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Nanogel-based transdermal delivery systems for neuropathic pain management

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Abstract

Neuropathic pain is a chronic condition arising from lesions or dysfunction of the somatosensory nervous system and remains difficult to treat with conventional oral medications due to poor bioavailability and systemic side effects. Transdermal delivery provides a promising alternative that bypasses hepatic first-pass metabolism and allows sustained drug release. In recent years, nanogel based systems three dimensional, hydrophilic polymeric networks of nanoscale size have emerged as versatile carriers capable of encapsulating both hydrophilic and lipophilic drugs. Their large surface area, tunable porosity, and responsiveness to physiological stimuli enhance skin penetration and enable controlled release at targeted sites. Key emphasis is placed on polymer selection, transdermal permeation mechanisms, preclinical outcomes, and translational challenges. Current evidence suggests that nanogel systems containing gabapentin, pregabalin, and lidocaine demonstrate superior pharmacokinetic profiles and patient compliance compared with conventional gels. However, large scale manufacturing, stability, and regulatory standardization remain critical hurdles. Continuous innovation in polymer design and stimuli-responsive nanogels is expected to expand their clinical potential in chronic neuropathic pain therapy.

Keywords: Controlled Release; Gabapentin; Nanogel; Neuropathic Pain; Transdermal Drug Delivery; Polymer Nanocarrier

1. Introduction

Neuropathic pain is a chronic disorder resulting from injury or dysfunction of the peripheral or central nervous system, often characterised by burning, tingling, and shooting sensations that significantly impair quality of life[1]. Conventional pharmacotherapy primarily oral anticonvulsants, antidepressants, and opioids frequently provides incomplete pain relief because these drugs exhibit poor penetration to damaged neurons and are associated with systemic adverse effects including dizziness, somnolence, and gastrointestinal irritation[2]. Consequently, there is a growing need for alternative delivery approaches that can enhance localised drug concentration while reducing systemic toxicity[3].

Transdermal drug delivery has emerged as an attractive, non-invasive route for long term neuropathic pain management, as it bypasses hepatic first-pass metabolism, maintains steady plasma concentrations, and improves patient compliance[4]. However, the stratum corneum forms a major barrier that restricts permeation of most therapeutic molecules, particularly hydrophilic compounds and drugs with high molecular weight[5]. To overcome this limitation, advanced carrier systems are required to facilitate deeper skin penetration and sustained release[6].

Nanogels three dimensional, cross-linked polymeric networks capable of entrapping hydrophilic and lipophilic drugs have recently gained attention as promising transdermal carriers due to their high water content, nanoscale dimensions, and tunable physicochemical properties[7-10]. Their ability to hydrate the stratum corneum, interact with

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skin lipids, and provide controlled drug release makes them suitable candidates for improving the therapeutic management of chronic neuropathic pain[11-13].

2. Pathophysiology of Neuropathic pain

Neuropathic pain originates from structural or functional damage to the somatosensory nervous system, leading to abnormal signal processing and exaggerated pain perception[14,15]. Peripheral sensitisation occurs when inflammatory mediators-prostaglandins, bradykinin, tumour necrosis factor-α, interleukin-1β, and nerve growth factor-lower the threshold of nociceptor activation[16]. Up-regulation of voltage-gated sodium and calcium channels in damaged neurons Increase spontaneous discharge and amplifies pain signalling[17]. Central sensitisation involves enhanced excitability of spinal dorsal-horn neurons caused by continuous peripheral input. This leads to overactivation of NMDA receptors, increased glutamate release, and diminished GABA-mediated inhibition [18]. Activated microglia and astrocytes release cytokines that further promote synaptic plasticity and neuronal hyperresponsiveness[19,20]. Neurochemical imbalances in monoamines such as serotonin and noradrenaline worsen pain transmission. The cumulative effect manifests clinically as allodynia and hyperalgesia[21,22]. Consequently, localised delivery systems capable of providing sustained therapeutic concentrations directly at the site of nerve injury are being explored[23]. Among these, nanogel-based transdermal formulations offer a promising strategy by combining controlled release, enhanced skin permeation, and improved patient compliance[24].

