International Journal of Science and Research Archive
eISSN: 2582-8185
Cross Ref DOI: 10.30574/ijsra
Journal homepage: https://ijsra.net/

(REVIEW ARTICLE)

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Transdermal drug delivery approaches for neuropathic pain: Formulation strategies and clinical potential of amitriptyline hydrochloride and meloxicam

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International Journal of Science and Research Archive, 2026, 18(03), 470-483

Publication history: Received on 15 January 2026; revised on 01 March 2026; accepted on 02 March 2026

Article DOI: https://doi.org/10.30574/ijsra.2026.18.3.0415

Abstract

Neuropathic pain, including sciatica, is a chronic condition that imposes a significant global burden through mechanisms like dysfunction of the peripheral or central nervous system, sodium channel dysregulation, and neurogenic inflammation, affecting 7-10% of the population globally. Conventional oral Amitriptyline hydrochloride, a tricyclic antidepressant exerting sodium channel blockade along with serotonin/norepinephrine reuptake inhibition, and Meloxicam, a selective cyclooxygenase-2 inhibitor targeting inflammatory prostaglandins, deliver symptomatic relief but are limited by systemic adverse effects such as sedation, dry mouth, gastrointestinal ulcers, and renal impairment. Transdermal drug delivery systems (TDDS) have emerged as a patient-centric alternative, enabling localized, sustained drug release through matrix or reservoir designs with permeation enhancers to overcome the stratum corneum barrier while minimizing first-pass metabolism and plasma fluctuations. This review explores recent advancements in transdermal formulation strategies for Amitriptyline hydrochloride and meloxicam, polymer selection, permeation enhancement methods, and advanced carriers like microneedles and nanostructures tailored for neuropathic pain applications. Additionally, the article highlights the need for further research in this field to develop more effective and targeted therapies for neuropathic pain management.

Keywords: Neuropathic Pain; Sciatica; Transdermal Drug Delivery; Amitriptyline Hydrochloride; Meloxicam; Sustained Release; Matrix; Inflammatory Pain

1. Introduction

1.1. Neuropathic pain epidemiology

Neuropathic pain is a complex chronic pain condition resulting from injury or dysfunction of the sensory nervous system. It significantly impairs quality of life and functional capacity, with global prevalence estimates ranging from 7-10% of the population [1]. Patients experience symptoms such as burning, tingling, and shooting pain, which substantially impair quality of life and daily functioning [2]. Among neuropathic pain disorders, sciatica represents one of the most frequent clinical manifestations, caused by compression or inflammation of lumbosacral nerve roots. Epidemiological studies suggest that sciatica affects a substantial portion of the population, with lifetime prevalence estimates typically ranging from about 10% - 40%. Due to its chronic nature and poor response to conventional analgesics, neuropathic pain poses a considerable clinical and socioeconomic burden worldwide [3].

In India, low back pain is widely reported across different age groups and occupations, often linked to physically demanding work, long hours of sitting, and poor ergonomic habits. Depending on the region and the population studied, reported prevalence rates vary between rang from around 6% to 40%. [4].

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1.2. Limitations of oral therapy:

Oral medications are still the most used treatment for managing the neuropathic and inflammatory components of sciatica. Among them, Amitriptyline hydrochloride, a tricyclic antidepressant, is frequently prescribed because of its effectiveness in relieving neuropathic pain. However, its long-term use is often limited by side effects such as drowsiness, dry mouth, constipation, dizziness, and potential cardiovascular problems, which can reduce patient comfort and treatment adherence [5, 6].

Meloxicam, a non-steroidal anti-inflammatory drug, is widely used to relieve inflammatory pain, but long-term oral therapy is linked to side effects such as stomach irritation and bleeding, kidney dysfunction, and increased cardiovascular risk. In addition, NSAIDs taken by mouth often provide limited relief for the neuropathic component of radicular pain, reducing their overall effectiveness in sciatica management [7].

1.3. Advantages of the transdermal drug delivery system

Transdermal drug delivery systems (TDDS) are increasingly being explored as an alternative approach for long-term pain management, allowing medications to be absorbed through the skin into the bloodstream or directly into underlying tissues. This method avoids first-pass liver metabolism, enables prolonged and controlled drug release, and helps reduce systemic side effects while improving patient compliance. By maintaining more stable drug levels in the body and allowing targeted application to painful areas, TDDS are particularly well-suited for treating chronic neuropathic and musculoskeletal conditions such as sciatica [8].

