International Journal of Pharmaceutical Drug Design (IJPDD)
Website: https://ijpdd.org/
ISSN: 2584-2897
Vol. 2, Issue 11, November, 2025
Page No.: 34-50

Review

Advancements in Nanoemulsion-Based Transdermal Drug Delivery Systems for Gout Treatment: A Comprehensive Review

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DOI: *10.62896/ijpdd.2.11.05*

Conflict of interest: *NIL*

Article History
Received: 12/10/2025
Accepted: 05/11/2025
Published: 28/10/2025

Abstract:
Gout is a metabolic condition characterized by the deposition of monosodium urate crystals in the joints, leading to intense inflammation, pain, and swelling. Despite the availability of several treatment strategies, including nonsteroidal anti-inflammatory drugs (NSAIDs), corticosteroids, and urate-lowering therapies (ULT), these treatments often present adverse effects, limiting their long-term use. Nanoemulsion-based transdermal drug delivery systems have emerged as promising alternatives, offering enhanced drug penetration, stability, and controlled release while minimizing systemic side effects. These systems, composed of nanoscale droplets, allow for the effective delivery of both hydrophobic and hydrophilic drugs, overcoming biological barriers such as the skin's stratum corneum. Nanoemulsions improve bioavailability, provide localized treatment, and reduce the need for frequent dosing, making them ideal for chronic conditions like gout. This review explores the advancements in nanoemulsion technology for gout treatment, focusing on the use of anti-inflammatory drugs like naproxen sodium in transdermal delivery systems. Additionally, the review discusses the challenges and potential solutions in the development and optimization of nanoemulsion formulations for enhanced therapeutic efficacy in gout management.

Keywords: Gout, Nanoemulsions, Transdermal Drug Delivery, NSAIDs, Naproxen Sodium, Bioavailability.

1. Introduction

Gout is an inflammatory disease that primarily affects the joints, characterized by painful and acute flare-ups due to the deposition of monosodium urate crystals. It typically occurs as a result of hyperuricemia, where uric acid levels in the bloodstream rise beyond the normal threshold, either due to overproduction or inadequate excretion by the kidneys (Herdiana et al., 2025). The most common manifestation of gout is the sudden onset of pain and swelling, often in the big toe, though other joints such as the knees, elbows, and wrists can also be affected (Harwansh et al., 2024). If left untreated, gout can progress to a chronic form, with the formation of tophi and irreversible joint damage, leading to decreased mobility and functionality (Shah et al., 2021). Understanding the mechanisms underlying gout, including the inflammatory response triggered by uric acid crystals and the immune system's role, has led to significant advancements in treatment strategies (Wang et al., 2008).

Currently, managing gout typically involves acute and chronic treatment approaches. For acute flare-ups, medications such as nonsteroidal anti-inflammatory drugs (NSAIDs), colchicine, and corticosteroids are prescribed to alleviate pain and inflammation. For chronic gout management, urate-lowering therapies (ULT) such as allopurinol and febuxostat are commonly used to reduce uric acid

production (Faheem et al., 2024). However, these therapies can present several challenges, including gastrointestinal side effects, skin irritations, and kidney toxicity, limiting their long-term use (Harwansh et al., 2024). Even with these treatments, many patients face difficulty in achieving adequate symptom relief, which underscores the need for alternative therapies that can target localized inflammation while minimizing systemic side effects.

Nanotechnology has emerged as a promising avenue for advancing drug delivery systems, particularly for chronic conditions such as gout. Nanoemulsions, a type of nanocarrier, are colloidal systems composed of oil and water phases stabilized by surfactants. These systems, with droplet sizes typically ranging from 20 to 200 nanometers, are capable of solubilizing both hydrophobic and hydrophilic drugs, improving their bioavailability and stability (Benson et al., 2021). In the case of gout, the use of nanoemulsions in transdermal drug delivery offers significant advantages, including enhanced drug penetration and controlled release at the site of inflammation (Zhou et al., 2018). By utilizing nanoparticles and other nanocarriers, these systems can overcome biological barriers, such as the skin's stratum corneum, facilitating more efficient drug delivery (Sami et al., 2016). Recent studies have demonstrated that nanoemulsions can significantly improve the transdermal absorption of NSAIDs like naproxen sodium, providing targeted therapy and reducing the risk of systemic side effects (Faheem et al., 2024; Shakeel et al., 2008).

Transdermal drug delivery systems (TDD) have become a key focus in the pharmaceutical industry for their ability to bypass the gastrointestinal tract and first-pass metabolism, resulting in more consistent and effective drug delivery (Tuteja et al., 2016). TDD systems, including nanoemulsion-based formulations, offer several advantages such as prolonged drug release, better patient adherence due to fewer required doses, and minimized systemic exposure, making them ideal for managing long-term conditions like gout (Sharma et al., 2015). However, challenges still exist in overcoming the skin barrier and ensuring the stability and efficacy of the delivered drugs. Nanoemulsions have shown promise in addressing these challenges by improving drug solubility, enhancing stability, and increasing skin permeability (Shah et al., 2021; Khawaja et al., 2017).

