Review Article

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Transdermal Delivery of Ketoprofen for Osteoarthritis Treatment and Management: A Literature Review on Current Progression

Dwi Asih Ramadhani, Yahdiana Harahap, Erny Sagita , Kartika Citra Dewi Permata Sari, Rr. Kirana Andranilla, Jessica Trisina, Gabriella Frederika Punu, Delly Ramadon*
Faculty of Pharmacy, Universitas Indonesia, Depok, West Java, Indonesia

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ABSTRACT

Arthritis, a diverse spectrum of joint disorders, is characterized by chronic pain and inflammation. Osteoarthritis (OA), the most prevalent form, leads to disabling pain, functional limitations, and reduced mobility. Nonsteroidal anti-inflammatory drugs (NSAIDs) are widely used for managing OA pain, with ketoprofen recognized as one of the effective options. However, oral administration of ketoprofen may cause gastrointestinal irritation. Addressing this issue, Transdermal Drug Delivery Systems (TDDS) emerge as a promising alternative route of administration. TDDS facilitates delivery of various drugs through the skin without undergoing first-pass metabolism. Recent studies have centered on enhancing ketoprofen's transdermal delivery, particularly focusing on different methods (such as patches, gels, electroporation technology, and *stratum corneum* bypass methods), with microneedles emerging as a promising approach for delivering anti-inflammatory drugs through transdermal routes. This review aims to explore recent advancements in transdermal drug delivery systems for managing OA. The utilization of transdermal ketoprofen presents innovative opportunities for future research and development in novel drug delivery systems.

Keywords: *transdermal; ketoprofen; osteoarthritis; drug delivery system*

**corresponding author*
Email: delly.ramadon@farmasi.ui.ac.id

INTRODUCTION

Osteoarthritis (OA) is a prevalent form of arthritis characterized by the continuous degeneration of the joints. The deformation of joint tissue will result in discomfort around the joint cartilage, along with other clinical symptoms, such as edema and stiffness around the joints (Jang et al., 2021; Santos et al., 2023). Recent research has highlighted various factors contributing to the development of OA, including trauma, inflammation, biochemical responses, and metabolic abnormalities. These factors exacerbate the condition over time, ultimately leading to disability in individuals with OA (Long et al., 2022; Mora et al., 2018). The primary goals of treating osteoarthritis are to alleviate pain, reduce stiffness, and preserve physical function, as there is currently no known cure for this condition (Sardana et al., 2017).

OA treatment strategies aim to reduce patient discomfort and slow disease progression. According to the American College of Rheumatology guidelines (Kolasinski et al., 2020), Nonsteroidal Anti-inflammatory Drugs (NSAIDs) are among the preferred options for managing OA-related pain. NSAIDs including ibuprofen, ketoprofen, naproxen and diclofenac are commonly used to alleviate OA pain (Magni et al., 2021). Ketoprofen stands out as one of the most potent NSAIDs for OA pain relief, demonstrating strong clinical efficacy and good tolerability (Atzeni et al., 2021). Its pharmacodynamic activity involves inhibiting the production of prostaglandins (PGs) and thromboxane through the blockade of cyclooxygenase (COX) pathway (Ghlichloo & Gerriets, 2022). Especially, ketoprofen exhibited superior efficacy in inhibiting PG synthesis compared to other NSAIDs, such naproxen and indomethacin. Previous study reported that ketoprofen is 6 times more potent than naproxen and 12 times more potent compared to indomethacin (Rençber et al., 2009). Additionally, ketoprofen has been shown to be effective and well-tolerated in treating various forms of arthritis pain (Atzeni et al., 2021).

Oral NSAIDs or glucocorticoids are commonly recommended for patients with OA symptoms (Wang et al., 2022; Kolasinski et al., 2020). However, a long-term oral NSAIDs use carries risks, such as gastrointestinal bleeding and cardiovascular events, including myocardial infarction (Rother et al., 2007; Ghlichloo & Gerriets, 2022). Studies by Rannou et al. (2016) indicated that both topical and oral NSAIDs have comparable efficacy in treating OA, with fewer adverse events associated with topical NSAIDs.