In this regard, this review focuses on the growing potential of the transdermal drug delivery system in the management of neuropathic pain. It covers epidemiology and clinical burden of neuropathic and radicular low back pain, along with the pharmacological limitations of commonly prescribed oral therapies such as amitriptyline hydrochloride and meloxicam. The review further explores formulation strategies for transdermal delivery, including polymer selection, penetration enhancers, and methods to achieve sustained drug release, drug combinations, and barriers influencing the drug release and therapeutic outcomes, while suggesting future directions for developing safer, more effective, and targeted therapies, and targeted therapies for neuropathic pain management.

2. Pathophysiology of neuropathic pain

2.1. Mechanisms of Peripheral and Central Sensitization in Neuropathic Pain

Neuropathic pain develops because of injury or dysfunction within the somatosensory nervous system and is marked by long-lasting changes in both peripheral and central pain pathways. **Peripheral sensitization** occurs when sensory neurons at the site of nerve damage become increasingly sensitive, largely due to the release of inflammatory mediators that reduce activation thresholds and heighten nociceptor excitability. After nerve injury, immune cells release cytokines and prostaglandins such as PGE_2, which further amplify nerve sensitivity and sustain ongoing pain signaling [9, 10].

Central sensitization refers to a state in which neurons within the spinal cord and brain become overly responsive following repeated or intense pain signals. During this process, communication between nerve cells is strengthened, normal inhibitory controls are weakened, and even mild sensory inputs begin to trigger strong pain responses. Consequently, sensations that would not usually cause pain can produce exaggerated discomfort, and pain may spread beyond the original site of injury [11, 12].

Voltage-gated sodium (Na_v) channels. Sodium channels help nerves send pain signals in the body. When a nerve is injured, these channels often become more active and increase in number. This causes the nerve to fire repeatedly without strong stimulation, leading to continuous pain. Certain types of sodium channels, such as $Na_v1.7$ and $Na_v1.8$, are especially involved in this process. As a result, the nerves become overly sensitive and keep sending pain messages, which contributes to long-term neuropathic pain [13].

COX-2-Mediated Inflammation in Sensitization: COX-2 is an enzyme that increases during injury and inflammation. It produces prostaglandins that make pain-sensing nerves more sensitive and strengthen pain signals (Fig.1). This increased COX-2 activity in tissues and the spinal cord worsens pain and helps neuropathic pain continue for a long time [10, 14].

