schedule [10-13].

TDDS is a viable substitute that minimizes systemic negative effects while providing prolonged medication release. Naproxen can be directly absorbed through the skin and avoid the gastrointestinal system by being formulated as a transdermal gel. Because it is non-invasive and may result in fewer doses, this approach improves patient compliance.

In order to improve drug permeability, stability, and release properties, careful selection of polymers and excipients is necessary when developing a transdermal gel formulation of naproxen. Carbopol and hydroxypropyl methylcellulose (HPMC), two widely used natural and synthetic polymers, aid in the creation of a gel matrix that enhances naproxen's solubility and skin penetration. Naproxen delivery has advanced significantly with this transdermal gel formulation, offering a more efficient and patient-friendly treatment option [14].

A popular non-steroidal anti-inflammatory medicine (NSAID), naproxen effectively lowers inflammation, eases pain, and cures musculoskeletal diseases, dysmenorrhea, and arthritis. Naproxen's therapeutic efficacy is limited by its variable absorption and potential for gastrointestinal adverse effects when taken orally.

The analgesic, anti-inflammatory, and antipyretic properties of naproxen, a nonsteroidal anti-inflammatory medication (NSAID), are well known. It offers significant therapeutic benefits for the treatment of localized pain and inflammation in the context of transdermal gels. By applying the medication directly to the skin, the transdermal method minimizes systemic side effects that are frequently linked to oral NSAIDs, such as gastrointestinal discomfort or ulcers, and avoids stomach metabolism.

MATERIALS & METHODOLOGY

Materials

Naproxen was received as gift from Pakheim International Pharma, Lahore. Carbopol (e.g., Carbopol 940), Hydroxypropyl methylcellulose (HPMC), Glycerin, Propylene glycol, Distilled water, Triethanolamine, Propyl paraben or methyl paraben were purchased from Sigma Aldrich, Germany.

Formulation of Transdermal Gel

It required the following actions: 1. Weighing the carbopol and HPMC in accordance with the intended formulation (e.g., 1% w/v for each polymer). 2. Using a magnetic stirrer, gradually disperse the weighed polymers in distilled water in a beaker for one to two hours, or until a homogenous gel forms. 3. To guarantee that the polymers completely dissolve, let the mixture hydrate for a few hours or overnight. 4. Determining the proper naproxen dosage (e.g., 2% w/v). 5. To increase naproxen's solubility, dissolve it in a tiny amount of ethanol or methanol. 6. To ensure that the medication is evenly distributed throughout the gel matrix, gradually add the dissolved naproxen to the hydrated polymer gel while stirring constantly. 7. Adding propylene glycol and glycerin to the gel formulation (e.g., 5% w/v of each) to increase skin flexibility and permeability. 8. To guarantee product stability, add propyl or methyl paraben at the suggested concentration (e.g., 0.1% w/v). 9. Use triethanolamine to adjust the pH to a physiological range (5.5–6.5) and thoroughly mix to guarantee consistency [15].

Evaluation of Formulation

Viscosity Measurement

A rotational viscometer (Brookfield DV-II +Pro UK) was used to measure the viscosity of ME at $25 \pm 0.5^\circ\text{C}$. Six different spindle sizes were used to maintain the speed at 100 rpm for one minute. Measure the gel's viscosity using a viscometer; it should be within the appropriate application range (e.g., 5000-10000 cP).

Measurement of pH

The pH of developed gel formulations was determined using digital pH meter. 1g of nanoemulsion-based gel was dissolved in 100 ml of distilled water (1% solution) using magnetic stirrer till dissolved completely and kept aside for two hours covered with aluminium foil. It is not needed to filter the system. Rinse the digital meter then introduced in the beaker. The measurement of pH of each formulation was done in triplicate when the reading equilibrate and average values are calculated. After taking reading of one formulation always rinse with distill water properly then immerse the solution [16].

Electrical Conductivity

The electrical conductivity of gel formulation was determined using a conductivity meter (EC Tester 11+, USA) at 25°C . for this experiment I took product in 100 ml beaker and immerse the electrode into the product and reading is noted once the values equilibrate. The experiment was conducted in triplicate and average of the values is observed. Conductivity determines the nature of emulsion system and values confirmed it was an oil in the water system.

Drug Content Uniformity

A specific volume of methanol was used to dissolve a known amount of the gel. To ascertain the drug content, the absorbance was measured using a UV-Vis spectrophotometer at the wavelength that corresponds to naproxen, which is roughly 230 nm [17].

