Does OTC Diclofenac Gel Meet Therapeutic Needs? A Dose-Response Review in Neuropathic & Inflammatory Pain Management

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Abstract

Diclofenac (VOLTAREN) was synthesized in 1973 and is the most widely prescribed NSAID worldwide. Subsequently, transdermal diclofenac sodium (TDS) emerged as a promising therapeutic option for localized pain management, offering a targeted approach with negligible plasma/systemic exposure. Through a comprehensive analysis of applicable pharmacokinetic and biopharmaceutic studies, this review aims to clarify the dose and formula optimization of TDS preparations. Our findings suggest that TDS 1.5-2% may not only enhance local bioavailability and analgesic efficacy, but may also relieve neuropathic pain—a novel application for this drug class. To validate our inferred conclusions, further investigation into the dose-response and antiangiogenic attributes of transdermal NSAIDs are required to substantiate the applicability of TDS in neuropathy.

Introduction

The localized management of musculoskeletal and neuropathic pain remains a complex challenge, driven by the intricate interplay of somatic, neurochemical, and psychosocial factors. Nociception is marked by its diverse biochemical mechanisms, often resulting in insufficient pain relief and patient dissatisfaction. Neuropathic signal transmission involves both peripheral and central biochemical mechanisms; its multimodal, pro-inflammatory nature makes it difficult to sustain antineuropathic satisfaction with conventional therapies. The recent surge in transdermal dose-response and drug delivery studies in arthritic and neuropathic conditions indicates an urgent desire for safe, efficacious, and targeted analgesic therapy. Topical NSAIDs, such as diclofenac sodium (DS) gel, not only provide comparable local pain relief vs oral formulations, but also improve safety outcomes. By modifying the dosage form and optimizing dosage of NSAIDs, healthcare providers and pharmacists can expand the therapeutic potential of these "tried and true" drugs.

Transdermal Delivery of NSAIDs [4-11,14,28]

Transdermal NSAIDs present a promising therapeutic option for specific patient populations where oral NSAIDs may pose significant risks or limitations, or in which systemic NSAID use is contraindicated or requires caution. Emerging data overwhelmingly supports the potential for transdermal NSAIDs to address these therapeutic gaps, paving the way for further research into their role as a safer, targeted pain management strategy.

Multiple head-to-head trials have demonstrated that topical nonsteroidal anti-inflammatory drugs (NSAIDs), including topical diclofenac, provide *at least* equivalent analgesia, improvement in physical function, and reduction of stiffness compared with oral NSAIDs in osteoarthritis and have fewer associatef systemic adverse events.

Therapeutic Equivalence: Drug levels within local tissues after transdermal administration are comparable to those observed with oral dosing; however, systemic plasma concentrations remain markedly lower with application to the skin. This transdermal phenomenon, often likened to a "Swiss cheese" effect, reflects the skin's selective permeability, which impedes the free diffusion of the drug into the systemic circulation. The reduced plasma drug concentration directly correlates with a minimized risk of systemic adverse events, such as gastrointestinal or renal complications, while maintaining therapeutic efficacy at the site of application. This pharmacokinetic advantage positions transdermal NSAIDs as a strategic option for optimizing localized drug delivery and minimizing systemic toxicity/treatment-limiting side effects.

Diclofenac Sodium [1-5,20,25]

Diclofenac, first synthesized in 1973, is among the most frequently prescribed NSAIDs worldwide. An oral dosage form of diclofenac sodium (DS) was first approved by the FDA in July 1988; DS was released under the trade name Voltaren (manufactured by Novartis). Nearly twenty years later, diclofenac sodium topical gel 1% (formerly Voltaren Gel) was FDA-approved in 2007. The popularity of topical diclofenac sodium ("TDS") and widespread development of similar NSAIDs is owed to their ease of use, impressive tolerability, and profound analgesic efficacy. In 2020, an Rx-to-OTC switch was authorized; the FDA granted approval of OTC Voltaren Arthritis Relief to GlaxoSmithKline. Diclofenac sodium topical gel 1% became the first (and is still the only) FDA approved transdermal NSAID the United States.

Currently available TDS *gel* products are listed below:

- **OTC Voltaren Arthritis Relief** (diclofenac sodium gel 1%) is indicated for temporary relief of arthritis pain in the hand, wrist, elbow, foot, ankle, or knee.
- **Diclofono (†diclofenac sodium gel 1.6%)** is a product by Nubratori Rx, a 503b Outsourcing Facility. Although not available on the mass market, Diclofono presents intriguing advancement potential for neuropathic pain relief.
- **Solaraze (diclofenac sodium gel 3%)** is indicated for the treatment of acitinic keratosis only. Solaraze contains ingredients which prevent cutaneous locomotion, as its formula was designed to work on the surface of the epidermis.

