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Review

Topical and Transdermal Delivery of Nonsteroidal Anti-Inflammatory Drugs (NSAIDs) for Inflammation and Pain: Current Trends and Future Directions in Delivery Systems

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Abstract: The use of topical and transdermal drug delivery systems for nonsteroidal anti-inflammatory drugs (NSAIDs) has transformed pain management, inflammation, and skin conditions. This analysis highlights the topical and transdermal applications of ibuprofen, ketoprofen, and flurbiprofen, highlighting their excellent skin permeability and localized pain relief, as well as an evaluation of their safety in such applications. Their compatibility with diverse formulations, minimal systemic side effects, and widespread use in commercial products makes them ideal candidates for skin research and targeted therapy. Advances in transdermal delivery processes, such as the use of chemical enhancers, Solid Lipid Nanoparticles, vesicular systems, and hydrogels, have enhanced NSAID penetration and bioavailability. Physical techniques like iontophoresis and sonophoresis further enhance the transport of drugs across the stratum corneum of the skin. These approaches and processes enable more efficient and localized treatment of inflammatory conditions. The review emphasizes the need for continued innovation, interdisciplinary processes, and collaboration to overcome existing challenges. Future developments in nanotechnology and advanced drug delivery systems have the capability to enhance the effectiveness and safety of NSAIDs, paving the way for novel therapeutic solutions in managing pain and inflammation.

Keywords: NSAIDs; skin; topical delivery; transdermal systems; ibuprofen; ketoprofen; flurbiprofen; pain management; inflammation; nanotechnology

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Academic Editor: Paolo Trucillo

Received: 28 January 2025
Revised: 7 March 2025
Accepted: 17 March 2025
Published: 19 March 2025

Citation: Drosopoulou, K.; Kosheleva, R.I.; Ofrydopoulou, A.; Tsoupras, A.; Mitropoulos, A. Topical and Transdermal Delivery of Nonsteroidal Anti-Inflammatory Drugs (NSAIDs) for Inflammation and Pain: Current Trends and Future Directions in Delivery Systems. *Processes* **2025**, *13*, 907. https://doi.org/10.3390/pr13030907

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1. Introduction

The skin, the body's largest organ, acts as the main defense barrier against external factors [1] and maintains homeostasis [2]. It is a highly multilayer composite, and it comprises three key structural components: epidermis, dermis, and hypodermis (Figure 1). The epidermis consists of five layers composed of epithelial cells, one of which is the topmost layer of the skin, known as the Stratum Corneum (SC) [1]. The SC is usually 10 to 20 μm thick, it contains 15% water, and it is made up of two essential structural elements: the corneocytes and the intercellular lipids [3]. Elias (1983) introduced the "brick and mortar" concept, where corneocytes represent bricks embedded in a lipid-based mortar [4].

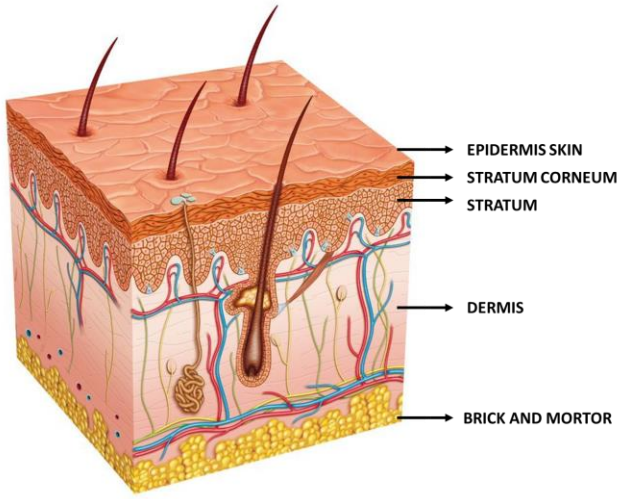


Figure 1. Schematic representation of the multi-layer composition of skin (retrieved from pinterest.com: https://gr.pinterest.com/pin/41376890326483798/, accessed on 8 January 2025).

As highlighted by Scheuplein and Blank (1971), the SC functions as the main protective layer to percutaneous absorption, with its keratinized structure significantly reducing permeability to water-soluble substances [5].

The key roles of SC are to prevent water loss from the epidermis while also blocking external molecules from penetrating; therefore, cosmetologists and pharmacologists are particularly interested in how it can facilitate or enhance. For this reason, studies show that there are various approaches to enhance SC penetration by the molecules (Figure 2) [6]:

i. The intercellular, which enables a winding penetration, like a "zig-zag" route, through the lipids located between corneocyte cells.
ii. The transcellular, which allows penetration through the keratinized corneocytes.
iii. The intrafollicular, which enables drug passage via hair follicles.
iv. The polar, meaning through pores with polar properties located between cells and encased by polar lipids.

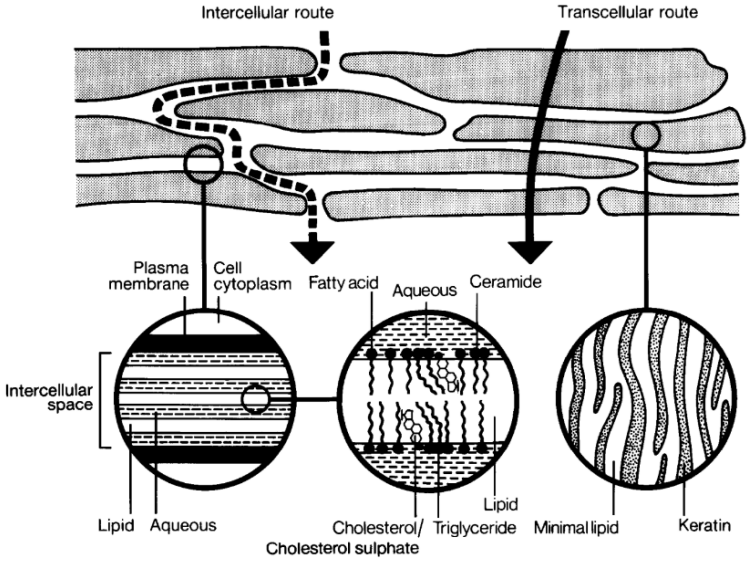


Figure 2. Potential pathways for drug penetration through the skin—intercellular or transcellular pathways [7].

In general, transdermal drug delivery systems offer notable benefits in medical applications for drugs having a specific target action in the human body and are assumed

as some of the best routes for active ingredient administration. They reduce systemic side effects, control and prolong drug delivery, and can serve as an alternative to oral administration, which presents challenges for drugs with inconsistent absorption in the digestive system. For example, this method can be used for managing inflammatory diseases, such as dermatitis, erythematous lupus, and psoriasis [8–11]. However, to penetrate deeper skin layers, the drug must overcome the SC barrier. For that to happen, drug substances should be small, under 500 Da, compatible, and both water-and fat-soluble [12,13].

Any disruption or damage to the skin caused by medical conditions, physiological disorders, or trauma is termed a wound [14]. Based on the affected skin region and the depth of skin layers involved, wounds can be categorized into (i) Superficial wounds, when the epidermis is affected, (ii) Partial thickness wounds, when the deeper dermis layers are involved, and (iii) Full-thickness wounds, extend to deeper tissues. In addition, wounds can be classified as acute wounds, chronic wounds, and complicated wounds [15]. The process of wound healing is considered to occur in three stages: inflammation, proliferation, and remodeling. In particular, the first step begins with blood hemorrhage and clot formation for about 48 h [16].

Inflammation is the body's natural response to injury or infection, which is essential for eliminating harmful agents and restoring tissue structure and function [17]. Inflammation can be caused either by chronic wounds, including diabetic foot ulcers, or simply by a natural response to injury like burns. Many biological processes work in order to repair the skin tissue after an injury. The quality of wound healing is dependent on multiple factors, one of which is the inflammatory response to injury [18].

Chronic wounds, however, may not adhere to this healing process, and often remain stuck in the inflammatory stage, preventing progression to the healing phase. This lack of progression can be because of difficulty in recruiting the necessary cells to regenerate tissue, protect the wound, or address harmful substances that have entered the body [19]. The keratinocytes at the SC play a key role in initiating inflammation while also regulating it by producing anti-inflammatory cytokines [20].

