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Current trends in treatment and management of Neuropathic pain: Use of carrier approaches

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Abstract: - Neuropathic pain arises from a lesion or disease of the somatosensory nervous system and can substantially impair quality of life. Incomplete pain relief and adverse effects associated with conventional pharmacotherapy have prompted research into carrier-based strategies designed to improve drug delivery. This narrative review summarizes the pathophysiology of neuropathic pain and examines lipid-based, polymeric, and biomimetic carriers, with particular emphasis on intranasal nose-to-brain delivery. The platforms reviewed include liposomes, solid lipid nanoparticles, nanostructured lipid carriers, nanoemulsions, polymeric nanoparticles, hydrogels, extracellular vesicles, and cell membrane-coated nanoparticles. Depending on their composition and route of administration, these systems can improve drug solubility and stability, sustain release, and increase exposure at target sites. Intranasal formulations may improve nasal residence and mucosal permeation, while transport along olfactory and trigeminal pathways offers a potential route to the central nervous system that can bypass the blood–brain barrier. Preclinical studies suggest that selected formulations can increase brain drug exposure or prolong analgesic effects. Clinical translation requires confirmation of efficacy and long-term safety in humans, alongside reproducible manufacturing and consistent nasal dosing. Carrier-based delivery offers a promising approach to neuropathic pain management, with clinical studies needed to determine which formulations and patient populations are most likely to benefit.

Keywords: Neuropathic pain, carrier-based drug delivery, intranasal delivery, nose-to-brain delivery, blood–brain barrier, nanocarriers, hydrogels.

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1. Introduction:

Pain is an unpleasant sensory and emotional experience that can have a significant impact on a person's quality of life, general health, psychological health, and social and economic wellbeing. The members of the committee formed by the International Association for the Study of Pain (IASP) in 2020 redefined the Pain as an unpleasant sensory and emotional experience associated with, or resembling that associated with, actual or potential tissue damage. This could not only impact the quality of life, general and psychological health but also the economic and social wellbeing. On the other hand, Neuropathic Pain is defined as the pain induced by a disease or lesion of the somatosensory system that can affect central nervous system as well as peripheral nervous system (Baron et al., 2010; Campbell & Meyer, 2006; Raja et al., 2020). Management and treatment of the neuropathic pain is strictly associated with its accurate diagnosis which is carried out by screening questionnaires, clinical symptoms and the presence as well as quality of

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pain. Following the diagnosis, pharmacological management of neuropathic pain is initiated using antidepressants, anticonvulsants and topical analgesics. These drugs are considered as first line therapy of neuropathic pain, but their use is limited due to their lesser efficacy and adverse effects in some patients. Neuroleptic drugs are also studied as potential treatment for neuropathic pain, but their use is limited as they are not recommended as first line of treatment leading to the horizon of novel carrier-based drug delivery system.

2. Pathophysiology of Neuropathic Pain:

Neuropathic pain can be defined as a chronic and complex pain that occurs as a result of damage or malfunctioning of any component of Nervous system whether it is central nervous system or Peripheral Nervous System. As a result, damaged nerve fibers send incorrect signals to pain centers (Svokos & Goldstein, 2009) In another words pain caused without the participation of nociceptors is called neuropathic pain (Petroianu et al., 2023). Neuropathic pain occurs when tissue damage occurs, pronociceptive mediators are released, which sensitize peripheral nerve terminals (peripheral sensitization), changing the phenotype of sensory neurons and increasing the excitability of spinal cord dorsal horn neurons (central sensitization). Furthermore, nociceptive responses are modulated by descending supraspinal systems. It is now recognized that pain pathways involve a wide range of receptors, transmitters, second messenger systems, transcription factors, and other signaling molecules. Neurotrophic factors released during tissue damage, such as nerve growth factor (NGF), inflammatory mediators, such as ATP, PGE2, 5-HT, bradykinin, epinephrine, and adenosine, or pro-inflammatory cytokines, such as interleukin-1β (IL-1 β) and tumor necrosis factor-α (TNF-α), can all cause peripheral sensitization. Intense, repetitive, or protracted action potential production in primary sensory afferents is also linked to peripheral sensitization. This phenomenon is mediated by changes in the expression and activity of voltage-gated sodium and calcium channels. Nociceptors' activation threshold is lowered and their firing rate is increased as a result of peripheral sensitization. Furthermore, the development and upkeep of central sensitization are significantly influenced by peripheral sensitization. Various pathways showing the physiology of occurrence of neuropathic pain are shown in figure 1 (Boyce-Rustay & Jarvis, 2009; Smith, 2004). Bernatoniene et al. (2023) defined neuropathic pain as an abnormal signaling within the nerve system causes neuropathic pain, a crippling disorder that causes persistent and frequently severe pain feelings. It can result from a number of conditions, such as neuropathy, acute nerve injury, and specific illnesses.