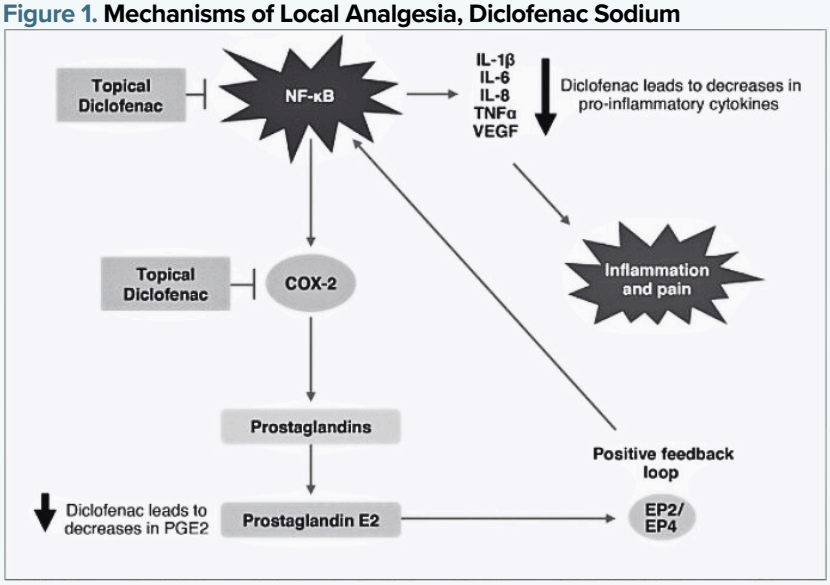
†Diclofono (diclofenac sodium topical gel) 1.6% is available commercially from Nubratori RX, a 503b FDA outsourcing facility. Diclofono is listed in all national drug databases. Medications can be prescribed and dispensed when in the opinion of the health care provider it is clinically significant over other commercial available medications.

Local Mechanism of Action

1. Cyclooxygenase Inhibition [1-4,22,28]

Diclofenac exerts its anti-inflammatory activity via inhibition of cyclooxygenase-1 (COX-1) and cyclooxygenase-2 (COX-2) enzymes. While it inhibits both enzymes, diclofenac shows some selectivity towards COX-2; as a result, diclofenac is considered a preferential option for treating acute pain and inflammation. DS exerts its anti-inflammatory effects by reducing the production of inflammatory prostanoids, particularly: prostaglandin E2 (PGE2), prostacyclins, thromboxanes. Diclofenac may also decrease levels of substance P—a nociceptive neuropeptide. As a result of selective COX-2 inhibition, diclofenac is proven to alleviate inflammation and pain associated with conditions like osteoarthritis and rheumatoid arthritis. Additional mechanisms of analgesia have been discovered recently, including promising anti-VEGF activity. *See Figure 1*

Figure 1. Mechanisms of Local Analgesia, Diclofenac Sodium



Modified Image.Bariguian Revel, F., Fayet, M. & Hagen, M. Topical Diclofenac, an Efficacious Treatment for Osteoarthritis: A Narrative Review. Rheumatol Ther 7, 217–236 (2020). https://doi.org/10.1007/s40744-020-00196-6. [10]

2. Anti-Angiogenesis [8,32-35]

Vascular endothelial growth factor (VEGF) is the key regulator of *angiogenesis* (the process by which new blood vessels form from existing vasculature) and neovascularization. These angiogenic processes are known to be essential for *tissue repair*, *wound healing*, growth, and development. VEGF receptors (VEGFRs) are widely distributed throughout the body, making them a considerable therapeutic interest across a multitude of pathologies. Recently, VEGF blockade has been a novel target in the development of topical analgesia. At the molecular level, VEGF binds to VEGFR-1 and VEGFR-2 on endothelial cells with high affinity, thereby activating signal transduction pathways which result in nociceptor sensitization. VEGF activation influences numerous physiological processes, including localized inflammation, which has sparked growing interest in VEGF and VEGFR as potential drug targets. *See Figure 2.*

While VEGF inhibition has traditionally been employed in anticancer therapies, emerging research highlights VEGF expression as a valuable biomarker and potential therapeutic target for conditions such as neuropathic pain, musculoskeletal pain, and inflammation. The VEGF family comprises five members, with VEGF-A and VEGF-B being the most prominent. These bind to VEGFR1 and VEGFR2 expressed in nociceptors, inferring the relevance of angiogenesis in neuropathic and inflammatory pain. VEGF blockade has been shown to reduce pain and improve synovitis, the primary cause of arthritic joint pain. VEGF expression also mediates the activation of macrophages, fibroblasts, and neutrophils. In a perpetual feedback loop, the increased production of inflammatory biomarkers aggrandizes cytokine and VEGF production, prolonging nociceptive transduction along not only *inflammatory* pathways, but also *neuropathic* pathways.