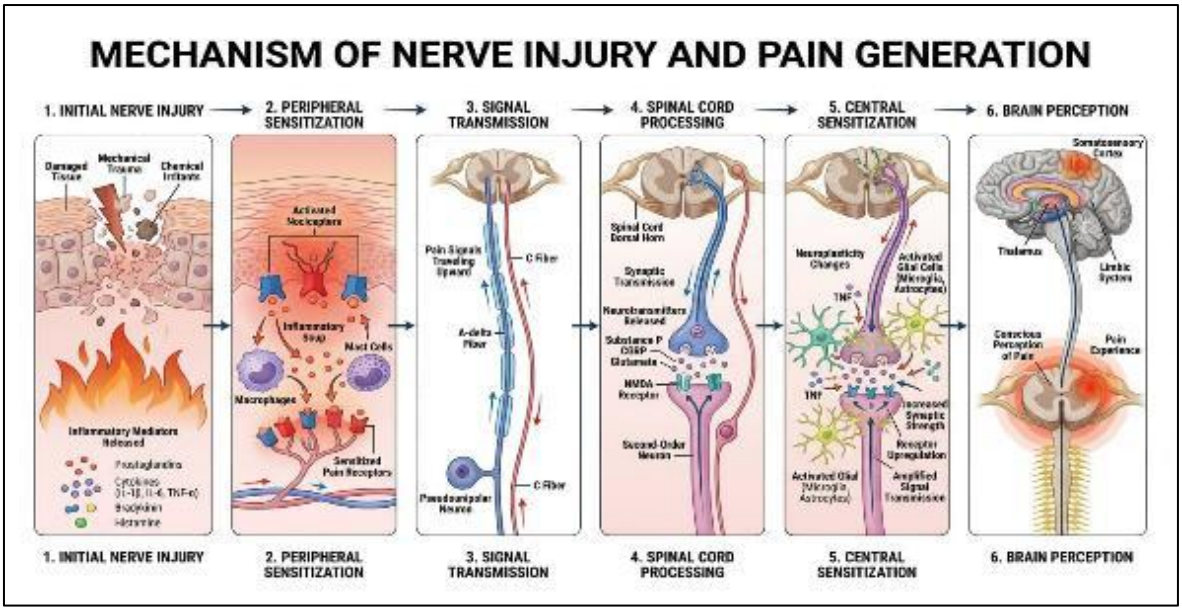

Figure 1 Mechanism of Nerve Injury and Pain Generation

2.2. Pharmacological Roles: Amitriptyline hydrochloride and Meloxicam

Amitriptyline, a tricyclic antidepressant, is widely used in neuropathic pain management because it acts on both central and peripheral pain pathways. It increases serotonin and norepinephrine levels in the brain and spinal cord, strengthening natural pain-inhibitory mechanisms, while also blocking sodium channels in sensory nerves to reduce abnormal nerve firing and nerve sensitivity. These combined actions help to control persistent nerve-related pain more effectively [15, 16].

Meloxicam is a preferential cyclooxygenase-2 (COX-2) inhibitor that reduces inflammation by limiting prostaglandin production, which plays a major role in pain and nerve irritation in sciatica [17]. By decreasing inflammatory sensitization around compressed nerve roots, meloxicam helps relieve pain and swelling. Its COX-2 selectivity generally results in fewer gastrointestinal side effects than older NSAIDs, although prolonged use still carries renal and cardiovascular risks [18].

2.3. Rationale for Transdermal Synergistic Therapy in Sciatica

2.3.1. Sciatica involves both nerve and inflammatory pain processes

Sciatica occurs when nerve roots are compressed and inflamed, which leads to abnormal nerve signaling and increased pain sensitivity. Because both nerve dysfunction and inflammation contribute to pain, effective treatment should address both mechanisms together [19].

2.3.2. Single drug therapy produce low therapeutic effect

Medications that reduce inflammation alone may not fully control nerve-related pain, while drugs aimed at neuropathic pain do not reduce swelling around irritated nerves. Combining therapies helps manage pain more effectively by targeting multiple pathways at the same time [20].

2.3.3. Drug combinations can work better together

When drugs with different actions such as nerve stabilizers like amitriptyline and anti-inflammatory agents like meloxicam are used together, they can enhance pain relief while allowing lower doses of each medication, which helps reduce side effects [21].

2.3.4. Transdermal delivery provides steady and localized treatment

Delivering drugs through the skin allows continuous release directly to affected tissues and into the bloodstream. This helps maintain consistent drug levels and avoids first-pass metabolism, improving treatment effectiveness and safety [22].

2.3.5. Fewer systemic side effects and better patient adherence

Transdermal therapy reduces stomach, heart, and nervous system side effects commonly seen with long-term oral medications, making it more suitable for chronic pain conditions like sciatica [23].

2.3.6. Supports a targeted multimodal pain approach

A single transdermal patch containing both neuropathic and anti-inflammatory agent offers a practical and focused strategy to manage the complex causes of sciatica pain more efficiently [22, 23].

3. Fundamentals of transdermal drug delivery

3.1. Skin barrier and Stratum Corneum

The skin serves as the body's main protective barrier, and the stratum corneum is the outermost layer that most strongly limits drug entry. It is made up of dead, keratin-rich cells called corneocytes surrounded by a lipid matrix, often compared to a "brick-and-mortar" structure. This tightly packed arrangement prevents most large and water-soluble molecules from passing through, while allowing only small and moderately lipophilic drugs to penetrate efficiently [24, 25].

Most drugs move across the skin through the lipid spaces between cells, although smaller amounts may also pass directly through the cells themselves or via hair follicles and sweat glands [25].