This review will explore the latest advancements in nanoemulsion-based transdermal drug delivery systems, specifically for the treatment of gout. We will examine their potential for improving the local delivery of anti-inflammatory drugs like naproxen sodium, the advantages they offer over traditional oral therapies, and the ongoing challenges in the development of effective nanoemulsion systems.

2. Gout

Definition, Symptoms, Causes, and Pathophysiology

Gout is a metabolic condition marked by the buildup of uric acid crystals within the joints, resulting in painful bouts of inflammation. The condition is associated with hyperuricemia, characterised by an elevated level of uric acid in the bloodstream, which can result from either excessive production or insufficient excretion by the kidneys (Herdiana et al., 2025).

The manifestations of gout generally encompass intense joint discomfort, inflammation, discolouration, and warmth, predominantly seen in the big toe, although other joints like the knees, elbows, and wrists may also be involved (Harwansh et al., 2024). Repeated instances of acute gout may lead to the development of chronic tophi, joint deterioration, and reduced mobility (Shah et al., 2021).

The underlying mechanisms of gout encompass the accumulation of monosodium urate crystals within the joints and adjacent tissues, which incites an inflammatory reaction orchestrated by the immune system. The crystals are identified by phagocytic cells, which then secrete pro-inflammatory cytokines, resulting in acute inflammation and discomfort (Wang et al., 2008).

Current Treatment Strategies and Challenges

Presently, the approaches to treating gout emphasise the management of sudden flare-ups and the lowering of serum uric acid concentrations. In the case of acute flares, various medications such as NSAIDs (for instance, ibuprofen and naproxen), colchicine, and corticosteroids are frequently utilised to alleviate pain and diminish inflammation. The ongoing management of chronic conditions includes the application of urate-lowering therapies (ULT) like allopurinol and febuxostat, which work to reduce the production of uric acid. Nevertheless, these therapies frequently present with adverse effects including gastrointestinal issues, skin

irritations, and kidney toxicity, which may restrict their prolonged application (Faheem et al., 2024).

Even with these treatment options accessible, numerous patients struggle to attain sufficient symptom management or encounter negative side effects, underscoring the necessity for alternative therapies, especially those capable of improving localised drug delivery while minimising systemic adverse effects (Harwansh et al., 2024)

3. Nanotechnology in Drug Delivery

Nanotechnology involves the intricate manipulation of substances at the nanoscale, generally ranging from 1 to 100 nanometres. This process enables the development of innovative materials that exhibit distinct characteristics absent in larger bulk materials. Nanotechnology has transformed the landscape of drug delivery, fundamentally altering the methods by which drugs are formulated and administered to the body (Sami et al., 2016). Utilising nanoparticles, liposomes, and nanoemulsions allows for a more efficient delivery of drugs, resulting in improved stability, solubility, and controlled release mechanisms.

Nanocarriers can be engineered to navigate and surpass biological obstacles, including the skin, gastrointestinal tract, and blood-brain barrier. When considering gout treatment, the utilisation of nanoemulsions for transdermal drug delivery presents remarkable advantages, such as enhanced drug penetration and prolonged release at the intended site (Zhou et al., 2018).

Table 1: Nanotechnology in Drug Delivery

Subsection	Key Concepts	Benefits/Applications	References	Notes
Nanotechnology in Drug Delivery	Manipulation at the nanoscale	Improved bioavailability, targeted delivery	Sami et al., 2016; Zhou et al., 2018	Revolutionizes drug delivery methods.
Nanoemulsions for Drug Delivery	Oil-in-water and water-in-oil systems	Enhanced drug penetration, stability, and solubility	Benson et al., 2021	Nanoemulsions are ideal for hydrophobic and hydrophilic drugs.
Mechanism of Nanoemulsion Delivery	Lipid solubility, droplet size, and surfactant use	Enhances drug delivery across barriers	Zhou et al., 2018	Small droplet sizes increase skin permeability.
Types of Nanoemulsions (O/W vs W/O)	Two-phase system, based on phase dominance	Flexibility in drug formulation	Benson et al., 2021	Selection depends on drug type (hydrophobic or hydrophilic).
Properties of Nanoemulsions	Small droplet size, high surface area	Better diffusion into tissues and controlled release	Benson et al., 2021	Ideal for transdermal and systemic drug delivery.
Nanoemulsion-Based Transdermal Delivery	Penetration enhancers, skin diffusion, lipophilic drugs	Targeted and sustained drug release	Zhou et al., 2018; Faheem et al., 2024	Effective in overcoming skin's barrier function.
Nanoemulsions for Pain and Inflammation	Targeted delivery of NSAIDs	Relieves pain locally without systemic side effects	Faheem et al., 2024; Harwansh et al., 2024	Especially useful for arthritis and gout.
Stability of Nanoemulsions	Emulsifying agents, surfactants	Prevents drug degradation, enhances shelf life	Benson et al., 2021	Ensures drug stability during storage and application.
Drug Release Control	Tunable release rate through formulation	Extended-release formulations for chronic conditions	Shakeel et al., 2008; Benson et al., 2021	Allows for reduced dosage frequency