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Furthermore, findings from multicenter randomized controlled trials by Rother et al. (2007) and Conaghan et al. (2013) on the efficacy and safety of ketoprofen in transfersome gel (IDEA-033) versus oral celecoxib and placebo in knee of OA patients suggested that IDEA-033 was superior to placebo and comparable to celecoxib in relieving OA pain. Moreover, their study also suggested that topical NSAIDs should be the preferred treatment option for OA patients aged more than 75 years with co-morbidities. Ketoprofen also demonstrated a high level of efficacy and good tolerability in elderly patients on long-term medication since there is no significant relationship between side effect incidence and age or cumulative dose (Sarzi- Puttini et al., 2011).

In the studies by Wolff et al. (2021) and Bhargava et al. (2019), topical diclofenac and ketoprofen were identified as the most extensively researched topical NSAIDs for treating knee OA, showing significant improvements in function and pain reduction. Although no statistically significant improvements was found in the analgesic efficacy between transdermal ketoprofen (20 mg) and diclofenac (200 mg) patches, patients reported lower maximal pain intensity with ketoprofen transdermal patch application. Currently, diclofenac is the only topical NSAID authorized for over-the-counter usage in the US and widely available worldwide (Wolff et al., 2021). Therefore, the development of topical and transdermal ketoprofen offers a promising alternative drug delivery method, bypassing first-pass metabolism, reduce the systemic toxicity, providing sustained drug release, and improving compliance and long-acting analgesia for effective pain management (Jadhav et al., 2018; Mills et al., 2020).

Transdermal Ketoprofen Research Progressiveness

TDDS is a painless method that is applied to healthy parts of the skin which appears to be a desirable alternative to undergo the problems in oral administration for several reasons, including increased patient compliance, avoid first-pass metabolism, controlled or sustainable drug release system, reduced side effects, and dose flexibility (Tanner & Marks, 2008). Several enhancement strategies have been developed, including both passive and active methods. Passive methods involve the use of chemical enhancers and drug-vehicle interactions which can enhance drug penetration through the skin. However, active methods utilize external devices, such as microneedle technology, iontophoresis, and thermal ablation (Ramadon et al., 2022).

Transdermal ketoprofen facilitates a simple, effective, and safe therapeutic option for OA treatment. Various studies have focused on the development of transdermal ketoprofen, and the research progressivity related to transdermal ketoprofen was depicted in Figure 1. The study about transdermal ketoprofen was initiated by Panus et al. (1997) who first delivered ketoprofen on *in vitro* studies in anodic and cathodic iontophoresis then verified on humans using clinical iontophoresis values (0.28 mA/cm^2), and a 300 mg/mL ketoprofen concentration applied at the human wrist. The iontophoretic method involves the use of an electric current to enhance the drug to permeate into the skin. The result of *in vitro* studies using anodic and cathodic iontophoresis was higher than passive intracutaneous of ketoprofen. This was subsequently verified on human's transdermal iontophoresis of ketoprofen in humans can achieve systemic circulation after 40 minutes. The amount of ketoprofen excreted in the urine after 16 hours after iontophoresis was 790±170 µg. This research was also the first utilization of a commercial iontophoretic device.