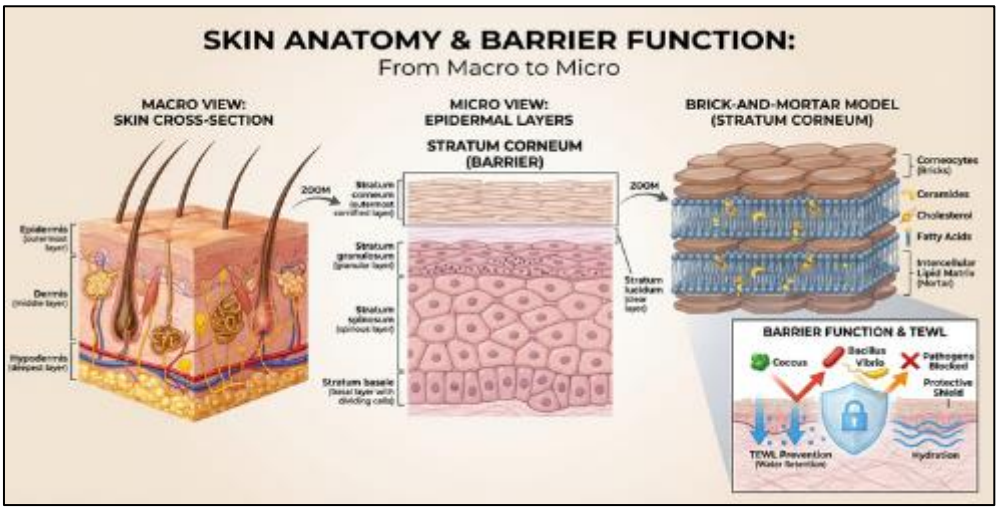

Figure 2 Skin Anatomy & Barrier Function

3.2. Fick's Law of Diffusion

Transdermal drug transport is primarily governed by Fick's first law of diffusion, which states that drug flux (J) across the skin is proportional to the concentration gradient (ΔC), diffusion coefficient (D), and partition coefficient (K), and inversely proportional to membrane thickness (h).

It shows that higher drug concentration, better lipid solubility, and smaller molecular size enhance permeation of the drug, while thicker skin reduces drug flux.

$$J = \frac{D.K.\Delta C}{h}$$

Where:

J = drug flux across the skin (amount passing per unit area per time)

D = diffusion coefficient of the drug in the skin

K = partition coefficient between formulation and skin

ΔC = concentration difference across the skin

h = thickness of the skin barrier [26].

3.3. Passive vs Active Transdermal Systems

Passive systems depend only on natural diffusion of the drug across the stratum corneum. These include transdermal patches (such as matrix or reservoir types) and topical formulations like gels and creams. They are suitable mainly for drugs having good skin-penetrating properties [27].

Active enhancement systems use physical techniques to improve drug transport through the skin barrier. Microneedles create tiny, painless openings in the skin that allow drugs to pass more easily [28]. Iontophoresis uses a small electrical current to push charged drug molecules across the skin, while sonophoresis (ultrasound) increases permeability by temporarily disrupting the lipid layers of the stratum corneum [29].

3.4. Physicochemical Requirements for Transdermal Delivery

For drugs to pass effectively through the skin by passive diffusion, they should generally have a small molecular size (below about 500 Da), moderate lipid solubility (log P between 1 and 3), good balance of water and lipid solubility, and strong potency so only low doses are needed [26, 27].

Amitriptyline hydrochloride has a suitable molecular weight for transdermal delivery and is highly lipophilic. However, its high lipid solubility can limit its ability to dissolve in water, so special formulation approaches such as permeation enhancers or optimized polymer systems are often required [30].

Meloxicam also falls within the ideal molecular weight range for transdermal delivery and has moderate lipophilicity, making it suitable for skin permeation. Its main limitation is low water solubility, which can affect how quickly it is released from a transdermal formulation [31].

Table 1 Pharmacokinetics and physicochemical properties of amitriptyline hydrochloride and meloxicam

Parameter	**Amitriptyline hydrochloride**	**Meloxicam**
Molecular weight (g/mol)	349.87 [32]	351.4 [32]
Log P	4.9 (base) [33]	3.4 [34]
pKa	9.4 [33]	4.1 [34]
Water solubility	Low to moderate [33]	Very low [34]
Oral bioavailability	30-60% [35]	89% [34]
Plasma protein binding	95% [35]	99% [34]
Half- life	15-25 hours [35]	15-20 hours [34]
Metabolism	Hepatic (CYP2D6, CYP2C19) [35]	Hepatic (CYP2C9) [34]
Elimination	Renal & fecal [35]	Renal & fecal [34]

4. Formulation strategies for transdermal delivery of amitriptyline hydrochloride

Amitriptyline hydrochloride, a tricyclic antidepressant, is commonly recommended as a first-line treatment for neuropathic pain because it helps regulate pain signaling in the central nervous system. It works by increasing serotonin and norepinephrine levels while reducing abnormal nerve excitability through sodium channel blockade. Recent international clinical guidelines continue to support the use of amitriptyline for neuropathic pain, particularly in patients who do not respond adequately to standard pain medications **[36].**

4.1. Gels and creams

These are widely used for fast and localized delivery through the skin. These semi-solid formulations are usually prepared with hydrophilic polymers such as Carbopol, hydroxypropyl methylcellulose, or sodium carboxymethyl cellulose to create a stable base. Solvents like ethanol and propylene glycol are added to improve drug solubility and keep the formulation in close contact with the skin, while permeation enhancers such as oleic acid or natural terpenes disrupt the lipid structure of the stratum corneum and increase drug diffusion. Although these systems provide rapid pain relief and are comfortable for patients, they generally offer limited sustained drug release when compared with transdermal patches **[37, 38]**

4.2. Transdermal Patches

Transdermal patches are widely explored for delivering amitriptyline hydrochloride in a sustained and controlled manner through the skin. These systems are designed to maintain consistent drug levels over extended periods, which is particularly beneficial for chronic neuropathic pain management.

