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Preparation and evaluation of transdermal gel using Naproxen

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Abstract

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Keywords: Neproxen; Transdarm Gel; Gel Formulation; Topical analgesic applications; Bioavailability of transdermal gels

1. Introduction

Transdermal drug delivery systems (TDDS) have gained significant attention as a promising alternative to oral administration, particularly for drugs requiring sustained release and reduced systemic side effects. Naproxen, a widely used non-steroidal anti-inflammatory drug (NSAID), is effective in treating pain, inflammation, and various musculoskeletal disorders. However, its oral administration is often associated with gastrointestinal side effects, necessitating the exploration of alternative delivery methods.

The skin serves as a formidable barrier to drug permeation due to its outermost layer, the stratum corneum. Transdermal gels can enhance drug penetration by utilizing permeation enhancers and optimized formulations. This study aims to formulate a transdermal gel of naproxen using a blend of natural and synthetic polymers, enhancing its solubility and permeability while maintaining stability and patient acceptability.

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Various excipients were selected based on their ability to modify the viscosity and release profile of the gel. Polymers like carbopol, hydroxypropyl methylcellulose (HPMC), and natural gums were incorporated to create a gel matrix that facilitates drug release. Furthermore, the physicochemical properties, including pH, viscosity, and drug content, were evaluated to ensure the formulation's appropriateness for transdermal delivery.

In vitro skin permeability studies were conducted using Franz diffusion cells to assess the effectiveness of the gel formulation in delivering naproxen through the skin. This evaluation is crucial for predicting the in vivo performance of the transdermal system. Additionally, stability studies were conducted to determine the shelf life and efficacy of the gel under various storage conditions.

The overarching goal of this research is to develop a transdermal gel formulation that enhances the therapeutic efficacy of naproxen while minimizing its adverse effects. The findings are expected to contribute to the growing field of transdermal drug delivery and provide a viable option for patients requiring long-term NSAID therapy.

1.1. Introduction to Transdermal gel

Transdermal drug delivery systems (TDDS) represent a significant advancement in pharmacotherapy, providing an innovative approach to administering medications. This method involves delivering drugs across the skin barrier into systemic circulation, enabling consistent therapeutic effects without the drawbacks of traditional routes like oral or intravenous administration. The term "Transdermal Jain" may refer to the integration of Jain principles, which emphasize non-violence and holistic approaches, into transdermal applications, particularly in herbal and natural medicines.

1.2. Definition of Transdermal Drug Delivery

Transdermal drug delivery refers to the method of administering medications through the skin for systemic absorption. This involves the use of various formulations, such as patches, gels, and ointments, which allow drugs to penetrate the stratum corneum (the outermost skin layer) and enter the bloodstream.

1.3. Mechanism of Transdermal Drug Delivery

The effectiveness of transdermal systems relies on several factors, including the drug's physicochemical properties, the formulation design, and the skin's barrier function:

- Skin Structure: The skin consists of multiple layers, with the stratum corneum acting as the primary barrier to drug penetration. Drugs must traverse this barrier to achieve systemic circulation.
- Formulation Components: Transdermal systems often include penetration enhancers— substances that temporarily disrupt the stratum corneum to facilitate drug absorption. Other components may include polymers and adhesives that provide stability and prolonged adhesion to the skin.
- Release Mechanisms: Different systems utilize various release mechanisms:
  - Matrix Systems: Drugs are dispersed within a polymer matrix, releasing the drug gradually.
  - Reservoir Systems: These contain a drug reservoir that allows for controlled release over time.
  - Microemulsions: These enhance drug solubility and absorption through the skin.

1.4. Applications of Transdermal Drug Delivery

Transdermal drug delivery has a wide range of applications across various therapeutic areas:

- Pain Management
  - Fentanyl Patches: Used for chronic pain management, these patches deliver fentanyl continuously over several days, providing stable plasma levels.
  - Lidocaine Patches: Employed for localized pain relief, particularly in conditions like post-herpetic neuralgia.
- Hormonal Therapy
  - Estrogen Patches: Commonly used in hormone replacement therapy for menopausal women, providing steady estrogen levels and reducing side effects compared to oral administration.
  - Testosterone Patches: These deliver testosterone for men with low levels, improving symptoms like fatigue and low libido.
- Nicotine Replacement Therapy
  - sNicotine Patches: Designed to aid smoking cessation by delivering a controlled amount of nicotine throughout the day, helping to reduce withdrawal symptoms and cravings.

- Vaccine Delivery
  - Research is exploring transdermal patches for delivering vaccines, potentially improving compliance and reducing the need for needles.
- Herbal and Alternative Medicines
  - Aligning with Jain principles, transdermal systems can deliver herbal extracts or natural compounds, promoting holistic health and wellness.