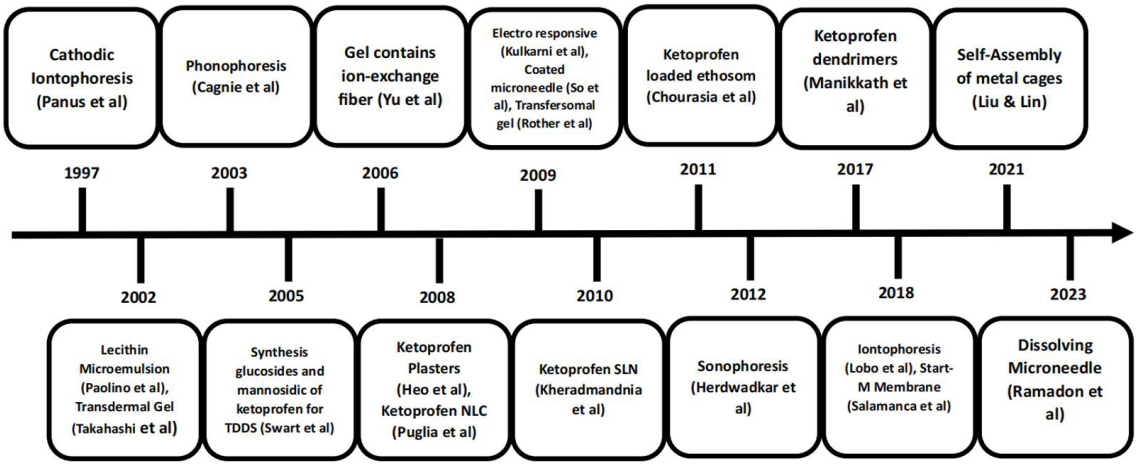

Figure 1. Summary of transdermal ketoprofen's progression

Table 1. Main finding and limitation of each study

Year	System	Main Finding	Limitations	References
1997	Cathodic iontophoretic	Cathodic iontophoresis in humans (0.28 mA/cm^2) using ketoprofen concentration 300 mg/mL which was performed at the wrist can achieve systemic circulation after 40 minutes.	The practical feasibility of the Ketoprofen Cathodic Iontophoretic may be limited as it requires specialized equipment and expertise that may not be readily available.	Panus et al.
2002	Lecithin microemulsion	In comparison to conventional formulations (w/o emulsion, o/w emulsion, and gel), One-gram ketoprofen loaded to lecithin microemulsion, which is proposed as a dermal and transdermal delivery system, showed that it can improve permeability through human skin (AUC: 893.92±56.25 µg.h/mL).	The study does not explicitly mention that oleic acid addition to the formulation of microemulsion may not significantly improve percutaneous absorption.	Paolino et al.
2002	Transdermal gel	The bioavailability of ibuprofen and ketoprofen were significantly higher when released from xyloglucan gels (AUC: 10.81±2.06 µg.h/mL for ibuprofen and 10.38±2.15 µg.h/mL for ketoprofen) compared to pluronic F127 gels (AUC: 1.02±0.32 µg.h/mL for ibuprofen and 0.47±0.19 µg.h/mL for ketoprofen)	The formulations are designed to form gel using in situ gelling, which can lead to stability problems due to chemical degradations.	Takahashi et al.
2003	Phonophoresis	In a clinical trial involving three groups that were administered ketoprofen gel (Fastum gel), phonophoresis of ketoprofen allows the attainment of higher local concentrations, whereas systemic exposure is lower. This was confirmed by using continuous ultrasound (1 MHz, 1.5 W/cm^2) for group A, pulsed ultrasound (100 Hz, 20% duty cycle) for group B, and five minutes of sham ultrasound for group C.	Phonophoresis of ketoprofen appears to be superior to local application rather than transdermal application.	Cagnie et al.
2005	Synthesis glucosides and mannosidic derivates of ketoprofen	The transdermal flux of the parent ketoprofen is at least a factor 10 higher than those of the ketoprofen glucosides or ketoprofen mannosidic.	The parent ketoprofen often faces issues with low solubility, moreover if it is administered transdermally.	Swart et al.
2006	Gel containing ion-exchange fiber as a controlling device for iontophoresis	Ketoprofen's fluctuating release rate from the vehicles was significantly less than that of basic gels; however, the inclusion of ions and iontophoresis might enhance the rate, extent of ketoprofen delivery and provide a regulated drug delivery.	The practical feasibility of the ketoprofen iontophoretic may be limited. The total concentration delivered of ketoprofen in the study is comparatively less.	Yu et al.
2008	Ketoprofen plasters	Ketotop-P (60 mg ketoprofen/70 cm^2) shown a greater and more sustained anti-inflammatory effect compared to ketotop-L (30 mg ketoprofen/70 cm^2), mainly due to its ability to attain a higher plasma concentration of ketoprofen.	The limited information about potential efficacy and safety of ketoprofen plasters to other pharmaceutical dosage form.	Heo et al.
2008	Ketoprofen NLC (Nanostructured Lipid Carrier)	Ketoprofen NLC provides a more prolonged anti-inflammatory action and extended drug release in the epidermis compared to the free drug formulation.	Ketoprofen NLC may have limited of targeting selectivity, which can limit the precision in delivering drugs to specific tissues or cells.	Puglia et al.