Matrix-type patches are the most commonly investigated formulation, where the drug is evenly distributed within a polymeric film. Polymers such as hydroxypropyl methylcellulose (HPMC), Eudragit RL/RS, polyvinylpyrrolidone, and ethyl cellulose are frequently used either alone or in combination. Drug release from these systems occurs gradually as the drug diffuses through the polymer network, and by modifying the polymer ratio and composition, it is possible to control release kinetics, flexibility, and mechanical strength **[39].**

Reservoir-type patches, in contrast, store the drug in a liquid or gel reservoir that is separated from the skin by a rate-controlling membrane. This design can provide a more uniform drug release profile; however, it involves more complex manufacturing processes and requires strict quality control to prevent dose dumping in case of membrane failure **[37].**

4.3. Quality by Design (QbD) for Polymer Ratio and Enhancer Optimization

Quality by Design (QbD) is a systematic formulation approach that focuses on understanding critical material attributes (CMAs) and critical process parameters (CPPs) to achieve consistent product quality **[40].** In transdermal patch development, QbD is used to optimize polymer composition, permeation enhancer concentration, plasticizer content, and patch thickness.

Experimental designs such as factorial design and Box-Behnken design help evaluate the combined effects of polymer ratio and enhancer level on drug release, permeation, and mechanical properties **[41]**. This structured approach ensures reproducible performance while minimizing trial-and-error formulation.

5. Formulation strategies for transdermal delivery of meloxicam

Meloxicam is a selective cyclooxygenase-2 (COX-2) inhibiting nonsteroidal anti-inflammatory drug that is not typically considered a primary treatment for neuropathic pain. It can target the inflammatory processes that frequently coexist with nerve damage and enhance pain sensitization. Experimental animal studies have demonstrated that meloxicam reduces neuroinflammatory responses, inhibits microglial activation, decreases oxidative stress, and alleviates neuropathic pain-like behaviors after nerve root compression. These findings support its potential role as an adjunct therapy by regulating peripheral inflammatory mechanisms involved in neuropathic pain [42].

Meloxicam is a lipophilic BCS class II drug that freely partitions into lipid membranes but exhibits very low water solubility and a strong tendency to remain crystalline, which can hinder uniform dispersion and sustained release in polymer-based delivery systems [43].

Meloxicam has been formulated into various transdermal systems to improve skin permeation and achieve sustained therapeutic levels. Emulgels and lipogels provide enhanced solubilization of the lipophilic drug and prolong the skin contact, resulting in improved permeation compared with conventional gels [44].

Vesicular carriers, including conventional liposomes and highly deformable transfersomes, have demonstrated superior penetration through the stratum corneum and increased drug retention in deeper tissues, making them promising candidates for localized joint targeting in inflammatory conditions [45].

For controlled systemic delivery, matrix-type transdermal patches prepared using polymers such as polyvinyl alcohol (PVA) and hydroxypropyl methylcellulose (HPMC) regulate drug diffusion and enhance mechanical stability, allowing prolonged release of meloxicam across the skin [46].

6. Formulation strategies to improve skin permeation

6.1. Polymers

Enhancing drug transport across the skin remains a central objective in transdermal drug delivery, as the stratum corneum imposes substantial resistance to molecular diffusion. Optimization of the polymer matrix plays a critical role in overcoming this barrier, where blending hydrophilic polymers such as HPMC with hydrophobic polymers like ethyl cellulose or PVA regulates hydration, mechanical strength, and drug diffusion pathways. Experimental permeation studies have shown that such polymer combinations significantly increase drug flux across excised skin while maintaining sustained release profiles, demonstrating improved permeation efficiency compared with single-polymer systems [47].

The selection and proportion of polymers in a transdermal patch strongly influence its mechanical strength, hydration behavior, and drug release characteristics. Hydrophilic polymers such as HPMC tend to absorb moisture and swell, creating aqueous channels that promote faster drug diffusion, whereas hydrophobic polymers like ethyl cellulose or Eudragit restrict molecular movement and slow drug release. By blending these polymer types, formulators can fine-tune release kinetics while maintaining suitable flexibility and film integrity. In practical permeation studies, Latif and coworkers demonstrated that HPMC - ethyl cellulose matrix films produced controlled, near zero-order release patterns, and increasing the proportion of ethyl cellulose significantly reduced cumulative drug release over a 24-hour period [48].