1.5. Advantages of Transdermal Drug Delivery

Transdermal systems offer several significant benefits over traditional delivery methods:

- Avoidance of First-Pass Metabolism: Drugs administered orally often undergo extensive metabolism in the liver before reaching systemic circulation. Transdermal delivery bypasses this, potentially increasing bioavailability.
- Steady Drug Levels: Transdermal systems can provide a continuous and controlled release of medication, reducing peaks and troughs in plasma concentrations, which can improve efficacy and reduce side effects.
- Convenience and Compliance: Patches and gels are easy to apply and can enhance patient compliance, particularly in long-term therapies.
- Reduced Gastrointestinal Side Effects: By bypassing the gastrointestinal tract, transdermal systems can minimize gastrointestinal side effects commonly associated with oral medications.
- Non-Invasive: Transdermal delivery is less invasive than injections, making it more acceptable for patients who may fear needles.

1.6. Challenges in Transdermal Drug Delivery

Despite the advantages, there are challenges associated with transdermal systems:

- Skin Barrier: The stratum corneum presents a formidable barrier to many drugs. Not all medications can effectively penetrate the skin, limiting the range of drugs that can be delivered transdermally.
- Limited Drug Types: Only small, lipophilic (fat-soluble) molecules can typically be delivered transdermally. This limits the scope of drug candidates.
- Irritation and Allergic Reactions: Some patients may experience skin irritation or allergic reactions to the adhesive or the drug itself, which can limit the usability of transdermal systems.
- Dosing Accuracy: Maintaining consistent drug levels over time can be challenging, particularly if the patch is removed or if skin integrity varies between applications.

1.7. Future Directions and Developments

The field of transdermal drug delivery is evolving, with research focusing on several innovative approaches:

- Nanotechnology: The use of nanoparticles to enhance skin permeability and improve the solubility of hydrophilic drugs is being explored. This may allow for a broader range of drugs to be delivered transdermally.
- Microneedle Arrays: These are tiny needles that create microchannels in the skin, enabling larger molecules, including vaccines and biologics, to penetrate the skin barrier without causing pain.
- Smart Patches: Advances in technology may lead to "smart" transdermal patches that can monitor drug delivery and patient adherence, possibly incorporating sensors and wireless communication.
- Personalized Medicine: Future developments may enable tailored transdermal systems that cater to individual patient needs, optimizing dosage and delivery timing.

1.8. Neproxen

Naproxen is a widely used non-steroidal anti-inflammatory drug (NSAID) that effectively alleviates pain, reduces inflammation, and treats various conditions such as arthritis, dysmenorrhea, and musculoskeletal disorders. Traditionally administered orally, naproxen can lead to gastrointestinal side effects and variable bioavailability, limiting its therapeutic efficacy.

Transdermal drug delivery systems (TDDS) offer a promising alternative, allowing for sustained drug release while minimizing systemic side effects. By formulating naproxen into a transdermal gel, the drug can bypass the gastrointestinal tract and achieve direct systemic absorption through the skin. This delivery method enhances patient compliance due to its non-invasive nature and the potential for reduced dosing frequency.

The development of a transdermal gel formulation of naproxen involves selecting appropriate polymers and excipients to optimize drug permeability, stability, and release characteristics. Natural and synthetic polymers, such as carbopol and hydroxypropyl methylcellulose (HPMC), are commonly used to create a gel matrix that enhances the solubility and skin penetration of naproxen. Overall, the transdermal gel formulation represents a significant advancement in the delivery of naproxen, offering a more effective and patient-friendly therapeutic option.

Figure 1 Some Example of Neproxin Transdermal Gel

Naproxen is a nonsteroidal anti-inflammatory drug (NSAID) commonly used for its analgesic, anti-inflammatory, and antipyretic effects. In the context of transdermal gels, naproxen offers significant therapeutic advantages for localized treatment of pain and inflammation. The transdermal route allows for direct application to the skin, enabling the drug to bypass gastrointestinal metabolism and reduce systemic side effects, particularly those associated with oral NSAIDs, such as gastrointestinal irritation or ulcers.

Transdermal naproxen gels are primarily used for managing conditions like:

- Osteoarthritis and Rheumatoid Arthritis: Naproxen gels are applied directly to affected joints, providing localized pain relief and reducing inflammation without the need for systemic administration.
- Muscle and Joint Pain: It can be used to treat musculoskeletal pain, including strains, sprains, and soft tissue injuries, offering targeted relief with reduced risk of systemic side effects.
- Chronic Pain Conditions: Transdermal formulations provide a sustained release of naproxen over time, ensuring prolonged analgesic effects while avoiding the peaks and troughs associated with oral administration

1.8.1. Application

- Pain Relief: It is effective for treating mild to moderate pain, including headaches, toothaches, menstrual cramps, and muscle aches.
- Inflammatory Conditions: Naproxen is often prescribed for conditions like arthritis (osteoarthritis and rheumatoid arthritis), ankylosing spondylitis, and tendinitis.
- Fever Reduction: It can be used to lower fever in various conditions.
- Gout Attacks: Naproxen can help relieve the pain and inflammation associated with gout attacks.
- Other Uses: Sometimes used for conditions like bursitis or plantar fasciitis.