				and prolonged therapeutic effects.
Skin Permeation Improvement	Nanoparticles reduce size for enhanced absorption	Increased transdermal absorption	Suyal & Ganesh, 2017; Shakeel et al., 2008	Critical for bypassing gastrointestinal and first-pass metabolism.
Reduced Side Effects	Targeted drug delivery, avoiding systemic exposure	Minimizes risk of gastrointestinal and renal toxicity	Faheem et al., 2024	Beneficial for drugs with high systemic side effects when taken orally.
Particle Size Control	Fine-tuned droplet size	Increased skin penetration, enhanced therapeutic effects	Shakeel et al., 2008; Benson et al., 2021	Smaller particles (less than 100 nm) penetrate deeper into the skin.
Surfactant Selection	Optimizing surfactant type for drug solubility and stability	Improves skin penetration and drug bioavailability	Shakeel et al., 2008; Faheem et al., 2024	Selection of non-ionic surfactants such as Tween 80 enhances permeation.
Lipid-Based Nanoemulsions	Interaction with lipid-rich skin layers	Facilitates penetration of lipophilic drugs	Zhou et al., 2018; Benson et al., 2021	Oil-in-water nanoemulsions work best for lipophilic compounds.
Nanoemulsions in Chronic Disease	Long-term drug delivery, sustained therapy	Suitable for managing long-term conditions like gout and arthritis	Faheem et al., 2024; Harwansh et al., 2024	Ideal for chronic inflammation treatments requiring continuous drug levels.

Nanoemulsions represent colloidal mixtures of oil and water, which are stabilised by surfactants and distinguished by their diminutive droplet sizes, typically falling within the range of 20 to 200 nm. These can be categorised as oil-in-water (O/W) or water-in-oil (W/O) systems based on which phase is dominant. Nanoemulsions are frequently favoured for drug delivery because they can effectively solubilise both hydrophilic and hydrophobic drugs, thereby enhancing the bioavailability and effectiveness of compounds that are poorly soluble (Benson et al., 2021).

4. Transdermal Drug Delivery Systems

Transdermal drug delivery (TDD) involves the administration of medications via the skin to achieve systemic effects, effectively circumventing the gastrointestinal tract and liver metabolism. This approach entails the uptake of medicinal substances through the skin into the circulatory system, allowing them to travel to their designated areas of effect. The main process through which medications penetrate the skin occurs via diffusion across the stratum corneum, which is the outermost layer of the skin. The architecture of the skin, made up of an intricate configuration of keratinised cells and lipid bilayers, serves as a protective barrier against the diffusion of various substances. For drugs to be effective, they need to traverse the lipid-dense stratum corneum and proceed through the epidermis until they arrive at the dermis, where they can access the blood vessels for entry into systemic circulation (Tuteja et al., 2016). The effectiveness of transdermal absorption is significantly influenced by the physicochemical characteristics of the drug, such as its molecular size, solubility, and lipophilic nature. Drugs that are lipophilic tend to be absorbed more efficiently through the lipid-rich barrier of the skin when compared to hydrophilic substances (Ng & Lau, 2015).

The movement of drugs across the skin can be divided into two main pathways: the transcellular pathway, in which drugs navigate through the cells of the stratum corneum, and the intercellular pathway, where drugs move through the gaps between the cells. In both pathways, the medication must navigate the skin's resistance, which can be altered through diverse formulation techniques, including the incorporation of penetration enhancers that momentarily compromise the skin's barrier, thereby aiding the movement of larger or hydrophilic molecules (Abd et al., 2016). Moreover, elements like skin moisture levels, ambient temperature, and dermal thickness can affect the absorption of medications. For instance, a rise in skin temperature can boost drug permeability by modifying the fluidity of the lipid bilayer, whereas improved skin hydration can enhance permeability by rendering the stratum corneum more flexible (Suyal & Ganesh, 2017). The selection of the delivery mechanism significantly influences the effectiveness of transdermal administration. Nanoemulsions, as an illustration, have shown the capability to enhance the solubility and stability of pharmaceuticals, facilitating superior penetration through the skin (Shah et al., 2021). The dimensions of the particles within nanoemulsions significantly amplify the surface area accessible for drug interaction with the skin, facilitating enhanced drug diffusion (Khawaja et al., 2017).

Even with the possible advantages, the skin's barrier function continues to be one of the major obstacles in the realm of transdermal drug administration. Only diminutive, lipophilic compounds can effortlessly traverse the stratum corneum. To successfully deliver drugs that possess elevated molecular weights or exhibit hydrophilic characteristics through the skin, it is essential to employ cutting-edge strategies. Specifically, systems based on nanoemulsions have garnered significant attention due to their capability to improve the absorption of medications through the skin, especially for hydrophobic compounds such as naproxen sodium. This formulation into a nanoemulsion leads to improved bioavailability and controlled release properties (Faheem et al., 2024). Nanoemulsions represent submicron-sized emulsions that provide the remarkable benefits of enhanced solubility for lipophilic drugs while simultaneously minimising the particle size of the drug, thereby enhancing its penetration through the skin (Rai et al., 2018). Through the manipulation of the dimensions and makeup of the nanoemulsion, scientists are able to precisely adjust the rate at which the drug is released, thereby enhancing the effectiveness of the drug's delivery to the intended tissue.