2. Materials and Methods

The Scholar and the PubMed databases were used to locate pertinent research. The search included the following terms: "Skin", "Drug Delivery", "Nonsteroidal anti-inflammatory drugs", "NSAIDs", "Ibuprofen", "Ketoprofen", "Flurbiprofen", "Stratum Corneum", "Wound healing", "Skin Barrier", "Transdermal", "Topical", "Inflammation", "Chronic wound", "Chronic pain", "Prostaglandins", "Hydrogels", "Gel", "Nanogel", "Patch", "Cream", "Skin permeability", "Permeability enhancement", "Chemical techniques", "Physical techniques", "Iontophoresis", "Sonophoresis", "Electroporation", "Chemical Enhancers", "Solid Lipid Nanoparticles", "Nanostructured Lipid Carriers", "Nanosized vesicular systems", "Vesicles", "Liposomes", "Transfersomes", "Polymeric Nanoparticles", "Nanoemulsion", "Microemulsion", "Oil in water", "Water in oil", "Clinical trials", "Clinical study", "in vitro", "in vivo", "Nanobubbles", with the use of and/or their combinations. The search was performed using these keywords in article titles, abstracts, and keywords from November 2023–November 2024.

The criteria for selection were based on available data from Scopus, and PubMed, while studies that met these requirements were included: (i) to be research articles (ii) to be written in English, (iii) to be accessible, and (iv) to be published between 2000 and 2024. A limited amount of important information from review papers and books, as well as other articles before 2000, which were not thoroughly previously reviewed, were also included.

To assess the quality and relevance of articles, we initially examined their title and abstracts, discarding those that were irrelevant. The remaining studies were thoroughly analyzed to determine their suitability and usefulness for this review.

3. Processes for Increasing the Efficacy of NSAIDs Through Topical and Transdermal Applications

3.1. NSAIDs

For the decrease in inflammatory disease states and an inhibitory effect on the wound recovery process, commonly nonsteroidal anti-inflammatory drugs (NSAIDs) are used. Those kinds of drugs are recommended after soft-tissue damage or surgical procedures to help manage the pain and diminish the inflammation by inhibiting cyclooxygenase (COX) [21], the isozymes, which are responsible for converting arachidonic acid into prostaglandins, including thromboxane and prostacyclin [22].

COX-1 is consistently present in the majority of cells and plays a role in prostaglandin synthesis. The latter provoke physiological functions, such as gastric epithelial cytoprotection and homeostasis, while COX-2 is activated by inflammation, hormones, and growth signals. COX-2 is responsible for the synthesis of proinflammatory prostaglandins and in conditions involving abnormal cell growth, like cancer [23,24]. Each NSAID inhibits the COX enzymes at varying degrees [25].

More specifically, NSAIDs attach to and deactivate the COX enzyme site at only one monomer within the COX dimer (the two COX isoforms, COX-1 and COX-2) and this effectively stops prostanoid synthesis. The second monomer seems to have an allosteric role [26]. As mentioned before, NSAIDs are commonly used to inhibit prostaglandin production (Figure 3). Prostaglandins (PGs) have a very important role in the regeneration of the inflammatory response [27], in pyrexia, and in pain sensation [22].

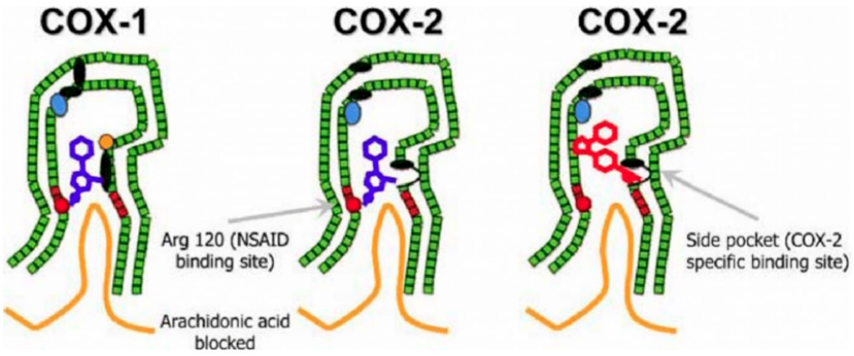


Figure 3. Diagram illustrating how a non-selective NSAID blocks COX 1 (**left**), of the inhibition of COX-2 by a nonselective NSAID (**middle**), and of the COX 2 suppression by a selective NSAID (**right**) [28].

The population that is exposed to NSAIDs is critically large, as these drugs have been used for over 3500 years, with an annual production of about 40,000 metric tons of aspirin, the most common anti-inflammatory drug, consumed [29]. For conditions involving moderate pain, an alternative to oral administration of NSAIDs would be topical use. It is considered safer, particularly regarding gastrointestinal or kidney-related adverse effects [30]. However, due to the fact that NSAIDs also affect the local immune reactions, which are essential for effective wound healing post-operatively, they result in some undesirable complications, like wound dehiscence, infection, and impaired collagen synthesis; thus, their use is controversial [19,31]. Among others, NSAIDs, Ibuprofen (IBU), Ketoprofen (KTP), and Flurbiprofen (FB) have been studied (Figure 4).

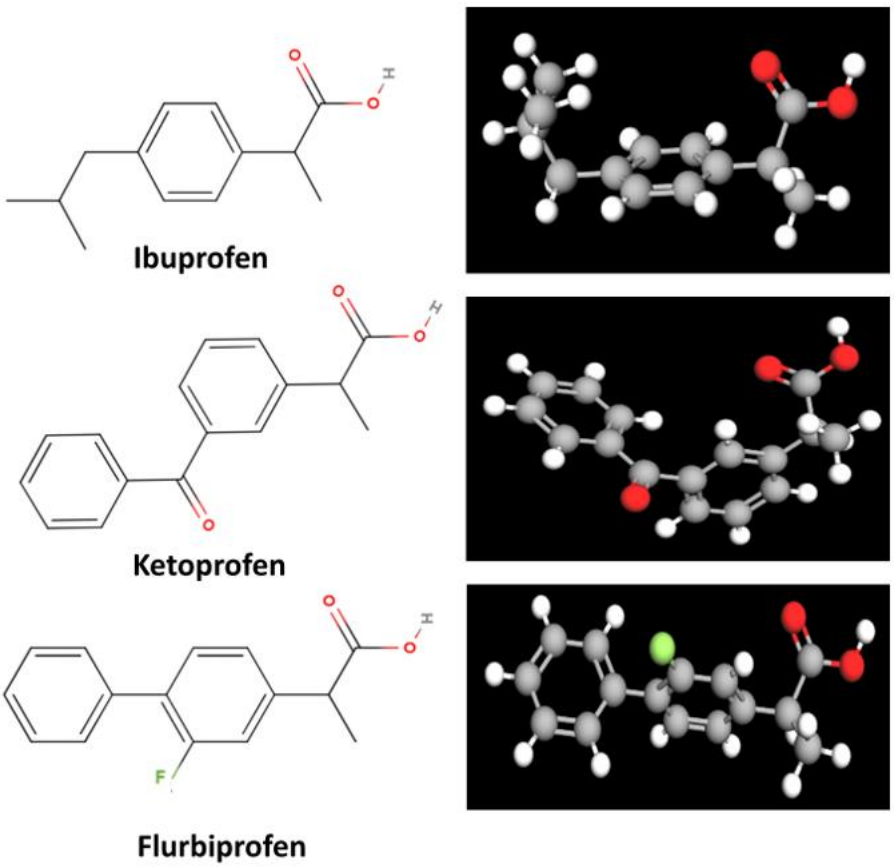


Figure 4. Chemical Structures (2D and 3D) of Ibuprofen, Ketoprofen, and Flurbiprofen (retrieved from molview.org: https://molview.org/, accessed on 8 January 2025).

3.1.1. Ibuprofen

IBU is one of the most common examples of NSAIDs used in several dermal applications. IBU is a moderately lipophilic compound with poor solubility. It was developed as a superior alternative to aspirin for treating rheumatoid arthritis by a team of researchers at Boots the Pure Drug Company Ltd. in Nottingham, UK, in the 1960s. The way IBU works across various treatments is well understood. The racemic mixture of IBU is a non-selective COX inhibitor, where the S (+) enantiomer specifically inhibits COX-1, while R (−) ibuprofen has minimal pharmacological activity [32].

As it was discussed previously, some drugs cause negative effects on the gastrointestinal system, as shown in Table 1; therefore, the need for different methods arose. Later on, in 1983, the first topical IBU preparation started [33]. In particular, Seth (1993) [34] used three IBU-containing topical forms: gel, water-based ointment, and cream in order to compare them with the effectiveness of the oral form. The blood samples collected at various times showed that the gel formulation led to the highest blood levels within 24 h of use, peaking at 4.8 h after application, followed by the cream at 6.8 h, and finally the hydrophilic ointment at 7 h.

