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TRANSDERMAL ADMINISTRATION OPTIMIZATION: INCREASINGNAPROXEN SODIUM'S EFFICACY IN A TOPICAL HYDROGEL FORMULATION

MASTER THESIS

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Nour Saaydeh01.05.2024

DEDICATION

I dedicate this thesis to my dear family, especially my beloved mother (Faten Qadri) and my brothers, sisters, and friends, who have continuously supported me in all aspects of my life. Their support has truly inspired me to become the best version of myself. I am forever grateful for everything they have done for me. May their love and encouragement always guide me towards success and fulfilment. This thesis is a testament to their influence, a tribute to their enduring presence in my heart and mind.

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LIST OF SYMBOLS AND ABBREVIATIONS

HPLC	High Performance Liquid Chromatography
NS	Naproxen Sodium
HPMC	Hydroxypropyl Methylcellulose
NSAID	Non-steroidal Anti-inflammatory Drug
MeOH	Methanol
DMSO	Dimethyl Sulfoxide
TDDS	Transdermal Drug Delivery System
SC	Stratum Corneum
L	Liters
ML	Milliliters
G	Grams
Mg	Milligram
µg	Microgram
M	Molar
mM	Millimolar
PH	Potential of Hydrogen
°C	Celsius
WHO	World Health Organization
w/w	Weight to weight
vivo	Within the living
in vitro	Within the laboratory
%	Percent sign
Jss	The steady-state flux
Q	The cumulative amount
RA	Rheumatoid arthritis
SC	Stratum corneum
Rpm	Rounds per minute
hrs	Hours

cm−2	Centimetre power–2
SD	Standard Deviation

ABSTRACT

Transdermal Administration Optimization: Increasing Naproxen Sodium's Efficacy in a Topical Hydrogel Formulation. Yeditepe University, Institute of Health Science, Department of drug and Cosmetic Technology, MSc thesis, Istanbul.

The transdermal drug delivery (TDDS) system is a promising alternative to conventional oral administration, particularly for pain management medications like naproxen sodium. The main challenge in developing a TDDS is overcoming the many barriers the skin poses. These include its physical characteristics, such as its thickness and the presence of hair follicles; biochemical characteristics, such as the composition of the stratum corneum; and immunological characteristics, such as the presence of immune cells in the skin. [53] Rheumatoid arthritis (RA) is a medical disorder characterized by an abnormal immune response. Symptoms include joint swelling, redness, chronic inflammation, discomfort, and decreased strength. The World Health Organization (WHO) has documented an increased global prevalence of arthritis among women (18%) compared to men (9.6%). [54] This study presents a novel approach within the Transdermal Drug Delivery System (TDDS) field by combining innovative methods. This approach incorporates a naproxen microemulsion formulated as an Emulgel, 30% dimethyl sulfoxide (DMSO) and facilitated by dermaroller application. This study investigated the enhancement of skin permeation for the lipophilic drug naproxen (5%). We achieved this by incorporating a naproxen microemulsion containing 2% lecithin (C10NE) into a 10% hydroxypropyl methylcellulose (HPMC) hydrogel formulation (Emulgel). A separate formulation (C10ND 30%) was also prepared by adding 30% dimethyl sulfoxide (DMSO) to the 10% HPMC hydrogel containing Naproxen. The study evaluates the fluxes of different hydrogel formulations containing Naproxen over a 24-hour, administered via dermaroller application, and assesses their penetration through pig skin using the Franz diffusion method. Statistical analysis reveals a notable increase in the transdermal penetration of Naproxen (5%) hydrogel formulations on pig skin and cellulose membranes. A comparative study between a commercially available Naproxen gel (MG) and formulations coded as C10NE and C10ND 30% demonstrates an approximate 25% increase in transdermal penetration for both coded formulations ($p < 0.001$). Further comparison with a hydroxypropyl methylcellulose (HPMC) hydrogel (C10N) containing Naproxen indicates a threefold enhancement in transdermal penetration for formulations coded as C10NE and C10ND 30% ($p < 0.0001$), compared to both the plain HPMC (10%) (C10N) hydrogel formulation and a commercially available gel

formulation (MG). These findings suggest that the C10NE and C10ND 30% formulations hold

promise for enhancing the efficacy of Naproxen sodium.In conclusion, this research is a significant step forward in the field of transdermal drug delivery systems (TDDS). It not only presents a novel approach but also proposes a viable strategy for improving the therapeutic efficacy of Naproxen sodium and potentially other drugs across various therapeutic applications. Our study also observes increased (5%) Naproxen fluxes with the chemical enhancer dimethyl sulfoxide (DMSO) (30%) compared to existing market formulations, further highlighting the potential of our approach.

Key Words: Naproxen sodium, Transdermal Drug Delivery System, Dimethyl Sulfoxide, PigSkin, Hydroxypropyl Methylcellulose

ÖZET

Transdermal Yolla Verimin Optimizasyonu: Topikal Hidrojel Formülasyonunda Naproksen Sodyumun Etkisinin Arttırılması Yeditepe Üniversitesi, Sağlık Bilimleri Enstitüsü, İlaç ve Kozmetik Teknolojisi Anabilim Dalı, Yüksek Lisans Tezi, İstanbul.

Transdermal ilaç taşyıcı sistemler 'Transdermal Drug Delivery Systems' (TDDS), özellikle naproksen sodyum gibi ağrı yönetimi ilaçları için geleneksel oral uygulamaya alternatif bir yöntem olarak umut vaat etmektedir. Bir TDDS geliştirmenin ana zorluğu, derinin birçok engelini aşmaktır. Bunlar, fiziksel özellikleri, stratum corneumun bariyer oluşturması, kalınlığı ve saç foliküllerinin varlığı gibi; biyokimyasal özellikleri, stratum korneumun bileşimi gibi; ve immünolojik özellikleri, derideki bağışıklık hücrelerinin varlığı gibi. Romatoid artrit (RA), anormal bir bağışıklık yanıtı ile karakterize edilen bir tıbbi bozukluktur. Belirtiler arasında eklem şişliği, kızarıklık, kronik iltihaplanma, rahatsızlık ve güç azalması bulunur. Dünya Sağlık Örgütü (WHO), kadınlar arasında (%18) erkeklere (%9,6) göre artrit yaygınlığında artış olduğunu belgelemiştir. Araştırmamız, TDDS alanını devrim niteliğinde değiştirebilecek potansiyele sahiptir. Baz olarak Hidroksipropil metilselüloz (HPMC) %10 hidrojel (C10N) formülasyonları hazırlanıp, yenilikçi yöntemler kullanarak, Naproksen mikroemülsiyon (Emulgel) ve 30 % dimetil sülfoksit (DMSO) ilavesi ve dermaroller uygulamaları ile lipofilik ilaç naproksenin (%5) deriye geçişini başarılı bir şekilde artırdık. Bu formülasyonlar, dimetil sülfoksit (DMSO) gibi deriden emilimi arttırıcı özelliği ve bir emülsiyon hidrojel formülasyonu gibi deri penetrasyonunu iyileştirecek şekilde tasarlanmıştır. Ayrıca bu çalışmada domuz derisi ve selüloz membranlara uygulandığında Naproksen hidrojel formülasyonlarının deri penetrasyonunda önemli bir artış göstermiştir. Naproksen ile hazırlanan farklı hidrojel formülasyonları özellilkle 24 saatlik bir süre boyunca değerlendirilmiştir. Naproksen mikro emülsiyon formülasyonu soya lesitini (2%) yardımıyla hazırlanıp, HPMC (10%) hidrojele dahil etmek suretiyle Emulgel ($C10N^E$) hazırlanmıştır. İkinci başarılı formülasyon ise naproksen içeren HPMC (10%) hidrojele 30 % DMSO (C10ND 30%) ilavesi şeklindedir. domuz derisinde yapılan ve dermaroler uygulaması ile v Franz difüzyon penetrasyon çalışması ile elde edilen Naproksen konsanrasyonu (24 saat sonunda) istatiksel olarak değerlendirilmiştir. Piyasada bulunan bir Naproksen jel (MG) formülasyonu ile C10NE kodlu formülasyonu ve C10ND 30% kodlu formülasyonu karşılaştırıldığında her iki formülayon için Naproksenin transdermal penetrasyonu yaklaşık 25 % oranında artığı gösterilmiştir ($p < 0,001$). $C10N^E$ kodlu

formülasyon ve C10ND 30% kodlu formülasyonu naproksen içeren HPMC (10%) hidrojel (C10N) karşılaştırıldığında Naproksenin transdermal penetrasyonu üç kat arttığı gözlenmiştir ($p < 0,0001$). Bu çalışmada elde edilen sonuçlar göstermiştir ki naproksen sodyumunun etkinliğini artırmak için çalışmada kullanılan C10NE ve C10ND 30% kodlu formülasyonların umut verici yaklaşımlar olduğu düşünülmektedir.

Anahtar Kelimeler: Naproksen sodyum, Transdermal İlaç Dağıtım Sistemi, Dimetil Sülfoksit,Domuz Derisi, Hidroksipropil Metilselüloz

1. INTRODUCTION

Percutaneous delivery provides a noninvasively path for administering drugs for localized and systemic purposes, although its effectiveness is curtailed by the skin's natural resistance to foreign substances. The stratum corneum (SC), The epidermis, the outermost layer of the skin, isthe primary obstacle to preventing absorption. By thoroughly evaluating parameters such as the potency of the active component, its physicochemical properties, the formulation, and delivery techniques, it is feasible to improve penetration to achieve both medical and aesthetic advantages. [55] Drug delivery through the skin offers a needle-free option for local and systemic treatment but is limited by the protective barrier of the skin. The SC, the outermost layer of the skin, mainly hinders the absorption of drugs. By strategically selecting the drug's concentration, its physical and chemical properties, the type of formulation, and the delivery method, penetration through the skin can be improved, enabling both therapeutic and cosmetic effects. [55] Utilizing dermal permeation enhancers can increase the rate at which drugs traverse the skin layers, boosting the absorption of compounds that might otherwise exhibit low systemic or topical uptake. Selecting the appropriate enhancer and optimizing its efficacy necessitates an understanding of its mechanisms and how they synergize with the physicochemical properties of the drug and its delivery system. In order to enhance the transdermal absorption of naproxen, the use of penetration enhancers and appropriate vehicles/cosolvents is necessary. otherwise, only minimal quantities of naproxen can permeate the skin. [30] Multiple penetration enhancers are successful in elevating the permeation speed through the skin and enhancing the delivery of drugs that are typically poorly absorbed when administered systemically or topically.

Determining the most suitable enhancer and fine-tuning its ability to enhance penetration involves comprehending how the enhancer works in conjunction with the physicochemical attributes of both the active drug and the carrier used. [56] The use of certain agents can improve the speed of drug penetration through the skin, aiding the absorption of medications that typically do not absorb well through traditional systemic or topical methods. The right choice of such an agent, along with adjustments to maximize its penetration-enhancing properties, requires knowledge of how it interacts with the drug's physical and chemical nature and its formulation.

This thesis aims to employment of specific compounds can enhance the transdermal absorption rate, facilitating better uptake of drugs that generally have low absorption via oral or topical pathways. This process involves carefully selecting a compatible enhancer and tailoring its use toaugment its effectiveness in concert with the drug's inherent properties and the composition of the delivery vehicle.

The significance of this research lies in its potential to advance transdermal drug delivery systems, not only for naproxen sodium but also for other drugs with similar delivery challenges. By overcoming barriers to effective transdermal delivery, this study aims to contribute to improved patient care and outcomes in pain management and beyond.

1.1. Aim of the Study

The biggest challenge with transdermal drug delivery is to avoid first pass past effect. It is also,is control medication penetrating through the skin. The stratum corneum (SC), The epidermis, the outermost layer of the skin, is the primary obstacle to preventing absorption. So itneeded trigger effect like physical and chemical enhancer. The primary objective of this investigation is to formulate a hydrogel containing Naproxen sodium, utilizing two carrier polymers—Hydroxypropyl methylcellulose (HPMC) at concentrations of 8%, 10%, and 12%, and Pluronic F-127 at concentrations of 20%, 23%, and 26%. Additionally, the study aims to explore the potential benefits of incorporating dimethyl sulfoxide (DMSO) as a permeation enhancer at varying concentrations (10%, 20%, and 30%) in the HPMC gel. The overarching goal is to enhance the transdermal delivery of Naproxen sodium, a non-steroidal anti- inflammatory drug (NSAID), by overcoming the barrier properties of the stratum corneum (SC) and the epidermis, the outermost layer of the skin, which serve as primary obstacles to drug absorption.