Fig 2. Cytokines with direct effects on sensory *neurons* and other inflammatory markers

Modified Image. Source: Topical Diclofenac, an Efficacious Treatment for Osteoarthritis: A Narrative Review

Cytokine	Pain at rest	Pain on movement	Total WOMAC	Mechanical hypersensitivity	Direct effects on sensory neurons
TNFα	(+) Leung [85]	(+) Leung [85]	(+) Gallelli [25]	(+) Richter [86] (preclinical)	(+) Richter [86] (preclinical) and Miller [88] (review)
IL-1β	NE	(−) Leung [85]	NE	NE	(+) Miller [88] (review)
VEGF	NE	NE	(+) Gallelli [25]	NE	NE

(+) positive association, (-) negative (inverse) association, IL interleukin, NA no association identified, NE not evaluated in the articles identified. TNFα tumor necrosis factor alpha, VEGF vascular endothelial growth factor

Modified Image. Original; Bariguian Revel, F., Fayet, M. & Hagen, M. Topical Diclofenac, an Efficacious Treatment for Osteoarthritis: A Narrative Review. Rheumatol Ther 7, 217–236 (2020). https://doi.org/10.1007/s40744-020-00196-6 [10]

Pharmacokinetics of TDS

Upon application to the skin, drugs must permeate the stratum corneum, the most significant barrier to absorption, and subsequently pass through the epidermis and dermis. This multilayered locomotion significantly limits plasma/systemic absorption, while allowing therapeutic drug concentrations to accumulate in the tissue, where it exerts its analgesic activity. Topical diclofenac is absorbed through the epidermis, allowing diclofenac sodium to dissolute and penetrate into subdermal tissues, including synovial tissue, to act directly at the site of pain and inflammation.

Transdermally-applied formulas capitalize on the unique pharmacokinetic (PK) properties of transcutaneous drug delivery, which inherently improve safety outcomes by limiting systemic exposure.

Structure-Activity Relationship (SAR) [1-4,7,15-17]
Diclofenac is a phenylacetic acid derivative and non-steroidal anti-inflammatory drug (NSAID). Its structure, characterized by a phenylacetic acid moiety and a chlorine substitution on the phenyl ring, plays a significant role in its pharmacokinetic behavior and therapeutic activity. *See Figure 3*

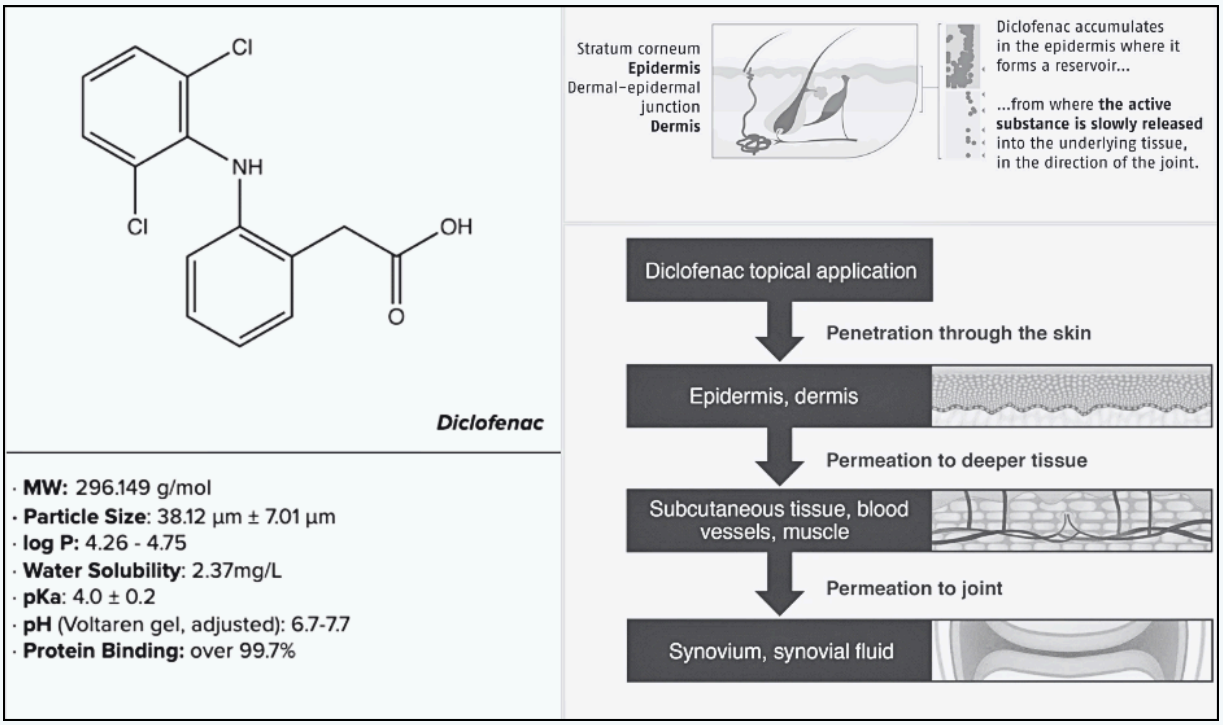
The lipophilicity of diclofenac, primarily due to its aromatic rings and chlorine substitution, enhances its ability to penetrate biological membranes, making it suitable for transdermal delivery. The presence of the chlorine atom in particular increases the compound's hydrophobicity, facilitating its partitioning into the skin's lipid-rich layers.