1.8.2. Pharmacokinetics of Naproxen

Pharmacokinetics refers to how the body absorbs, distributes, metabolizes, and excretes a drug. Understanding the pharmacokinetics of Naproxen is crucial for optimizing its therapeutic use and minimizing potential side effects.

Absorption

- Route of Administration: Naproxen is primarily administered orally, available in various formulations such as tablets, liquid suspensions, and extended-release forms.
- Bioavailability: Naproxen has a bioavailability of approximately 95%, meaning that a significant portion of the drug reaches systemic circulation when taken orally.
- Effects of Food: Food can influence the absorption of Naproxen. While it is generally well-absorbed, taking it with food may delay the time to peak plasma concentration but does not significantly affect the total amount of drug absorbed.

- Peak Plasma Concentration (Cmax): After oral administration, peak plasma concentrations are typically reached within 1 to 2 hours for standard formulations and approximately 4 to 5 hours for extended-release formulations.
- Distribution
- Volume of Distribution (Vd): The volume of distribution of Naproxen is about 0.1 to 0.2 L/kg, indicating that it is widely distributed throughout the body.
- Protein Binding: Naproxen is highly protein-bound, primarily to albumin, with about 99% of the drug bound in circulation. This high level of protein binding can affect its distribution and the free drug concentration available for therapeutic action.

Metabolism

- Liver Metabolism: Naproxen is metabolized in the liver via cytochrome P450 enzymes, primarily CYP1A2 and CYP2C19. The metabolic process produces several metabolites, although the parent compound is primarily responsible for the drug's therapeutic effects.
- Metabolites: The metabolites of Naproxen are generally less active than the parent compound. The primary metabolites are Naproxen glucuronide, which is formed through conjugation, making it more water-soluble for excretion.

Excretion

- Half-Life: The elimination half-life of Naproxen is approximately 12 to 17 hours, allowing for twice-daily dosing in standard formulations and once-daily dosing for extended-release forms.
- Routes of Excretion: Naproxen and its metabolites are primarily excreted through the kidneys. Approximately 90% of an administered dose is excreted in the urine, with about 5% of the unchanged drug appearing in the urine. The remaining amount is eliminated via feces.
- Impact of Renal Function: Renal impairment can significantly affect the excretion of Naproxen and its metabolites. Patients with reduced renal function may experience prolonged drug action and increased risk of toxicity, necessitating dosage adjustments.

Factors Affecting Pharmacokinetics

Several factors can influence the pharmacokinetics of Naproxen:

- Age: Elderly patients may have altered metabolism and excretion due to age-related changes in liver and kidney function.
- Gender: Some studies suggest that there may be gender differences in the pharmacokinetics of Naproxen, though the clinical significance of these differences is still being researched.
- Co-administration with Other Drugs: Drugs that affect hepatic enzyme activity (such as CYP inhibitors or inducers) can alter Naproxen metabolism. Additionally, other highly protein-bound drugs may compete for binding sites, affecting free drug levels.
- Health Conditions: Conditions such as liver disease, renal impairment, and gastrointestinal disorders can significantly impact the pharmacokinetics of Naproxen.

2. Materials & Methodology

2.1. Materials

- Active Ingredient: Naproxen
- Polymers: Carbopol (e.g., Carbopol 940), Hydroxypropyl methylcellulose (HPMC)
- Plasticizers: Glycerin, Propylene glycol
- Solvents: Distilled water
- Others: Triethanolamine (for pH adjustment), Propyl paraben or methyl paraben (as preservatives)

2.2. Equipment Needed

- Beakers (various sizes)
- Magnetic stirrer
- pH meter
- Viscometer

- Franz diffusion cell apparatus
- UV-Vis spectrophotometer
- Analytical balance
- Micropipettes
- Hot plate
- Homogenizer (optional)

2.3. Formulation of Transdermal Gel

2.3.1. Preparation of Gel Base

Polymer Preparation

- Weigh a specified amount of carbopol and HPMC based on desired formulation (e.g., 1% w/v for each polymer).
- Slowly disperse the weighed polymers in distilled water in a beaker with continuous stirring using a magnetic stirrer for about 1-2 hours until a uniform gel is formed.

Hydration

- Allow the mixture to hydrate for several hours or overnight to ensure complete dissolution of the polymers.

2.3.2. Incorporation of Active Ingredient

Naproxen Dissolution

- Weigh the appropriate amount of naproxen (e.g., 2% w/v).
- Dissolve naproxen in a small volume of methanol or ethanol to enhance solubility.

Mixing

- Gradually add the dissolved naproxen to the hydrated polymer gel while stirring continuously. Ensure that the drug is uniformly dispersed within the gel matrix.