1.2. Skin Anatomy

The skin, the most significant part of the body, maintains homeostasis by acting as a barrier to prevent water loss. Its large surface area and easy accessibility make it essential for medication delivery. [19] The intricate structure of the skin, also known as the integumentary system, functions as a remarkable barrier, safeguarding the body from external threats. This complex composition is a fantastic protective barrier, presenting a promising platform for developing innovative drug delivery systems. The outermost layer of the skin is referred to as the stratum corneum. Alternatively, horny layer coating of the skin, with a thickness that varies from 10 to 20 μm. The substance has a high density of 1.4 g/cm³ when dry and lower hydration levels of 10%–20% compared to the roughly 70% seen in other bodily tissues. This layer is the skin's primary barrier despite being just 10–15 cells thick. The skin regulates water loss and serves as abarrier, blocking the entry of hazardous chemicals and bacteria. [18]

Understanding the layers and composition of the skin is pivotal in appreciating the potential of TDDS. This method harnesses the skin's unique attributes to administer therapeutic agents in a controlled and non-invasive manner. Unlike other tissues in the body, the stratum corneum comprises corneocytes. These corneocytes predominantly comprise aggregated keratin filamentsenclosed in a cornified envelope. They are surrounded by an extracellular environment of lipids organised in numerous lamellar bilayers. Structured lipids act as a protective barrier to prevent excessive water loss from the body. They also restrict the absorption of most topically applied drugs, save for those that are both soluble in lipids and have a small molecular size. Delivering medications via the skin, whether for localised effects on the skin or for systemic therapy by penetrating shallow blood vessels in the skin, poses a significant challenge. [1] The epidermis, the outermost layer, consists of a specific cluster of cells known as keratinocytes. These cells have the role of producing keratin, a sturdy protein providing protective characteristics. The dermis, acting as an intermediary layer, primarily comprises collagen, a robust fibrous structural protein. It houses small clusters of fat cells called lipocytes, positioned above the subcutaneous tissue, also identified as the panniculus. These strata's thickness varies considerably, depending on the body's geographical location and anatomical structure. [68]

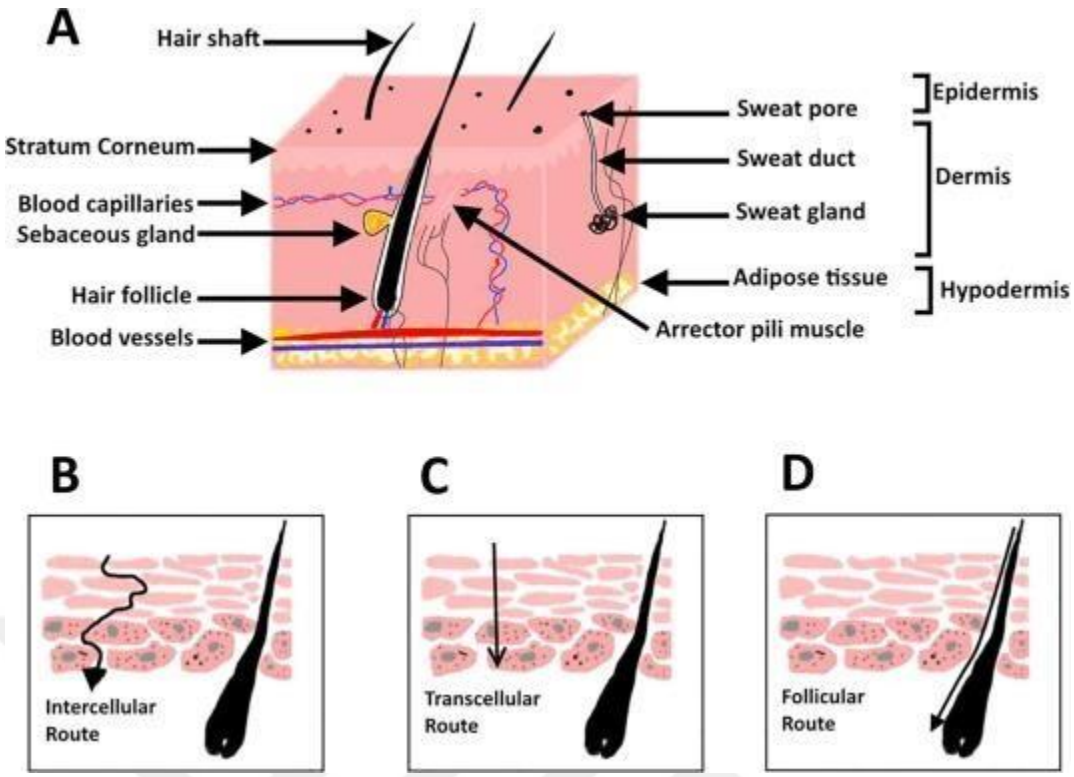

Figure 1.2. A model of human skin layers showing how nanoparticles can enter the body. [68]

1.2.1. Skin Barrier and Drug Penetration

Comprehending the complex characteristics of the skin barrier is essential. It is vital to fully grasp how it functions in reducing water and solute loss from the body. Moreover, the importance of having extra barriers becomes evident in certain circumstances. The outermost protective layer ofthe skin, referred to as the stratum corneum (SC), may not always provide sufficient hindrance, especially in cases of specific skin conditions or with substances that the SC does not typically impede. [39] The skin barrier, consisting of the stratum corneum, epidermis, and dermis layers, serves as a robust defence mechanism, controlling the movement of water, electrolytes, and otherchemicals between the body and the outside world. The stratum corneum plays a crucial role in restricting the entry of potentially dangerous substances due to its dense structure of corneocytes embedded in a lipid matrix. [40] Moreover, the epidermis contains immune cells that play a role in the skin's defence processes. [41] The skin barrier serves as both physical protection and a dynamic interface that interacts with the external environment and reacts to different stimuli. A comprehensive comprehension of the complexities of the skin barrier is essential for the

development of efficient transdermal drug delivery systems. This is because it directly affects thepenetration and absorption of therapeutic substances applied externally, such as in the case of the investigation into the enhanced delivery of NSAIDs, specifically Naproxen sodium, using DMSOin hydrogel formulations.

1.3. Transdermal Drug Delivery System: Hydrogel Formulation

The complex structure of the skin acts as a robust defence system, protecting the body and providing a suitable surface for advanced medication delivery techniques. To grasp the potential of transdermal medication administration, it is essential to comprehend the layers and compositionof the skin. [43]

The stratum corneum's outermost layer possesses remarkable barrier properties due to its unique composition of corneocytes surrounded by organized lipids. Unlike other tissues in the body, thislayer comprises corneocytes, primarily aggregated keratin filaments enclosed in a cornified envelope. [44] Surrounding these corneocytes is an extracellular environment of lipids organized into multiple lamellar bilayers. These organized lipids serve as a protective barrier, preventing excessive water loss from the body and restricting the entry of most topically applied drugs, except for those that possess lipid solubility and low molecular weight. The challenge in drug administration through the skin lies in overcoming this formidable barrier, whether the drugs are intended for localized effects on the skin or systemic treatment after entering the superficial dermalcapillaries. [1]

Beneath the stratum corneum lies the epidermis, composed of keratinocytes responsible for producing protective keratin. The intermediate layer, the dermis, predominantly consists of collagen, a fibrous structural protein. The dermis overlays the subcutaneous tissue, housing clusters of fat cells. The thickness of these layers varies significantly based on body location and anatomical structure. [2]

The transdermal patch delivery system signifies a groundbreaking innovation in medication administration, offering a non-invasive means of transferring medicinal substances through the skin into circulation. This approach provides notable benefits, including enhanced patient compliance and sustained release. This thesis aims to comprehensively explore TDDS, covering fundamental principles, challenges, and recent advancements. The increasing demand for effective

and user-friendly drug delivery methods has fueled interest in transdermal systems, reshaping how medication is approached compared to conventional methods like oral ingestion and injection. Transdermal patches distinguish themselves by gradually releasing medication over an extended period, allowing controlled drug release administered intravenously, bypassing the gastrointestinaltract. [3]

Advancements in TDDS encompass first-generation patches, second-generation chemical enhancers and iontophoresis for small molecules, and third-generation physical enhancers (ultrasound, thermal ablation, and microneedles), enabling transdermal delivery of macromolecules and vaccines. [3]

Theoretical advantages of transdermal drug delivery system (TDDS):

Enhanced adherence from patients.

Enhanced efficiency achieved by continuous discharge.

Diminished toxicity by avoiding concentration peaks and lowering the overall absorbed dosage.Avoid hepatic first-pass effect.

Minimise the probability of gastrointestinal adverse effects and local metabolic reactions.Reduced frequency of administration.

Minimise the discomfort caused by injections.

Reduced expenses for patients resulting from decreased: (a) overall dosage and (b) frequency ofdosage (enhanced efficiency). [1]

Hydrogels, intricate three-dimensional networks formed by natural or synthetic polymers, represent a significant advancement in drug administration. They offer a non-invasive and patient- friendly approach to TDDS, featuring high water content and biocompatibility. Hydrogels facilitate the gradual and controlled release of medicines, overcoming challenges associated with oral administration and reducing systemic adverse effects. These formulations, adaptable to the skin's surface, enhance contact and improve medication absorption. The growth of pharmaceuticalresearch benefits from the creation and optimization of transdermal hydrogel formulations, providing practical and patient-centred options across various therapeutic fields. [9]

1.3.1. Transdermal Penetrations and Franz Different Cell

Transdermal penetration is a vital component of drug delivery, where therapeutic compounds areabsorbed via the skin to reach the circulation. The Franz diffusion cell is a widely used in vitro model for assessing this process. A popular tool for evaluating drug release and skin absorption is the Franz diffusion cell. This lab instrument allows scientists to assess how effectively various topical formulations, like gels, creams, and transdermal patches, permeate excised skin tissue. [10] A membrane, typically made of exfoliated animal or human skin, separates the system's donor andreceptor compartments. [10] [58,59] Alternatively known as Liquid Scintillation Counting (LSC). [60,61] Due to its potential benefits, transdermal drug delivery is becoming increasingly popular as an alternative to other routes of administration. The benefits of this approach include needle- free administration, less tissue harm, improved patient adherence, and the ability to provide continuous or regulated drug delivery. [60,62] The Franz diffusion cell is a two-chambered device used to assess drug permeation across a barrier. The donor chamber contains the formulation with the active component, while the receptor chamber contains a dissolving media. A piece of skin or a synthetic membrane separates these chambers, mimicking the biological barrier. The entire setupis typically placed on a magnetic stirrer with a heating plate to maintain a constant temperature. The solution in the receptor compartment is continuously stirred at a predetermined speed to facilitate drug movement. [63,64] Commonly, researchers utilize Franz diffusion cells to assess drug permeation. The permeated amount is then measured using analytical techniques like High-Performance Liquid Chromatography (HPLC) or ultraviolet (UV) methods. [65] These Franz diffusion cell experiments provide valuable insights into the complex interactions between the skin, the medication itself, and the formulation used to deliver it. This information is crucial throughout the formulation development process to guarantee the efficacy and safety of novel topical treatments. Franz diffusion cells can also be used in toxicity testing and quality control procedures. [66,67]

Figure 1.3.1. displays the configuration of the Franz diffusion cell system. this cell facilitates the evaluation of in-vitro and ex-vivo drug release from topical formulations. Studying the relationships among the formulation, the active medicinal component, and the skin provides essential information. The Franz cell is crucial for the toxicity assessment and quality control of

pharmaceutical goods. It may be used to masure medication penetration into the skin, gather dataon chemicals that cause skin irritation, and understand the molecular processes involved in skin penetration. In conclusion, the Franz diffusion cell plays a pivotal role in skin permeation studies,offering a dependable method for measuring drug release, assessing skin permeability, and evaluating the effectiveness and safety of TDDS. [10]

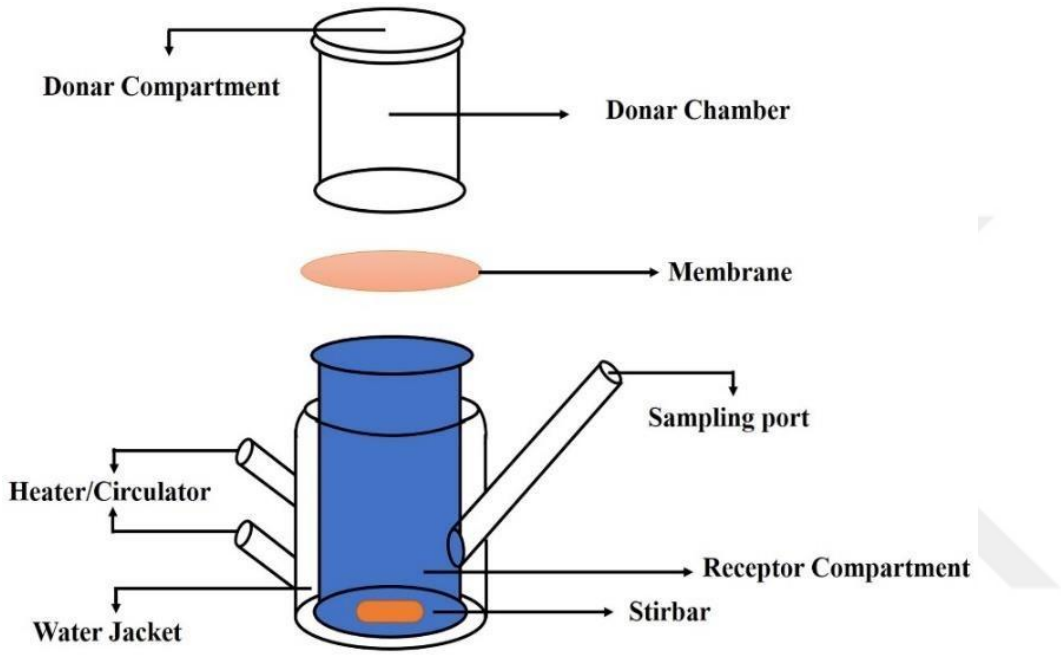

Figure 1.3.1. A graphical illustration of the Franz diffusion cell. [10]

1.4. Enhancement of Transdermal Penetration

In order to enable the movement of medications and big molecules through the skin, it is required to use strategies that include physical or chemical augmentation. [70] Various chemical and physical approaches have been utilized to enhance the rate and extent of absorption, each with differing levels of effectiveness. Physical approaches include iontophoresis, sonophoresis, microneedle array technology, electroporation, microporation, laser technology, thermal ablation, and magnetophoresis. [71] Delivering medication through the skin transdermal delivery offers

significant benefits over pills or injections. It's painless, avoids initial processing by the liver first-pass metabolism, and provides a steady release of the drug. To make this method even more effective, scientists are developing new techniques to improve how medications pass through the skin's outermost layer stratum corneum. [69] The advancement of new chemical combinations and intelligent physical instruments has been employed to enhance the effectiveness of transdermal delivery in a manageable manner. This analysis explores different methods for skin penetration that facilitate transdermal delivery, encompassing chemical mixtures like enhancers, peptides, transfersomes, and liposomes, along with combined techniques such as microneedles.[69] Understanding the link between enhancers and the top layer of skin as well as the links between enhancer composition and effectiveness will be very important for creating enhancers that have the qualities we want and don't pose a high risk of toxicity. [11]

1.4.1. Chemical Enhancement

A penetration enhancer, also referred to as a chemical enhancer, is a substance employed to increase the permeability of medications or other substances through biological barriers, such as the skin. Chemical enhancers are pharmacologically inactive chemicals that penetrate and spread through the skin, interacting with elements of the stratum corneum. They are generally regarded as safe for usage. [73] One commonly used method includes adding chemical enhancers to dermal and transdermal formulations to increase drug delivery via the skin. Nevertheless, selecting an appropriate penetration enhancer poses challenges, and thus far, no penetration enhancer has been identified as ideal. [14] Chemical penetration enhancers play a reversible role in altering the skin's structure to enhance the permeation of drugs through the skin. The Lipid-Protein-Partition (LPP) Theory provides insight into their mechanism of action. [72] Chemical enhancers increase drug penetration through many mechanisms: they interact within the intracellular pathway, participate in interactions within the intercellular pathway, and modify the solubility or distribution within the outermost layer of the skin, known as the stratum corneum. Within the intercellular route, the solute can interact with the polar head group within the aqueous regions of intercellular bilayers and interact within the lipid regions of intercellular bilayers. [74] The chemical methods for penetration enhancement deliberated upon in this review show considerable promise. Emphasis

should be placed on evaluating skin irritation, aiming to identify penetration enhancers that offer optimal enhancement effects with minimal impact on skin irritation. [8]

1.4.1.1. Chemical Enhancement Approaches

Most studies investigating the impact of enhancers on skin permeability have relied on in vitro diffusion tests, using different kinds of diffusion cells. Among these, the Franz diffusion systems are widely recognized. These systems consist of two compartments—the donor and receptor compartments—with the skin positioned between them (the donor compartment positioned above the receptor). Usually, the skin is prepared beforehand with a solution that contains the chemical enhancer being tested. [16]

The mechanism of action of chemical enhancers involves:

1) Disrupting the structure of the stratum corneum lipid layer.
2) Interacting with intercellular proteins.
3) Enhancing the partitioning of the drug or compound. [75]

Examples of drugs administered via transdermal delivery with the aid of chemical enhancers are presented in Table1.5.2. [16] Lastly, the ideal chemical penetration enhancer should be aesthetically pleasing, ideally odourless and colourless, ensuring its acceptance in cosmetic applications. In essence, the optimal enhancer should harmonise effectiveness with safety, reliability, and user acceptability. [15] His field of research encompasses a spectrum of techniques and compounds that interact with the skin's structure, such as penetration enhancers, to facilitate the transdermal absorption of therapeutic agents. Comprehending and using chemical enhancement approaches has a substantial impact on the progress of drug delivery systems. They provide prospective answers to the difficulties related to the effectiveness and availability of different pharmaceutical formulations.