Local Bioavailability [13,19,20]
These structural characteristics allow DF to pass through the stratum corneum and to access deeper tissues, where it can exert its local analgesic and anti-inflammatory effects.

Within the dermal layers, diclofenac forms a reservoir in the skin, where it remains in a relatively high concentration. By maintaining a dermal reservoir, transdermal diclofenac offers prolonged, stable pain relief at the site of application, with minimal fluctuation in drug concentrations. Available data suggest that pain relief from topical diclofenac sodium begins within a few hours of application and is generally sustained over the 12-hour dosing interval, particularly with consistent use.

Local Biotransformation & Degradation *[1-4]*
Five primary metabolites of diclofenac have been identified in human plasma and urine. Of these, 4'-hydroxy-diclofenac is a major metabolite, although it exhibits weak pharmacological activity compared to the parent drug. The formation of 4'-hydroxy-diclofenac is primarily mediated by CYP2C9, a cytochrome P450 enzyme. Additionally, CYP2C8 contributes to oxidative metabolism, while CYP3A4 is involved in the formation of minor metabolites, such as 5-hydroxy- and 3'-hydroxy-diclofenac. Furthermore, acyl glucuronidation, mediated by UGT2B7, plays a role in the conjugation of diclofenac, facilitating its clearance and modulating its activity. These metabolic processes occur locally within the dermis and contribute to the pharmacokinetics of diclofenac following transdermal administration.

Fig 3. Transdermal Diclofenac Sodium & Inherent Attributes



Modified Image. Original; Bariguian Revel, F., Fayet, M. & Hagen, M. Topical Diclofenac, an Efficacious Treatment for Osteoarthritis: A Narrative Review. Rheumatol Ther 7, 217–236 (2020). https://doi.org/10.1007/s40744-020-00196-6 [10]

Discussion

This review was conducted in an effort to emphasize treatment gaps in dose-response, to improve analgesic outcomes, and to promote overall satisfaction in pain management, specifically in the unique case of acute and chronic neuropathic pain. It is critical to illuminate the overwhelming benefit and minimal risk associated with transdermal NSAIDs, and the ways in which they expand treatment options to specialized patient groups.

In studies of inflammatory pain, transcutaneous NSAID preparations have demonstrated noninferiority in the improvement of physical function and reduction of stiffness compared to equivalent dosage of oral NSAID. Regardless, few dose-optimization studies exist to determine if the transdermal route of NSAID delivery could not only provide equivalent analgesia, but **superior** and **sustained analgesia**. This discussion illustrates the results of our literary review, regarding dose and formula optimization, and biopharmaceutic implications of TDS products in neuropathy.