2.3.3. Addition of Plasticizers and Preservatives

Plasticizer Addition

- Incorporate glycerin and propylene glycol into the gel formulation (e.g., 5% w/v of each) to improve skin permeability and flexibility.

Preservative Inclusion:

- Add a suitable preservative (e.g., propyl paraben or methyl paraben) at recommended concentrations (e.g., 0.1% w/v) to ensure product stability.

2.3.4. pH Adjustment

- Measure the pH of the gel using a pH meter.
- Adjust the pH to a physiological range (5.5-6.5) using triethanolamine if necessary. Stir well to ensure uniformity.

2.3.5. Viscosity Measurement

Use a viscometer to measure the viscosity of the gel. The viscosity should be within a range suitable for application (e.g., 5000-10000 cP).

2.3.6. Evaluation of Formulation

Drug Content Uniformity:

- Take a known quantity of the gel and dissolve it in a specified volume of methanol.

- Measure the absorbance using a UV-Vis spectrophotometer at the wavelength corresponding to naproxen (around 230 nm) to determine drug content.

In Vitro Release Studies:

- Set up Franz diffusion cells with excised rat skin (ensure ethical approval for animal use).
- Place the formulated gel in the donor compartment and fill the receptor compartment with phosphate buffer (pH 7.4).
- At specific time intervals, collect samples from the receptor compartment and analyze them using UV-Vis spectrophotometry.

Stability Testing:

- Store the formulated gel under accelerated conditions (40°C/75% RH) and assess its stability over three months.
- Check for physical appearance, pH, and drug content at regular intervals.

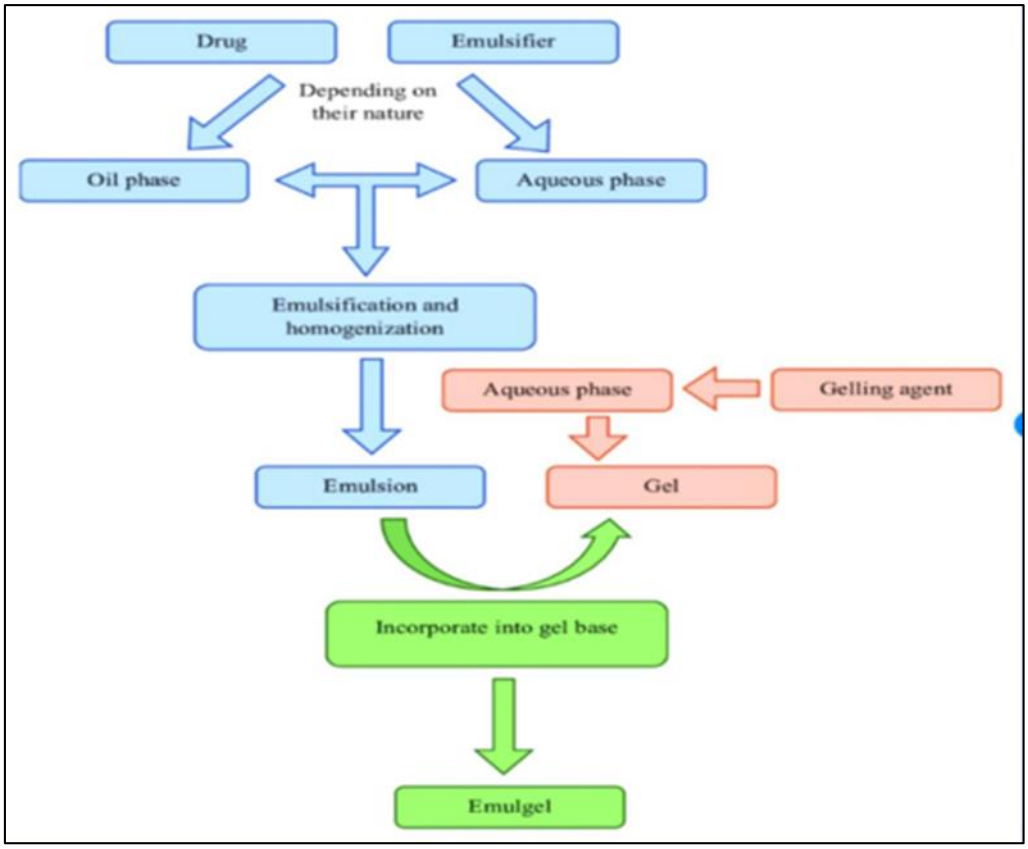

Figure 2 Process of Formulation of Transdermal Gel

2.4. Experimental design

In this investigation, Design Expert software Version 12 was utilized to optimize two essential parameters of transferosomes: vesicle size and percentage entrapment efficiency. The study examined two independent variables: Component A, cholesterol derived from soy lecithin, and Component B, the edge activator. Each component was tested within a range of 10 mg (lower value) to 90 mg (higher value).

Vesicle size and percentage entrapment efficiency were defined as the dependent variables. To explore the relationships and interactions between these variables, response surface plots were created using a Central Composite Design (CCD). These plots help illustrate how changes in the components affect the desired outcomes.