Over the course of years, even more studies were conducted so that the therapeutic concentration of IBU and its pharmacokinetics from topical preparation, could be determined. Berner et al. (1989) [35] reported plasma IBU concentrations in human subjects. Maximum plasma levels (0.2 μg/mL) were attained 11 h after the topical application of 10 mg/cm^2 IBU. Another group of patients, after applying 8 g of gel IBU to the skin, three times a day for 3 consecutive days, were found to obtain higher drug levels in muscle (20.32 μg/mL) compared to subcutaneous tissue (9.13 μg/mL). In this study, Berner et al. [35] were unable to detect any plasma IBU levels after 3 h, and at about 10 h, tissue drug levels were

approximately 100 times greater than plasma levels. In addition, Tegeder et al. (1999) [36] found plasma drug concentration to be much lower than in the case of oral administration. These results suggest that IBU applied topically achieves therapeutic levels in the deep epidermis and does not reach considerable levels in the bloodstream. That means that the transdermal application showcases a gradual drug release over time into systemic circulation, and formulating dosage forms that achieve both high and prolonged drug levels is the main challenge [37].

Transdermal formulations of IBU have been developed to provide localized anti-inflammatory and analgesic effects while minimizing systemic exposure. The effectiveness of these formulations is influenced by their ability to penetrate the skin barrier and deliver therapeutic concentrations to underlying tissues. An in vitro study comparing various 5% IBU topical formulations demonstrated significant differences in skin penetration efficiency. Formulations such as Ibuspray, Ibugel, and Ibumousse showed superior penetration, with approximately 2.5 times greater ibuprofen delivery through the skin over 48 h compared to formulations like Deep Relief Gel. These results emphasize the importance of the drug formulation composition in enhancing the percutaneous absorption and therapeutic efficacy of transdermal ibuprofen products [38].

3.1.2. Ketoprofen

KTP is another NSAID possessing pain-relieving, anti-inflammatory, and fever-reducing effects [39], which has also been used in such applications. It belongs to the propionics derived from arylcarboxylic acid. It works by COX 1 and COX 2 enzymes being inhibited reversibly, decreasing the synthesis of precursors to proinflammatory prostaglandins [40] and also KTP is considered one of the most powerful inhibitors of COX [41]. It was first synthesized in 1968 and marketed as an oral drug [24], and ten years later it was marketed in Europe as a topical product, like a topical patch and a gel delivery system. It is now available in more than 100 countries worldwide [39]. KTP is used to treat signs of inflammation and musculoskeletal disorders, as well as discomfort and elevated temperature in individuals of all ages [42–44]. Also, it is among the most widely used NSAIDs due to its rapid onset and effective pain relief [45]. Now, there are multiple different formulations, including capsules, rectal suppositories, injectable liquids, extended-release forms, topical gel, and many more [46].

As was previously discussed, the administration of NSAIDs from the oral route usually creates widespread side effects, particularly digestive issues (Table 2). For this reason, the idea of topical application of the active ingredient was developed between 1989 and 1994, when three patented formulations of topical KTP were successfully introduced to the French market [47,48]. In particular, pharmacokinetic studies reveal that the amount of KTP in the blood from a topical 2.5% gel is less than 1% of that from oral intake, offering effective pain relief while minimizing systemic side effects associated with oral NSAIDs. In one of the studies, topical KTP was administered daily for three consecutive days in patients, and by HPLC, KTP appeared in the blood for 2 h post-administration, maintaining steady levels for 12 h. As in the case of IBU, in this one, local tissue concentration was about 100 higher than the plasma concentration. This effect is attributed to direct absorption through the skin rather than diffusion through the bloodstream [41]. In clinical practice, there was a great use of topical KTP, and it was estimated to exceed three million patients/year even as early as 1986 [49].

However, the risk of using KTP directly on the skin should not be dismissed (Table 3). Although rare and, in most cases, mild, side effects occurring at both the application site and throughout the body associated with the administration of topical KTP have been reported [41]. In general, the most common adverse events include cardiovascular reac-

tions, central, dermatological, blood, liver, gastrointestinal, ophthalmic, renal, respiratory, and systemic [40], whereas in topical formulations the most significant one would be a photosensitivity reaction.

Skin photosensitivity is classified into phototoxicity [39] and photoallergy [50]. Photosensitivity reactions became such a potential risk related to NSAIDs that, since 2000, a designated symbol has been added to all medication packaging [30]. Some cases of photosensitivity have also resulted in chronic dermatitis following the topical KTP treatment [51,52]. To avoid this previous side effect, patients are guided to avoid sun exposure on the treated area while applying and for two weeks afterward [53].

Studies have indicated that KTP exhibits superior skin permeability compared to other NSAIDs. In vitro experiments demonstrated that ketoprofen gel achieved higher tissue penetration rates than diclofenac, niflumic acid, and piroxicam gels, with 21.9% of the active substance penetrating the tissue, compared to 11.2%, 4.4%, and 0.5% for the other gels, respectively. Additionally, using rats' models to study both short-term and long-term inflammation, KTP patches significantly reduced edema earlier and more effectively than other NSAID preparations. These results suggest that KTP's favorable skin permeability contributes to its strong pain-relieving and anti-inflammatory properties in transdermal applications [54].

3.1.3. Flurbiprofen

FB is a highly potent phenylalkanoic acid derivative with anti-inflammatory, analgesic, and antipyretic properties, as most NSAIDs, while it is mostly used to treat gout, osteoarthritis, rheumatoid arthritis, and sunburn. It can be administered orally; however, it can possibly cause stomach pain and other digestive issues and requires frequent dosing because its elimination half-life is relatively short at 3.9 h [55]. For these reasons, researchers have focused on improving the topical use of FB.

However, like it was discussed in the introduction, the intercellular lipid barrier in the SC provides strong resistance to penetration and most drugs cannot penetrate the skin easily. FB is one of those drugs. Although its physicochemical, pharmacokinetic, and pharmacodynamic properties make it well-suited for skin-based drug administration [56], among a group of lipophilic drugs, it is one of the least permeable through the skin [57].

FB, also formulated for transdermal delivery, has been evaluated for its skin permeation characteristics and therapeutic potential. A study assessing the percutaneous permeation of FB and KTP patches using a lateral sectioning approach in hairless rats revealed that both drugs' concentrations vary by depth, forming a gradient from the surface to the inner layers. Notably, FB achieved faster and increased drug levels in the deepest skin layer close to muscle tissue compared to KTP. This suggests that FB patches may effectively deliver the drug to deeper tissues, potentially enhancing its therapeutic efficacy in conditions involving deeper-seated inflammation or pain [58].

Table 1. Comparison of Transdermal Properties of IBU, KTP, and FB.

Drug	Skin Permeability	Anti-Inflammatory Efficacy	Optical Formulation	References
IBU	Variable; formulation-dependent	Effective; varies with formulation	Gel/Spray/Mousse	[38]
KTP	High	Superior	Patch/Gel	[54]
FB	Moderate to high; effective deeper tissue penetration	Effective	Patch	[58]

Table 2. Side effects of NSAIDs (IBU, KTP, FB).

Drug	General Side Effects	Topical Related Side Effects	References
IBU	Gastrointestinal issues	Impaired wound healing, infection, reduced collagen synthesis Suppressed local immune responses	[19,31,32] [19,31]
KTP	Rare systemic adverse events Gastrointestinal disorders	Photosensitivity reactions Chronic dermatitis in rare cases	[39,41,50] [51,52]
FB	Gastrointestinal discomfort	Poor skin permeability limits systemic absorption Limited topical effectiveness due to low permeability	[55,57] [57]

Table 3. Safety risks associated with prolonged use of IBU, KTP, and FB in transdermal applications.