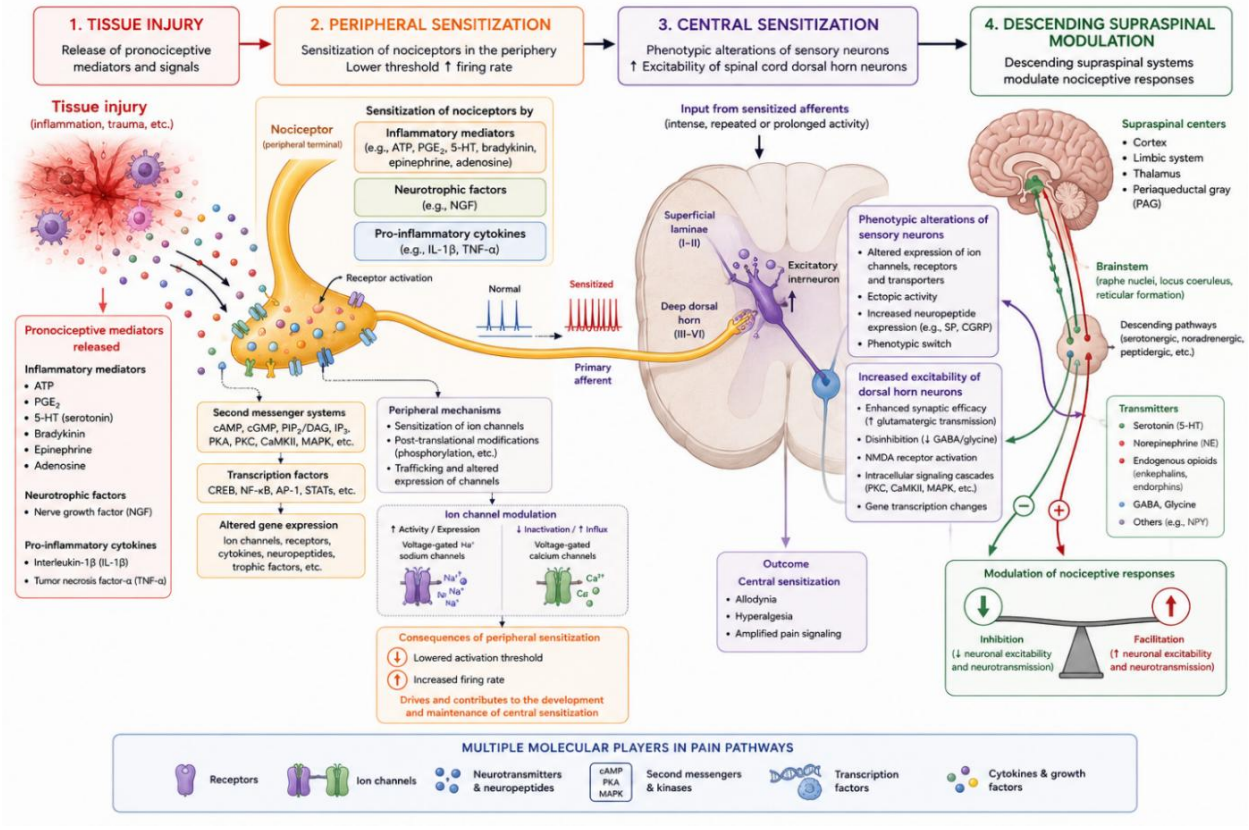


Figure 1: Pathways showing the pathophysiology of neuropathic pain

3. Carrier-Based Drug Delivery approaches

Conventional drugs are widely used in pharmaceutical industry, but due to their potential side effects, lower bioavailability and poor targeting efficiency led to open the horizon of new drug delivery system by which the utilization of microscopic vehicles for encapsulation, protection and transportation therapeutics to a particular tissues and control the release of drug at right time and right concentration to improve its bioavailability along with minimal side effects and enhance the therapeutic efficiency at molecular level, making the carriers as important as drugs (Losada-Barreiro et al., 2024; Rekha & Sharma, 2011) The rapid advancement of drug delivery technologies has had a substantial impact on the creation of more accurate and efficient therapeutic choices. Conventional drugs are released into the blood stream which have generalized effect on all the organs leading to potential toxicity to various organs as in case of conventional chemotherapy drugs. The carrier systems can be engineered to degrade gradually at the target site in response to stimuli (particular range of pH) leading to minimal systemic toxicity (Wu et al., 2016). Carrier systems enhance the pharmacokinetic properties without impacting the pharmacodynamic properties leading to enhance its bioavailability for the targeted site (Adepu & Ramakrishna, 2021; Glassman & Muzykantov, 2019; Sadar, 2020). The limitations of the traditional drugs facilitated the development of the carrier based system to precisely deliver the drugs to the target site.