Table .1.4.1.1. Chemical Permeation-Boosting Compounds in Topical Formulations. [16]

Original Component	Examples
Water	Water
Sulfoxides	Dimethyl sulfoxide, Dodecyl methyl sulfoxide
Ureas	Urea
Alcohols	Ethanol, Caprylic alcohol, Propylene glycol
Pyrrolidones	N-methyl-2-pyrrolidone, 2-pyrrolidone
Azone	Azone® (1-dodecylazacycloheptan-2-one)
Dioxolane	SEPA®
Surfactants	Sodium lauryl sulfate, Cetyltrimethyl ammonium bromide, Sorbitan monolaurate, Polysorbate 80, Dodecyl dimethyl, ammoniopropane sulfate
Terpenes	Menthol, Limonene
Fatty acids	Oleic acid, Undecanoic acid

1.4.2. Physical Enhancement Approaches

Most studies investigating the impact of enhancers on skin permeability have relied on in vitro diffusion tests, using different kinds of diffusion cells.Among these, the Franz diffusion systems are widely recognized. These systems consist of two compartments—the donor and receptor compartments—with the skin positioned between them (the donor compartment positioned abovethe receptor). Usually, the skin is prepared beforehand with a solution that contains the chemical enhancer being tested. [76] Physical enhancement transdermal delivery involves using several methods and technology to improve the penetration of medications through the skin barrier. Someof these approaches require the use of devices, which has the potential to significantly expand thetypes of pharmaceuticals that may be delivered via the skin. Encompassing water-soluble compounds and macromolecules.[1] Physical enhancement methods actively facilitate drug penetration across the skin layers.

Transdermal medication delivery is achieved by using physical enhancing methods:

1) Sonophoresis: Sonophoresis is a method of delivering medications via the skin using ultrasound to enhance absorption into the epidermis, dermis, and skin appendages. particularly suitable for hydrophilic molecules and macromolecules utilized as drugs.

2) Iontophoresis: Iontophoresis is a method of delivering drugs via the skin. It uses an electric current to transport a substance into skin tissue, overcoming the constraints of the skin barrier. Theskin is typically permeable only to lipid-soluble compounds with an approximate molecular weightof 500. An essential need for iontophoresis is ionising medicinal molecules to make them solublein water.

3) Microneedle: Microneedles are small-scale instruments that have the ability to mechanically penetrate the skin barrier. These microneedles can penetrate the stratum corneum and epidermis without reaching the nerve cells responsible for pain sensation. [21]

1.4.2.1. Microneedle (Dermaroller)

Microneedles represent a burgeoning area of research in transdermal drug delivery. To enhance the penetration of hydrophobic drugs, microchannels are formed through minimally invasive physical interaction. These microchannels enable the pharmaceuticals contained in themicroscopic needles designed to penetrate the deepest layers of the skin, reaching the dermal environment beyond the superficial layer of the skin, the SC. [69] They can potentially improve patient access to pharmaceuticals by replacing other administration methods. Microneedle technology utilizes tiny needles to painlessly transport medications through the skin's surface layerstratum corneum (SC) into deeper areas. The microneedles are available in various lengths, spanning from a few micrometres to 2 millimetres. [22] Despite variations in design based on function and medication, most microneedle patches share some similarities. These tiny needles typically come in a tapered cone shape with a sharp tip. Their dimensions vary from 150 to 1500 micrometres in length and 50 to 250 micrometres in width, with very slender tips measuring just

1 to 25 micrometres in thickness. The materials used to make microneedles include metals, silicon,polymers, glass, and even ceramic. [23]

Three distinct models of Dermarollers® were employed: C8 with needle lengths of 150 micrometres, CIT 8 with needle lengths of 500 micrometres, and MF 8 with needle lengths of 1500 micrometres. The Dermaroller® comes in many versions, including 24 circular arrays. Each arrayis made up of 8 needles, resulting in a total of 192 needles. These needles are placed in a cylindrical shape with a diameter and length of 2 centimetres. Refer to Figure 1 for a schematic representationof a Dermaroller®.[42]

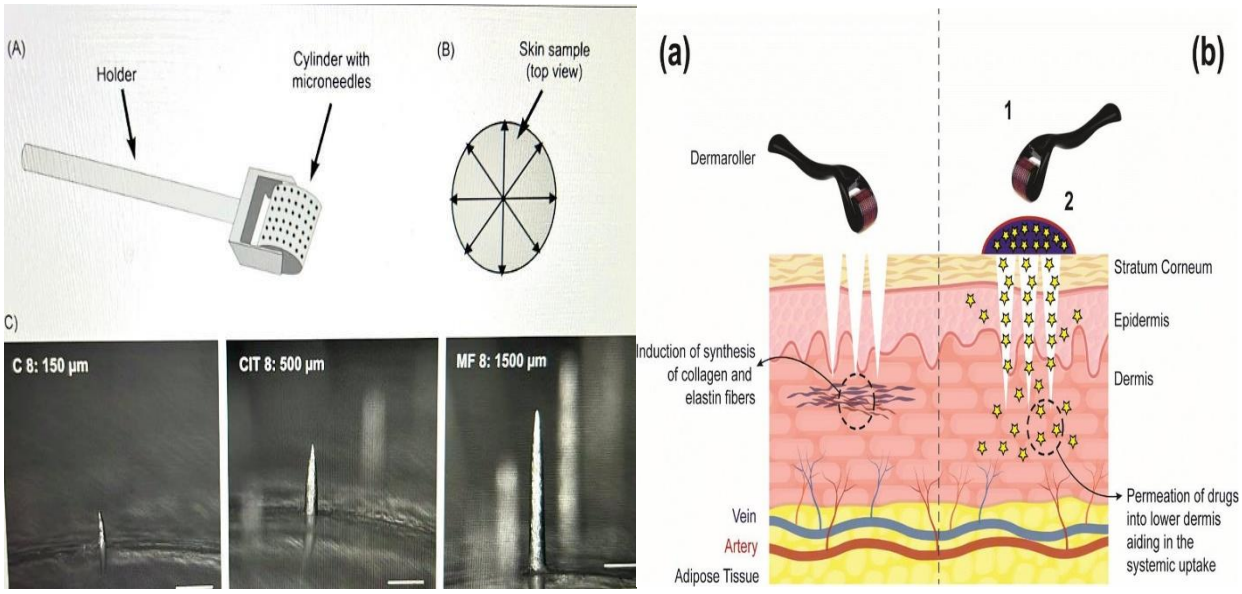

Figure 1.4.2.1.A. The text describes three different visual representations: an image of a Dermaroller®, a depictionof skin punctures, and stereo microscopic images of needles from different versions of Dermarollers® used in the study. The scale bars represent a length of 500 micrometres. [42] Summary of the utilization of derma rollers for (a) aesthetic and (b) transdermal purposes. In transdermal application, the skin undergoes pretreatment with the dermaroller (1) before applying the drug formulation (2). [86]

1.5. Naproxen Sodium

1.5.1. Pharmacological Effect of Naproxen Sodium

Non-steroidal anti-inflammatory drugs (NSAIDs), including both nonselective non-steroidal anti-inflammatory drugs (NSAIDs) and selective cyclo-oxygenase 2 NSAIDs (COXIBs), are widely prescribed pharmaceuticals worldwide. [45] Naproxen sodium (NS), a nonsteroidal anti- inflammatory drug (NSAID), has strong pharmacological effects by inhibiting cyclooxygenase enzymes, notably COX-1 and COX-2. NS exerts its effects by inhibiting the production of prostaglandins. The observed reduction in the in vivo synthesis prostaglandins in the central nervous system (CNS) implies an inhibitory impact on central prostaglandin synthesis by several NSAIDs. More precisely, diclofenac, indomethacin, and naproxen have shown a dose-dependent ability to block this particular aspect. Moreover, there is data indicating that diclofenac may also reduce the production of prostacyclin in the thalamus. [12] Which are important molecules involved in inflammation, pain, and fever. As a result, it has anti-inflammatory, analgesic, and antipyretic properties. The drug's pharmacological profile is further characterized by its long duration of action, enabling less frequent dosing and improved patient compliance. Furthermore, NS has been acknowledged for its ability to inhibit platelet aggregation, which enhances its usefulness in certain cardiovascular disorders. [46] Its efficacy in managing a spectrum of conditions, including arthritis, musculoskeletal disorders, and various pain syndromes, underscores its versatile pharmacological impact. As a critical component of this study, a thorough exploration of the pharmacological effects of naproxen sodium is imperative, aiming to contribute valuable insights to the broader understanding of its therapeutic potential and clinical applications.

1.5.2. Physico-chemical Properties of Naproxen Sodium

However, the limited capacity of many new potential drugs to dissolve in water may limit their ability to be absorbed into the body when taken orally, even if the active components have good permeability. [47] Exploring the physicochemical properties of Naproxen Sodium is essential for understanding its behaviour and interactions within pharmaceutical formulations. The cutaneous and transdermal delivery of medications heavily depends on the physicochemical properties of the compounds used. Naproxen sodium, an NSAID, exhibits certain characteristics that impact its stability, solubility, and overall efficacy in pharmaceutical delivery methods. The intrinsic dissolution rate of anhydrous sodium

naproxen (ASN) is higher than that of the dehydrated form.

[48] The investigation encompasses parameters such as crystalline structure, molecular weight, and solubility profile, shedding light on the drug's intrinsic properties. The anhydrate form can

undergo hydration to a dihydrate species through either crystallization from water or exposure to relative humidities exceeding 43%. Pharmaceutical solid materials may encounter water during several manufacturing phases, such as crystallization, lyophilization, wet granulation, aqueous film coating, or spray drying. Additionally, they may also be exposed to water when stored in settings with water vapour. [49] The solubility profile is pivotal for formulating effective dosage forms, guiding the selection of suitable excipients for optimal drug delivery. A comprehensive exploration of these physico-chemical properties lays the foundation for informed formulation strategies, ensuring the development of a Naproxen Sodium gel with enhanced transdermal delivery and therapeutic efficacy. The various dosage forms of naproxen exhibit bioequivalence concerning the extent of absorption (measured by area under the curve, AUC) and peak concentration, yet they vary in their absorption patterns. Naproxen and naproxen sodium are rapidly and completely absorbed from the gastrointestinal (GI) tract. Patients who are given naproxen may start to feel relief from pain after about 1 hour. However, those who are given naproxen sodium may find relief in as little as 30 minutes. Furthermore, the pain-relieving effectiveness has been noted to last for a duration of 12 hours. [50]

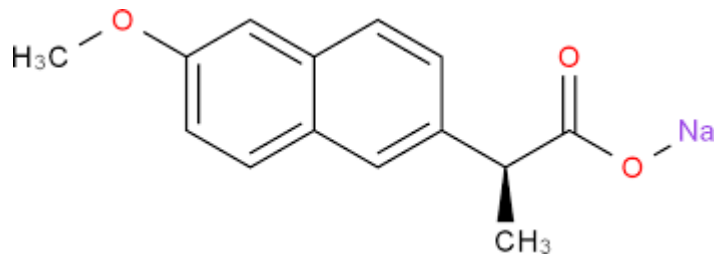

Figure 1.6. Chemical Formula for Naproxen sodium. [13]

1.5.3. Pharmaceutical Dosage Forms of Naproxen Sodium

Pharmaceutical dosage forms of naproxen sodium encompass a diverse range of formulations tailored to meet specific therapeutic needs and patient preferences. These formulations are specifically developed to enhance the administration of naproxen sodium, a powerful nonsteroidal anti-inflammatory medicine (NSAID), taking into account

parameters such as howwell it is absorbed by the body, how quickly it starts working, and how long its therapeutic effects last. Currently, naproxen medications are available in pharmaceutical markets solely in

the form of oral tablets, film-coated tablets, and rectal suppositories, gel. [51] Each formulation may vary in its composition, excipients, and release kinetics, aiming to achieve desired pharmacokinetic profiles and therapeutic outcomes. In addition, progress in pharmaceutical technology has resulted in the creation of new formulations, such as extended-release tablets andlipid-based formulations, which provide increased effectiveness, better patient adherence, and fewer adverse effects. Overall, the diversity of pharmaceutical dosage forms available for naproxen sodium underscores the importance of tailoring drug delivery to individual patient needs and treatment goals. [52]

1.5.4. Determination of Naproxen Sodium using HPLC

Incorporating specific substances can accelerate drug penetration through the skin, improving theintake of drugs that are not readily absorbed through standard systemic or topical routes. The optimal selection and calibration of these substances to boost their efficacy is key, and this requires a deep understanding of how they interact with the unique chemical and physical characteristics of the drug and its delivery medium. [57] The separation was accomplished by using an XDB-C18 column (4.6 × 150 mm, 3.5 microns, Agilent, USA) after the sample preparation. This solution was then subjected to UV detection at a wavelength of 230 nm. To quantify the total amount of naproxen sodium in the experiment, researchers measured the absorbance of each sample three times (in triplicate). They then used a calibration curve, created with known concentrations of naproxen sodium (ranging from 100 to 1500 nanograms per millilitre), to determine the unknown concentrations in the samples. The calibration curve generated from the standard solutions exhibited a near-linear relationship, which provided a reliable mathematical formula for subsequent calculations involving unknown concentrations.