Table 1. Continued

Year	System	Main Finding	Limitations	References
2009	Electroresponsive using PAAm-g-XG	The PAAm-g-XG hydrogels show promise as on-demand drug release transdermal drug delivery devices when triggered by an electric signal.	The hydrogel can lead to stability problem in different environments and the amount of drug loaded into hydrogel may be limited.	Kulkarni & Sa,
2009	Ketoprofen coated polycarbonate solid microneedle	The solid microneedle coated with ketoprofen gel can improve ketoprofen delivery efficiency and relative bioavailability, with a 1.86-fold and 2.86-fold increase in AUC (area under the curve) and C_{max} (maximum plasma concentration) compared with the ketoprofen gel alone group.	The solid microneedle led to sharp medical waste.	So et al.
2009	Ketoprofen in transfersomal gel	Diractin® (Ketoprofen in transfersomal gel) demonstrated significantly reduce pain in muscles contraction and muscle over-exercise.	A longer-term study may be needed to confirm the long-term safety and efficacy of Diractin ®.	Rother et al
2010	Ketoprofen loaded SLN (Solid Lipid Nanoparticle)	Ketoprofen loaded SLNs preparation with a mixture of beeswax and carnauba. Additionally, it was discovered that when compared to nanoparticles having a higher carnauba wax content in their structure, those with a higher beeswax content in their core showed faster drug release.	SLN have a low drug loading efficiency	Kheradmandnia et al.
2011	Ketoprofen loaded ethosom	Ketoprofen loaded ethosome in *in vitro* release study through the skin revealed higher transdermal flux compared to hydroalcoholic drug solution.	Potential risk to skin irritation of ethosome.	Chourasia et al.
2012	Sonophoresis	Ketoprofen was delivered using sonophoresis at 20 kHz and 6.9 W/cm^2, it greatly increased the drug's penetration into the skin, going from 74.87±5.27 µg/cm^2 when delivered passively to 491.37±48.78 µg/cm^2 when administered using sonophoresis.	Practical feasibility of the sonophoresis may be limited as it requires specialized equipment and expertise that may not be readily available.	Herwadkar et al.
2017	Dendrimers	Low-frequency ultrasound and PAMAM dendrimers both had an impact on the transdermal delivery of ketoprofen, increasing the drug's transdermal permeation when used separately, but when combined, the drug's skin penetration was significantly boosted.	Instability potential of the dendrimer. Dendrimer may experience degradation that can affect it stability.	Manikkath et al.
2018	Iontophoresis	To improve the drug's penetration through the skin, anodal and cathodal iontophoretic delivery of pure ketoprofen and ketoprofen choline chloride (KCC) was employed. Higher medication concentrations have been seen in KCC cases when compared to iontophoresis-based administration of ketoprofen.	Practical feasibility of the sonophoresis may be limited as it requires specialized equipment and expertise that may not be readily available.	Lobo & Yan.

Table 1. Continued

Year	System	Main Finding	Limitations	References
2018	Gel	Gel formulation gives higher permeation efficiencies than suspension formulation. The permeation studies using Strat-M membranes for semi-solid product or transdermal product represent a reproducible methodology.	The gel formulation can lead to stability problem.	Salamanca et al.
2021	Self-assembly of metal-cages	Ketoprofen's efficacy improved when combined with heterometallic cage compounds. So that, the heterometallic cage complexes are expected to be exceptional material for TDDS.	The self-assembly of metal-cages may suffer from a lack of stability.	Liu & Lin.
2023	Microneedle	Ketoprofen was developed using a dissolving microneedle method in combination with nanosuspension (NS) and co-grinding (CG). After 24 hours, the cumulative amounts of drug that permeated for NS and CG were 3.88 ± 0.46 µg and 8.73 ± 1.40 µg, respectively.	Further studies with clinical trials are necessary to fully evaluate the safety and efficacy of ketoprofen dissolving microneedle.	Ramadon et al.