***Formula Optimization** [5-10,19,22-27]*

Diclofenac sodium (DS) gel formulations offer distinct clinical advantages over alternative topical treatments such as DS solutions and patches, primarily due to superior tissue penetration and sustained local activity, which are mediated by its pharmacokinetic properties. Studies have shown that diclofenac gel exhibits higher flux compared to both patches and solutions, leading to enhanced bioavailability. In particular, a study by **Seth (1992)** demonstrated that a solution gel formulation of diclofenac sodium achieved significantly higher maximum plasma concentrations (Cmax: 81.33 ± 43.68 ng/mL) and area under the curve (AUC: 495.29 ± 218.43 h·ng/mL) compared to an emulsion gel formulation (Cmax: 39.36 ± 7.56 ng/mL, AUC: 321.92 ± 162.07 h·ng/mL). These results underscore the solution gel's superior systemic absorption and its potential for improved therapeutic efficacy. [27]

Kienzler et al. (2010) conducted a randomized three-way crossover study to evaluate the bioavailability and pharmacodynamic effects of diclofenac sodium (DF Na) across different topical formulations and dosing regimens. The high-strength topical gel dose (ii), involving 12 g applied four times daily to both knees and hands (TDD: 48 g), produced substantially greater systemic exposure (AUC_{0-24}: 807 ± 478 ng·h/mL) compared to the standard 1% gel dose (i) applied at 4 g four times daily to a single knee (TDD: 16 g; AUC_{0-24}: 233 ± 128 ng·h/mL). Additionally, regimen (ii) demonstrated significantly greater inhibition of both COX-1 and COX-2 enzymes than regimen (i), highlighting the enhanced efficacy of the high-strength topical gel over the standard formulation. [10]

Dimethyl sulfoxide (DMSO), an inactive ingredient in diclofenac sodium solution 1.5% products, plays a crucial role in enhancing skin penetration and drug permeability. As noted by **Hagen and Baker (2017)**, DMSO is a highly effective permeation enhancer that facilitates the transport of diclofenac through the stratum corneum into deeper tissues, significantly contributing to the solution's clinical efficacy. However, DMSO is also a known skin irritant, and its high concentration (45.5% w/w) in this formulation increases the potential for localized irritation and discomfort in some patients.

In contrast, newer formulations like Diclofono (diclofenac sodium gel 1.6%) gel provide high-strength diclofenac therapy without relying on irritating ingredients such as DMSO. Utilizing skin-friendly excipients minimizes irritation while maintaining effective drug delivery. High-strength DS gels are an appealing alternative for patients who require potent topical diclofenac treatment but are sensitive to irritants commonly found in solution-based formulations.

Dose Optimization [1-3,22-27,29-30]

Recent biopharmaceutic studies support the safety and efficacy of high-strength diclofenac gels in the targeted treatment of osteoarthritic, inflammatory, *and* neuropathic pain. Available TDS products (1% gel, 1.5-2% solution) have demonstrated suboptimal pain relief when studied in neuropathic conditions, thereby excluding diclofenac as an option for topical antineuropathic relief. Given the limited availability of FDA-approved transdermal NSAIDs (OTC or Rx), research into expanding these options is of pharmaceutical urgency. With only a single-strength diclofenac sodium gel available to the masses, investigators have yet to fully assess the therapeutic potential of transdermal NSAIDs. In this comprehensive review of the literature, we examine the antineuropathic dose-response activity of standard (1%) vs high-strength (1.5-2%) diclofenac sodium gels. Our results suggest that high-strength (1.5-2%) diclofenac sodium is not only increasingly efficacious and longer-lasting, but also equally safe vs the FDA-approved product. Standardized, large-scale studies must be conducted in the future to definitively optimize the therapeutic dose of diclofenac sodium in neuropathic pain relief.
This discrepancy in dosage highlights a critical gap between diclofenac concentration and analgesic response.

Higher-strength diclofenac formulations offer notable benefits in terms of patient *adherence and convenience*. By increasing the strength from 1% to 2%, the frequency of application can be reduced from four times a day to just twice daily, making the treatment regimen more manageable and improving patient compliance. This ease of use can lead to better adherence and, consequently, more effective treatment outcomes. Furthermore, topical diclofenac formulations with concentrations above 1%, such as 1.6% gels, have been shown to outperform some oral doses. These stronger gels exhibit enhanced flux, enabling more efficient skin penetration and faster onset of pain relief compared to solutions or lotions. This combination of improved efficacy and simplified dosing underscores the advantages of higher-strength topical diclofenac formulations.

Antineuropathic Potential: VEGF Blockade [8,31-35]

Nerve pain, unlike the slow progression of arthritic pain, often results from traumatic injuries, peripheral disease, or localized disease that ultimately results in often permanent disease or damage to the central nervous system.