1.6. Dimethyl Sulfoxide (DMSO) as a Chemical Enhancer

In order to accomplish this objective, penetration or diffusion enhancers such as DMSO might beused. DMSO, a molecule with a long history of use in the field of medicines, was first identified in the 19th century as a secondary product of the paper and wood industries. Since that time, it has been widely used as an industrial solvent. [33,34] Penetration

enhancers must exhibit compatibility with a range of topical formulations and be aesthetically pleasing to the user.

While no single compound has been demonstrated to possess all of these qualities, several, such as DMSO, exhibit many of them. [32] Thorough and systematic investigations are necessary to objectively evaluate the efficacy of DMSO as a diffusion or penetration booster in dermatopharmaceutics and cosmetics. The primary objective of these investigations should be toprecisely characterise the molecular-level interactions between DMSO and the lipids present in the stratum corneum. Concurrently, a portion of the lipids becomes solubilized. However, the degree of solubilization remains minimal, as evidenced by the slight increase in leakage at pH ten caused by 30% DMSO compared to that caused by 10% DMSO. Furthermore, no noticeableimpact on the lipid chains was seen. DMSO concentrates in the headgroup area, decreasing the lateral tensions between the ceramide molecules. [77]

1.6.1. The Molecular Mechanism of Dimethyl Sulfoxide's Action

Dimethyl sulfoxide (DMSO) is one of the first and most thoroughly studied substances promoting penetration. DMSO, a powerful aprotic solvent, forms hydrogen bonds with itself instead of water, which is widely employed in cell biology as an effective penetration enhancer, cell fusogen, and cryoprotectant. It lacks colour and scent and absorbs moisture, which is why it is known as a "universal solvent" and extensively used in medicinal applications. DMSO, when used externally, has traditionally been used in the management of widespread inflammation. The substance's exceptional efficacy as a penetration enhancer is obvious from its rapid absorption in the mouth within seconds upon skin contact. DMSO is effective, but it's important to acknowledge that using it comes with some difficulties. [8] The mechanism of action for Dermally Applied Penetration Enhancer, commonly referred to as DMSO (Dimethyl Sulfoxide), opens up intriguing possibilities in pharmaceutical and dermatological exploration. Serving as a potent skin penetration enhancer, DMSO plays a pivotal role in facilitating the enhanced deliveryof therapeutic agents across the skin barrier. Topical application of higher concentrations has been documented to exhibit anti-inflammatory effects [32].This sheds light on the potential for more effective absorption of topical medications into the systemic circulation. DMSO at lesser doses causes the thinning of the membrane and increases the fluidity of its hydrophobic core.

With increasing doses, DMSO induces the creation of temporary water channels in

the membrane. A continued increase in concentrations causes the release of individual lipid

molecules from the membrane, eventually leading to the breakdown of the bilayer structure. [4] DMSO demonstrates three distinct mechanisms of action, each operating within specific concentration ranges. DMSO induces membrane thinning and increases the fluidity of the hydrophobic core when found at low doses. At elevated doses, DMSO stimulates the creation of temporary water channels in the membrane. Continued increases in concentration cause the separation of individual lipid molecules from the membrane, resulting in the eventual breakdown of the bilayer structure. The reported occurrences of membrane thinning and, notably, pore formation offer a credible molecular-level explanation for the experimentally observed enhancement of permeation by DMSO. This is particularly evident for molecules with hydrophilic properties traversing lipid membranes. [5]

1.6.2. Navigating the Therapeutic Landscape of Arthritis with NSAIDs

The actual use of nonsteroidal anti-inflammatory drugs (NSAIDs) to address arthritis marks a notable advancement in the medical care of a condition marked by joint inflammation and discomfort. NSAIDs exert their effects by inhibiting COX-2, thereby impeding prostaglandin (PG)production at sites of inflammation or tissue damage. It is noteworthy that the inhibition of COX-1 in specific tissues, namely platelets and the lining of the stomach and duodenum, is linked to thetypical negative consequences of NSAIDs, such as bleeding and the formation of ulcers in the gastrointestinal tract. [6]

Arthritis, a complex and often persistent condition, has substantial consequences for joint function and general quality of life. Nonsteroidal anti-inflammatory medicines (NSAIDs) have become essential in the treatment of arthritis, offering pain relief and targeting the inflammatory components linked to this common musculoskeletal disorder.

The mechanism of action for NSAIDs involves the inhibition of cyclooxygenase enzymes (COX), pivotal players in the synthesis of prostaglandins responsible for the inflammatory response and pain signaling. By disrupting this enzymatic process, NSAIDs effectively alleviate inflammation, offering symptomatic relief and enhancing joint mobility for individuals dealing with arthritis.

This pharmacological category includes a range of choices, from easily accessible over-the-counter solutions like ibuprofen and Naproxen to more potent prescription medications. Such variability allows healthcare practitioners to customise treatment programmes based on the particular requirements and intensity of each patient's arthritis. Despite the efficacy of NSAIDs, the oral administration of naproxen sodium is linked to several side effects, including nausea, vomiting, gastrointestinal bleeding, ulcers in the stomach, headaches, and chest pain. As a result of these related adverse effects, alternate methods of administration, such as transdermal delivery, have been devised. Dermal drug administration is an effective method of transferring medicationsvia the skin, providing therapeutic benefits that are similar to oral delivery but with a safer option.[7]

2. MATERIALS AND METHODS

2.1. Materials

2.1.1. The Active Ingredient

Naproxen Sodium was a kind gift from **Neutec** - Turkey.
kind gift from Neutec Pharmaceuticals (Istanbul, Turkey) and used as a reference product.

2.1.2. Devices and Instruments

Table 2.1.2 Comprehensive Overview of Research Tools: Equipment, Devices, and Manufacturing Details.

Instrument Name	**Company Name**	**Origin Country**
HPLC	Agilent Technologies 1100 infinity	USA
Franz diffusion cell	Permegear	USA
PH meter	Hanna instrument	Romania
Weighting Device	Analytical Plus OHAUS	USA
Ultrasonic Bath	Bandelin Sonorex Super RK 156 BN	Germany
Ultrasonic- Homogenizer	Bandelin Sono Plus Ultrasonic Homogenizer	Germany
Hot plate	Heidol ph (MR 3004 Safty)	Germany
Vacuum Pump	Sartorius stedim	Germany
Ultrapure Type I Water Machine	Simplicity UV Merck Life Science	Germany
Magnetic stirrer	Scilogex	USA
Analytical balance	Ohause explorer	Switzerland
Viscometer	Kinexus series SERIES Redefining rheometer capabilities	UK
Homogenizer	Heldol PH Silent Crusher M Homogenizer	Germany

Ultrasonic- Homogenizer	Bandelin Sono Plus Ultrasonic Homogenizer	Germany
Microscopes	Carl Zeiss AxioLab A1	Germany
Microscopes	AxioCam ERc5s	Germany

2.1.3. Chemical and Compounds used

Table 2.1.3. The listed chemicals were employed with due respect and in adherence to the research objectives.

Chemical Name	**Company Name**	**Origin Country**
Acetonitrile HPLC	Sigma	Germany
Methanol	Carlo Erba	France
Phosphoric acid	Sigma	Germany
Hydroxypropyl methylcellulose	Sigma	USA
Pluronic F-127	Sigma	USA
Methylparaben	Fluka	Switzerland
Glycerin	Sigma	Germany
Ethanol HPLC	Isolab	Germany
Carbopol 934	Serva	Germany
L-α-Phosphatidylcholine (Lecithin)	Sigma	USA
Sodium Hydroxide	Merck-Millipore	Germany
Citric acid	Merck-Millipore	Germany
Disodium phosphate	Isolab	Germany
Monosodium phosphate	Isolab	Germany

2.2. Methods

2.2.1. Hydrogel Formulation with Excipients and their coded

Table 2.2.1. Compositions (%, w/w) of Naproxen gel, each formulation containing 5 % of Naproxen Sodium (NS)

Formulation code	HPMC	Pluronic	Glycerine	Methylparaben	Water	DMSO	Lecithin
P20N	----	20	5	0.15	25	---	---
P23N	----	23	5	0.15	25	---	---
P23ND 10%	----	23	5	0.15	25	10	---
P23ND 20%	----	23	5	0.15	25	20	---
P23ND 30%	----	23	5	0.15	25	30	---
P26N	----	26	5	0.15	25	---	---
C8N	8	----	5	0.15	30	---	---
C10N	10	----	5	0.15	30	---	---
C10ND 10%	10	----	5	0.15	30	10	---
C10ND 20%	10	----	5	0.15	30	20	---
C10ND 30%	10	----	5	0.15	30	30	---
C12N	12	----	5	0.15	30	---	---
$C10N^{E}$	10	----	5	0.15	30	---	2

N Naproxen Sodium, P Pluronic F-127, HPMC Hydroxypropyl methyl cellulose, D Dimethyl sulfoxide, E Emulgel

2.2.2. Analysis of Naproxen Sodium using High Performance Liquid Chromatography (HPLC)

The pharmaceutical ingredient Naproxen sodium (NS) was analysed using the high-performance liquid chromatography (HPLC) technique (Agilent Technologies 1260 Infinity analytical equipment) combined with a diode array detector (DAD) from Agilent Tech, Germany.

Separation was achieved by using an XDB-C18 column (4.6 × 150 mm, 3.5 microns, Agilent, USA). The isocratic mobile phase consisted of a buffer solution comprising phosphoric acid (H3PO4) as type II distilled water, coupled with pure acetonitrile (ACN) in a volumetric ratio

of 60:40. Before use, the mobile phase underwent filtration by a vacuum pump through a 0.45 μm membrane filter. Additionally, it was exposed to ultrasonic degassing for a period of 20 minutes. The eluent was then under UV detection at 230 nm. "The temperature of the column was maintained at a constant 25°C throughout," while the efflux of samples occurred at a flow rate of 1 mL/min. A 5 μL injection volume of the sample was utilised, revealing an NS retention time of
5.1 minutes.

The mobile phase was a buffer solution made up of phosphoric acid (H3PO4), type II distilled water, and pure acetonitrile (ACN) in a 60:40 volumetric ratio. Before use, the mobile phase underwent filtration by a vacuum pump through a 0.45 μm membrane filter. Additionally, it was exposed to ultrasonic degassing for a period of 20 minutes.

2.2.3. Preparation of Naproxen Sodium Hydrogel

2.2.3.1. Pluronic F-127 Hydrogel Preparation of Naproxen Sodium

The gel formulations were developed using a modified cold method. For thermogelling systems, comprising exclusively Pluronic F-127, the polymer was introduced into cold distilled water at varying concentrations (20%, 25%, 30% w/w). After thorough stirring and cooling, this mixture was combined with the remaining components. The continuous mixing process was maintained, and the resultant mixture was refrigerated at 4 °C overnight. Subsequently, the necessary quantityof the active ingredient, NS, was integrated by dissolving it in a blend of water and glycerol. The gel was then added until it reached the final weight of 100g. This resulting mixture underwent vigorous stirring overnight.

2.2.3.2. HPMC (Hydroxypropyl Methylcellulose) Hydrogel Preparation of Naproxen Sodium

Preparation of HPMC gel with concentrations of 8%, 10%, or 12%. Begin by measuring the specified quantity of HPMC and dispersing it in hot water. It's crucial to add the HPMC gradually to the hot water while consistently stirring the mixture. Continue stirring until the HPMC is entirely dissolved, ensuring that no lumps remain in the solution. Complete dissolution of the HPMC is essential to guaranteeing a seamless and uniform gel. After achieving full dissolution, allow the solution to cool down to room temperature before adding

the NS after dissolving it in distilled water and glycerol. The pH of the solution is adjusted if necessary to optimise drug stability and release characteristics. The gel was then added until it reached the final weight of 100g. This resulting mixture underwent vigorous stirring overnight.

2.2.3.3. Emulgel Hydrogel Preparation of Naproxen Sodium

The Emulgel was prepared by measuring the specified quantity of Lecithin and dispersing it in distilled water. Dissolving it entirely in the water and keeping it at a cooled temperature overnightis crucial. After that, we used the ultrasonic homogenizer for 5 minutes using the ice to make surethe temperature was not elevated. Then, we add the 5% naproxen sodium while stirring in until the

NS is entirely dissolved, ensuring that no lumps remain in the solution. Then again, we will use the ultrasonic homogenizer to ensure a clear solution without turbidity. After measuring the particle size, we will add 10% of the HMPC gel until it reaches the final weight of 100g. This resulting mixture underwent vigorous stirring overnight. The pH of the solution is adjusted if necessary to optimize drug stability and release characteristics.

2.2.4. Pig Skin Preparation

The initial phase was a comprehensive pig skin cleansing by eliminating subcutaneous fat.Following that, the skin was divided into samples measuring 4x4 cm2. These skin samples were stored at −18°C, and a day before the experiments, they were placed at 4 °C after I mentioned a solution of phosphate-buffered saline with a pH of 7.4. The specimens were placed in a refrigerator for the duration of the night. To ensure maximum preservation. Subsequently, the skin membraneswere dried using absorbent paper and placed flat between parafilm sheets. On the day of use, a derma roller with a 2 mm length was employed to create pores in the skin. To prepare for the experiments, the skin was pre-equilibrated in phosphate buffer solution (PBS) at 25°C two hours prior. [20] Ultimately, a round piece of skin was carefully positioned between the two sections of the Franz diffusion cell, ensuring that the skin's outermost layer faced the area where the substancewas being released.

2.2.5. In Vitro Permeation Study

Researchers studied skin permeation in vitro using cellulose membranes in Franz diffusion cells. These cells have an effective diffusion area of 4.906 cm2 and a receptor chamber capacity of about20 mL. The cellulose membranes were cut into discs and positioned between the donor and receptorcompartments of the Franz cell. The receptor compartment, filled with PBS at pH 7.4, was submerged in a water bath maintained at 35 ± 0.5°C. The donor solution consisted of 2 g of each formulation, including HPMC 10% and Pluronic F-127 with varying concentrations of DMSO, and1 g of the control formulation, which was a commercial product. All formulations contained 5% (w/w) naproxen.To avoid evaporation, the donor chamber was sealed using parafilm. Periodically, naproxen content in all samples was ascertained using HPLC. Additionally, in vitro skin

permeation studies used pig skin in Franz diffusion cells, incorporating derma rollers (2 mm) to create perforations.