After 5 years ahead, Paolino et al. (2002) conducted a study examining the permeation of ketoprofen-loaded lecithin microemulsions. Their findings revealed that the ketoprofen-loaded microemulsion exhibited better permeability through human skin compared to the conventional formulations such as w/o emulsion, o/w emulsion, and gel. The steady-state flux (Js) value of ketoprofen-loaded microemulsion was 4.511 ± 0.001 µg/cm^{2}h, with an area under the curve (AUC) of 893.92 ± 56.25 µg.h/mL. This enhanced permeability can be attributed to the formulation's lecithin's content, which influences lipid-fluidization, thereby reversibly affects barrier function. Furthermore, this study also assessed the tolerability of a ketoprofen-loaded microemulsion on human volunteers in good physical condition. The results indicated that the microemulsion formulation presented the highest skin tolerability compared to the conventional formulation. Specifically, only 2 samples showed a visible reaction after 24 h during the human skin irritancy test, compared to 12 samples were for the control group.

In the same year, Takahashi et al. (2002) also developed a sustained released transdermal gel containing ketoprofen and ibuprofen, comparing the properties of Pluronic F127 and xyloglucan derived from tamarind seed as gelling agents, and evaluating both through *in vitro* and *in vivo* tests. They examined that ibuprofen was able to penetrate excised skin at a higher rate compared to ketoprofen when released from both gels. However, the bioavailability of ibuprofen and ketoprofen was significantly higher when released from xyloglucan gels compared to pluronic F127 gels (AUC: 1.02±0.32 µg.h/mL for ibuprofen and 0.47±0.19 µg.h/mL for ketoprofen with pluronic F127 gels, versus AUC: 10.81±2.06 µg.h/mL for ibuprofen and 10.38±2.15 µg.h/mL for ketoprofen with xyloglucan gels). This differences in release rates between Pluronic F127 and xyloglucan gels containing ibuprofen and ketoprofen can be attributed to the variances in gel structures, leading to the significantly higher bioavailability of both drugs from xyloglucan gels.

In 2003, Cagnie et al. conducted a clinical trial to examine the influence of phonophoresis, a physical therapy modality that involves the use of ultrasound to enhance the delivery of drugs through the skin, versus topical application of ketoprofen in 26 patients with knee disorders by comparing the concentrations found after continuous and pulsed application. The subject was divided into three groups: group A received continuous ultrasound (1 MHz, 1.5 W/cm^2) for five minutes to phonophoresis a ketoprofen gel; group B received the same procedure but with pulsed ultrasound (100 Hz, 20% duty cycle); and group C is a control group received five minutes of topical application of ketoprofen.

The plasma level of ketoprofen were consistently very low across all three groups, but there were significant variations in ketoprofen concentrations in adipose and synovial tissues. Group C exhibited different ketoprofen concentrations in synovial tissue compared to group A and B. Group B had a consistently higher level of ketoprofen in both adipose and synovial tissue as compared to group A. The study suggests that while systemic exposure is minimized, pulsed phonophoresis allows for higher local concentrations of ketoprofen. These findings suggest that continuous or pulsed phonophoresis may yield higher local concentrations while minimizing systemic exposure, suggesting that phonophoresis ketoprofen appears to be superior to topical application.

Over the next two years, Swart et al. (2005) synthesized glucosides and mannosidic derivates of ketoprofen and revealed that the transdermal flux of ketoprofen, ketoprofen glucoside, and ketoprofen mannosidic is 8.951±2.32 µg/(cm^{2}h), 0.342±20.15 µg/(cm^{2}h) and 0.329±0.38 µg/(cm^{2}h) respectively. They concluded that the transdermal flux of the parent ketoprofen was at least a factor 10 higher than those of the glucosides or mannosidic. In the next year, Yu et al. (2006) developed a gel containing ion-exchange fiber for iontophoresis, as a controlling device for ketoprofen delivery. Their study aimed to assess the effectiveness of the system in delivering ketoprofen through the skin. In their investigation, they found that the flux significantly increased with the electrically aided action, suggesting that the use of ion-exchange fibers on iontophoresis may be able to get through the skin barrier and obtain a promising approach.