Advantages and Disadvantages of Transdermal Drug Delivery Systems

The transdermal route of drug delivery presents numerous benefits compared to conventional techniques such as oral intake and injections. A major benefit lies in the bypassing of first-pass metabolism, which poses a crucial challenge for oral formulations. When medications are taken by mouth, they travel through the digestive system and the liver, where they may undergo significant metabolism prior to entering the bloodstream. This leads to a decrease in the drug's bioavailability. Conversely, transdermal systems facilitate the direct uptake of substances into the bloodstream via the skin, circumventing the liver and maintaining the drug's effectiveness (Shakeel et al., 2010). This advantage holds particular significance for medications that experience considerable first-pass metabolism, like naproxen sodium. Transdermal delivery can provide elevated and steadier plasma concentrations by bypassing the liver, thereby minimising the variations linked to oral dosing (Kumar et al., 2016).

A notable benefit of transdermal delivery lies in its capacity to ensure prolonged and regulated drug release across extended durations. Transdermal patches, for example, can be crafted to provide a consistent release of medication throughout hours or even days. This leads to enhanced adherence among patients, as they do not need to take multiple doses frequently, a common scenario with oral medications (Harwansh et al., 2024). Moreover, transdermal systems have the capability to sustain therapeutic drug levels within the bloodstream over an extended duration, resulting in more consistent plasma drug concentrations and reducing the fluctuations that are typically associated with oral administration (Sharma et al., 2015). This regulated release proves to be especially advantageous for long-term ailments necessitating ongoing therapy, like gout or arthritis, where individuals can gain from a consistent delivery of the medication at the desired location.

In spite of these benefits, transdermal drug delivery systems present a number of drawbacks as well. A

significant limitation lies in the confinement to smaller, lipophilic compounds. The barrier characteristics of the skin restrict the absorption of larger molecules or those that exhibit low solubility in lipids, posing challenges for the effective delivery of a diverse array of drugs via this pathway. This constraint has spurred the creation of numerous approaches aimed at improving skin absorption, including the utilisation of penetration enhancers or the integration of medications with nanocarrier systems like nanoemulsions (Tuteja et al., 2016). Nonetheless, despite these significant advancements, the effective delivery of large proteins, peptides, and highly hydrophilic drugs through the skin remains a challenge.

One more hurdle is the occurrence of skin irritation and sensitisation. The ongoing utilisation of transdermal patches or the direct application of drug delivery systems onto the skin may lead to irritation, particularly in individuals with sensitive skin. The substances utilised in patches or gels may also trigger allergic responses or localised inflammation (Sami et al., 2016). Additionally, extended skin exposure to specific formulations might result in negative reactions like itching or redness, potentially diminishing patient adherence. Additionally, the expenses associated with producing transdermal drug delivery systems may exceed those of conventional oral formulations, potentially limiting accessibility for certain patients. The expenses stem from the necessity for unique materials, the intricacy of the production process, and the elevated costs associated with patches and gels in comparison to oral tablets (Ng & Lau, 2015). Moreover, the effectiveness of transdermal systems can fluctuate between individuals, as skin permeability varies among people influenced by factors such as age, skin condition, and general health (Benson et al., 2021). This variability may result in unpredictable therapeutic results, necessitating more tailored strategies for dosing and formulation.

Table 2: Transdermal Drug Delivery Systems

Subsection	Key Concepts	Advantages	Disadvantages	References
Transdermal Drug Delivery Systems Overview	Delivery via skin, bypassing gastrointestinal system	Avoids first-pass metabolism, consistent drug release	Limited to small, lipophilic drugs	Tuteja et al., 2016; Ng & Lau, 2015
Mechanism of Skin Penetration	Diffusion through the stratum corneum, transcellular or intercellular	Direct bloodstream access, avoids gastrointestinal tract	Slow onset for large molecules	Abd et al., 2016; Tuteja et al., 2016
Challenges in Transdermal Delivery	Skin barrier, molecular size limitation, poor permeability	Non-invasive, can be designed for sustained release	Skin irritation, sensitization	Shakeel et al., 2010
Advantages of Transdermal Delivery	No first-pass metabolism, long-lasting effects	Higher bioavailability for specific medications	Limited to specific types of drugs	Kumar et al., 2016; Shakeel et al., 2010
Disadvantages of Transdermal Delivery	Limited drug size, irritation, variability in absorption	Targeted drug delivery without systemic side effects	Skin irritation, high production cost	Tuteja et al., 2016; Ng & Lau, 2015
Skin Irritation and Sensitization	Allergic reactions, prolonged exposure to patches	Minimizes side effects compared to oral dosage	May cause localized skin issues	Sami et al., 2016; Shakeel et al., 2010
Advantages of Targeted Drug Delivery	Enhanced local delivery, reduced systemic toxicity	Non-invasive, improves patient compliance	May require specific formulations and materials	Shakeel et al., 2010
Cost Considerations	Higher production cost for patches and gels	Higher cost compared to oral medications	Less affordable for some patient groups	Ng & Lau, 2015