6.2. Plasticizers (film flexibility & diffusion)

The addition of plasticizers such as PEG-400, propylene glycol, and glycerol plays an important role in improving the flexibility of transdermal films and enhancing drug diffusion through the polymer matrix. By increasing polymer chain mobility, plasticizers soften the patch structure and form microscopic pathways that facilitate drug movement. This effect not only minimizes film brittleness and cracking during handling but also promotes uniform drug release and improved skin adhesion, ultimately leading to better permeation performance [49]. Moderate levels of PEG-400 (about 1–2% w/w) have been shown to yield uniform HPMC films, while very low or high concentrations alter mechanical strength. [50].

6.3. Permeation enhancers and excipients

Transdermal drug absorption can be improved by adjusting both the formulation components and the conditions at the skin surface. Various chemical permeation enhancers, including terpenes, fatty acids, surfactants, and sulfoxides, promote drug transport by temporarily disrupting the lipid structure of the stratum corneum or interacting with keratin proteins, which lowers skin barrier resistance and enhances diffusion [51].

Moisture-enhancing excipients such as polyols and humectants further support permeation by increasing hydration within the stratum corneum. This hydration causes swelling of skin cells and loosening of lipid packing, creating pathways that allow greater molecular movement [52].

Increasing the thermodynamic activity of a drug can significantly enhance its ability to permeate through the skin. This can be achieved by using supersaturated formulations or selecting appropriate solvent systems that create a stronger concentration gradient across the skin barrier. A higher concentration gradient promotes greater drug diffusion without permanently damaging the structure of the stratum corneum. It is important to carefully optimize the concentration of permeation enhancers, as excessive levels may lead to skin irritation or unwanted barrier disruption [53].

7. Clinical evidence and trials

7.1. Amitriptyline clinical evidence in neuropathic pain

Randomized controlled clinical studies have shown that amitriptyline provides significant pain relief in patients with painful diabetic neuropathy. In double-blind trials, treatment with amitriptyline resulted in approximately 30–40%

reductions in pain intensity over an eight-week period compared with placebo, with only three to five patients needed treatment to achieve meaningful improvement [54].

Comparative crossover studies evaluating amitriptyline against nortriptyline and placebo demonstrated that both tricyclic antidepressants produced significantly greater pain relief than placebo, indicating that their analgesic effects are independent of their antidepressant action [55].

With respect to safety, commonly reported adverse effects include dry mouth, drowsiness, and constipation. In some clinical trials, these side effects led to treatment discontinuation in roughly 20–30% of patients, reflecting tolerability limitations despite therapeutic benefits [56].

7.2. Meloxicam clinical evidence in neuropathic pain

NSAIDs, including meloxicam, have not consistently demonstrated effectiveness in treating neuropathic pain in randomized clinical trials. Evidence from systematic reviews indicates that high-quality studies do not support NSAIDs as being superior to placebo for neuropathic conditions such as post-herpetic neuralgia, diabetic neuropathy, or pain arising from nerve compression [57].

In clinical studies involving patients with mixed pain types such as osteoarthritis or chronic low back pain with neuropathic features, meloxicam was associated with improvements in overall pain intensity. However, when neuropathic pain components were analyzed separately, the drug did not show significant advantages over non-NSAID treatments, suggesting its benefit is primarily related to its anti-inflammatory action rather than direct neuropathic pain control [58].

8. Challenges in transdermal delivery

8.1. Skin Barrier Limitation

The main barrier to transdermal drug absorption is the stratum corneum, which consists of a tightly packed lipid-protein matrix that strongly limits the passage of most therapeutic molecules. As a result, only drugs with relatively small molecular size (generally below 500 Da), suitable lipophilicity, and high pharmacological potency can effectively penetrate the skin through passive diffusion [22, 24]

8.2. Poor Permeability of Drugs across the skin

Hydrophilic, ionized, and poorly soluble drugs generally exhibit very low permeability across the skin, resulting in inadequate transdermal drug flux for therapeutic effectiveness. Even compounds with favorable lipophilicity may encounter delivery limitations due to slow or incomplete release from formulation matrices, which can lead to variable and inconsistent drug levels in systemic circulation [22].