Drug	Local Skin Reactions	Systemic Absorption and Toxicity	Delayed Wound Healing and Skin Barrier Damage	Allergic Reactions	Potential Drug Interactions	References
IBU	Mild irritation, redness, and itching	Can lead to renal impairment, especially in prolonged use or high doses	May slow down skin repair due to prostaglandin inhibition	Possible cross-reactivity in aspirin-sensitive individuals	Can interact with anticoagulants	[19,31,32]
KTP	Higher risk of photosensitivity reactions	Risk of kidney and liver toxicity in patients with preexisting conditions	Can impair wound healing and cause dryness or sensitization	Higher chance of photoallergic reactions, leading to long-term skin sensitivity	Risk of bleeding and kidney damage when combined with other NSAIDs	[39,41,50–52]
FB	Moderate irritation; risk of allergic contact dermatitis	Higher cardiovascular risks, linked to hypertension, heart attack, and stroke	Moderate risk of skin barrier disruption	May cause hypersensitivity reactions	Can interfere with blood pressure medications and increase cardiovascular strain	[55,57]

3.2. Hydrogels

The commonly used various topical dosage forms, including ointments, creams, gels, patches, films, etc., that are commercially available, unfortunately also have limitations. They cannot always release the medicine at the desired rate and extent [59]. To overcome this, research in recent years has emphasized controlled-release drug technologies such as hydrogels [60]. Hydrogels are three-dimensional structures formed by cross-linking natural and synthetic polymers [61]. These have been utilized across multiple medical fields, such as heart disease, cancer treatment, immune responses, wound care, and pain relief. They contain a significant proportion of water, typically around 70 to 99%, which resembles biological tissues, is highly biocompatible, and effectively encapsulates water-soluble drugs. In addition, they have a cross-linked polymer network, which makes hydrogels solid-like; thus, they have various physical and mechanical characteristics. In general, hydrogels vary in size and structure, and these characteristics influence their suitability for drug delivery [62].

Hydrogels can be categorized using different criteria, most commonly based on their source [57]. Natural hydrogels, derived from biological sources, are preferred for their high biocompatibility. On the other hand, synthetic hydrogels, created using artificial gelling agents, often offer more adaptability in modifying their composition and mechanical properties but do not offer similar biocompatibility compared to natural hydrogels [58]. Multiple NSAIDs, including IBU, KTP, and FB, have been found to be suitable for incorporation into hydrogels. For example, the physical hydrogels developed by Corrente et al. (2009) [63] using carboxymethylscleroglucan calcium ions were tested for their potential use in topical formulations with IBU, KTP, and diclofenac [59]. Another example would be Mahmood's et al. (2021) [64] IBU-loaded Chitosan-Lipid Nanoconjugate Hydrogel for controlled transdermal delivery, aiming to enhance patient compliance and drug efficacy by improving skin permeability and providing sustained release [60].

In addition, Mikušová et al. (2022) prepared hydrogels from 11 distinct types of gelling polysaccharides that differed by their polarities and charges, in order to study their influence on the gel properties and IBU diffusion profiles, while chitosan proved to be an effective modifier of diffusion profiles, enabling prolonged drug release [65]. In 2024, Mohseni et al. introduced hydrogels using O-carboxymethyl chitosan and Gelatin type A in a 1:2 ratio with β-glycerophosphate at varying percentages, proving once again that these hydrogels, carrying NSAIDs like IBU, are potential treatments for inflammatory conditions like osteoarthritis [66].

3.3. Topical and Transdermal Drug Delivery

The two main types of skin-based drug delivery are topical and transdermal methods. Benefits associated with both include non-invasive application, bypassing first-pass metabolism, extended drug activity, reduced dosing frequency, stable plasma drug levels, improved patient compliance, and more. However, their goals, mechanisms, and outcomes differ significantly [67–69].

3.3.1. Topical Drug Delivery

Topical drug delivery occurs from the formulation into the skin, reaching the target site before being cleared via diffusion, metabolism, and circulation. Topical treatments, originally simple formulations, have evolved into advanced delivery mechanisms. While some drugs are not appropriate for skin-based delivery, at least 96 drugs currently meet the criteria and are available in various dosages, including patches, gels, ointments, and solutions. Essential criteria for topical medications to be effective are their ability to penetrate through and/or into the skin, and subsequently to be delivered to the target tissue site where the active compound of the drug will exert its effect(s) [70].

3.3.2. Transdermal Drug Delivery

Transdermal drug delivery enables a drug to penetrate the skin and enter the systemic circulation to achieve therapeutic effects [71]. It enables a regulated release of the drug into the inner region while stabilizing the plasma concentration, avoiding severe side effects. It is generally considered an easy administration for vulnerable groups, including children and older adults [72].

The main problem exists in overcoming the SC's highly effective barrier, which hinders drug absorption. Numerous efforts have been undertaken for this to happen, both with physical and chemical methods, which will be discussed shortly. The most well-known method is the use of drug delivery systems, such as the use of chemical enhancers (i.e., Solid Lipid Nanoparticles (SLNs), vesicular systems, and hydrogels), and physical techniques (i.e., ion-tophoresis and sonophoresis), which enhances drug transport across the skin by enhancing, for example, drug solubility, drug distribution, and membrane fluidity [73].

3.4. Enhancement of Skin Permeability

For a drug molecule to penetrate the skin without resistance in transdermal delivery, ideally, the drug must weigh less than 500 Da and show balanced fat solubility. Large and water-soluble drugs, including peptides, often fail to pass through the SC [74]. For this reason, some prospective strategies, including physical and chemical techniques that enhance skin permeation, have been investigated [74,75].

Prausnitz and Langer (2008) described three generations of Transdermal Drug Delivery (TDD) [10]. The first generation consists of passive dosage forms, for small, lipophilic drugs. The second generation includes dosage forms using chemical enhancers and iontophoresis. The third generation is characterized by systems that rely upon the disruption of SC, mainly to assist with the permeation rather than the penetration enhancement [10,74].

Both physical and chemical approaches have successfully delivered various drugs; however, chemical enhancers may irritate the skin or cause permanent damage, while physical enhancement techniques can be painful, costly, and may not always be patient-friendly. So, choosing a method depends on specific circumstances [76]. Although both types of techniques are equally important, this review will emphasize Chemical Enhancement Techniques using nanoscopic systems.

3.4.1. Physical Enhancement Techniques

Physical Enhancement Techniques are usually energy-based methods that employ electrical devices to boost drug absorption through the skin. As previously mentioned, these techniques belong to the second and third generations [77].

Iontophoresis

In iontophoresis, drug permeation is increased using low electrical current, from 0.5 to 20 mA, as illustrated in Figure 5 [77]. This system operated on the principle of charge variation in the electrodes used: the anode and the cathode [78]. Factors such as formulation, the application site, drug properties, and duration of application can influence iontophoresis-based drug delivery [79]. Iontophoresis has demonstrated efficacy for the delivery of various pharmacological agents, including NSAIDs [80]. More specifically, iontophoresis relies on the use of electric currents, which reduces the dependence of drug absorption on biological parameters, thereby offering a distinct advantage over many conventional drug delivery systems [81]. However, limitations include potential skin irritation, the need for specialized equipment, complexity, and high costs [77,82].

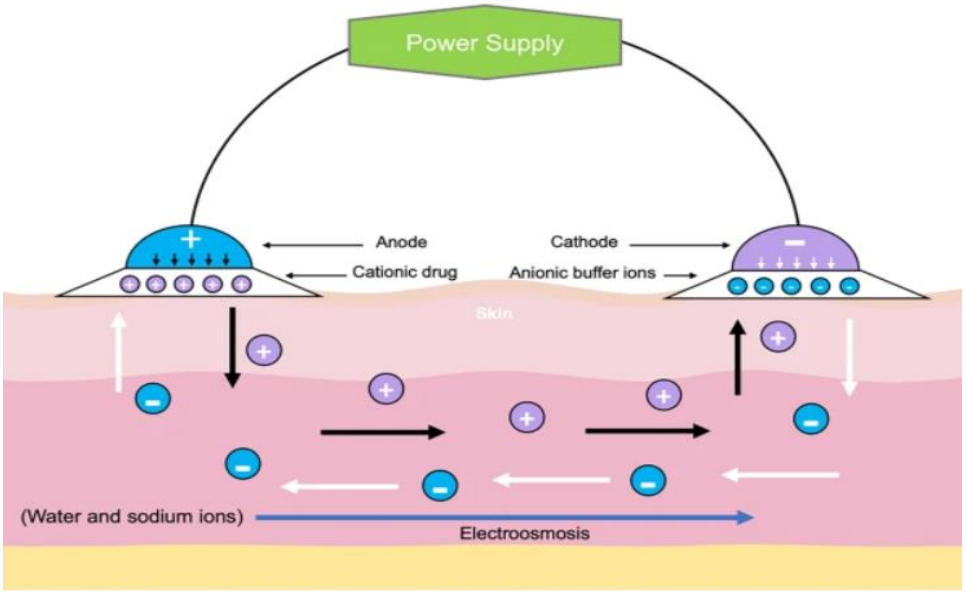


Figure 5. A schematic representation that illustrates the mechanism of cationic drug delivery via iontophoresis, where black arrows depict the drug's movement from the solution toward the cathode and white arrows indicate anion migration from the buffered solution beneath the cathode and the anode [77].