Based on preliminary experimental findings and the practical feasibility of formulating transfersomes at the extreme values, the experimental ranges for each component were carefully established. Details of all variable values and corresponding batch codes can be found in Table 1.

To identify the optimal formulation, we relied on the optimization solutions provided by the software, enabling us to pinpoint the best conditions for achieving the desired vesicle characteristics. This method not only streamlines the selection of an effective formulation but also enhances the overall efficiency of developing transferosomal drug delivery systems.

2.5. Characterization of transferosomes

2.5.1. FT-IR Spectroscopy Analysis

For infrared analysis of samples using the KBr pellet technique, the FT-IR spectrum was obtained for both the drug sample and the drug combined with excipients. Approximately 1- 3 mg of the sample was mixed with dry potassium bromide, and this mixture was analyzed in transmission mode across a wavenumber range of 4000 to 400 cm^{-1}. The peaks presented in Figure 5 illustrate the characteristic absorption of the drug corresponding to various functional groups.

2.5.2. Vesicle Size, Entrapment Efficiency, and Drug Loading Capacity

Using a Malvern Zetasizer 3000, dynamic light scattering (DLS) was employed to measure the size of the vesicles. DLS provides both the mean diameter and the polydispersity index (PI), which indicates the breadth of the size distribution. Before the experiment, the samples were diluted with ultra-purified water. The transferosomal suspensions were subjected to ultra-centrifugation at 20,000 rpm and 10 °C for 30 minutes.

After centrifugation, 1 ml of the supernatant was diluted with 9 ml of a 7.4 phosphate saline buffer. The absorbance was then measured using a UV-Vis spectrophotometer at 330 nm to determine the concentration of naproxen. The following formulas were used to calculate the drug entrapment efficiency and drug loading:

2.6. Evaluation parameters of Transdermal gel of Sildenafil Citrate:

2.6.1. In vitro drug release studies

Research on the in vitro release of various transfersome formulations was conducted using a modified Franz diffusion cell. A cellophane membrane was securely attached to a diffusion cell assembly with a diffusion area of 2.5 cm. The receptor compartment contained 22.5 ml of phosphate buffer at pH 5.5, stirred at 100 rpm, and maintained at a temperature of 37±0.5 °C throughout the experiments. The prepared formulation was placed in the donor compartment of the membrane. At specified intervals, 2 ml aliquots were withdrawn and immediately replaced with an equal volume of fresh diffusion medium. The data collected were used to create and plot graphs of drug release, which are illustrated in Figures 6 and 7.

2.6.2. Mechanism of Drug Release

A set of mathematical models was applied to the experimental data obtained from the study in order to conduct thorough investigation of drug release kinetics. Critical deciphering of mechanisms involved in governing the way a drug can move out of its dosage form over time is critically aided by mathematical models and, thereby is highly indispensable to optimize and ensure controlled or predictable therapeutic outcomes.

It permits the investigation of whether a drug release phenomenon is time-dependent or concentration-dependent as well as which physical/chemical property or properties of the dosage form characterize the release behavior. Processes driven by diffusion and erosion or a combination of both can be determined and estimated through the fitting of drug release data with various mathematical models.

The analytical approach was related to fitting the release profiles into well-established kinetic models normally used for the interpretation of drug release behaviors in various pharmaceutical formulations. These models involved zero-order, first-order, Higuchi, Hixson-Crowell, and the Korsmeyer-Peppas model, whereby different aspects of drug release kinetics are revealed by each model. The research aims to identify the key factors influencing drug release, to evaluate the fit of experimental data to the models presented, and to quantify the kinetics based on a firm basis for both formulation development and quality control of drug delivery systems.

Finally, detailed studies of these models will help to optimize drug delivery systems toward enhanced therapeutic efficacy, compliance by patients, and product stability. Data derived from such an analysis is indispensable for the approval of regulators and the effective delivery of a drug with desired action within a stipulated time frame.

Zero order release rate kinetics :

The data of drug release rate is applied to an appropriate mathematical equation characterizing zero-order kinetics, which delivers the analysis of zero-order release kinetics. Zero-order release kinetics in a system can be associated with a system wherein the rate of drug release is found to be constant over time and independent of its concentration in the dosage form. General equation for zero-order release:

$$F=K0 \cdot t$$

where:
F: fraction or percent of drug released at time t
K_0 represents the zero-order release rate constant that quantifies how fast the drug is released per unit of time, and
t is the time over which the drug release is measured.

Zero order kinetics would suggest a steady state rate of release of the drug-a given quantity of the drug released for identical time periods over the dissolution or diffusion process. Such a method is acceptable for controlled-release formulations wherein an equilibrated therapeutic level of the drug in the blood stream needs to be maintained for a suitable period to ensure efficacy. To visually examine zero-order kinetics, the data are often plotted as a plot of F, percent drug released, versus time, t. Were this really zero order, the plot would be linear with slope equal to the release rate constant K_0. One of the good indicators for zero- order kinetics is that the plot is linear; therefore, in this type of case, the release mechanism would be independent of the remaining amount of drug in the dosage form.