Researchers are still working to elucidate the multimodality of neuropathic signal transduction. Historically, topical formulations present a unique challenge, particularly in neuropathic pain management. Emerging evidence of anti-VEGF activity, as well as the potential for additional nociceptive signal modulation, encourages investigational pharmacologists to determine the impact of DS dosage on therapeutic applicability.

Although FDA-approved topical diclofenac products are *not* currently labeled with indications related to neuropathic pain, emerging evidence provides insight into the angiogenic implications of neuropathy. Our review of the literature supports the efficacy, safety, and applicability of TDS 1.5-2% gel in localized neuropathic relief.

A study published in *Anesthesiology* in 2015 assessed the efficacy of a 1.5% topical diclofenac formulation for managing neuropathic pain in patients. The study involved 28 participants (12 male, 16 female) with a mean age of 48.8 years. After two weeks of topical application, the group using the 1.5% diclofenac formulation reported a lower overall visual pain score compared to the placebo group (4.9 [1.9] vs. 5.6 [2.1]) and a reduction in burning pain (2.9 [2.6] vs. 4.3 [2.8]). No significant differences were observed between the groups for constant shooting pain or hypersensitivity over the painful area. These self-reported improvements were supported by a reduction in pain summation, as detected by quantitative sensory testing. There were no notable changes in functional status or complications across the groups. These findings suggest that a 1.5% topical diclofenac formulation could be an effective treatment option for patients suffering from neuropathic pain, particularly in conditions like postherpetic neuralgia and complex regional pain syndrome (CRPS).

Antineuropathic Potential: KP Modulation [31-33]
The kynurenine pathway (KP) plays a significant role in the pathophysiology of neuropathic pain, particularly in the modulation of inflammation and pain processing. The KP is responsible for the metabolism of tryptophan, with key metabolites such as kynurenine and its downstream products influencing neuroinflammation and pain perception. In the context of neuropathic pain, alterations in the KP have been linked to increased neuroinflammation and the sensitization of pain pathways, contributing to heightened pain sensitivity and chronic pain conditions.

A recent publication, Debbag et al. (2023), via the European Review for Medical and Pharmacological Sciences, examined the effects of diclofenac treatment in a rat model of neuropathic pain. The results indicated that diclofenac treatment led to both nociceptive improvements and alterations in the kynurenine pathway.

These results indicate that diclofenac may also exert antinociceptive activity by modulating the kynurenine pathway. Although this study was conducted in a systemic animal model, it raises the possibility that a topical diclofenac formulation could similarly influence the KP pathway in local tissues. The localized application of diclofenac could alter the KP metabolites within the dermal or local tissue environment, potentially contributing to its analgesic effects in a way that is distinct from the systemic effects seen with oral formulations. However, further research is needed to confirm whether the modulation of the KP pathway occurs in a dermal environment, as the penetration of diclofenac into deeper tissues and its ability to affect these local biochemical pathways would require further investigation.

Conclusion

Transdermal NSAIDs present a promising therapeutic option for specific patient populations where oral NSAIDs may present significant risks or limitations. Research is ongoing to develop improved methods of drug delivery which mitigate these systemic concerns. Through the expansion of 503a compounding pharmacies and 503b outsourcing facilities, providers and pharmacists are able to proactively increase therapeutic applications, and expand the accessibility of anti-inflammatory drugs to patients nationwide.

In addition to the well-established benefits of transdermal diclofenac sodium (DS) gel, recent theories regarding anti-VEGF (vascular endothelial growth factor) and kynurenine pathway (KP) modulation further support its antineuropathic potential. The modulation of VEGF through topical DS gel may reduce vascular permeability and neuroinflammation, which are key contributors to neuropathic pain. These mechanisms could promote local tissue healing and pain relief without the risks associated with systemic therapies. By influencing the KP, topical DS gel could reduce neuroinflammation and normalize pain processing at the local level, further enhancing its utility in managing conditions like postherpetic neuralgia and complex regional pain syndrome.

In personalizing transdermal formulations and dosing regimens, researchers seek to enhance the precision of analgesic interventions, particularly in neuropathic pain, where localized anti-inflammatory and analgesic effects may offer significant advantages. The results of our literary review are in support of the development of diclofenac sodium gel 1.5-2% as a safer, more effective, and longer-lasting alternative to diclofenac sodium topical gel 1%. Although early evidence suggests antineuropathic success, further dose-response, locomotive, neuropathic, and formulation studies are essential to the expansion and optimization of transdermal NSAID products.

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