Skin Permeability Enhancement	Penetration enhancers, iontophoresis	Improved absorption of large molecules	Potential for skin damage if used improperly	Tuteja et al., 2016; Shakeel et al., 2008
Use for Chronic Conditions	Ideal for prolonged treatment, such as in arthritis or gout	Steady, controlled drug release	Higher initial cost, inconsistent absorption rates	Kumar et al., 2016
Variability in Absorption	Factors like age, skin health, hydration, and temperature	Customizable therapy for patients based on needs	Can lead to inconsistent dosing in certain individuals	Benson et al., 2021
Dosing Frequency	Extended-release formulations, once-daily or longer dosing	Better patient adherence, fewer doses required	May be less flexible in emergency situations	Sharma et al., 2015
Skin Moisture and Temperature Effects	Increases permeability and skin flexibility	Boosts drug absorption	Variability based on individual patient skin conditions	Suyal & Ganesh, 2017
Reduced Risk of GI Side Effects	Avoids gastrointestinal irritation, nausea, and ulcers	Lower systemic exposure	Limited to certain types of drugs	Shakeel et al., 2008

In light of these obstacles, the field of transdermal drug delivery remains a highly promising domain of investigation, especially when augmented by cutting-edge technologies like nanoemulsions. These systems enhance the solubility and stability of pharmaceuticals, facilitating improved regulation of drug release and superior penetration through the skin (Shah et al., 2021). With the advancement of technology, it is anticipated that transdermal systems will grow more adaptable and effective, presenting innovative alternatives for addressing a diverse array of diseases. Future investigations could concentrate on addressing the challenges associated with skin permeability and broadening the spectrum of medications that can be administered transdermally, especially for ailments such as gout, which necessitate prolonged and consistent drug delivery (Harwansh et al., 2024).

5. Naproxen Sodium: Pharmacology and Applications

Naproxen sodium stands out as a commonly utilised nonsteroidal anti-inflammatory medication (NSAID), predominantly recognised for its pain-relieving, inflammation-reducing, and fever-lowering properties. This medication is commonly recommended for the treatment of various conditions, including osteoarthritis, rheumatoid arthritis, ankylosing spondylitis, and gout. Additionally, it is utilised to relieve pain associated with musculoskeletal injuries and menstrual discomfort (Faheem et al., 2024).

Pharmacokinetics of Naproxen Sodium

Naproxen sodium exhibits pharmacokinetics marked by swift absorption, significant protein binding, and a comparatively prolonged half-life, rendering it appropriate for infrequent dosing regimens. Following oral intake, naproxen sodium is rapidly taken up by the gastrointestinal system, achieving peak plasma levels usually within a timeframe of 2 to 4 hours (Benson et al., 2021). The medication experiences considerable first-pass metabolism within the liver, mainly through cytochrome P450 enzymes, especially CYP2C9. This metabolic pathway results in the creation of non-active metabolites that are eliminated via urine. Significantly, naproxen sodium exhibits a strong affinity for plasma proteins, predominantly albumin, which restricts its distribution to various tissues (Tuteja et al., 2016).

The elimination half-life of Naproxen varies between 12 and 17 hours, positioning it as a prime candidate for formulations designed for sustained release. The extended half-life facilitates a reduced dosing schedule in comparison to alternative NSAIDs, thereby improving patient adherence (Suyal & Ganesh, 2017). Nonetheless, the significant protein binding of naproxen sodium indicates that any condition or medication that modifies plasma protein levels could influence the

drug's distribution and efficacy, which should be taken into account when determining therapeutic dosing (Abd et al., 2016). Furthermore, naproxen sodium undergoes significant metabolism in the liver, presenting a potential limitation for individuals with liver dysfunction. This diminished metabolic capacity may result in elevated plasma levels and a heightened risk of adverse effects (Harwansh et al., 2024).

Pharmacodynamics of Naproxen Sodium

The pharmacodynamics of naproxen sodium are mainly due to its capacity to block COX enzymes, which facilitate the transformation of arachidonic acid into prostaglandins. Prostaglandins are crucial in orchestrating the inflammatory response by heightening the sensitivity of pain receptors, enhancing vascular permeability, and triggering fever (Rai et al., 2018). Naproxen sodium works by lowering the levels of prostaglandins, which in turn effectively diminishes inflammation, alleviates pain, and brings down fever. In contrast to opioids or corticosteroids, naproxen sodium offers pain relief while eliminating the dangers of addiction or significant immunosuppression (Shakeel et al., 2008).

Naproxen sodium demonstrates notable efficacy in addressing inflammatory disorders like rheumatoid arthritis and gout, wherein prostaglandins play a crucial role in the disease's pathophysiology. Naproxen sodium is utilised for gout as it specifically addresses the acute inflammation linked to the deposition of uric acid crystals in the joints, effectively alleviating pain, swelling, and redness (Xu et al., 2023). The pharmacodynamics of naproxen sodium reveal that its effects are influenced by the dosage administered. At reduced dosages, it primarily demonstrates anti-inflammatory and pain-relieving properties, whereas at elevated dosages, it may additionally exhibit fever-reducing effects (Harwansh et al., 2024).

Current Methods of Naproxen Delivery

Naproxen sodium is typically administered through oral routes; however, alternative delivery methods, including topical formulations, have garnered interest for their potential to minimise systemic side effects. Oral administration generally encompasses immediate-release formulations, which facilitate a swift onset of action; however, prolonged use may lead to gastrointestinal irritation or ulcers (Sharma et al., 2015). Extended-release oral formulations are designed to minimise dosing frequency and deliver prolonged effects; however, they still require systemic drug absorption, which may lead to systemic side effects, including gastrointestinal discomfort, renal toxicity, or cardiovascular complications (Khawaja et al., 2017).