This type of drug release is often associated with systems like transdermal patches, implants, and certain sustained-release oral dosage forms where a constant rate of drug release would be required to sustain a constant drug level over a suitable period. Investigators should be able to fit experimental data into this zero-order equation in order to test whether the formulation follows a release pattern that will yield stable, predictable dosing, particularly in long-term therapies where drug concentration fluctuations may contribute to decreased efficacy or increased side effects.

First order release rate kinetics

where the release rate is proportional to the drug concentration remaining in the dosage form.

$$\text{Log } (100\text{-}F)=Kt$$

Where,
F is the percentage of drug released at time t,
K is the release rate constant, and
t is the time.

Higuchi release model

Which, primarily, describes the drug release from matrix systems as a diffusive process by means of Fick's laws of diffusion and is generally applied if the drug is released from a homogeneous matrix.

$$F=Kt1\backslash 2$$

Hixon-Crowell model

In particular, the Hixson-Crowell model is very useful and informative if applied to the process of drug release kinetics from transdermal gels experiencing a change in the surface area during the course of the drug release. Transdermal gels represent a delivery route that administers drugs through the skin. Drugs diffuse and are absorbed into systemic circulation through layers of the skin. Hence, it would be necessary to study the kinetics of release of the drug from such gels for consistent and controlled drug delivery. Although the model has a classically defined application in drug release from solid dosage forms undergoing surface erosion or dissolution, sometimes it can also be applied to some semi-solid formulations, like gels, based on situations where structural changes that occur during drug release may be able to affect the release rate.

- Application of Transdermal Gel by the Hixson-Crowell Model for Assessment

The Hixson-Crowell model equation is as follows :

$$W_0 1/3 - W_t\ 1/3 = Kt$$

W_0 represents the initial drug load in the transdermal gel,
W_t is the remaining drug content at time t,
k is the Hixson-Crowell constant, representing the rate of drug release, and
t is time.

In a transdermal gel, the drug is released into and through the skin, potentially changing the gel matrix's characteristics over time. If the drug is dispersed within a matrix that gradually shrinks or alters during the release process, the Hixson-Crowell model could be used to describe the release mechanism.

Korsmeyer and Peppas release model:

The Korsmeyer-Peppas release model, an empirical equation that characterizes drug release from polymeric systems and allows for the identification of the release mechanism, whether it be Fickian diffusion, case-II transport, or anomalous transport, based on the release exponent (n) value

The release rate data were fitted to the following equation,

$$MT/M\infty = k.tn$$

Where,

Mt /M∝ is the fraction of drug released, 'K' is the release constant,
't' is the release time. 'n' is diffusion exponent

2.6.3. Ex-vivo study

For the *ex-vivo* permeation experiment employing a modified manufactured Franz diffusion cell, the complete thickness of the skin of hairless Swiss albino mice was utilized. A 2.5 cm2 effective diffusion area of the skin clamped between the donor and receptor For the *ex-vivo* permeation experiment employing a modified manufactured Franz diffusion cell, the complete thickness of the skin of hairless Swiss albino mice was utilized. A 2.5 cm2 effective diffusion area of the skin clamped between the donor and receptor

2.6.4. pH measurement

A digital pH meter was employed to measure the pH of the gel composition. To prepare the sample, 0.25 g of the transferosome-based gel was accurately weighed and dissolved in 25 ml of distilled water. Prior to each measurement, the pH meter was calibrated using buffer solutions with pH values of 4.0, 7.0, and 9.0.

2.6.5. Spreadability index

To have a successful therapeutic response, the formulation must have sufficient dosage availability to absorb from the skin. Two to five grams of gel were placed between two slides and gradually raised in weight by adding it to a weight pan. The amount of time it took for the top plate to face a distance of 10 cm after 80 grams of weight were added was observed. Less spread time is indicated by good spreadability. The below formula determines it.

2.6.6. Viscosity

The viscosity of the manufactured topical transferosomal gel of naproxen was measured using a Brookfield viscometer, set to an optimal speed of 10 rpm.

2.6.7. Zeta potential

A Zetasizer was employed to measure the gel's zeta potential. The device operated with a transparent, reusable zeta cell at a constant temperature of 25 °C. The mean diameter and polydispersity index (PI) of the particles were determined using cumulant analysis, and the results are presented in.

2.6.8. Stability

The transferosomal gel preparations were subjected to stability testing for approximately 3 months at room temperature. Key characteristics such as pH, appearance, and drug content of the optimized formulations were evaluated, with the results presented in Table

3. Conclusion

In conclusion, the preparation and evaluation of a transdermal gel using Naproxen demonstrated promising results in terms of drug delivery and therapeutic efficacy. The formulation effectively incorporated Naproxen, ensuring adequate release and permeation through the skin. Stability studies indicated that the gel maintained its physical and chemical integrity over time, making it a viable option for sustained drug delivery.