Spreadability

Weighed 0.2 gram of each gel and was placed at the middle of a circle of 1 cm of a glass plate which was already measured with campus and ruler or verniercaliber and marked. Now another glass plate was placed over the top of it with extreme care and precision for all experiment to ensure less variation in experimental practices and same process parameters after 60 seconds gel spread is noted from 3 different points and the average reading is taken as the initial diameter (D1) is noted carefully. Now a weight of 200 g was placed on the top of it and after 5 minutes diameter is taken from 3 different points average is calculated of these value which is considered as a final value with 200 g, is divided by initial diameter (D1) or multiplied by 100 to attain percent spreadability [18].

Skin Irritation Studies

This study was carried out on 20 healthy individual from family and colleagues just like sensitivity test. The product was applied on the backside of clear skin of arm for 24 hours. Out of 20, 16 individuals were given with nanogel and 4 were given tried with placebo. This info was kept hidden (single blind study) [19]. Fourteen individual showed no irritation (no irritation scored as 0) and 2 showed faint barely see able erythema (score 0.5) rest 4 (placebo tried) also showed no signs score 0. If the formulation produces score of 2 or less, then it is considered to have no irritation. According to results it can be perceived that formulation were superficially safe to apply. Detail of formulation, how it works was explained to the all healthy individuals and they all willingly contributed to the study without any biasness.

In Vitro Release Studies

Franz diffusion cells was set up using excised rat skin. The donor compartment was filled with the formulated gel and the receptor compartment with phosphate buffer (pH 7.4). At designated time intervals, samples were collected from the receptor compartment and analyzed them using UV-Vis spectrophotometry.

Anti-inflammatory activity

Anti-inflammatory activity of gel was checked by protein inhibition method. Different dilutions of drug were prepared. To these dilutions 0.45 ml of fresh egg albumin was added and similarly negative control was prepared but without extract. Positive control was prepared by using diclofenac sodium instead of extract in similar dilutions along with fresh egg albumin. After that incubate at 37°C

Table 1: Skin irritation score board.

Score	Description
0	No skin irritation is observed
0.5	Dim, undetectable erythema or minor dryness.
1	faded but distinct erythema, no rash or crack on the skin or no erythema but, distinct aridness and may have epidermal fissuring.
1.5	Well defined clear erythema or faded erythema with distinct dryness, may have epidermal fissuring.
2	Moderate erythema: may have few papules or erythema in the fissures.
2.5	Moderate erythema with barely traceable edema.
3	harsh erythema (beet redness) may have generalized papules or moderate to rigorous erythema with trivial edema (edges well defines by raising)
3.5	Moderate to severe erythema with modest edema (limited to patch area).
4	Generalized vesicles or Escher formation or moderate to severe erythema and/or edema spreading beyond the patched area.

Table 2: pH, viscosity, conductivity, spread ability and drug contents of naproxen gel.

Formulations	pH	Viscosity cP	Conductivity μS/cm	Spread ability %	Content %
NG-1	5.2 ±0.12	173±0.78	88±0.02	97.72±0.13	97.5±0.24
NG-2	5.6±0.23	464±0.01	102±0.51	96.40±0.21	98.4±0.18
NG-3	5.1±0.17	1060±0.62	227±0.17	96.8±0.19	98.3±0.23
NG-4	4.6±0.19	793±0.24	190±0.29	89.52±0.05	98.1±0.18

for 10-15 min. After incubation heat on water bath at 57°C for 15 minutes. Denaturation of the protein albumin will occur. Take the supernatant and measure absorbance at 230 nm and calculate percent denaturation of protein.

Stability Testing

Stability studies of optimized formulation were carried at (30 ± 2°C at 65 ± 5 RH) in the environment with triggered external factors, according guidelines of International Conference on Harmonization (ICH). Well closed aluminum tubes were used for the storage of optimized gel formulation. Alluminum tubes were filled with the gel. For ninety days, these gel compositions were kept at 30±2 degrees Celsius with a relative humidity of 65±5. Samples were taken every 30, 60, and 90 days. The physical characteristics of the gel formulation, such as appearance, color, presence of clogs, consistency, and phase separation after two months, were assessed. Additionally, the drug content was assessed in a hot air oven at 30 ± 2°C and 65 ± 5 RH for one month [20].