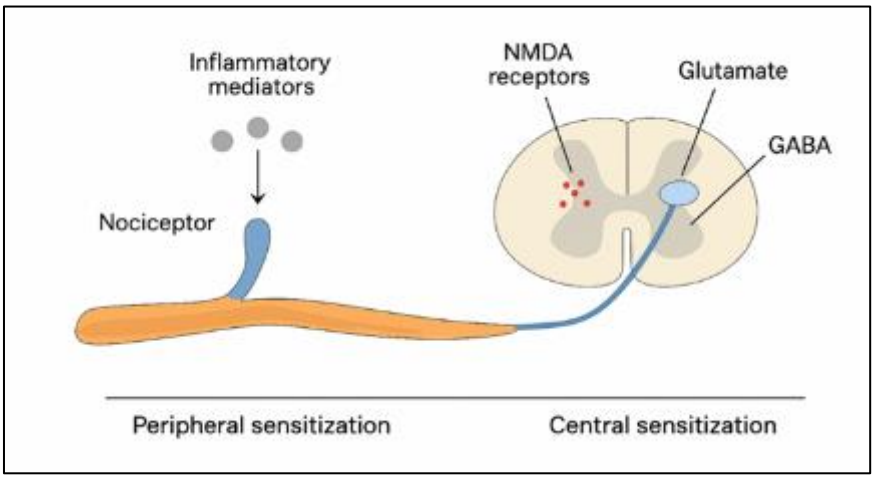

Figure 1 Pathophysiological mechanism of neuropathic pain showing peripheral and central sensitization pathways[15]

3. Nanogels-Composition and Mechanism

3.1. Definition and General Features:

Nanogels are nanosized hydrogel particles composed of a three-dimensional, cross-linked polymeric network capable of swelling in aqueous environments without dissolving[25]. Their particle size usually ranges between 20 – 200 nm, which allows enhanced penetration across biological membranes and improved pharmacokinetic behaviour[26].

3.2. Types of Polymers Used

3.2.1. Natural Polymers

Natural polymers are widely preferred because of their biodegradability, low toxicity, and resemblance to extracellular matrix components[27].

- Chitosan
- Alginate
- Dextran
- Gelatin and Collagen[28].

3.2.2. Synthetic Polymers

Synthetic polymers allow precise control over particle size, cross-linking density, and degradation rate, enabling reproducibility in formulation[29].

- Poly(N-isopropylacrylamide) (PNIPAM)
- Polyethylene Glycol (PEG)
- Polyvinyl Alcohol (PVA)
- Poly(lactic-co-glycolic acid) (PLGA)[30].

3.2.3. Semi-Synthetic and Copolymer Systems

Hybrid polymer systems combine natural and synthetic components to achieve both biocompatibility and tunability. For example, chitosan-PEG or alginate-PNIPAM copolymers enhance mechanical strength while maintaining biodegradability. These systems are being explored for responsive release based on external stimuli such as temperature or pH[31].

3.3. Mechanism of Drug Loading and Release

Drugs are incorporated within nanogels through physical entrapment, ionic interactions, or covalent conjugation depending on the physicochemical characteristics of the active molecule[32]. Hydrophilic drugs occupy the aqueous core, while lipophilic ones are embedded within hydrophobic domains. Drug release may follow diffusion-controlled, swelling-controlled, or degradation-controlled mechanisms[33]. Stimuli-responsive nanogels react to pH, temperature, or ionic strength to provide site-specific, on-demand drug release[34].

3.4. Methods of Preparation

Nanogels can be prepared using several techniques depending on the type of polymer, desired particle size, and application. Each method influences the structural integrity, porosity, and drug-loading efficiency of the final formulation.

3.4.1. Emulsion Polymerisation

This is one of the most common techniques, involving polymerisation of monomers in a continuous oil or water phase with surfactants[35].

3.4.2. Self-Assembly Techniques

Self-assembly utilises non-covalent interactions (hydrogen bonding, electrostatic forces, hydrophobic effects) to form nanogels spontaneously under physiological conditions[35].

3.4.3. Green and Microwave-Assisted Synthesis

Recent advances focus on eco-friendly fabrication using natural solvents, plant extracts, or microwave radiation[36].

4. Transdermal delivery using nanogels

4.1. Principles of Transdermal Drug Delivery

The skin consists of the epidermis, dermis, and subcutaneous tissue, with the stratum corneum acting as the primary barrier to drug permeation[37]. Traditional patches and gels depend on passive diffusion of small, lipophilic molecules, which limits therapeutic options[38]. To enable delivery of hydrophilic or large molecular weight drugs, carriers such as nanogels have been introduced[39].