Sonophoresis

Sonophoresis implements ultrasound at frequencies ranging from 20 kHz to 16 MHz to modify the lipid bi-layer arrangement of the SC. This allows the skin temperature to increase, leading to increased drug penetration into the skin, as shown in Figure 6 [77]. Lower-frequency ultrasound achieves better results, as it enhances drug transport by creating a water-filled pathway through which the drug may be introduced [83]. The

principle of this system lies in the fact that the drug solution is positioned beneath the ultrasound probe, and a specified ultrasound frequency is applied to facilitate penetration, and so, the microbubbles and cavities are generated, disrupting the lipid bi-layer of the SC [84,85]. Parameters like the application time and the gap between the ultrasound probe and the skin affect the success of sonophoresis [86].

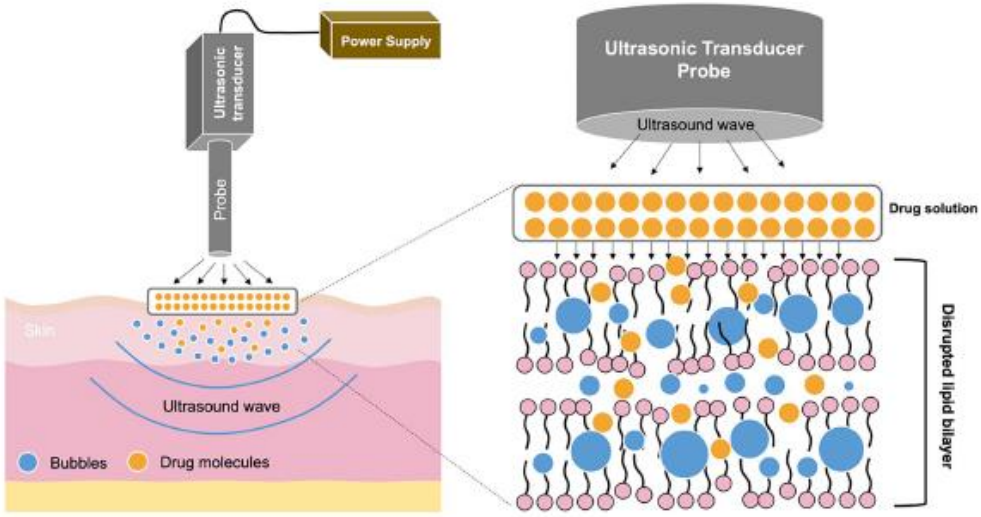


Figure 6. A schematic diagram that illustrated how ultrasound application facilitates drug movement into the dermis [77].

Research has demonstrated that sonophoresis effectively enhances the transdermal delivery of KTP and other drugs from different classes [86]. However, some disadvantages of this technique are that it is time-consuming, it requires specific instrumentation, and the skin needs to be in a healthy condition during application [68].

Electroporation

In contrast to sonophoresis, electroporation employs strong electrical pulses that generate short-lived micropores in the skin, varying between 5 and 500 V for brief periods [78,87]. Those pores in the lipid bi-layer allow micro and macro molecules to reach the inner layers of the skin, as depicted in Figure 7 [77,88]. This technique is highly safe and non-painful; however, some of the drawbacks include small delivery loads, massive cellular perturbation, heat-induced drug damage, etc. [88].

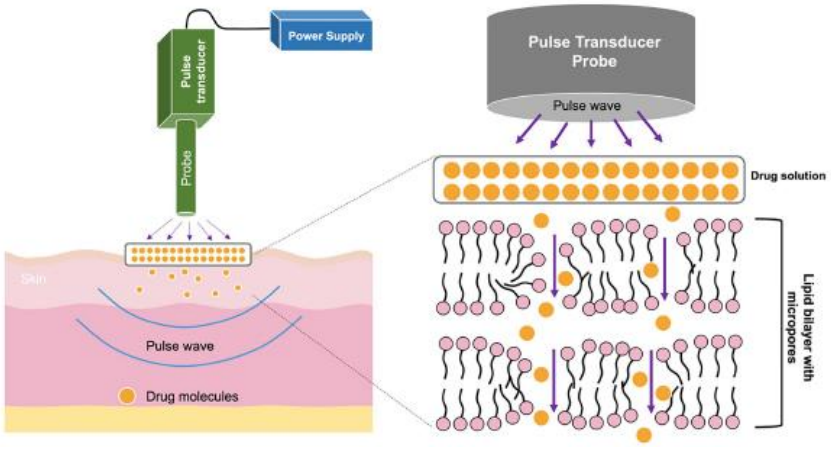


Figure 7. A schematic illustration that shows how electroporation aids transdermal drug delivery by facilitating penetration into the dermis [77].

3.4.2. Chemical Enhancement Techniques

Chemical approaches are widely studied due to their affordability and ease of formulation into creams, gels, and patches [89].

Chemical Penetration Enhancers

Chemical Penetration Enhancers (CPEs) are substances studied for their effectiveness in enhancing skin drug delivery. They mostly work by breaking down the lipid layers in the SC, interacting with cell membranes or intercellular proteins, or altering the drug's distribution between phases [90]. Over 300 substances have been used as CPEs [91]; however, not all chemicals can be used as one. They should be stable, non-toxic, non-allergenic, and non-irritating, which is actually the biggest problem with using CPEs, and they must allow the skin to restore its protective function soon after the chemical is eliminated [77,92]. Some examples of CPEs include sulfoxides, azone, pyrrolidone, fatty acids, alcohols, surfactants, urea, and terpenes [77].

The slow process for IBU transdermal delivery [37] can be avoided by using these CPEs. The most common examples of IBU enhancers are ethanol and propylene glycol [90]. In particular, propylene glycol activity in topical lipophilic IBU formulations has been studied, and they indicate that propylene glycol's skin penetration directly correlates with its concentration, impacting IBU's ability to dissolve within the skin's protective layer [93]. In addition, Bednarczyk et al. (2023) found out that oleic acid and allantoin demonstrated the greatest IBU absorption, proving their efficiency in drug delivery enhancement [94]. Specifically, patches with oleic acid exhibited permeation with a value of 163.306 $\mu g/cm^2$, and patches with 5% allantoin exhibited nearly 2.8 times higher absorption compared to enhancer-free patches after 24 h.

Similarly to IBU, FB is often combined with special CPEs in order to improve its permeability. Common examples of permeation enhancers for FB would be propylene glycol (PG), polyethylene glycol (PEG) [95], and nanostructured lipid carriers (NLC) [96]. In addition, unsaturated fatty acids, which produce large increases in the partition coefficient of flurbiprofen, are powerful enhancers [95,97]. Gadad et al. (2020), in their studies, showed that ethanol improves vesicle penetration through the SC by enhancing both intercellular and intracellular permeability [98], which is explained more in the section "Vesicles".

Solid Lipid Nanoparticles (SLNs)

Solid Lipid Nanoparticles (SLNs) are solid, submicron-sized particles [99,100] ranging from 50 to 1000 nm [101] that act as carriers and consist of natural lipids ideal for treating irritated or injured skin [99,100]. The SLNs are inexpensive and nontoxic [102]. Those characteristics, in combination with their capability to encapsulate both lipophilic and hydrophilic compounds, make them ideal candidates for delivering cosmetic and medicinal compounds through the skin [99,100].

SLNs are a subcategory of Lipid Nanoparticles, similar to Nanostructured Lipid Carriers (NLCs), with the difference that the first ones only consist of solid lipids and surfactants instead of solid lipids, liquid lipids, and surfactants as the latter [103]. SLNs may appear as spheres, disks, or flattened [104]. For ibuprofen-SLN (Figure 8), crystals were observed forming on the particle's surface, likely resulting from drug precipitation due to the crystalline reorganization of the lipid matrix [105]. Hair follicles and intercellular gaps serve as primary diffusion routes of nanoparticles, such as SLNs, across the SC [106].