Heo et al. (2008) examined research on the pharmacokinetics and pharmacodynamics of ketoprofen plasters (ketotop-P and ketotop-L) and found that ketotop-P (60 mg ketoprofen/70 cm^2) was able to achieve a higher plasma concentration of ketoprofen compared to ketotop-L (30 mg ketoprofen/70 cm^2), exhibiting a higher and more consistent anti-inflammatory effect. Concurrently, in the same year, Puglia et al. (2008) investigated the utilization of ketoprofen-loaded nanostructured lipid carriers (NLC) for skin inflammation, revealing a longer duration of anti-inflammatory effect and extended drug release in the epidermis compared to the drug solution.

In 2009, Kulkarni & Sa initiated the development of a transdermal drug delivery system for ketoprofen using electro-sensitive hydrogels comprising poly(acrylamide) (PAAm) and xanthan gum (XG). Their study revealed a significant increase in drug permeation through the skin in response to electrical stimulus compared to passive diffusion. Histological analysis of the skin indicated structural changes in cells and *stratum corneum* structure occurred following the electrical stimulation. These findings underscores the potential of the PAAm-g-XG (poly(acrylamide-grafted-xanthan gum) hydrogel as an electrically actuated platform for on-demand release, thereby enhancing drug bioavailability. This technology held promise for controlled and sustained drug delivery, reducing the frequency of dosing and maintaining therapeutic drug concentrations.

In the same year, So et al. (2009) prepared a gel containing ketoprofen (24mg/kg) embeded in a coated polycarbonate solid microneedle. *In vivo* studies on rats demonstrated that the solid microneedle coated with ketoprofen gel significantly improved ketoprofen delivery efficiency and relative bioavailability, resulting in a 1.86-fold increase in the area under curve (AUC) and a 2.86-fold increase in maximum plasma concentration (C_{max}) compared to the ketoprofen gel alone group. Toward the year's end, Rother et al., (2009) introduced diractin®, a transfersomal gel product designed to release ketoprofen into deep epidermal layers to alleviate pain and inflammation resulting from eccentric muscle contractions and muscle over-exercise. The findings revealed that diractin® significantly reduced pain in muscle contraction and muscle over-exercise compared to standard topical treatments and oral ketoprofen. Further clinical trials are warranted to validate and assess the efficacy of this product across various conditions, such as knee OA.

Kheradmandnia et al. (2010) formulated ketoprofen-loaded SLNs (solid lipid nanoparticles) using a mixture of beeswax and carnauba. Their study unveiled that nanoparticles with a higher beeswax content in the core exhibited accelerated drug release compared to formulation with a higher concentration of carnauba wax. Subsequently, Chourasia et al. (2011) developed nanosized ethosomes containing ketoprofen to enhance drug delivery. Ethosomal formulation emerged as a promising vehicle for transdermal ketoprofen administration. Results of *in vitro* skin release investigation indicated that ethosomal formulations displayed higher transdermal fluxes than hydroalcoholic drug solutions.

Later, Herwadkar et al. (2012) investigated the efficacy of ketoprofen delivery across the skin using low-frequency sonophoresis operating at 20 kHz at 6.9 W/cm^2. *In vitro* studies utilizing Franz diffusion cells were conducted on shaved and hairless rat skin for 24 hours. The use of sonophoresis significantly enhanced ketoprofen penetration rates from 74.87±5.27 µg/cm^2 with passive delivery to 491.37±48.78 µg/cm^2. Furthermore, the concentration of ketoprofen in skin layers rose from 34.69±7.25 µg/cm^2 with passive permeation to 212.62±45.69 µg/cm^2 with sonophoresis. These findings

underscored the effectiveness of 20 kHz sonophoresis as a viable approach to enhance transdermal and topical ketoprofen distribution.