4.2. Mechanism of Skin Penetration by Nanogels

Nanogels enhance skin permeation through multiple mechanisms[40]: hydration of the stratum corneum, occlusion to improve retention, electrostatic interaction with skin lipids, and controlled diffusion providing sustained release.

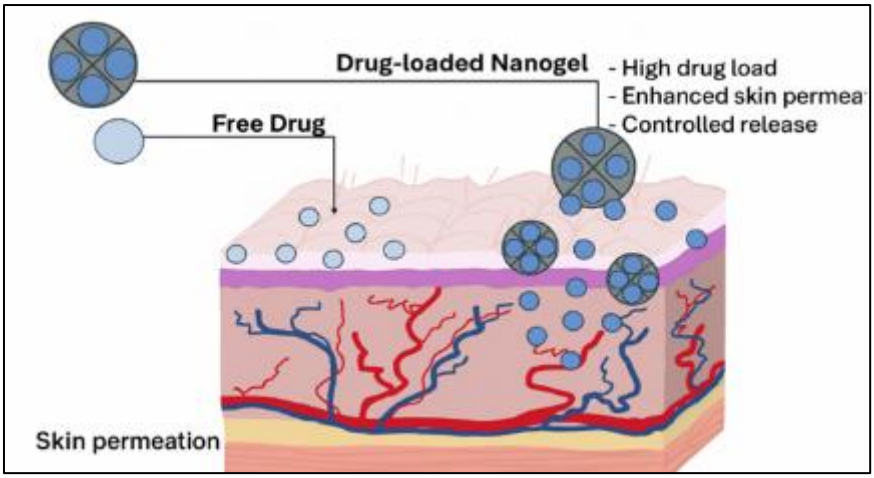

Figure 2 Drug-loaded nanogels enhancing Skin permeation and controlled release[9]

4.3. Formulation Parameters Influencing Delivery

Effective transdermal delivery depends on polymer concentration, particle size, cross-linking density, and pH[41]. Incorporation of permeation enhancers such as ethanol or surfactants can further improve flux[42].

4.4. Evaluation and Characterisation

Nanogels are evaluated for particle size, zeta potential, viscosity, pH, drug content, and in-vitro diffusion using Franz diffusion cell[43]. In-vivo studies in neuropathic pain models confirm their pharmacodynamic efficacy[44].

4.5. Benefits over Conventional Transdermal Systems

Compared with standard gels or patches, nanogels provide controlled release, deeper dermal penetration, and minimal skin residue[45]. They improve patient comfort due to their non-greasy texture and offer higher bioavailability with reduced systemic toxicity[46].

5. Applications in neuropathic pain management

5.1. Overview of Nanogel Applications in Pain Therapy

Neuropathic pain commonly arises from diabetic neuropathy, postherpetic neuralgia, spinal cord injury, chemotherapy-induced neuropathy, and multiple sclerosis[47]. Oral pharmacotherapy using anticonvulsants or antidepressants provides limited efficacy due to poor bioavailability and adverse systemic reactions. Nanogel-based transdermal drug delivery offers a targeted, non-invasive solution with enhanced local concentration and minimal systemic toxicity[48]. The small particle size of nanogels enables deeper penetration into the skin layers, while their hydrophilic structure allows gradual release of the encapsulated drug, ensuring sustained analgesic action[49].

5.2. Gabapentin Nanogels

Gabapentin, a structural analogue of γ-aminobutyric acid (GABA), is one of the most widely used drugs for neuropathic-pain management but suffers from low and variable oral bioavailability due to saturable intestinal absorption. Encapsulation of gabapentin into chitosan-carbopol or alginate-based nanogels significantly enhances its skin permeability and allows a steady, prolonged release profile[50,51].

5.3. Lidocaine and Other Local Anaesthetic Nanogels

Lidocaine is a fast-acting sodium-channel blocker used for local anaesthesia and postherpetic neuralgia. However, topical creams have a short duration of action and require repeated application. Incorporation of lidocaine into thermo-responsive PNIPAM nanogels provides sustained, controlled release for several hours, maintaining stable local drug levels and patient comfort[52].

5.4. Pregabalin and Duloxetine Nanogels

Pregabalin, a structural analogue of gabapentin, binds to the $\alpha_2\delta$ subunit of voltage-gated calcium channels, reducing neurotransmitter release and hyperexcitability of neurons [53,54]. Duloxetine-loaded hybrid nanogels, prepared using PEG–PNIPAM copolymers, allow bypass of first-pass metabolism and reduce gastrointestinal side effects while maintaining antidepressant and analgesic efficacy[55].