8.3. Skin Irritation and Toxicity

Prolonged use of transdermal drug delivery systems often leads to irritation at the site of application due to continuous interaction between the skin and formulation ingredients [37]. Although chemical permeation enhancers such as oleic acid, ethanol, and DMSO facilitate drug passage across the skin by modifying the stratum corneum lipid layers, they may simultaneously provoke inflammatory reactions such as redness and discomfort [38]. Continuous or repeated patch application can impair the natural protective function of the skin, increasing the risk of cumulative local toxicity for long-term use [51].

8.4. Limited Drug Dose Capability

The stratum corneum strongly resists drug movement; only a small fraction of the drug can pass through the skin. Therefore, transdermal delivery is generally suitable only for potent drugs that are effective at low doses (generally 10-20 mg/day) and unsuitable for medications that require higher therapeutic doses to the systemic circulation [59, 60].

8.5. Drug Stability and Crystallization Issues

Drug stability in transdermal systems depends greatly on the formulation environment. Factors such as moisture, heat, oxygen, and light can accelerate degradation reactions like hydrolysis and oxidation, reducing drug potency and altering release behavior [61]. Additionally, interactions between the drug and formulation components, including polymers and plasticizers, may influence drug solubility and long-term stability [62].

Another major concern is drug crystallization within the matrix. When drugs are present in a supersaturated state, they may undergo nucleation and recrystallize during storage, which lowers their thermodynamic activity and reduces diffusion across the skin [63]. This can lead to decreased drug flux and inconsistent dose delivery. As a result, ensuring proper drug–polymer compatibility and using crystallization inhibitors are essential to maintain formulation stability and performance throughout shelf life [64].

8.6. Variability in Skin Permeability Among Individuals

Skin permeability differs widely from person to person and even between different areas of the body, which makes drug absorption through the skin difficult to predict. Characteristics such as age, level of skin moisture, lipid content, body temperature, health of the skin, and genetic makeup can alter the structure of the stratum corneum, which directly affects drug diffusion rates through the skin [65].

9. Advances and future perspectives in neuropathic pain management

Neuropathic pain results from injury or dysfunction of the nervous system and is characterized by persistent and often debilitating symptoms. Conventional oral pharmacotherapy frequently provides suboptimal pain control due to inconsistent bioavailability and the development of systemic adverse effects. Consequently, recent advancements in transdermal drug delivery systems (TDDS) have focused on improving cutaneous drug permeation, achieving sustained analgesic concentrations, and enabling localized targeted therapy, thereby enhancing therapeutic efficacy and patient compliance [66].

9.1. Microneedle-based transdermal system

Microneedle (MN) systems enhance transdermal drug delivery by creating microscopic and reversible channels within the stratum corneum, which significantly improves skin permeability without stimulating pain receptors or causing tissue damage [67]. This approach allows efficient transport of both low-molecular-weight drugs and larger therapeutic molecules that are typically unable to penetrate the intact skin barrier [68].

For neuropathic pain treatment, MN platforms enable localized and sustained drug release at the site of nerve involvement, which helps maintain consistent analgesic effects while reducing systemic drug exposure and associated adverse effects [69]. In addition, the painless nature of microneedle application improves patient comfort and long-term adherence to therapy, which is essential for managing chronic pain conditions [68].

9.2. Energy-Assisted Transdermal Techniques for Neuropathic Pain Management

Physical enhancement approaches such as iontophoresis, electroporation, and sonophoresis have been developed to temporarily disrupt the skin barrier and promote faster transport of analgesic drugs across the stratum corneum. The major advantage is that it increases drug flux and provides more efficient and predictable transdermal absorption compared with a conventional passive system [29, 70]. These techniques use electrical current or ultrasound energy to increase skin permeability without causing permanent tissue damage, allowing drugs that normally exhibit poor passive diffusion to reach therapeutic levels in deeper tissues [71]. In addition, these methods provide rapid onset of analgesic action, making them particularly useful for managing flare-ups of neuropathic pain where immediate relief is required [72].

Another important benefit is the ability to control drug dosing by adjusting electrical intensity or ultrasound exposure, enabling precise regulation of drug input into systemic circulation [71]. Clinical and experimental studies have demonstrated enhanced transdermal transport of local anesthetics such as lidocaine as well as anti-inflammatory and analgesic agents using iontophoresis and sonophoresis, supporting their effectiveness in neuropathic pain therapy [72, 73]

9.3. Nanocarrier-Based Transdermal Formulations

Recent advancements in nanotechnology have enabled the development of transdermal systems in which analgesic drugs are incorporated into nano-sized lipid and polymer carriers to enhance skin permeation and therapeutic performance [74]. These nanocarriers improve drug solubility and protect active molecules from degradation, resulting in more consistent and sustained drug release profiles across the skin [75].