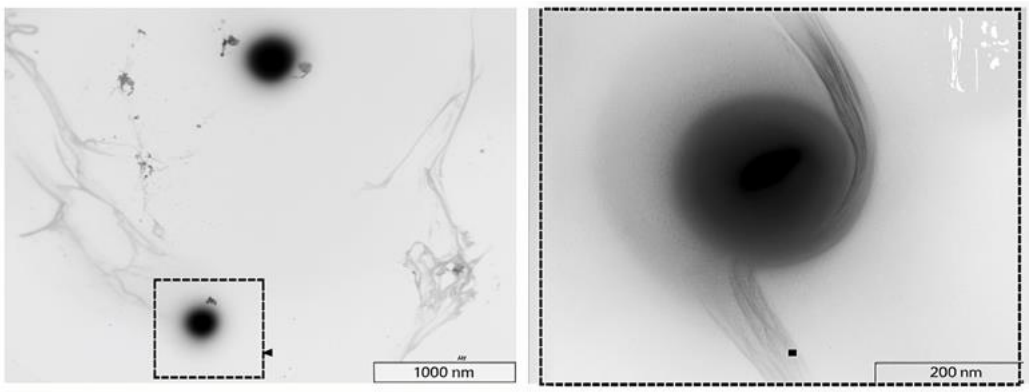


Figure 8. TEM images that reveal the presence of solid particles of an ibuprofen-SLN. The image on the right represents a magnified section within the dashed rectangle from the left image. Scale bar: 1000 nm [105].

SLNs form a film on the skin, minimizing moisture loss while enhancing skin hydration [107]. Their reduced size increases the contact surface of drugs with the skin, thereby improving NSAID permeation [108]. In particular, research on dermal delivery of IBU has shown promising results, particularly in encapsulation efficiency and controlled release [55,107,109,110]. It also has been used in oral delivery for cancer chemoprevention [111]. Three-dimensional imaging (Figure 8) and cross-sectional analysis show an uneven, rough structure, consistent with TEM observations of unloaded nanoparticles (Figure 9). Loaded and empty particles showed no significant differences. Using multiple analytical methods gave additional insights into SLN characteristics [105].

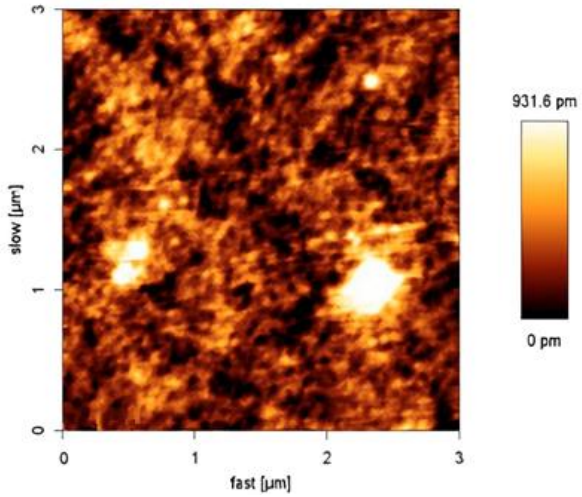


Figure 9. AFM image of IBU-SLNs [105].

Additionally, Pham et al. (2020) prepared SLN solutions with elevated IBU concentrations, and they were successfully incorporated into a stable and uniform network [112]. This facilitated the demonstration of in vitro studies that enhanced IBU permeation through rat skin and improved local anti-inflammatory and analgesic effects compared with those of commercial products. After 1 h of incubation, the drug-loaded SLN was detected within the cells, primarily in the cytoplasm (Figure 10) [105].

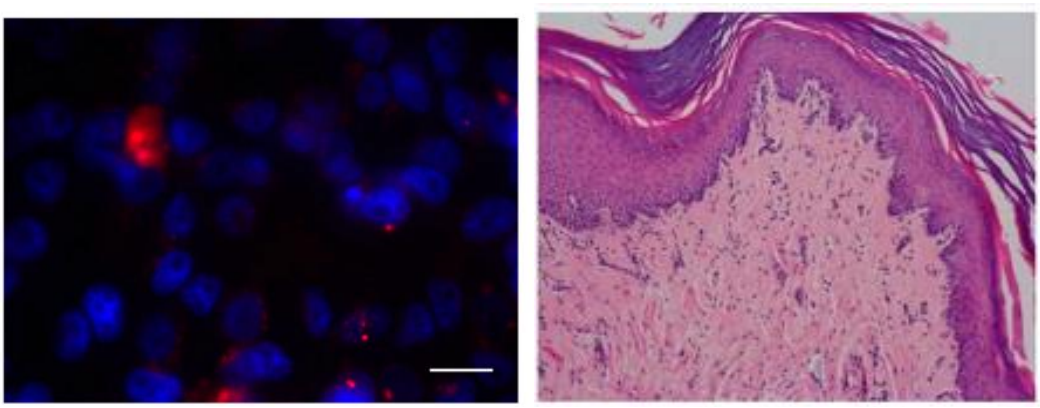


Figure 10. Fluorescent micrographs of IBU-loaded SLN in HaCaT cells (**left**). Scale bar: 50 μm [105]. Sample images of rat paw tissue sections stained with H&E of IBU-SLN hydrogel (**right**). Magnification 100× [105].

Lastly, Burki et al. (2023), synthesized FB-loaded SLNs, for transdermal drug delivery by the solvent emulsification method [113]. Lower viscosity, reduced surface tension, and lipid-loving properties enhance drug penetration in both coated and uncoated SLN formulations. Scanning Electron Microscopy (SEM) of SLNs from indicative studies showcases their size and shape uniformity, supporting their good applicability and penetration efficiency (Figure 11), while SEM images of FB SLNs with spherical particles of varying sizes below 250 nm have also been documented [114].

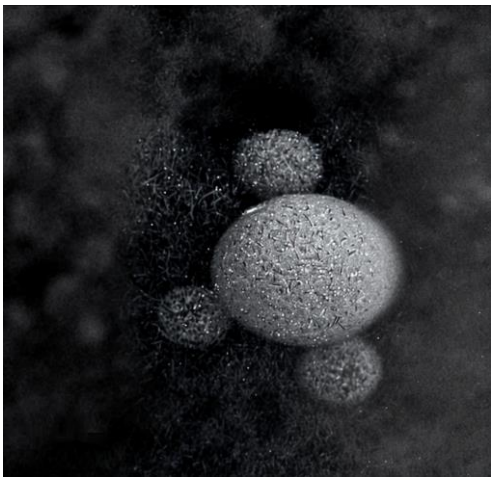


Figure 11. SEM image of SLNs [113].

Vesicles

Among the most promising chemical approaches is the use of nanosized vesicular systems, which consist of self-assembled amphiphilic bilayers in an aqueous environment [76]. So, they are able to transport both hydrophilic substances, contained within an internal water phase, while lipid-soluble drugs are stored in the bilayer [115]. Those systems increase the bioavailability of encapsulated drugs and increase drug resistance time in the epidermis while also modulating systemic absorption [116,117]. Vesicle systems are categorized into different types, such as liposomes, transfersomes, ethosomes, etc., as demonstrated in Figure 12 based on the characteristics of the materials included [117].

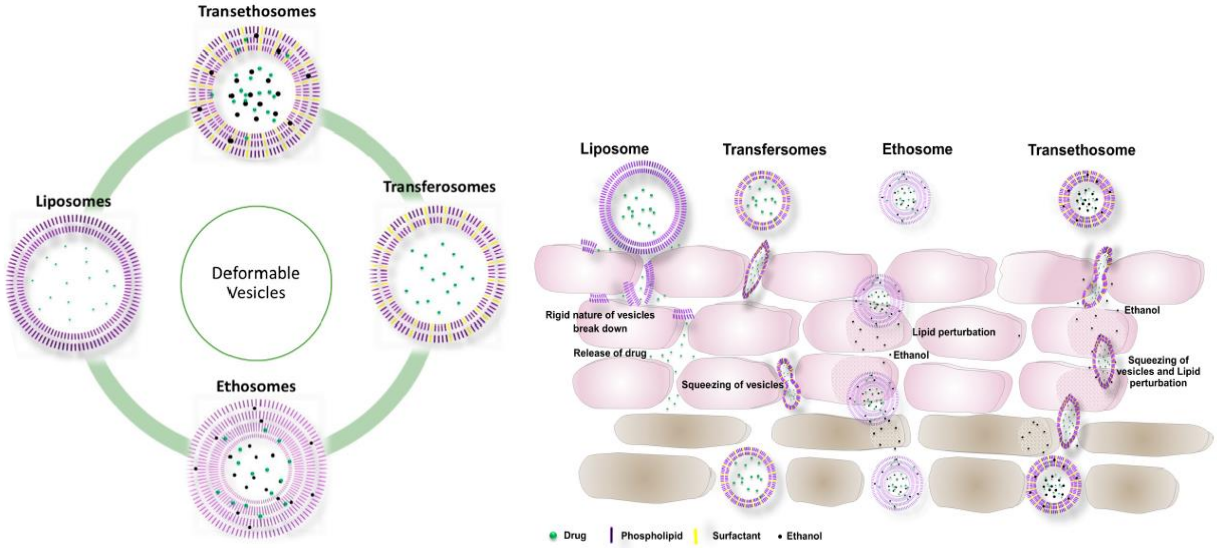


Figure 12. Schematic representation of the different types of layered vesicle-based drug carriers and compositions (**left**). The process by which vesicular carriers penetrate the SC (**right**) [118].