This essay could explore the use of DMSO in drug formulations, discussing its properties and potential benefits. Additionally, it could delve into the challenges of using DMSO, such as its potential toxicity and limited solubility. The essay could also discuss alternative solubilizing agentsand their advantages and disadvantages.

This essay could explore the use of DMSO in drug formulations, discussing its properties and potential benefits. Additionally, it could delve into the challenges of using DMSO, such as its potential toxicity and limited solubility. The essay could also discuss alternative solubilizing agents and their advantages and disadvantages. 2. Comparing HPMC and Pluronic F-127 in Drug Formulations This essay could compare the use of HPMC and Pluronic F-127 in drug formulations, discussing their properties and how they affect drug delivery and efficacy. Additionally, it could delve into the challenges of formulating drugs with these polymers, such as their potential interactions with other excipients. The essay could also discuss novel approaches for optimizing drug formulations with these polymers.

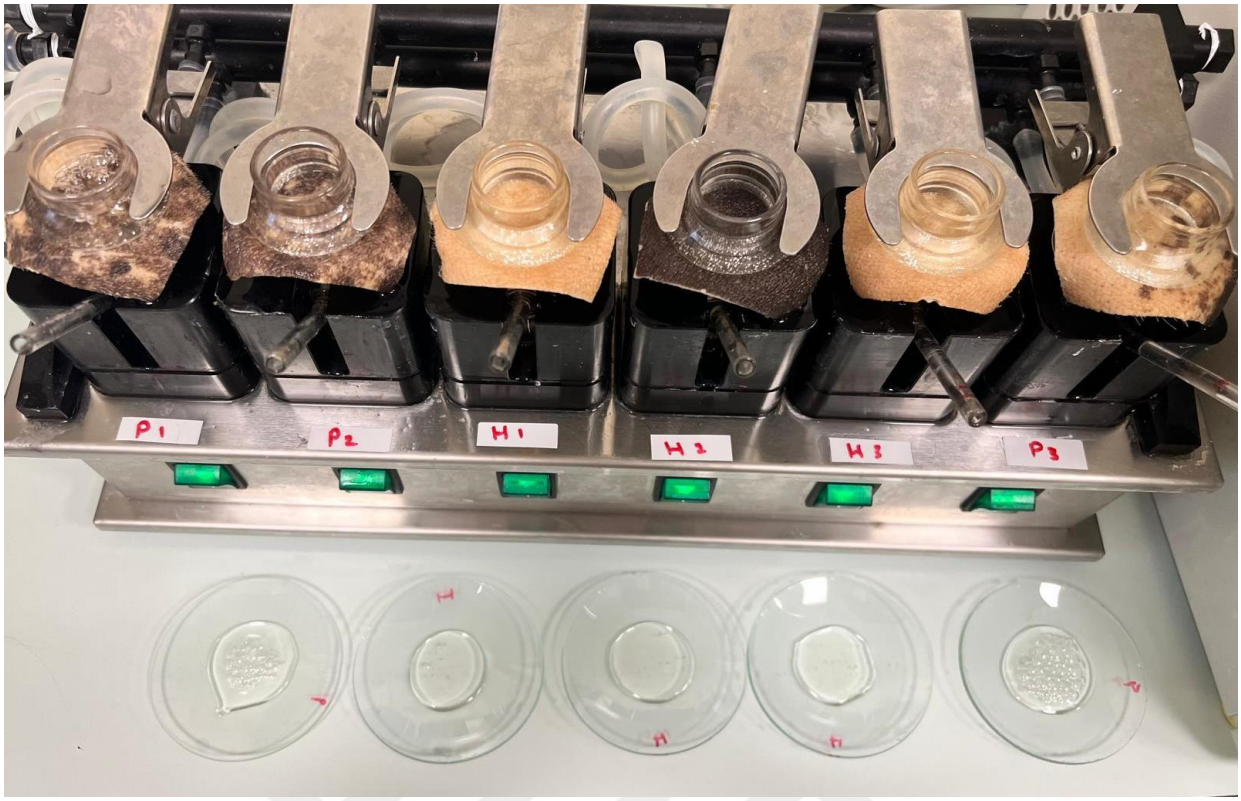

Figure 2.2.5. Franz diffusion cells set up Naproxen sodium gel formulations.

2.2.6. Naproxen Sodium Permeability Studies using Franz Cell Diffusion Method

This research used the Franz cell diffusion technique to investigate the permeability of Naproxen sodium across artificial and pig skin membranes. In vitro evaluations of drug release often utilize synthetic membranes, while natural membranes derived from humans or animals are employed for permeation studies. [82] For the pig skin membrane, due to its established histopathological similarity to human skin, pig skin is frequently used as a first step in evaluating how well topical medications penetrate the skin. [35,36] This study enhances our overall comprehension of drug permeability, providing valuable insights for the advancement of more efficient and precise drug delivery methods. The validity of this method has been established through previous research. There was a strong correlation between the apparent permeability measured in vitro using this artificial membrane and the actual fraction of the drug absorbed by humans. This validation included a range of drugs (including naproxen) encompassing the entire spectrum of human absorption rates. Notably, these drugs represent a significant portion of those listed by the FDA

for validating in vitro permeation methods. [83]

2.2.7. Naproxen Gel Features

2.2.7.1. Thermodynamic Stability

Thermodynamic stability is a fundamental property of a material that provides accurate information about the processes that cause phase formation or breakdown when equilibrium is achieved. Ensuring the physical stability of a formulation is crucial for its efficacy, since it mightbe affected by the settling of the active component within the excipient mix. In order for a material to be deemed stable under certain circumstances, it's essential that all potential phase separation and phase transition reactions are thermodynamically discouraged. [25] The Naproxen sodium gel formulations were subjected to three weeks of stability testing to determine the most efficient NS gel formulation. Six heating and cooling cycles have been performed upon these formulations, involving 48 hours of cooling at 4°C accompanied by 48 hours of heating at 40°C. Aftercentrifugation at 3000 rpm for 20 minutes, the samples were then subjected to two freeze-thaw stress cycles, which also involved 48 hours of freezing at -4°C followed by 48 hours of thawing at40°C. After each cycle completion.

2.2.7.2. Assessing Visual Observation of the Naproxen gel

Each of the created formulations was evaluated to establish their suitability as in-situ gelling systems, with an emphasis on their ability to form a gel, the time it takes for gelation to occur, andtheir viscosity. To evaluate gelling capacity, a drop of each formula was introduced into a vial containing 2 ml of freshly prepared simulated tear fluid. Visual examination was used to monitorthe process of gel formation, documenting both the time it took for the gel to develop and the length of time it remained intact before dissolving. [37,38]

2.2.7.3. Determination of Rheological Characteristics

2.2.7.3.1. Gel Viscosity

A rheometer was used to study further the rheological properties and behaviours of the formulations of choice (gel with DMSO 30%, gel with microemulsion and naproxen blank

gel alone). The rheological properties (viscosity, flow) of the hydrogel and Emulgel were observed and recorded using the Kinexus series SERIES Redefining rheometer capabilities (UK). The viscosity was determined by imposing steady shearing deformations on a stress-controlled rotational rheometer using a cone-and-plate (CP).[80] while shear rate, which is the difference in velocity between two layers within the bulk of material divided by a distance, was applied to the formulation between 10 and 100 rpm at 25°C ± 0.5°C. The viscosity of the formulations was measured in mPa.s.

2.2.7.3.2. Gel Spreadability

A crucial characteristic of topical dental gels for successful application to the oral mucosa is their spreadability. [84] Spreadability is assessed by the time required to detach two slides under a defined load. A shorter detachment time signifies a gel's superior spreadability characteristics. [81]The gel sample was loaded into a conical receiver to create a smooth, air-free upper surface. A complementary conical probe was pre-positioned above the gel for subsequent analysis. Two replicate analyses were performed at room temperature for each sample, providing the same conditions for each measurement. Spreadability was evaluated using a custom-designed apparatus. Two 6 x 2 cm glass slides were employed. A specific weight was placed on the upper slide, sandwiched between the two pre-cleaned slides. The time taken for the slides to separate under this weight was recorded as the spreadability value. Lower separation times indicated superior spreadability characteristics of the gel. Following measurement, the weight was removed, and excess gel adhering to the slides was discarded. The lower slide was secured to the base of the apparatus, while the upper slide was attached to a string connected to a pulley system capable of exerting an 80-gram load. The separation time was measured as the duration it took for the upperslide, under a defined weight, to fully traverse a 6 cm distance and detach from the lower slide. This experiment was repeated, and the average of three such measurements was calculated for

each gel formulation. [85]

3. RESULTS and DISCUSSION

3.1. Data Analysis for Naproxen Sodium and Marketed Gel

Total naproxen sodium regarding the experiment, absorbance was measured and noted for each sample as triplicate, and a calibration curve was calculated using naproxen sodium (100–1500 ng/mL) where the average determination coefficient R2 value was closest to 1 and the plot of the standards was linear providing the necessary formulation to further conduct calculations.

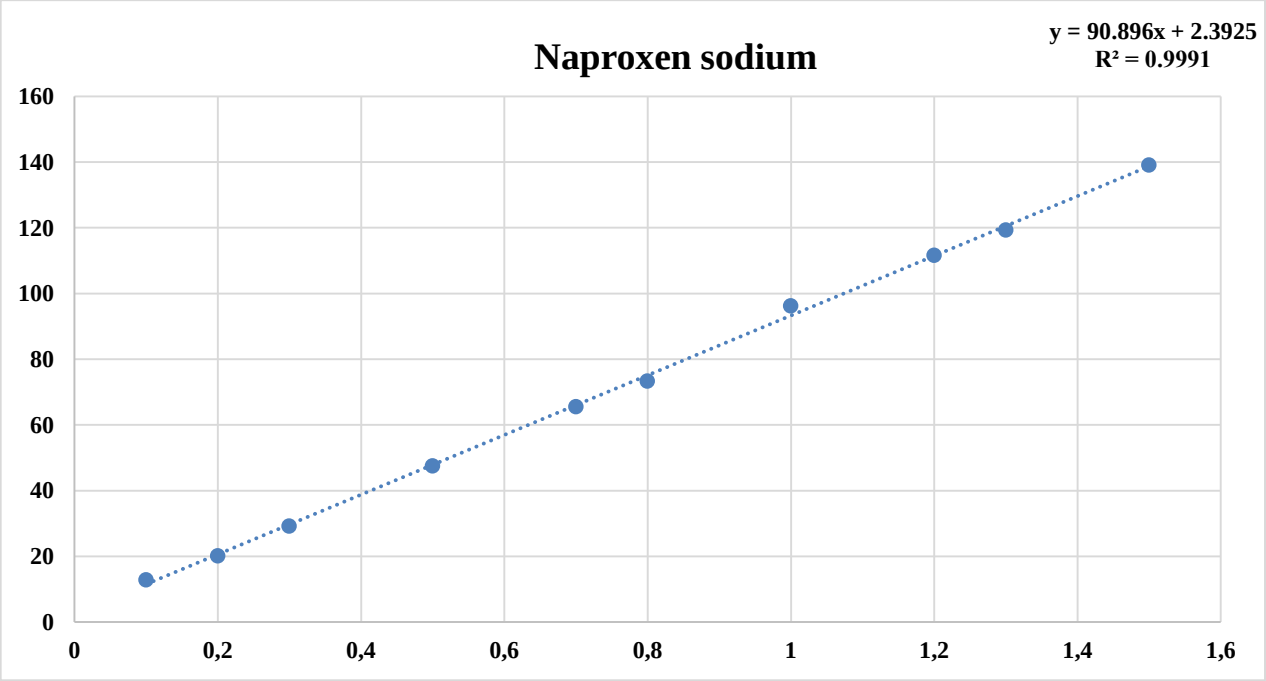

Figure 3.1.A. Calibration curve of naproxen sodium (absorbance of 230 nm).

After preparing a gel, it closely resembles the commercially available gel in terms of its composition and properties, absorbance was measured and noted for each sample as triplicate, a calibration curve was calculated naproxen sodium (100–1500 ng/mL) where R2 value was closest

to 1 and the plot of the standards was almost linear providing us with the necessary formulation tofurther conduct calculations.

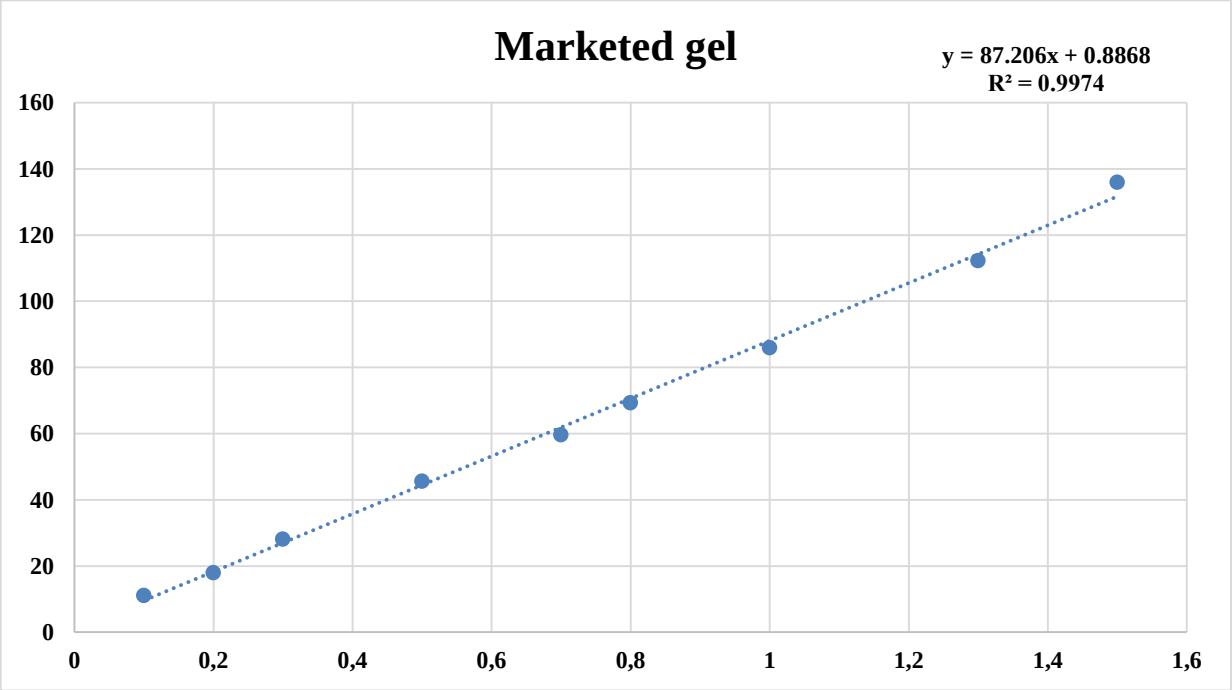

Figure 3.1.B. Calibration curve of marketed gel (absorbance of 230 nm).