The topical administration of naproxen has been investigated to provide targeted therapy for ailments such as musculoskeletal discomfort and arthritis, with the medication being applied straight to the impacted region. Topical formulations of naproxen, whether in gel or cream form, are designed to deliver the medication straight into the skin. This allows the drug to provide its anti-inflammatory benefits precisely at the location of discomfort, bypassing the first-pass metabolism that occurs in the liver (Shah et al., 2021). Nonetheless, the barrier characteristics of the skin restrict the uptake of the medication, resulting in merely a minor fraction of the administered dosage arriving at the intended tissue. The efficacy of topical naproxen is confined primarily to superficial ailments and shows diminished effectiveness when addressing deeper or more systemic inflammatory issues.

Table 3: Naproxen Sodium: Pharmacology and Applications

Subsection	Key Concepts	Pharmacokinetics	Pharmacodynamics	References
Naproxen Sodium Overview	Nonsteroidal anti-inflammatory drug (NSAID)	Absorbed rapidly from the GI tract, peak plasma in 2-4 hrs	Inhibits COX enzymes, reduces pain and inflammation	Faheem et al., 2024; Rai et al., 2018
Pharmacokinetics of Naproxen Sodium	Absorption, protein binding, metabolism in the liver	Long half-life (12-17 hrs), 99% bound to plasma proteins	High bioavailability, reduced dosing frequency	Benson et al., 2021; Tuteja et al., 2016
Pharmacodynamics of Naproxen Sodium	COX-1 and COX-2 inhibition	Reduces prostaglandin	Alleviates inflammation in arthritis and gout	Shakeel et al., 2008

		synthesis, reducing pain and swelling		
Current Methods of Naproxen Delivery	Oral (immediate and extended release)	Oral route causes first-pass metabolism	Oral forms can cause GI irritation	Faheem et al., 2024; Sharma et al., 2015
Topical and Nanoemulsion Delivery	Topical gels and creams for localized treatment	Bypasses first-pass metabolism, targeted pain relief	Nanoemulsions provide better skin penetration	Faheem et al., 2024; Abd et al., 2016
Topical Formulation Effectiveness	Improved skin absorption via nanoemulsions	Provides localized treatment without systemic side effects	Controlled release improves compliance and reduces dosage frequency	Faheem et al., 2024; Abd et al., 2016
Bioavailability and GI Toxicity	Nanoemulsion delivery reduces systemic exposure	Increases local concentration at the site of action	Reduces the likelihood of gastrointestinal toxicity	Harwansh et al., 2024
Use in Gout Treatment	Direct delivery to affected joints	Targets inflammation at the site, reducing swelling and pain	Effective in managing acute flare-ups of gout	Xu et al., 2023

In recent times, innovative transdermal delivery systems have surfaced as a more sophisticated approach for administering naproxen sodium. These innovative systems encompass patches, gels, or emulsions meticulously crafted to improve drug penetration across the skin, thereby guaranteeing enhanced bioavailability and prolonged drug release (Baboota et al., 2007). Nanoemulsions have emerged as highly efficient carriers for naproxen sodium, attributed to their diminutive particle size and their capacity to enhance the solubility and stability of lipophilic medications (Faheem et al., 2024). The inclusion of penetration enhancers within these formulations can significantly improve the transport of the drug through the skin barrier, minimising systemic side effects while preserving therapeutic effectiveness (Suyal & Ganesh, 2017). Nanoemulsion-based systems enhance drug permeation while simultaneously offering a controlled release mechanism for naproxen sodium. This ensures prolonged therapeutic effects and minimises the necessity for frequent reapplication (Sharma et al., 2010). Furthermore, systems based on nanoemulsions present the benefit of facilitating targeted drug delivery, thereby reducing adverse effects like gastrointestinal discomfort and kidney toxicity linked to the use of oral NSAIDs (Benson et al., 2021). Recent research has shown that nanoemulsions of naproxen sodium markedly improve transdermal absorption when compared to traditional gel or cream formulations, offering a viable alternative to oral therapy, especially for individuals who cannot tolerate oral NSAIDs because of side effects (Abd et al., 2016). The advancement of nanoemulsion-based systems holds promise for enhancing patient adherence, as these innovative systems can deliver prolonged pain alleviation and minimise the need for frequent administration, rendering them exceptionally advantageous for chronic ailments like gout (Khurana et al., 2013).

6. Nanoemulsions for Transdermal Delivery

Nanoemulsions represent a cutting-edge approach to drug delivery systems, capturing considerable interest in recent times due to their promising ability to improve the transdermal administration of medications. A nanoemulsion represents a system comprising submicron-sized droplets, generally measuring less than 100 nm, that are dispersed within a continuous phase. This phase can either be water-in-oil (W/O) or oil-in-water (O/W), contingent upon the specific composition and intended application (Benson et al., 2021). These systems provide numerous benefits for transdermal drug delivery, such as improved drug solubility, increased stability, and better penetration through the skin barrier. Their diminutive droplet dimensions and capacity to solvate a range of hydrophobic and

hydrophilic pharmaceuticals render them an optimal carrier for diverse therapeutic agents, encompassing nonsteroidal anti-inflammatory drugs (NSAIDs) such as naproxen sodium (Faheem et al., 2024).