The most commonly used vesicle systems are liposomes. Liposomes are round vesicles made of phospholipids and cholesterol, key components of cell membranes, contributing to their high safety and compatibility [119]. They enhance drug transport by adsorption onto the skin, merging with the skin's lipid structure of the SC, and lipid exchange between vesicular and cellular membranes [120]. Xu et al. (2022) compared normal creams or gels to liposome drug carriers and proved that the latter provides a better option for the transdermal delivery of IBU [121].

Kumar et al. (2024) prepared FB liposomes by thin film hydration technique and concluded that newly formulated controlled release liposomal drug delivery systems of FB may be ideal and effective in the management of arthritic pain in 24 h [122].

However, conventional liposomes do not significantly penetrate deep into viable skin or systemic circulation, making them primarily useful for topical, rather than transdermal, delivery [123,124].

For this reason, Cevc and Blume (1992) introduced the first generation of ultradeformable/elastic vesicles, called tranfersomes [125], considered to be one of the most outstanding transdermal drug carriers [115]. Besides phospholipids, their membrane includes single-chain surfactants, usually known as edge activators [125]. Edge activators weaken the lipid bilayer of vesicles, enhancing their flexibility and deformability [74]. In particular, they modify membrane flexibility, allowing for easier passage through skin pores easily [126] and spontaneously [127].

Many transfersome-based formulations have been evaluated in various clinical trial stages; for instance, research on KTP in transfersomes demonstrated greater effectiveness in pain relief of knee osteoarthritis and fewer adverse events, compared to a placebo [128].

Polymeric Nanoparticles (PNPTs)

With the evolution of nanotechnology in polymer science [129], Polymeric Nanoparticles have been investigated as carriers for pharmaceutical compounds for dermal and transdermal applications [130]. Polymeric Nanoparticles (PNPTs) are colloidal particles, between 1 and 1000 nm in size, and contain active pharmaceutical ingredients inside or absorbed into the polymer [131]. Produced through polymerization and cross-linking of biodegradable materials [132], most often chitosan [133], but also gelatin and polylactic acid [81,134–136]. PNPTs are distinguished by their high mechanical strength, yet they

are unable to penetrate openings equal to or smaller than their own dimensions. Despite this limitation, their usage is on the rise due to the inherent stability of these molecules, which makes them resistant to degradation. This characteristic allows drugs to be retained within the PNPTs for extended periods, facilitating their gradual release and diffusion into the deeper layers of the skin. [88]. In addition, they can overcome some limitations of other lipid-based carriers, safeguarding unstable drugs from breakdown while ensuring sustained release to minimize side effects [88,135]. Many studies that include IBU topical formulations have shown that, due to IBU's short half-life, PNPT technology is regarded as an effective method for controlled drug release [22].

However, it is important to conduct further investigations of the PNPTs in topical formulations, as skin toxicity is a significant concern, as additives used in polymerization and residual organic solvents may pose risks [137].

Nanoemulsions (NEs)

Emulsions consist of stable colloidal mixtures of oil droplets suspended in water or the other way around. Depending on their particle size, they could be characterized as microemulsions or nanoemulsions. Nanoemulsions are usually called emulsions with a particle size lower than 100 nm [138]. Nanoemulsions are categorized into three groups according to their composition. (i) oil in water (O/W), where the oil phase is dispersed in the aqueous phase [139]; (ii) water in oil (W/O), where the water phase is dispersed in the oil phase [140]; and (iii) bi-continuous/multiple emulsion, where some domains of oil and water phases are interdispersed in the system [127].

Nanoemulsions are preferred for skin drug delivery due to their rapid skin–cell interaction, facilitated by their fluidity and surfactant-stabilized structure [141]. They have been shown to serve as effective carriers for various drugs due to their composition and structure. Surface molecules act as CPEs and can enhance the solubility of poorly soluble compounds [127,142].

Extensive research has focused on developing and assessing NE-based systems for delivering NSAIDs, including IBU, KTP, and FB [12]. For example, Esmaeili, Baharifar, and Amani (2022) [143], among others, examined the anti-inflammatory activity of NEs-IBU in comparison to commercial products and provided TEM images of a nanoemulsion containing 5% IBU [143]. Oil-in-water NEs were presented as a successful model for skin delivery of hydrophobic drugs, as well as the in vivo studies confirm that NEs effectively deliver IBU through rat skin.

In addition, Lucca et al. (2019) produced a NE containing KTP and studied its skin permeation in vitro in comparison to a control group [144]. This resulted in 85% of KTP being released from the NE matrix, while only 49% was released from the control group after 8 h. NE enabled KTP to facilitate skin penetration and to prolong retention in the epidermis and SC.

Lastly, Hamzah (2020) developed and evaluated a nanoemulsion-based gel, nanogel, for the transdermal delivery of FB. Nanogels significantly improve drug permeation and anti-inflammatory effects compared to conventional gels, making them promising for transdermal delivery of FB [145].

4. Clinical Trials

The experimental techniques and mathematical models outlined by Scheuplein and Blank (1971) have greatly influenced subsequent research on skin permeability, establishing the groundwork for modern in vitro and in vivo studies [5]. Even though a lot of in vitro studies related to these applications exist, there is still a limited number of published clinical trials examining the efficacy and pharmacokinetics of various NSAID formulations,

focusing on their topical and systemic applications (Table 4). The studies reveal insights into the effectiveness of IBU, KTP, and FB in different contexts.

Table 4. Clinical Trials for Topical Use of Ibuprofen, Ketoprofen, and Flurbiprofen.

NSAID	Study Focus	Outcome	Conclusion	Ref.
IBU	The efficacy of IBU-containing foam dressing in partial-thickness burns in $N = 50$ patients with superficial second-degree burn wounds was evaluated.	➢ Wound recovery accelerated considerably in the group treated with IBU-infused foam dressings ($p = 0.010$). ➢ The total score on the Vancouver Scar Scale (VSS) was lower in the study group, but no statistical difference was observed.	➢ IBU-containing foam dressing provided effective pain management in patients with second-degree burns and increased patient comfort, while it did not show any negative effect on the wound healing process.	[146]
	The quantification of the analgesic efficacy of NSAIDs in a model of clinical pain applied in $N = 15$ volunteers.	➢ IBU gel significantly reduced ($p < 0.004$) the area of touch-evoked allodynia at constant skin temperature at 40 °C.	➢ IBU showed beneficial analgesic effects in a thermal-facilitated adaptation of the capsaicin model.	[147]
KTP	The study of the diffusion into the target tissues of 100 mg KTP from a new topical patch in $N = 10$ patients.	➢ An average plasma value of 52.8 ng/mL of KTP was obtained. ➢ In the subjects undergoing knee arthroscopy the tissue concentrations were 27.9 ng/g in the anterior fat pad and 239 ng/g in the synovial tissue, respectively.	➢ Application of KTP on the skin facilitated higher drug levels in subcutaneous and joint tissues than in plasma, achieving localized therapeutic effects. ➢ Blood levels of KTP were insufficient to cause systemic effects.	[148]
	To assess the possible postoperative sore throat attenuation by treatment with transdermal KTP on the anterior skin of the neck during operation in $N = 63$ patients	➢ The KTP group experienced a notable reduction in sore throat symptoms ($p < 0.05$).	➢ Topical KTP applied during surgery eases pain from tracheal intubation.	[149]
	To determine the drug concentrations and elimination rate of KTP in the SC following topical administration of two different formulations (tape or gel) in $N = 10$ human subjects.	➢ The KTP concentration in the SC decreased and the elimination half-life in the SC was comparable between tape and gel.	➢ KTP in the SC reaches the lower limit of quantitation 12–16 days after the removal of tape or gel.	[150]
	To evaluate the analgesic effect of 2.5% KTP gel administered in a 5 cm area on children between 7- and 18 years old presenting with ankle sprain versus a placebo gel.	➢ Median pain reductions both at 15 and 30 min were better in the case of KTP than the placebo groups. ➢ There were 7 rescue drug needs in the placebo group and 1 in the KTP group ($p = 0.83$).	➢ KTP gel was found to be superior to placebo in alleviating pain in children presenting with ankle sprains to the ED.	[151]
FB	To compare the tissue FB levels observed after skin application and oral intake in $N = 16$ patients.	➢ The FB concentration in the fat, tendon, muscle, and periosteum tissues was significantly higher ($p < 0.0330$) after topical application than after oral administration.	➢ Topical application was found to be a superior approach for administering FB, especially to surface-level soft tissues.	[152]