3.2. Selecting the Preferred Formulation

Selecting the best formulation is a critical factor that can significantly impact our goal of achieving optimal penetration. This study has altered the Naproxen sodium hydrogel formulation HPMC (8,10 and 12%) and Pluronic F-127 (21,23 and 26%). Through our study, and according to Franz diffusion permeation studies, it was found the HPMC 10% was the best hydrogel formulation overPluronic F127 26% due to its enhanced penetration capabilities on pig skin as seen in (Figure 3.2.)using chemical and physical enhancers. After thoroughly comparing both formulations, we found that HPMC 10% exhibited the most effective penetration characteristics. Our decision was based not only on the criteria of efficient drug delivery but also on the best outcomes in terms of skin permeation. This highlights the importance of selecting the most effective formulation to achieve the desired results in transdermal drug delivery. It emphasizes the significance of a formulation's ability to deliver the drug and penetrate the skin effectively. This careful selection process underscores

formulation's crucial role in the success of transdermal drug delivery. By prioritizing the formulation with the most favourable penetration characteristics, we are enhancing the efficiency of drug delivery and maximizing the therapeutic impact of the treatment. The meticulous evaluation and comparison of different formulations ultimately lead to identifying the most effective option, paving the way for improved outcomes and patient care in transdermal drug delivery.

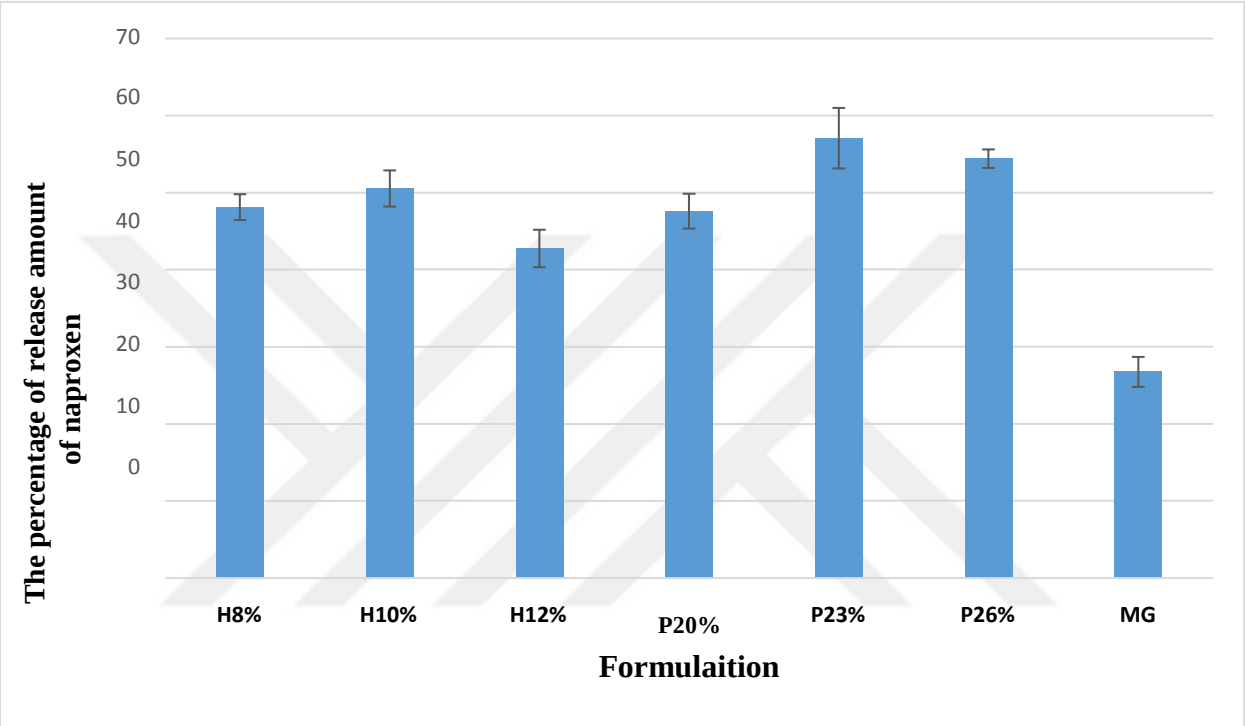

Figure 3.2. Naproxen sodium percentage release gel formula with HPMC (H) and Pluronic (P) compared with marketed gel (MG).

3.3. Evaluation Parameters of the Formulated Gels

3.3.1. Appearance

Initially, the mixture appeared cloudy because the Hydroxypropyl Methylcellulose (HPMC) solidified at high temperatures during the preparation process. However, after allowing the mixture to rest overnight, the cloudiness gradually dissipated, ultimately resulting in a mixture that was either entirely transparent or slightly translucent.

3.3.2. Determination of pH

The pH of the Naproxen sodium gel was determined at room temperature (20 - 25ºC), and after equipment stabilization. The potentiometer for the hydrogel was Hanna®.The pH values of the selected formulations were determined using a digital pH metre. The pH values of all formulated products fell within the range of 6.81±0.12 to 6.95±0.02, which is within the acceptable range to minimize the potential for skin irritation upon application.

3.4. Rheological Studies

3.4.1. Determination of hydrogel viscosity

In order to fully understand the composition of our gel formulation, we performed detailed tests on its flow properties rheology. These tests were done under precise conditions, maintaining a constant temperature of 25°C. Shear rate, which is the difference of velocity of two layers within the bulk of material divided by a distance, we applied a controlled shearing force to the gel, mimicking how it might flow when used. This force steadily increased from very slow (0.1 rpm) to quite fast (100 rpm), and we carefully measured how easily the gel flowed (its viscosity) at eachstep.

The constricted radius was used to calculate the shear stress and shear rate, assuming there was noadditional flow of material between the roughness elements, unlike recent observations in parallel plate geometries. [79] The formulations exhibited characteristic non-Newtonian pseudoplastic properties, in thick gel the speed at which particles slip past the wall depends on how easily the liquid part of the hydrogel flows. This finding applies to both simple liquids and those that thin out when sheared (like some thickening agents). [78] Significantly, a noticeable change inviscosity occurred with a certain shear rate, resulting in improved flow characteristics. An increase in viscosity that is directly proportionate to the temperature rise was observed, which aligns with the results of a comparable investigation on the rheological properties of Carbopol. [95] DMSO did not alter the viscosity of the gel. [87] The temperature-induced viscosity increase could be

interpreted in various ways, and one article proposed that the strengthening of solvent-polymerinteractions with temperature is a key factor explaining this observed rise in viscosity.

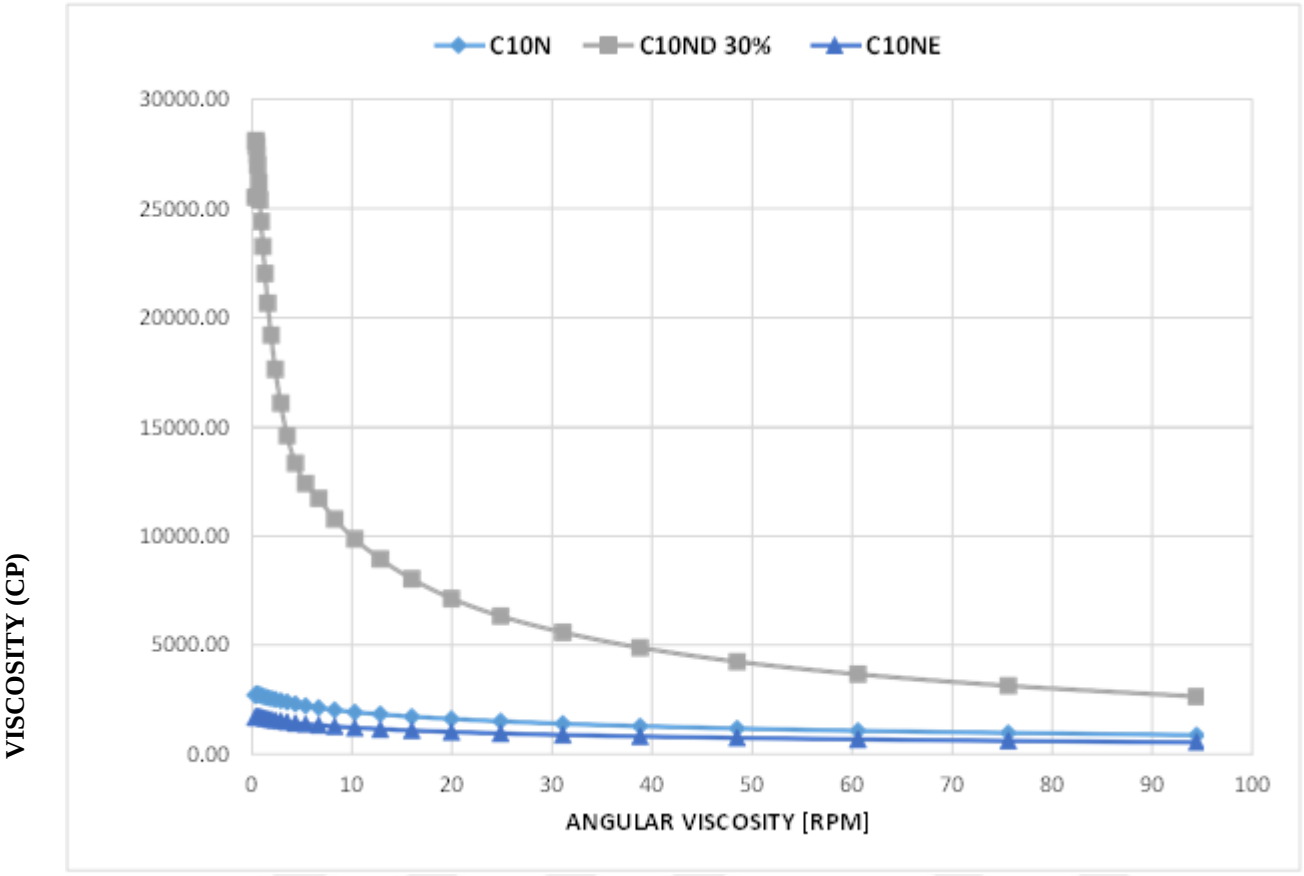

Figure 3.4.1. The viscosity of naproxen hydrogel formulation, in relation to the angular velocity at room temperature(n=3)

The provided data in Table 3.4.1.A. offers a detailed insight into the physicochemical propertiesof the Naproxen sodium hydrogel formulations. These characteristics include appearance in general, viscosity, pH, and droplet size (for emulsions only). There was a high degree of homogeneity evident in the smooth and homogenous appearance that was seen in all formulations. Viscosity readings at 50 rpm showed results that suggested a gel-like consistency that would work well for topical application. Additionally, the pH levels stayed within the permissible range, guaranteeing that skin contact caused the least amount of irritation. Regarding

formulations based on emulsions, the droplet sizes measured in nanometers confirmed the durability and efficacy of the emulsion for specific drug delivery. These characteristics are essential for assessing the hydrogel formulations' stability and

efficacy in-depth, particularlywhen considering improved transdermal distribution.

Property	HPMC 10% Naproxen sodium alone and DSMO 30%		Emulgel
	C10N	**C10ND 30%**	**C10N^{E}**
Appearance	Clear	Clear	Clear
Viscosity (cp) at 50 (rpm)	1.40	3.59	0.75
pH	6.81±0.12	6.95±0.02	6.55±0.05
Droplet size (nm) (emulsion only)	e	e	25.6 ± 3.1

Table 3.4.1.A. Physicochemical Properties of Naproxen Sodium Hydrogel Formulations.
C10N Naproxen HPMC hydrogel alone .. C10ND 30% Naproxen HPMC hydrogel+ 30% DMSO.. C10NE Naproxen Emulgel

3.5. Franz Diffusion Naproxen Sodium Release Studies

Importantly, drugs may both permeate and accumulate in the skin. While the opposite behaviour is intended for transdermal delivery systems, the accumulation in the skin with minimal penetration is desired for topical delivery methods [88]. In the case of anti-inflammatory drugs, faster and greater permeation is most often preferred, with less accumulation in the skin. Figure
3.5 shows the percentage release of Naproxen sodium hydrogel formulations in ex vivo after 24 h of penetration. The lowest precent release values were obtained for [C10N] ,[C10ND 10%] and[MG]: 6.133, 19.397 and 19.849 respectively. The data highlight the efficiency and effectiveness of each hydrogel formulation in delivering the drug. By comparing the release, this analysis provides valuable insights into the performance of each formulation, informing the optimization process for enhanced transdermal delivery of Naproxen sodium.