Liposome-based formulations have been widely reported to increase drug accumulation within the epidermis and dermis, thereby prolonging local analgesic action while limiting systemic absorption [76]. Similarly, nanostructured

lipid carriers provide higher drug loading capacity and improved physical stability compared with conventional lipid systems, leading to extended pain relief and reduced irritation [77].

9.4. Controlled-Release and Long-Acting Transdermal Patches

Recent developments in transdermal patch technology have focused on using polymeric matrix systems, pressure-sensitive adhesives, and drug reservoir designs to deliver analgesic drugs at a steady rate for extended periods, typically ranging from 24 to 72 hours. [37]. This controlled release helps to maintain stable plasma drug concentrations, reducing the fluctuations commonly associated with oral dosing and improving overall pain control in chronic conditions [78].

By providing prolonged drug delivery, these patches decrease dosing frequency and enhance patient adherence, which is particularly important for individuals suffering from long-term neuropathic pain [37, 78]. Clinically available long-acting lidocaine and high-concentration capsaicin patches have demonstrated significant effectiveness in relieving peripheral neuropathic pain by delivering localized and sustained analgesia directly to the affected area [79, 80].

9.5. Future Perspectives

Neuropathic pain is increasingly treated using neuromodulation techniques that directly regulate abnormal nerve signaling responsible for chronic pain. Spinal cord stimulation and peripheral nerve stimulation deliver controlled electrical impulses to interrupt pain transmission pathways, leading to significant and sustained pain relief while reducing dependence on systemic analgesics and opioids [81]. Recent progress in neuromodulation systems allows automatic adjustment of stimulation parameters based on real-time neural feedback, further improving therapeutic precision and long-term outcomes in patients with refractory neuropathic pain [82].

In parallel, advanced drug delivery technologies are improving the effectiveness and safety of pharmacological treatment by enabling localized and sustained drug release. Transdermal platforms, microneedle-assisted systems, and nanotechnology-based carriers enhance skin permeability and maintain stable drug levels over extended periods, minimizing plasma fluctuations and systemic toxicity. These approaches are particularly beneficial for chronic neuropathic pain, where long-term therapy is required, and oral medications often cause adverse effects or inconsistent bioavailability [22].

Beyond symptomatic relief, emerging regenerative and molecular therapies aim to modify the underlying disease process by repairing nerve damage and suppressing persistent pain signaling. Approaches such as stem cell therapy, neurotrophic factor delivery, and gene-silencing strategies using small interfering RNA have shown promising potential to reduce neuroinflammation and restore neuronal function in preclinical and early clinical studies [83]. These innovations represent a shift toward disease-modifying treatments rather than lifelong symptom control.

Looking forward, the future of neuropathic pain management is expected to combine personalized medicine with smart therapeutic technologies. Intelligent drug delivery systems integrated with biosensors may allow real-time monitoring of physiological pain markers and trigger drug release only when needed, optimizing dosing while minimizing overdose risk. Additionally, multimodal therapeutic platforms that integrate pharmacological treatment, neuro modulation, and regenerative strategies may offer synergistic pain control and improved quality of life for patients suffering from chronic neuropathic disorders [84].

10. Conclusion

Transdermal drug delivery systems have emerged as an effective and patient-friendly strategy for managing neuropathic pain, particularly in long-term treatment settings. By enabling continuous drug release through the skin and avoiding gastrointestinal and hepatic metabolism, these systems maintain consistent therapeutic drug levels and reduce the risk of peak-related adverse effects commonly observed with oral medications. Their non-invasive application and improved tolerability make them especially suitable for individuals requiring prolonged pain control.

The combined use of amitriptyline hydrochloride and meloxicam provides a complementary therapeutic approach by targeting both neural dysfunction and inflammatory mechanisms involved in neuropathic pain. Amitriptyline hydrochloride acts on central pain modulation pathways, while meloxicam limits inflammatory responses that exacerbate nerve damage and pain sensitivity. This dual-mechanism strategy has the potential to enhance analgesic outcomes while minimizing dose-dependent side effects.

Advancements in transdermal formulation technologies and permeation-enhancing techniques continue to expand the feasibility of delivering multiple drugs effectively through the skin. As research progresses, dual-drug transdermal

systems may substantially decrease reliance on conventional oral therapies and, in selected cases, offer a viable alternative for neuropathic pain management. Further clinical investigations are required to confirm their long-term efficacy, safety, and therapeutic superiority.

Compliance with ethical standards

Disclosure of conflict of interest

No conflict of interest to be disclosed.

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