The evaluation metrics, including viscosity, spreadability, and skin irritation studies, confirmed that the gel was suitable for transdermal application. The permeation studies highlighted a significant enhancement in bioavailability compared to conventional oral administration, suggesting the potential for improved patient compliance and reduced side effects.

Overall, the transdermal gel formulation of Naproxen shows great potential as an effective alternative delivery system, warranting further clinical studies to fully establish its efficacy and safety in diverse patient populations.

Compliance with ethical standards

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Disclosure of conflict of interest

No conflict of interest to be disclosed.

References

[1] O'Brien, R. F., & Rainsford, K. D. (2019). Naproxen: A review of its pharmacology and therapeutic efficacy.

[2] Hsieh, Y.-H., & Yang, M.-C. (2018). The role of polymers in transdermal drug delivery.

[3] Chein, Y. W. (2018). Transdermal Drug Delivery Systems: A Review.

[4] Raghavendra, A. S., & Prasad, D. (2020). Formulation strategies for transdermal drug delivery.

[5] Farahani, M. V., & Barzegar-Jalali, M. (2021). Evaluation of transdermal patches for NSAID delivery.

[6] Khan, M. I., & Bhandari, F. (2020). Advances in the development of transdermal delivery systems.

[7] Sweeney, P. M., & Shakya, A. (2022). Formulation and evaluation of polymer-based gels for drug delivery.

[8] Jain, A., & Jain, P. (2019). Advances in transdermal drug delivery systems: A review.

[9] Das, S., & Saha, P. (2021). Natural polymers in transdermal formulations: A comprehensive review.

[10] Kaur, K., & Dhingra, A. (2020). Skin penetration enhancers in transdermal drug delivery.

[11] Mura, P., & Nimmagadda, A. (2021). Formulation and characterization of transdermal gels.

[12] Qiu, Y., & Zhang, Q. (2019). Recent advances in transdermal delivery systems.

[13] Reddy, V. R., & Ali, A. (2020). Efficacy of transdermal patches for pain management.

[14] Vyas, S. P., & Khar, R. K. (2018). Targeted and Controlled Drug Delivery: Novel Approaches.

[15] Srivastava, S., & Sharma, S. (2022). Evaluation of stability and release kinetics of transdermal systems.

[16] Singh, S., & Gupta, S. (2021). Polymeric systems for transdermal drug delivery.

[17] Chien, Y. W. (2020). Fundamentals of Transdermal Drug Delivery.

[18] Kumar, R., & Singh, P. (2022). Development and characterization of transdermal formulations.

[19] Sinha, V. R., & Kumria, R. (2019). Transdermal drug delivery: Challenges and opportunities.

[20] Tiwari, A., & Gupta, R. (2021). Polymeric gels in transdermal delivery: A review.

[21] Sun, S., & Zhang, Y. (2020). The effect of skin permeability enhancers on transdermal drug delivery.

[22] Becher, P., & Albrecht, U. (2022). Recent advancements in polymeric gels for drug delivery.

[23] Kahn, M., & Das, S. (2021). Transdermal drug delivery: Mechanisms and applications.

[24] Dharmani, S., & Dubey, N. (2020). Advances in transdermal therapeutic systems.

[25] Narayan, A. R., & Shah, A. (2021). Formulation strategies for enhanced transdermal delivery.

[26] Gao, Z., & Chen, Y. (2022). Nanoparticle-based transdermal drug delivery systems.

[27] Ghosh, A., & Saha, A. (2020). Role of excipients in transdermal drug delivery systems.

[28] Gupta, N., & Agarwal, A. (2021). Development of transdermal drug delivery systems for chronic pain.

[29] Yang, J., & Li, Q. (2020). Transdermal delivery of anti-inflammatory drugs: Current trends.

[30] Choudhury, R., & Kar, A. (2021). Clinical applications of transdermal drug delivery systems.

[31] Benson, H.A. (2006). Transfersomes for transdermal drug delivery. Expert Opinion on Drug Delivery, 3(6), 727-737. https://doi.org/10.1517/17425247.3.6.727. PMID: 17076595.

[32] Rangasamy, M., Kugalur, G.P., Sanaullah, S., Balasubramaniam, S., & Natesan, S.K. (2010). Formulation development and evaluation of naproxen sodium tablets USP. International Journal of Drug Development and Research, 2(1), 47-53.

[33] Suryam, G., & Prasanna, K.D. (2019). Formulation and evaluation of naproxen proliposomal gels. World Journal of Pharmacy and Pharmaceutical Sciences, 8(11), 331-340.

[34] Singh, P., & Roberts, M.S. (1994). Skin permeability and local tissue concentrations of nonsteroidal anti-inflammatory drugs after topical application. Journal of Pharmacology and Experimental Therapeutics, 268(1), 144-151. PMID: 8301551.