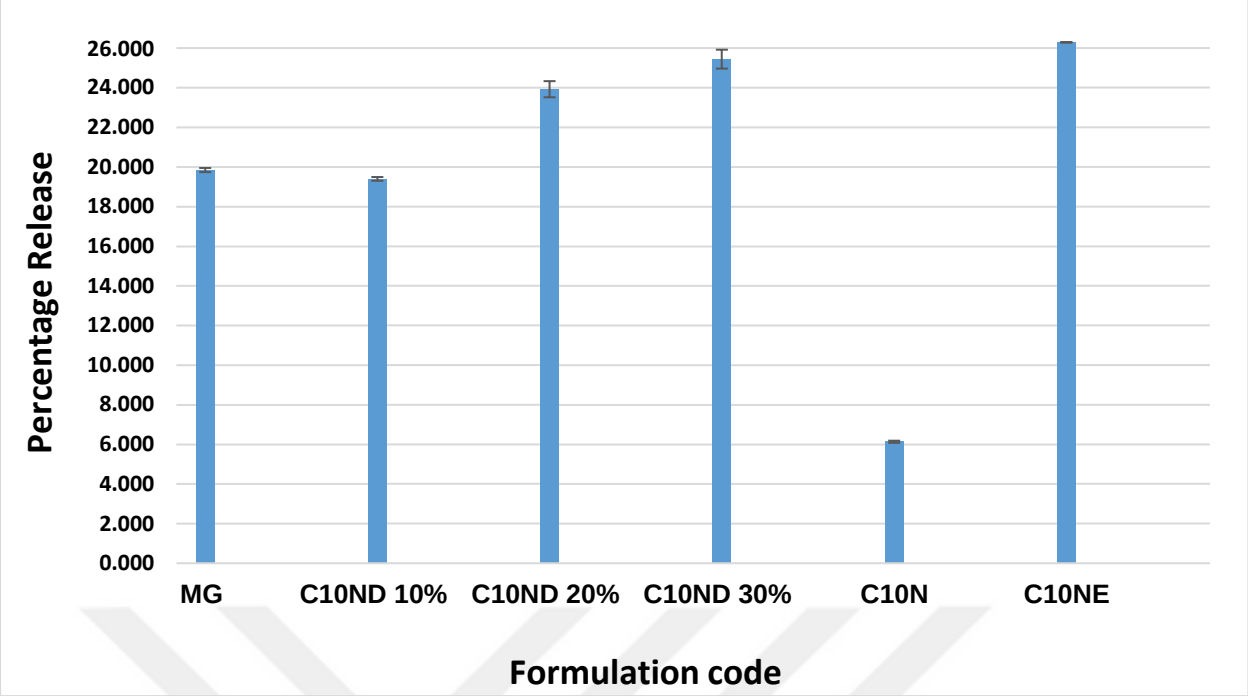

Figure 3.5. Comparative analysis of Naproxen sodium release across formulation codes within the skin throughout 24-hour period of penetration for pig skin before using the dermaroller. Statistical analysis, employing the ANOVA test, determined any significant differences observed (Mean ± SD, n = 3)

3.6. The results of ex vivo Skin Permeation of Naproxen

Naproxen is a potent nonsteroidal anti-inflammatory medication (NSAID) for many inflammatory conditions. Naproxen exhibits gastrointestinal side effects, while its cardiovascular risks might be lower than similar medications within its class. [27] An alternative method to alleviate the adverse effects of naproxen is to involve administering it topically. [28] Certain

anti-inflammatory drugs, such as naproxen, are anticipated to quickly enter the skin, leading to aprompt therapeutic reaction. [29] However, the stratum corneum, primarily composed of lipids such as cholesterol, ceramides, and fatty acids, is a barrier that restricts the infiltration of these chemicals. [30] Different penetration enhancers improve skin permeation rates and enhance the

delivery of poorly absorbed drugs. Selecting and optimising enhancers requires a comprehensive knowledge of how they function and the features of the medication and vehicle. [31]

Considering all time points, the cumulative mass of the tested compounds in the acceptor fluid ispresented in (Figure 3.6.1.). (Table 3.6.A.) summarises the concentration of naproxen and its derivatives in the acceptor fluid collected throughout 24 hours of permeation. The cumulative mass of the individual formulation, determined after 24 h of permeation, was as follows: [Emulgel] > [DMSO 30%] > [MG] > [DMSO 20%] > [DMSO 10%]. The cumulative mass of all naproxen formulations in the acceptor phase after 24 hours of permeation exhibited a marked increase compared to 10% DMSO. The Emulgel formulation demonstrated the most notable improvement in the rate of permeation. The cumulative amounts of naproxen sodium permeated throughout the 24-hour study were 25986.48, 23956.94, 19314.89, 22959.41, and 25890.66 µg, respectively (Table 3.6.A.).

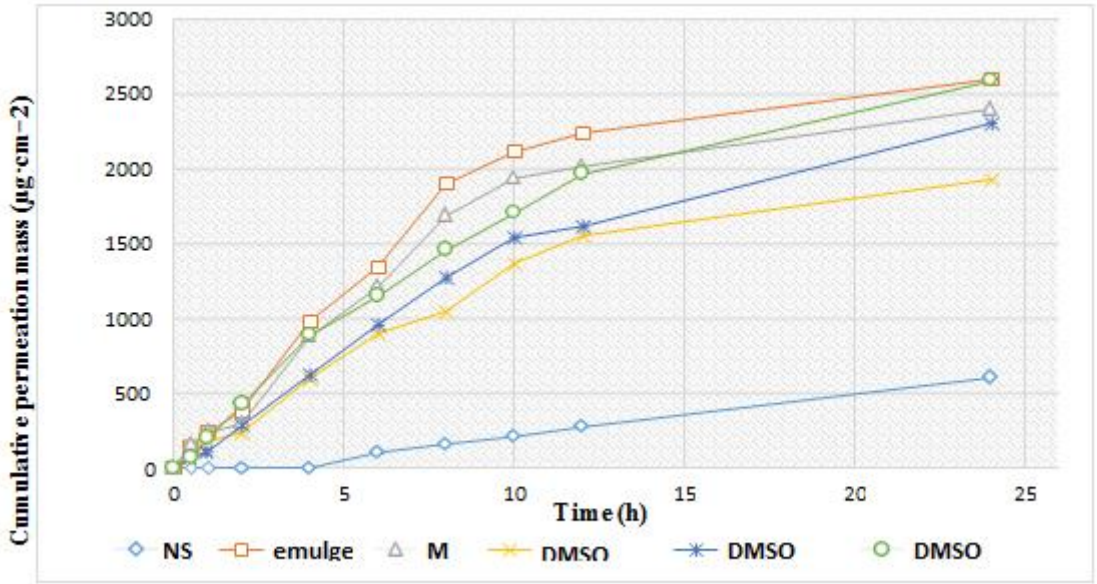

Figure 3.6.1. The 24-hour permeation study tracked the cumulative mass of Naproxen and its different formulation over time. Statistical analysis, employing the ANOVA test, determined any significant differences observed (Mean

± SD, n = 3).

	Emulgel	MG	DMSO 10%	DMSO 20%	DMSO 30%	NS
Cumulative Permeation Mass ($\mu g \cdot cm^{-2}$)	25986.48	23956.94	19314.89	22959.41	25890.66	6070.55

Table 3.6.A. The cumulative mass of Naproxen and its different formulation was measured ($\alpha = 0.05$, mean ± SD, n = 3). Statistical significance was determined through ANOVA testing.

The results of the ex vivo efficiency permeation experiments related to naproxen and other formulation are summarized in (Table 3.6.B.) the permeation parameters such as flux, apparent permeability coefficient, lag time, percent drug permeated after 24 h, and enhancement factor were calculated using the equations as Mukesh et al. [86] A marked difference in the flux for the naproxen alone, and instead formulation was immediately evident: the transdermal flux of the hydrogel formulation with the enhancer was from 4.80 to 6.50 times higher than that of the 5% naproxen alone (164.73 for [C10ND 10%], 203.18 for [C10ND 20%], 216.05 for [C10ND 30%],
223.30 for [C10NE] vs 34.31 μg cm−2 h−1, respectively). The permeability coefficient (KP), a quantitative measure of the rate at which a molecule can cross the skin, was also determined. KP is composed of factors related to both the drug and the barrier and their interaction. This parameter eliminates the effect of compound concentration. For the tested compounds, KP values were from 3.194 to 4.33 times higher than for naproxen hydrogel alone. These results suggest that the compounds under study can promote repartition in the skin.

Table 3.6.B. Skin permeation parameters for naproxen sodium, HPMC 10% and Emulgel. n = 3.

Compound	J_{SS}, µg cm^{-2} h^{-1}	$K_P \cdot 10^3$, cm/h	L_T, h	Q%$_{24\,h}$	EF
[NS]	34.31	1.03	-	6.133	1
[C10ND 10%]	164.73	3.29	0.61	19.40	3.16
[C10ND 20%]	203.18	4.06	0.57	24.13	3.93
[C10ND 30%]	216.05	4.32	0.52	25.43	4.14
[C10N^{E}]	223.30	4.46	0.19	27.07	4.41
[MG]	168.57	3.37	0.62	19.84	3.23

J_{SS} steady-state flux; **K_P** permeability coefficient; **L_T** lag time; **Q** the percentage of the applied dose, **EF** enhancement factor.

In Figure 3.6.A, the ex-vivo release amounts of Naproxen sodium after 24 hours for various formulations (before the dermaroller application) were compared to the C10N formulation, representing Naproxen sodium-HPMC 10% hydrogel. A noticeable increase in drug release wasobserved between C10N and formulations C10ND 20%, C10ND 30%, and C10NE Emulgel. These evaluations showed a significant difference statistically between all Naproxen hydrogel formulation about (3 times, p <.0001) incernment and this suggests that the inclusion of 20% and 30% DMSO in the C10ND formulations, as well as the Emulgel formulation, facilitates greater permeation of Naproxen sodium through the skin barrier compared to the base hydrogel formulation. The enhanced release from these formulations indicates the potential of DMSO as a permeation enhancer and highlights the unique delivery properties of the Emulgel formulation. These findings underscore the importance of formulation optimization in achievingefficient transdermal delivery of Naproxen sodium and suggest promising avenues for further enhancing drug permeation in topical applications.

While also Statistically, this forumulation C10ND 20%, C10ND 30%, and C10NE there were a significant difference between them and marketed gel (MG) also (before the dermaroller application) about 3 times more increment was observed p < 0.0001 as showen in Figure 3.6.B.

Specifically, The results indicate a significant improvement in drug release across all tested formulations (C10N, C10ND 10%, C10ND 20%, C10ND 30%, and C10NE) when

dermaroller application was employed. Notably, these formulations demonstrated over a three-fold increase in Naproxen sodium permeation compared to the base C10N hydrogel. This enhancement underscores the effectiveness of combining physical (dermaroller) and chemical (DMSO) permeation strategies, along with the unique properties of the Emulgel formulation, in optimizing transdermal drug delivery. Such synergistic approaches show considerable promise for improving the therapeutic efficacy of topical NSAID treatments as showen in Figure 3.6.C.

While In Figure 3.6.A, the ex-vivo release amounts of Naproxen sodium after 24 hours for various formulations, following dermaroller application, were compared to those of the marketed gel (MG). The results revealed that formulations C10ND 20%, C10ND 30%, and C10NE Emulgel provided significantly enhanced drug release compared to the marketed gel. These formulations showed a marked improvement, highlighting the effectiveness of using higher concentrations of DMSO as a permeation enhancer and the unique properties of the Emulgel formulation. This suggests that combining dermaroller application with optimized formulations can substantially improve the transdermal delivery of Naproxen sodium, potentially leading to better therapeutic outcomes.

The outcomes of this study are anticipated to offer remarkable insights into enhancing the penetration of a percentage amount of Naproxen sodium using an Emulgel formulation or DMSO (30%) as a chemical enhancer, potentially leading to more effective applications for topical pain relief. Moreover, the Franz diffusion cell study with pig skin before applying the formulation using the derma roller markedly increased the penetration of naproxen.

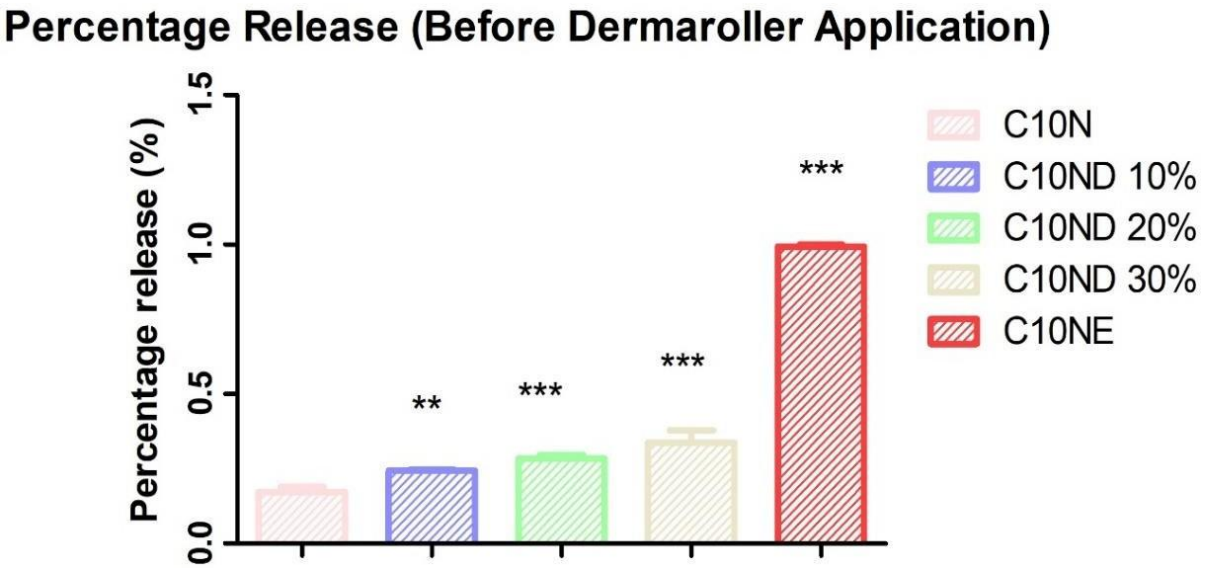

Figure 3.6.A. The ex-vivo release amounts of Naproxen sodium after 24 hours for different formulations (before the dermaroller application) were compared to the C10N formulation.

C10N Naproxen sodium-HPMC 10% hydrogel, C10ND 10% Naproxen sodium-HPMC 10% hydrogel + DMSO 10%, C10ND 20% Naproxen sodium-HPMC 10% hydrogel + DMSO 20%, C10ND 30% Naproxen sodium-HPMC 10% hydrogel + DMSO 30%,C10NE Naproxen sodium-HPMC 10% Emulgel.

** represents significantly higher than the control group (C10N) ** $p < 0.001$, *** represents significantly higher than the controlgroup (C10N) *** $p < 0.0001$.