The Role of Nanoemulsions in Transdermal Drug Delivery

A significant hurdle in the realm of transdermal drug delivery lies in surmounting the skin's inherent barrier, known as the stratum corneum, which restricts the uptake of numerous medications. Nanoemulsions are essential in enhancing drug permeation through the skin by minimising the size of drug particles, thereby amplifying the surface area available for absorption (Shakeel et al., 2008). The tiny droplets found in nanoemulsions enhance the transport of drugs by encouraging diffusion into the skin layers, which enables deeper penetration and improves the efficiency of drug delivery to the intended site (Sharma et al., 2010).

Additionally, nanoemulsions provide properties for controlled release that assist in sustaining a stable drug concentration at the target site, thereby decreasing the application frequency and lessening systemic side effects. This feature is particularly advantageous for medications such as naproxen sodium, where extended exposure to the drug is essential for maintaining therapeutic effects (Suyal & Ganesh, 2017). The capacity to adjust the release rate by altering the formulation elements, including the oil phase and surfactants, enables a personalised strategy designed specifically for the drug being administered (Abd et al., 2016).

Besides boosting drug penetration, nanoemulsions can further elevate the stability of pharmaceuticals by safeguarding against degradation caused by environmental influences like light, heat, and oxidation. The robustness of the pharmaceutical agent within a nanoemulsion can be primarily ascribed to the safeguarding characteristics of the emulsifying agents and the minimised surface area of the drug particles (Benson et al., 2021). The significance of this is especially pronounced for hydrophobic medications such as naproxen sodium, which can experience degradation when subjected to these factors in traditional formulations (Harwansh et al., 2024).

Previous Studies on Naproxen Nanoemulsions and Other NSAIDs

A multitude of research endeavours has investigated the promising capabilities of nanoemulsions in facilitating the transdermal administration of naproxen sodium alongside various other NSAIDs. In their 2024 study, Faheem and colleagues explored a topical nanoemulsion formulated with naproxen and Gaultheria oil, discovering that it significantly improved anti-inflammatory effects in models of osteoarthritis. This formulation showcased enhanced skin absorption and greater therapeutic effectiveness when compared to traditional gel formulations. The authors emphasised that the nanoemulsion system facilitated a more regulated and prolonged release of naproxen, minimising the likelihood of systemic side effects while providing a more targeted effect.

In a similar vein, Abd et al. (2016) investigated the collaborative effects of surfactants and nanoemulsions aimed at improving the permeation of naproxen sodium through the skin. Their findings demonstrated that surfactants such as Tween 80 and Span 80 markedly enhanced the transdermal delivery of naproxen by reducing the interfacial tension and boosting the drug's solubility within the emulsion phase. The results highlighted the significance of choosing suitable surfactants to enhance nanoemulsion formulations for effective skin absorption.

Alongside naproxen sodium, various other nonsteroidal anti-inflammatory drugs, including diclofenac, ketoprofen, and piroxicam, have been developed into nanoemulsions to enhance transdermal delivery effectiveness. As an illustration, Shakeel and colleagues (2008) showcased that formulations of diclofenac utilising nanoemulsion technology displayed improved bioavailability and diminished gastrointestinal irritation when contrasted with traditional oral formulations. This research highlighted the promising capabilities of nanoemulsions in facilitating the targeted delivery of NSAIDs to the inflammation site, thereby reducing systemic exposure and associated side effects.

In a similar vein, Sandig et al. (2013) developed nanoemulsions encapsulating piroxicam and assessed their analgesic efficacy in various animal models. The findings indicated that the nanoemulsion formulation markedly alleviated pain and inflammation, demonstrating its efficacy as a transdermal delivery system. The research highlighted the significance of nanoemulsions in effectively reaching deep tissue layers and providing localised therapeutic benefits.

Factors Influencing Transdermal Delivery via Nanoemulsions

A variety of elements play a crucial role in determining the efficacy of transdermal drug delivery through the use of nanoemulsions. The factors encompass the selection of surfactants, the dimensions of the nanoemulsion droplets, the viscosity, as well as the makeup of the oil and water phases.