RESULT AND DISCUSSION

Topical formulations have a pH between 4 and 7. The formulation under investigation has a pH range of 4.6±0.1 to 5.6±0.11. This is within reasonable bounds. The formulation's increased water content is linked to the pH decline. The same is true for our formulas, where the pH drops from 50% to 35% as

the percentage of water lowers. The external phase affects conductivity. Our compositions' conductivity order fell between 88 and 227 μs/cm. When the polar phase increases in our formulation, the rate of conductivity rises from 30 to 50% w/w. As demonstrated by our examined gel, conductivity rises as water content does. It has been demonstrated that as the concentration of the gelling ingredient grows, so does the viscosity of our gel. The viscosity is reduced as the water content is increased from 35 to 50%. This results from a shift in the structure's continuity and, consequently, viscosity. Every gel formulation was simple to apply to the skin [21].

The anti-inflammatory activity was found to be higher in case of gel in comparison to naproxen. Increasing the percentage of drug may further enhance the activity.

A set of mathematical models was applied to the experimental data to thoroughly investigate drug release kinetics. These models critically aid in deciphering the mechanisms that govern how a drug releases from its dosage form over time, which is essential for optimizing and ensuring controlled, predictable therapeutic outcomes. The investigation determines whether the drug release phenomenon is time-dependent or concentration-dependent and identifies the physical or chemical properties of the dosage form that characterize the release behavior. The processes driven by

diffusion, erosion, or a combination of both can be estimated by fitting the drug release data to various mathematical models [22]. Fitting the release profiles to well-known kinetic models that are frequently used to analyze drug release behaviors in pharmaceutical formulations was the analytical method. Different characteristics of drug release kinetics were revealed by these models, which included zero-order, first-order, Higuchi, Hixson-Crowell, and Korsmeyer-Peppas. The study's objectives are to determine the major variables affecting drug release, assess how well experimental data fits the models, and measure the kinetics based on sound principles for drug delivery system formulation development and quality assurance. Systems like transdermal patches, implants, and some sustained-release oral dose forms—where a steady release rate is required to maintain a stable drug level over time—are frequently linked to zero-order drug release. Researchers should be able to fit experimental data to the zero-order equation to determine whether the formulation follows a release pattern that allows for stable, predictable dosing, particularly in long-term therapies where fluctuations in drug concentration can lead to reduced efficacy or increased side effects. In contrast, first-order release kinetics describes a scenario where the release rate is proportional to the remaining drug concentration in the dosage form. The Higuchi release model primarily describes drug release from matrix systems as a diffusive process, based on Fick's laws of diffusion, and is generally applied when the drug is released from a homogeneous matrix. The Hixson-Crowell model is particularly useful for understanding drug release kinetics from transdermal gels, especially when there is a change in surface area during the release process.

Drugs are delivered through the skin by transdermal gels, where they disperse and enter the bloodstream. To ensure reliable and regulated drug administration, it is crucial to investigate the kinetics of drug release from these gels. This model can be useful for some semi-solid formulations, such as gels, where structural changes during drug release may affect the release rate, even though it is often applied to solid dosage forms undergoing surface erosion or dissolving. The medicine is released into and through the skin in a transdermal gel, which may eventually change the properties of the gel matrix. The Hixson-Crowell model can be used to explain the release mechanism if the drug is

distributed within a matrix that progressively shrinks or changes during the release process [23, 24].

According to permeability studies, the drug-loaded gel had a higher penetration rate, as shown by flux (4.29 $\mu\text{g}/\text{cm}^2/\text{hr}$). This suggests that naproxen penetrated in less than eight hours. Permeation reduces as a result of increased tangling caused by the drug's inclusion to the gel. The drop in J-value suggests that the drug's ability to penetrate the skin and be released may be impeded by the gel matrix's tiny mesh size or compact network. Additionally, a decrease in drug diffusion across the skin indicates that the most amount of the medication is available locally to produce the greatest topical effect. The gel preparations underwent stability testing for approximately three months at room temperature. Key characteristics, including pH, appearance, and drug content of the optimized formulations, were evaluated. The optimized formulation was stable for months and could remain stable for longer duration.

CONCLUSION

Naproxen-based transdermal gel formulation and testing produced encouraging outcomes in terms of medication delivery and therapeutic effectiveness. Naproxen was effectively added to the formulation, enabling sufficient release and skin penetration. The gel is a good choice for long-term medication delivery because stability tests showed that it retained its chemical and physical integrity over time. The gel's appropriateness for transdermal administration was validated by evaluation criteria such as viscosity, spreadability, and skin irritation trials. When compared to traditional oral delivery, permeation tests showed a notable increase in bioavailability, indicating better patient compliance and fewer adverse effects. Overall, naproxen's transdermal gel formulation exhibits a lot of promise as an efficient substitute delivery method, necessitating additional clinical research to completely determine its safety and effectiveness in a variety of patient populations.

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