The trials involving IBU demonstrate its efficacy in specific contexts. In Akgun and Alkin's research [146], an IBU-containing foam dressing, accelerated significantly wound healing in superficial second-degree burns, providing effective pain management without adverse effects on healing. McCormack, Kidd, and Morris' study [147] quantified its analgesic efficacy, showing that IBU gel reduced significantly touch-evoked allodynia, highlighting its potential in managing pain in a controlled thermal pain model. These findings suggest that IBU is particularly effective for topical pain management, benefiting both wound healing and comfort.

The KTP trials explore broader applications and pharmacokinetics. For instance, Osterwalder et al. showed that a 100 mg KTP patch achieves high tissue concentrations while maintaining low plasma levels, indicating a strong localized effect with minimal systemic side effects [148]. Similarly, Ozaki et al. highlight KTP's utility in alleviating postoperative sore throat, emphasizing its role in intraoperative pain management [149]. Furthermore, Serinken et al. demonstrate KTP gel's superiority to placebo for managing pain in pediatric ankle sprains [151]. These findings underscore KTP's versatility and efficacy in both local and systemic pain relief.

Kai et al. in their study involving FB, compare its tissue concentration after topical versus oral administration, finding significantly higher concentration in soft tissues after topical application [152]. This suggests that FB is especially effective for targeting tissues in the epidermis, making it a viable option for localized treatment.

5. Future Perspectives

The use of other nanosystems can be used in order to improve drugs' permeability on the skin. For example, a novel method using nanobubbles (NBs) may advance drug and cosmetic dermal delivery greatly [153].

These submicron gas-filled cavities are utilized in drug delivery due to their unique properties [153–157]. Firstly, NBs are completely transparent solutions, undetectable to the human eye, so an NB solution can be used in cosmetics. Secondly, they move according to Brown motion, giving them long-term stability after being produced [153,154,158–160]. Lastly, due to their high surface area, NBs can load the ingredients and the active substances between them and the solvent interface [153,154,161–163].

Mitropoulos et al. (2023) studied Oxygen NBs as a method to increase Hyaluronic Acid's (HA) permeability through the SC [154]. Using a synthetic membrane that resembles the human skin (Strat-M), he proved that O2-NBs enhance the absorption of cosmetic products through the skin faster than their non-NB counterparts. The suggested mechanism is shown in Figure 13.

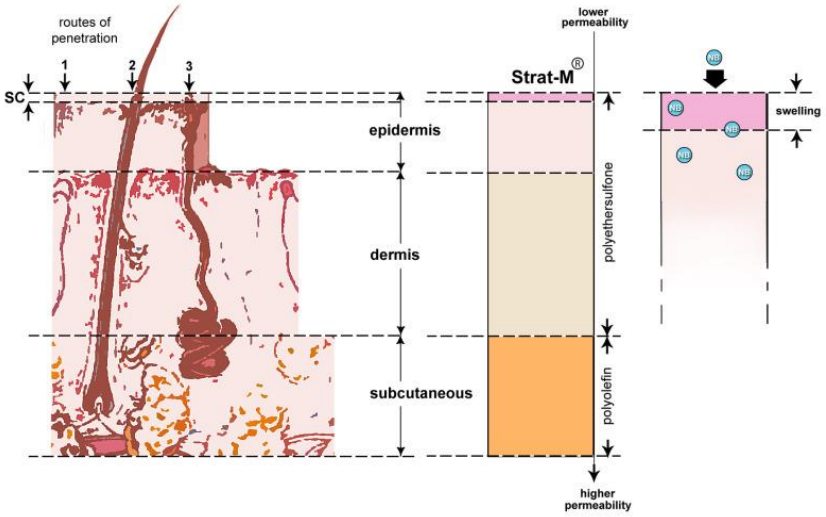


Figure 13. Schematic representation of human skin and comparison with STRAT-M membrane layers. The effect of NBs is shown in the right-hand drawing; by passing through the first layer of the epidermis, NBs expand this region due to their negative charge, thus leading to enhanced active ingredients penetrating down to deeper layers. Reprint from [154].

In particular, the same amount of product that passed through the membrane in 30 min using NBs needed 3 h without them. Although neither the mechanism of penetration nor the possible effects they may have on the skin have been fully studied, NBs are definitely an interesting option for enhancing skin permeation of NSAIDs, like IBU, KTP, and FB [154].

6. Conclusions

This review highlights the significant progress in the use of topical NSAIDs and transdermal drug delivery systems for managing pain, inflammation, and associated skin conditions. Ibuprofen, ketoprofen, and flurbiprofen stand out as effective candidates, each addressing specific therapeutic needs. Ibuprofen has demonstrated dual efficacy in promoting wound healing and pain relief, particularly in burn management. Ketoprofen's capability to reach high concentrations in target tissues while limiting systemic exposure, positions it as an ideal option for treating joint-related conditions and surgical or pediatric pain. Similarly, flurbiprofen excels in targeting soft tissues near the body surface, showing promise for localized treatment without the potential for widespread adverse reactions.

The advancements in transdermal delivery have been driven by innovations in both physical and chemical enhancement techniques. Chemical penetration enhancers, such as ethanol and propylene glycol, and nano-based systems, including Solid Lipid Nanoparticles (SLNs), liposomes, and nanoemulsions, have emerged as effective tools to bypass the strong protective function of the SC. Physical methods like iontophoresis and sonophoresis have further expanded the possibilities for administering medication via transdermal routes. Collectively, these technologies have addressed key challenges in topical drug delivery, enhancing the bioavailability, stability, and efficacy of NSAIDs while minimizing systemic exposure and adverse effects.

The review also emphasizes the versatility of hydrogels and vesicular systems as controlled drug delivery vehicles. These carriers have not only improved the pharmacokinetics of NSAIDs but have also demonstrated significant potential in controlling drug release over time while directing it to deeper skin layers. Despite their promise, issues such as skin irritation, photosensitivity, and long-term safety remain areas requiring further exploration.

The area of transdermal and topical NSAID delivery is an exciting blend of pharmaceutical advancements and real-world clinical use. By employing advanced delivery systems, we can customize treatments to enhance therapeutic results while reducing potential risks. Continued collaboration among different disciplines and further clinical research will play a key role in maximizing the effectiveness of these technologies, leading to safer, more effective, and patient-focused solutions for managing inflammation and pain-related issues.

Author Contributions: Conceptualization, A.T. and A.M.; methodology, A.T.; software, all authors; validation, A.T.; investigation, A.T. and K.D.; writing—original draft preparation, all authors; writing—review and editing, A.T., A.O., R.I.K. and A.M.; visualization, A.T. and A.M.; supervision, A.T., R.I.K. and A.M.; project administration, A.T. and A.M. All authors have read and agreed to the published version of the manuscript.

Funding: This research received no external funding.

Acknowledgments: The authors would like to thank the School of Chemistry of the Faculty of Sciences of Democritus University of Thrace for the continuous support.

Conflicts of Interest: The authors declare no conflicts of interest.

Abbreviations

The following abbreviations are used in this manuscript:

NSAIDs	Nonsteroidal Anti-Inflammatory Drugs
SC	Stratum Corneum
COX	Cyclooxygenase
PGs	Prostaglandins
IBU	Ibuprofen
KTP	Ketoprofen
FB	Flurbiprofen
TDD	Transdermal Drug Delivery
CPEs	Chemical Penetration Enhancers
PG	Propylene Glycol
PEG	Polyethylene Glycol
NLCs	Nanostructured Lipid Carriers
SLNs	Solid Lipid Nanoparticles
PNPTs	Polymeric Nanoparticles
NEs	Nanoemulsions
NBs	Nanobubbles
HA	Hyaluronic Acid

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