Five years later, Manikkath et al. (2017) investigated the potential of dendrimers as a delivery system for ketoprofen. Their research explored the influence of four PAMAM dendrimer generations (G1 to G4) on the skin penetration of 1.5% w/v ketoprofen. Further investigations were carried out utilizing sonophoresis, which involved the application of approximately 20 kHz ultrasound for 30 minutes, on the penetration of ketoprofen dendrimers. Simultaneous application of ketoprofen dendrimers and ultrasound significantly increased permeability compared to control and passive permeation methods. Furthermore, the highest penetration occurred with simultaneous application using G2-dendrimer (24 h = 210.43±17.20 μg/cm^2) compared to the control (24 h = 60.24±4.43 μg/cm^2). Nevertheless, the dendrimer pre-treatment substantially increased the permeability, with G4 dendrimer exhibiting the maximum permeation (24 h = 420.95±47.13 μg/cm^2). Simultaneous application and pretreatment, followed by ultrasound for 30 minutes, further enhanced skin penetration for G4 dendrimer (798.86±100.14 μg/cm^2) and 881.75±76.43 μg/cm^2, respectively. Moreover, the combination of dendrimer treatment and ultrasound application worked in synergy and significantly improved ketoprofen penetration into the skin.

The following year, Lobo & Yan, (2018) explored iontophoresis for transdermal delivery of NSAIDs. Anodal and cathodal iontophoretic delivery of pure ketoprofen and ketoprofen choline chloride (KCC) was employed to enhance drug penetration through the skin. Notably, KCC iontophoresis exhibited higher medication concentrations compared to iontophoresis-based administration of ketoprofen alone. This approach showed promising results in reducing symptoms of knee arthritis symptoms and holds potential for knee arthritis treatment. In the same year, Salamanca et al. (2018) conducted study on ketoprofen permeation using Strat-M membrane, a transdermal simulation model. This method offers a reproducible and reliable approach for evaluating the performance of semi-solid pharmaceutical product during the pre-formulation stage for topical or transdermal administration.

Liu & Lin (2021) introduced a novel approach for directing the self-assembly of metal cages in organic and transdermal drug delivery. Their investigation revealed the heterometallic cage compounds as exceptional materials for TDDS, particularly for the delivery of ketoprofen. In 2023, Ramadon et al. developed a novel combination of dissolving microneedles with nanosuspension (NS) and co-grinding (CG) techniques for transdermal delivery of ketoprofen. Furthermore, F5-MN-NS and F11-MN-CG formulations exhibited significant ketoprofen penetration rates of 3.88±0.46 μg and 8.73±1.40 μg, respectively, after 24 hours. These findings suggests that co-grinding method or nanosuspension into dissolving microneedles could be a promising strategy for transdermal delivery of ketoprofen. A summary of the main findings and limitations of these studies is provided in Table 1.

Despite significant progress in transdermal ketoprofen development since 1997, microneedles showed potential as a prospect to deliver ketoprofen through transdermal administration since it passes the first-pass metabolism, reduce the systemic toxicity, generate no biohazardous sharp waste, and enable patients to painlessly self-administer. Comprehensive investigation through preclinical and clinical research is essential to establish the safety and efficacy profiles of transdermal ketoprofen formulations.

CONCLUSION

Transdermal delivery of ketoprofen exhibits promising potential in effectively managing pain associated with osteoarthritis (OA). Advancements in TDDS are facilitating the easier administration of analgesics through transdermal routes. This approach is expected to gain wider acceptance and application since it offers a broader range of medications and enhanced transdermal drug delivery system. The transdermal route is the most promising field of innovative study in novel drug delivery systems compared to conventional oral treatments. TDDS emerges as the most effective, reliable, and user-friendly method for systemic medication delivery. To fully understand the potential of transdermal ketoprofen, comprehensive and longer-term clinical trials with higher scope are required.

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CONFLICT OF INTEREST

All authors declare that they have no competing interests.

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