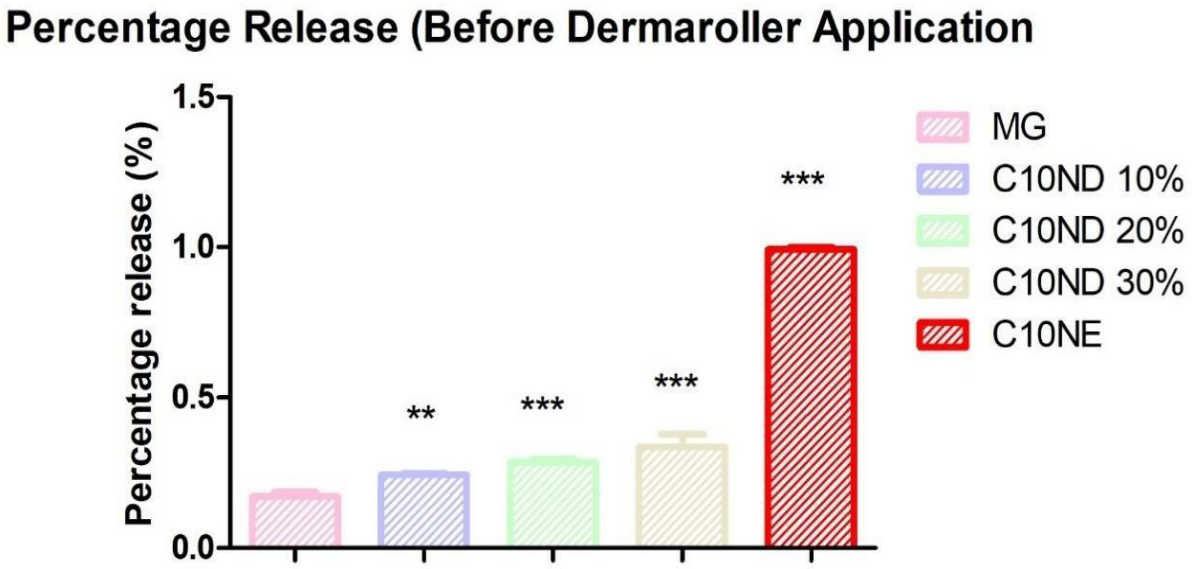

Figure 3.6.B. The ex-vivo release amounts of Naproxen sodium after 24 hours for different formulations (beforethe dermaroller application) were compared to those of the marketed gel.

MG Marketed gel, C10ND 10% Naproxen sodium-HPMC 10% hydrogel + DMSO 10%, C10ND 20% Naproxen sodium-HPMC 10% hydrogel + DMSO 20%, C10ND 30% Naproxen sodium-HPMC 10% hydrogel + DMSO 30%, C10NE

Naproxen sodium- HPMC 10% Emulgel.

** represents significantly higher than the control group (C10N) ** $p < 0.001$, *** represents significantly higher than the controlgroup (C10N) *** $p < 0.0001$

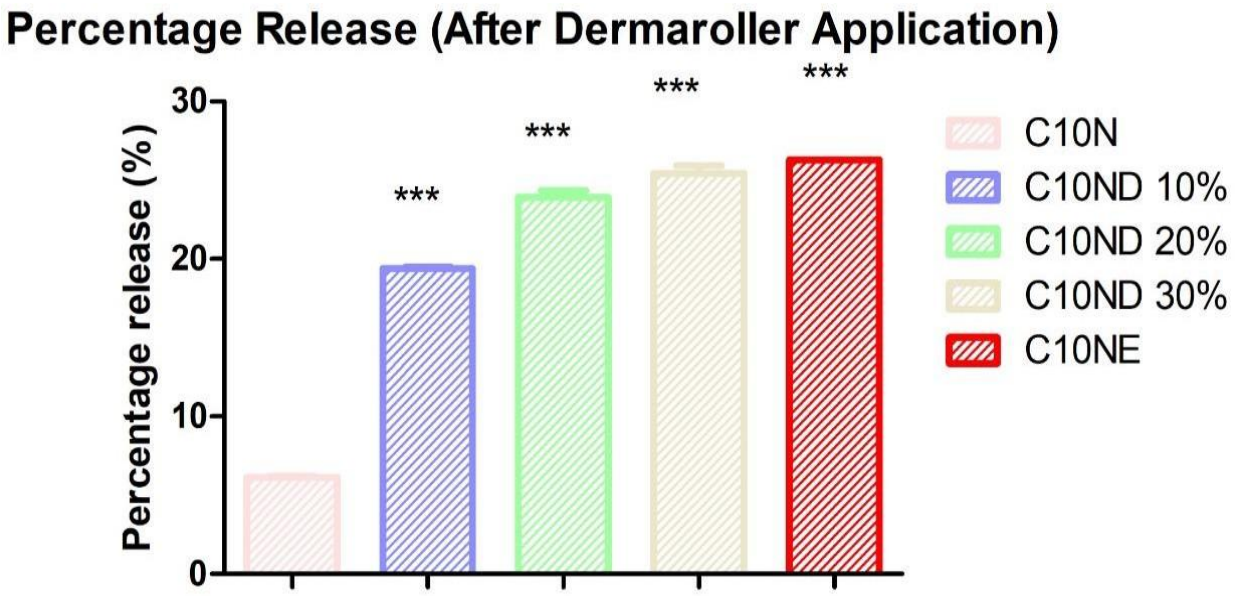

Figure 3.6.C. The ex-vivo release amounts of Naproxen sodium after 24 hours for differentformulations (after the dermaroller application) were compared to the C10N formulation.

C10N Naproxen sodium-HPMC 10% hydrogel, C10ND 10% Naproxen sodium-HPMC 10% hydrogel + DMSO 10%, C10ND 20% Naproxen sodium-HPMC 10% hydrogel + DMSO 20%, C10ND 30% Naproxen sodium-HPMC 10% hydrogel + DMSO 30%,C10NE Naproxen sodium-HPMC 10% Emulgel.

*** represents significantly higher than the control group (C10N), *** $p < 0.0001$.

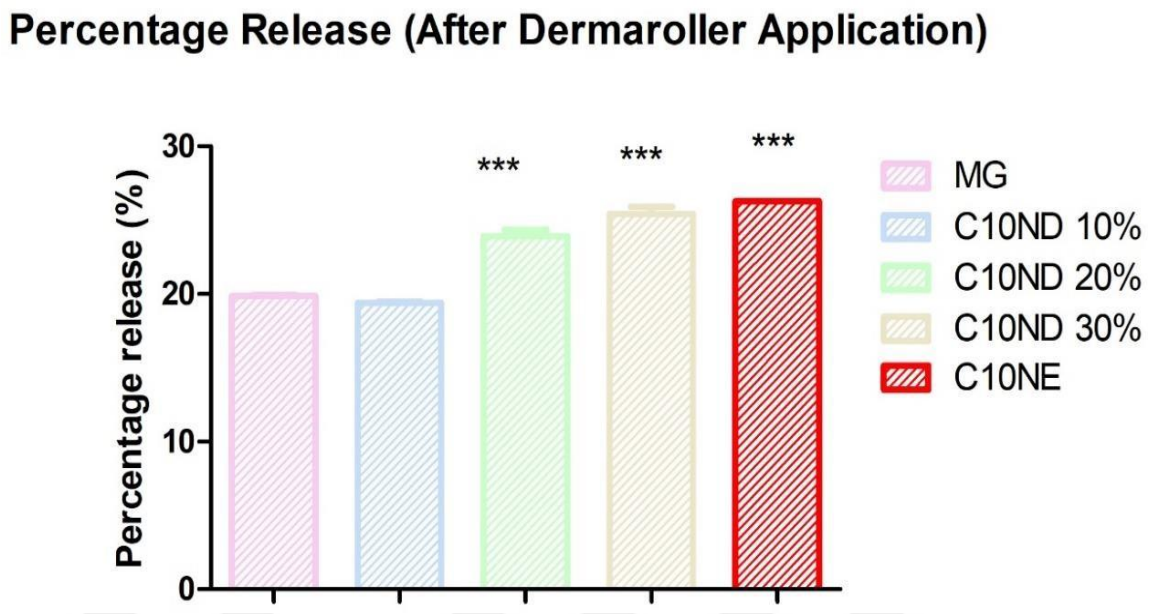

Figure 3.6.D. The ex-vivo release amounts of Naproxen sodium after 24 hours for different formulations (after the dermaroller application) were compared to those of the marketed gel.

MG Marketed gel, C10ND 10% Naproxen sodium-HPMC 10% hydrogel + DMSO 10%, C10ND 20% Naproxen sodium-HPMC 10% hydrogel + DMSO 20%, C10ND 30% Naproxen sodium-HPMC 10% hydrogel + DMSO 30%, C10NE Naproxen sodium- HPMC 10% Emulgel.

*** represents significantly higher than the control group (C10N) *** $p < 0.0001$.

3.7. The Dermaroller Application and Microchannel Evaluation Study on Pig Skin using Optical Microscopy

The microchannels that are created are transient in nature and spontaneously close a few hours after microporation; the length of the microneedles affects how long the sealing process takes. This transient property of microchannels provides important advantages for accurate dosing of medicinal or cosmetic materials. [89] In this study, researchers utilized a Dermaroller, a tool equipped with tiny needles, to create microchannels in pig skin. This process was employed to enhance the permeation of naproxen, a nonsteroidal anti-inflammatory drug (NSAID). Subsequently, before and after the application of the Dermaroller, ex vivo experiments using a Franz diffusion cell study were carried out. This allowed the researchers to investigate and

compare the diffusion of naproxen through the treated skin samples. In Figure 3.9.A, the process of preparing pig skin prior to creating microchannel pores using a derma roller is depicted. Subsequently, Figure 3.9.B illustrates clearly discernible microchannel pores with a size of 10 μm.

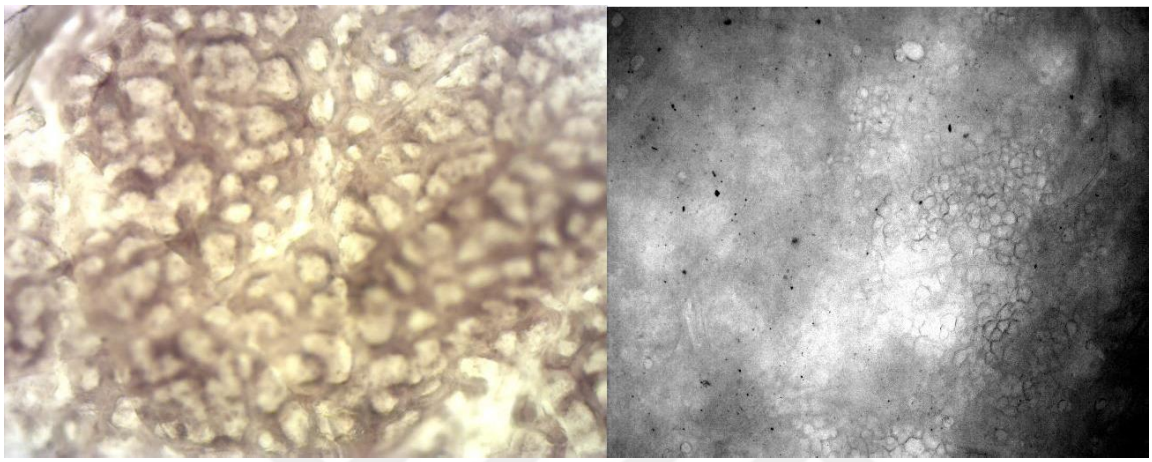

Figure 3.7.A. Pig skin morphology imaged by optical microscopy at magnifications (4 X and40 X).

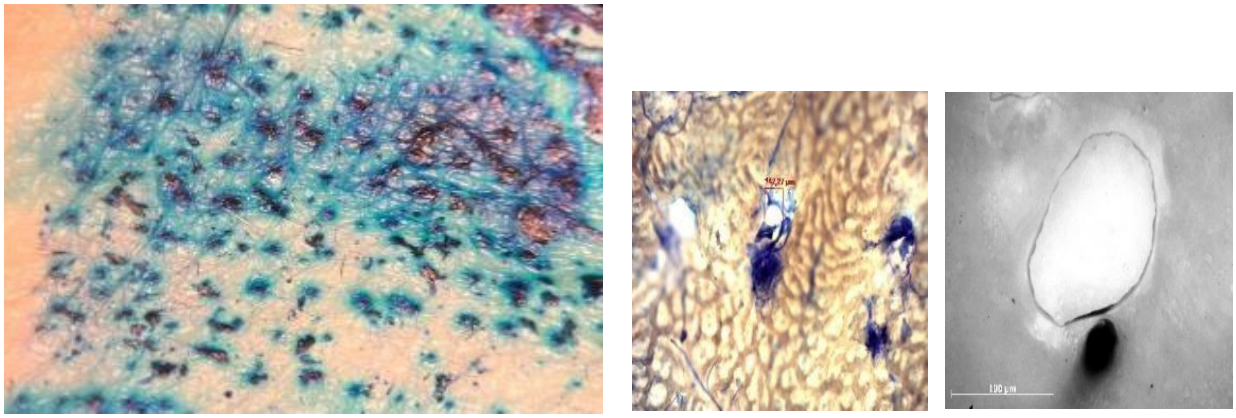

Figure 3.7.B. Pig skin microchannel morphology imaged by optical microscopy at magnitudes (4 X and 40 X).

CONCLUSION

The central objective of this thesis is to enhance the absorption of Naproxen sodium by incorporating it into a gel composition, addressing its limited transdermal permeation. This studysuccessfully optimized the transdermal administration of Naproxen sodium in a topical hydrogel formulation by utilizing Hydroxypropyl Methylcellulose (HPMC) with various concentrations ofdimethyl sulfoxide (DMSO) as a chemical permeation enhancer, as well as the incorporation of emulgul formulation with using the dermaroller for making microchannel to enhance the Naproxen penetration. The Emulgel and 30% DMSO significantly enhanced Naproxen sodium permeation through pig skin, showing statistically significant improvements over control formulations ($p < 0.0001$). Additionally, by incorporating 30% DMSO, Emulgel's formulation increased drug permeation by 25% compared to the marketed gel, highlighting DMSO's effectiveness as a permeation enhancer. Optimal hydrogel viscosity was achieved with a 10% HPMC concentration, balancing drug release and application ease. The use of a dermaroller further augmented drug penetration, indicating the potential of combining physical and chemical enhancers. These findings strongly suggest that the optimized formulation could lead to more effective topical pain relief applications, thereby underscoring the practical benefits of this research and warranting further research and clinical validation.

This study demonstrated that the tested Emulgel systems significantly augmented the permeation of naproxen sodium through pig epidermis. The enhanced permeation likely resulted from a synergistic effect of increased stratum corneum (SC) solubility and diffusivity. The higher SC solubility was attributed to incorporating the solutes within the formulation, facilitating their delivery into the SC.

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. CURRICULUM VITAE

Personal Informations

Name	Nour Saleh Mohammad	**Surname**	Saaydeh

Education

Degree	Department	The name of the Institution GraduatedFrom	Graduation year
Doctorate			
Master			
University	Pharmacy bachelor degree	Philadelphia University	2017
High school	Secondary certificate	Sakina Bint Al Hussein Secondary School	2013

Languages	Grades (#)
Arabic	Excellent
English	Excellent

Work Experience (Sort from present to past)

Position	Institute	Duration (Year - Year)
Community pharmacy		2018-2020
Agility logistics company		2020-2022

Computer Skills

Program	Level
Word microsoft	Excellent
Excel microsoft	Excellent
Power point	Excellent

***Excellent , good, average or basic**