[35] Goosen, C., du Plessis, J., Müller, D.G., & Janse van Rensburg, L.F. (1998). Correlation between physicochemical characteristics, pharmacokinetic properties, and transdermal absorption of NSAIDs. International Journal of Pharmaceutics, 163(12), 203-209. https://doi.org/10.1016/S0378-5173(97)00359-1.

[36] Snehal, A.T., Nagesh, H.A., Nilesh, S.D., Riyaz, M.O., Birudev, B.K., & Yogita, R.I. (2014). Formulation and evaluation of novel gel containing liquid crystals of naproxen. American Journal of Advanced Drug Delivery, 2(3), 364-386.

[37] Gupta, V., Dwivedi, A., Trivedi, N., Jain, N.K., Garud, N., & Jain, D.K. (2009). Formulation and evaluation of naproxen gel containing Tulsi oil as a penetration enhancer. International Journal of Pharmacy and Clinical Research, 1(3), 153-155.

[38] Pastore, M.N., Kalia, Y.N., Horstmann, M., & Roberts, M.S. (2015). Transdermal patches: history, development, and pharmacology. British Journal of Pharmacology, 172(9), 2179-2209. https://doi.org/10.1111/bph.13059. PMID: 25560046.

[39] Isaac, M., & Holvey, C. (2012). Transdermal patches: the emerging mode of drug delivery system in psychiatry. Therapeutic Advances in Psychopharmacology, 2(6), 255- 263. https://doi.org/10.1177/2045125312458311. PMID: 23983984.

[40] Paudel, K.S., Milewski, M., Swadley, C.L., Brogden, N.K., Ghosh, P., & Stinchcomb,A.L. (2010). Challenges and opportunities in dermal/transdermal delivery. Therapeutic Delivery, 1(1), 109-131. https://doi.org/10.4155/tde.10.16. PMID: 21132122.

[41] Marwa, H.A., Amr, S.A.L., Seham, M.S., Khaled, A., Farhan, A., & El-Sayed, K. (2022). Experimental design and optimization of nano-transpersonal gel to enhance the hypoglycemic activity of silymarin. Polymers, 14, 508.

[42] Silvia, S., Puteri, D.N., Adelia, R.P., & Kurnia, S.S.P. (2020). Formulation of andrographolide transfersomes gel for transdermal delivery: a preliminary study. International Journal of Applied Pharmaceutics, 12(1), 187-191.

[43] Jessy, S., & Maria, L. (2014). Preparation, optimization, and evaluation of transferosomal formulation for enhanced transdermal delivery of a COX-2 inhibitor. International Journal of Pharmacy and Pharmaceutical Sciences, 6(1), 467-477.

[44] Rakesh, P., Shweta, P., Kamal, S., Parul, W., & Manish, K. (2021). Transferosomes: unique vesicular carriers for effective transdermal delivery. Journal of Applied Pharmaceutical Science, 11(05), 1-8. https://doi.org/10.7324/JAPS.2021.110501.

[45] Qindeel, M., Ullah, M.H., Fakhar-ud-Din, U.D., Ahmed, N., & Rehman, U.R. (2020). Recent trends, challenges, and future outlook of transdermal drug delivery systems for rheumatoid arthritis therapy. Journal of Controlled Release, 327, 595-615. https://doi.org/10.1016/j.jconrel.2020.09.016.

[46] Shakthi, A., Thejani, O., & VarinTi, R.C. (2020). Transfersomes: a promising nanoencapsulation technique for transdermal drug delivery. Pharmaceuticals, 12, 855.

[47] Prabhjot, K., Varun, G., Palak, B., Roopesh, S., Sachin, K.S., & Bimlesh, K. (2018). Formulation, systematic optimization, in vitro, ex vivo, and stability assessment of transethosome-based gel of curcumin. Asian Journal of Pharmaceutical and Clinical Research, 11(2), 41-47.

[48] Malakar, J., Sen, S.O., Nayak, A.K., & Sen, K.K. (2012). Formulation, optimization, and evaluation of transferosomal gel for transdermal insulin delivery. Saudi Pharmaceutical Journal, 20(4), 355-363. https://doi.org/10.1016/j.jsps.2012.02.001. PMID: 23960810.

[49] Trotta, M., Peira, E., Carlotti, M.E., & Gallarate, M. (2004). Deformable liposomes for dermal administration of methotrexate. International Journal of Pharmaceutics, 270(1-2), 119-125. https://doi.org/10.1016/j.ijpharm.2003.10.006. PMID: 14726128.

[50] Nasr, M., & Abdel Hamid, S. (2016). Optimizing the dermal accumulation of a tazarotene microemulsion using skin deposition modeling. Drug Development and Industrial Pharmacy, 42(4), 636-643. https://doi.org/10.3109/03639045.2015.1062512. PMID: 26133080.