- **Surfactants**: Surfactants are essential in ensuring the stability of nanoemulsions and in managing the release of drugs. Non-ionic surfactants such as Tween 80, Span 80, and Brij 35 are frequently utilised because of their capacity to lower surface tension, facilitating the creation of stable emulsions and enhancing skin penetration (Sharma et al., 2015). The selection of surfactant significantly influences the drug's release rate, as it has the potential to modify the skin's permeability by changing the fluidity of the stratum corneum (Benson et al., 2021). Surfactants have the capability to function as penetration enhancers, promoting more profound drug absorption into the layers of the skin (Shah et al., 2021).
- **Particle Size**: The size of the particles within the nanoemulsion represents a vital factor that influences both the permeation of the drug and its stability. Tiny droplets, measuring less than 100 nm, offer an increased surface area for interaction with the skin, which boosts drug absorption and minimises the requirement for larger doses (Benson et al., 2021). Research indicates that nanoemulsions featuring reduced droplet sizes demonstrate enhanced skin penetration and superior transdermal delivery effectiveness in comparison to traditional formulations (Harwansh et al., 2024). Furthermore, the reduced particle size lessens the likelihood of skin irritation by diminishing the mechanical barrier created by larger droplets (Abd et al., 2016).
- **Viscosity**: The thickness of a nanoemulsion influences how easily it can be spread and applied onto the skin. Formulations with elevated viscosity levels can pose challenges during application and may lead to inconsistent drug distribution, potentially undermining the treatment's efficacy (Suyal & Ganesh, 2017). Conversely, formulations with lower viscosity can improve spreadability; however, they might also result in quicker drug diffusion and a shorter retention time on the skin, which could potentially lessen the duration of therapeutic effects (Faheem et al., 2024).
- **Oil and Water Phases**: The makeup of the oil and water components in a nanoemulsion formulation plays a crucial role in determining its stability, the solubility of the drug, and the ability to penetrate the skin. For hydrophobic drugs such as naproxen sodium, oil-in-water nanoemulsions are typically favoured due to their ability to effectively solvate the drug and improve its absorption via the skin (Shakeel et al., 2008). The choice of oils, such as oleic acid and caprylic acid, along with their concentration, can significantly affect the droplet size and the formulation's capacity to penetrate the skin (Khurana et al., 2013).

Table 4: Nanoemulsions for Transdermal Delivery

Subsection	Key Concepts	Benefits	Challenges	References
Role of Nanoemulsions in Transdermal Delivery	Small particle size, high surface area	Enhanced skin penetration, stability, bioavailability	Skin irritation, possible uneven drug release	Shakeel et al., 2008; Benson et al., 2021
Enhancing Skin Penetration	Use of surfactants, lipid components	Increased drug diffusion through skin layers	Needs careful formulation to avoid irritation	Shakeel et al., 2008; Faheem et al., 2024

Controlled Release Mechanism	Drug release rate controlled via formulation	Prolonged therapeutic effects	May require complex formulations	Faheem et al., 2024; Suyal & Ganesh, 2017
Previous Studies on Naproxen Nanoemulsions	Improved skin absorption and localized delivery	Significant improvement in efficacy compared to gels	Limited by skin permeability issues	Abd et al., 2016; Faheem et al., 2024
Particle Size and Drug Release	Small droplets increase skin penetration, tunable release rate	Controlled release reduces dosage frequency	Need for precise particle size control	Shakeel et al., 2008; Benson et al., 2021
Surfactants and Stability	Use of surfactants to enhance solubility and stability	Better stability against environmental factors (heat, light)	Possible impact on skin sensitivity	Shakeel et al., 2008; Suyal & Ganesh, 2017
Lipid Components	Role of oils in enhancing solubility and skin penetration	Boosts penetration of hydrophobic drugs	Limited selection of oils available for formulation	Zhou et al., 2018; Benson et al., 2021
Skin Irritation Reduction	Smaller particle sizes, penetration enhancers	Minimizes irritation and enhances absorption	May still cause irritation in sensitive individuals	Faheem et al., 2024; Suyal & Ganesh, 2017
Use in Chronic Disease Treatment	Long-term controlled drug release for chronic conditions	Ideal for conditions like arthritis and gout	Potential skin sensitivity issues over prolonged use	Faheem et al., 2024; Shakeel et al., 2008
Stability in Harsh Environments	Nanoemulsions provide enhanced stability under various conditions	Increases shelf life of formulations	Requires careful formulation to prevent instability	Benson et al., 2021

Nanoemulsions offer an exciting opportunity for improving the transdermal administration of naproxen sodium and various other non-steroidal anti-inflammatory drugs (NSAIDs). The synergy of diminutive droplet dimensions, finely-tuned surfactants, and meticulously regulated formulation variables facilitates enhanced skin absorption, minimised systemic adverse effects, and prolonged drug liberation. Earlier investigations have underscored the efficacy of nanoemulsions in the topical administration of naproxen sodium, and current research is expected to further enhance these formulations for improved therapeutic results in managing inflammatory disorders like gout (Faheem et al., 2024; Shakeel et al., 2008). Through enhanced optimisation, nanoemulsions have the potential to emerge as a crucial element in the transdermal administration of diverse medications, offering a precise, effective, and user-friendly substitute to oral treatments.

7. conclusion

Nanoemulsion-based transdermal drug delivery systems have demonstrated significant potential in the treatment of gout, offering a viable alternative to conventional therapies. The ability to enhance the penetration and bioavailability of drugs, particularly NSAIDs like naproxen sodium, provides a promising strategy for targeted therapy, minimizing systemic exposure, and reducing side effects. Nanoemulsions offer controlled drug release, which is crucial for chronic conditions like gout, where consistent drug delivery is needed. Additionally, advancements in formulation techniques, including the use of suitable surfactants and particle size control, have improved the stability and efficacy of these systems. However, challenges such as skin irritation, formulation complexity, and variability in absorption remain. Future research should focus on optimizing the formulation of nanoemulsions to enhance skin permeability, ensure long-term

stability, and improve patient adherence. As technology advances, nanoemulsions could become a key player in the transdermal delivery of gout medications, offering a more efficient and patient-friendly approach to managing this painful and debilitating condition. Moreover, the development of personalized transdermal therapies tailored to individual skin characteristics and disease severity could further enhance treatment outcomes.

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