5.5. Capsaicin, Clonidine

- **Capsaicin nanogels** deliver controlled, low-dose desensitisation of TRPV1 receptors, offering prolonged pain relief without the burning discomfort of conventional creams.
- **Clonidine nanogels** act on peripheral α_2-adrenergic receptors, reducing sympathetic outflow and peripheral sensitisation, thus decreasing allodynia in diabetic neuropathy[56].

5.6. Clinical Translation and Future Outlook

Although laboratory studies confirm improved efficacy and safety, clinical translation remains limited by issues such as manufacturing scalability, polymer toxicity, and regulatory validation[57]. New fabrication strategies 3D-printing-assisted nanogel scaffolds, stimuli-responsive smart polymers, and biodegradable cross-linkers are now under investigation to improve reproducibility and patient compliance.

6. Recent research and developments

6.1. Novel Polymer Innovations

From 2020 onward, the focus in nanogel research has shifted toward biodegradable and sustainable polymers to reduce toxicity and environmental impact. New hybrid polymers such as chitosan-PEG-PNIPAM, dextran-acrylate copolymers, and alginate-cellulose nanocomposites have been engineered for better mechanical strength and drug encapsulation efficiency[58]. A 2022 study demonstrated that dual-cross-linked nanogels with covalent and ionic bonds improved stability during storage and maintained a uniform particle size below 100 nm[59].

6.2. Stimuli-Responsive Smart Nanogels

Smart nanogels that respond to pH, temperature, redox potential, and enzymes have become a major research focus in the last five years. For neuropathic pain therapy, temperature-sensitive PNIPAM-based nanogels have been optimized to release drugs only at inflamed tissue regions, where local temperature is elevated[60].Similarly, pH-sensitive chitosan-alginate nanogels ensure controlled drug discharge under slightly acidic skin microenvironments associated with inflammation[61].

6.3. Clinical Trials and Regulatory Perspectives

Although preclinical data are highly promising, clinical trials involving nanogel-based transdermal systems are still in early stages[62,63]. Recent human pilot trials (2023–2024) with gabapentin-loaded nanogels reported faster onset of pain relief and higher patient satisfaction compared to oral formulations. However, challenges remain in regulatory validation, long-term safety evaluation, and standardization of polymeric excipients[64].

7. Advantages, limitations and future prospects

7.1. Advantages

- Biocompatible and patient-friendly platform[65].
- Enhanced skin permeation[66].
- Controlled and sustained drug release.
- Reduced systemic side effects.
- Ease of administration and patient compliance.
- Versatile drug compatibility[67].

7.2. Limitations and Challenges

Formulation instability, Polymer toxicity and biocompatibility concerns**,** Manufacturing complexity**,** Regulatory and ethical hurdles**,** Economic barriers[68].

7.3. Future Research Directions

Ongoing research focuses on resolving these issues by integrating advanced technologies and sustainable approaches:

- Smart stimuli-responsive systems
- Hybrid nanogel–microneedle patches
- AI and machine learning in formulation design
- Green synthesis and eco-friendly fabrication
- Translational and clinical evaluation[69].

8. Conclusion

Nanogel-based transdermal delivery systems represent one of the most promising frontiers in neuropathic pain management. Their unique combination of nanoscale dimensions, high drug-loading capacity, biocompatibility, and controlled-release behavior enables enhanced skin penetration and sustained localised therapy. Preclinical evidence strongly supports the potential of gabapentin, pregabalin, and lidocaine-loaded nanogels in delivering consistent analgesic action with superior pharmacokinetic profiles compared to conventional formulations. However, challenges such as scale-up reproducibility, long-term stability, polymer toxicity, and regulatory standardisation continue to limit clinical translation. Future research must focus on integrating AI-assisted formulation design, green synthesis methods, and hybrid microneedle or sensor-integrated systems to accelerate commercialisation. With continued interdisciplinary collaboration and standardised evaluation protocols, nanogel-based transdermal systems are poised to become the next-generation therapeutic platform for safe, effective, and patient-compliant management of chronic neuropathic pain.

Compliance with ethical standards

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Disclosure of conflict of interest

No conflict of interest to be disclosed.

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