4. Rationale for Carrier-Based Drug Delivery in Neuropathic Pain

According to research, 3–17% of people globally suffer with neuropathic pain and the number of patients is likely to increase in near future due to use of conventional medicines for number of diseases, increase in life expectancy and type 2 diabetes (De Moulin et al., 2014; Kuthati et al., 2020; Van Hecke et al., 2014; Zimmer & Rubin, 2016). Pharmacological treatments are presently the most followed approach for managing the neuropathic pain. For mild pain, anticonvulsants and antidepressants are the first line of treatment, followed by local anesthetics for moderate pain. When first- and second-line treatments fail, strong opioids are used as a third-line treatment for severe pain (Rugnath et al., 2024; Thouaye & Yalcin, 2023). Studies revealed that these treatments achieved low efficacy (50%) and effectivity (<50%) among patients (Finnerup et al., 2015; Rodrigues et al., 2023). To minimize the systemic toxicity, improvement in the pharmacokinetics and specificity, advanced technologies like drug carrier systems are designed to enhance the effectiveness and delivery of therapeutic agent. These systems are improving the bioavailability stability and targeted distribution along with reduced adverse effects. Personalized medication is likely to rule the drug delivery market globally with focus on drug carrier systems. Because of their characteristics, a variety of carrier-based systems are utilized to administer medications to treat neuropathic pain without causing adverse effects on other organs as discussed below:

4.1. Targeted delivery

Carrier based drugs are engineered to transport the therapeutics directly to the site of neuropathic pain with precision without systemic toxicity, hence minimizes the tolerance common with traditional medication (Dixit et al., 2025; J. Sun et al., 2025). Carrier based utilize different site-specific ligands or peptides or peptides which bind to receptors at the particular site of neural tissue. Carrier based drugs are designed to release therapeutic drug in response to particular ambient factors (enzymes, pH and temperature) of the specific damaged tissue (Bhansali et al., 2021; Tang et al., 2026; Yadav et al., 2025). There are numerous limitations of current medications like serious side effects, lack of specificity, Novel pain targets and innovative approaches to manage pain have been the subject of recent studies. Targeting the specific ion channels and inflammatory mediators and pain receptors are major advancements in pain management (Bhansali et al., 2021).

4.2. Sustained release

One of the biggest limitations of conventional drug is that these drugs are released in the blood stream. Circulation of drug particles throughout the body leads to lower drug concentration at the target tissue and expose other organs leading to the risk of adverse effect. Oral drugs may degrade in the gastrointestinal tract or in the liver during metabolism and elimination by renal excretion reducing the amount as well as time in the systemic circulation and target tissues hence show poor bioavailability at the targeted site (Stielow et al., 2023). (Adepu & Ramakrishna, 2021)Due to systemic release of drug, conventional formulations show peaks and troughs in blood results in toxicity at peak concentrations and reduced efficacy at lower concentration . On the other hand, systemic release of conventional drugs has shorter duration of action because of elimination. To compensate this, higher or repeated doses are required that again can cause toxic effects to other systemic organs. Conventional drugs also have limited interactions to the specific targeted sites. To address these limitations, numerous studies have been carried out to develop the carrier based drugs to enhance efficacy by protecting it from systemic degradation, improved solubility and facilitated targeted accumulation of therapeutic drug. To ensure appropriate and secure treatment, it is crucial to comprehend how medications are absorbed, transported, metabolized, and removed from patients' bodies. Stielow et al. (2023)reported the bioavailability is the key aspect of pharmacology influencing the effectiveness of the drug. Devi et al. (2024)

and Losada-Barreiro et al. (2024)explained the different kinds of pharmaceuticals are transported by cyclodextrin-based delivery systems through the formation of inclusion complexes, whose OH groups can be altered to incorporate other cargo molecules. Cyclodextrin based delivery system offer stability and sustained release of the cargo drug molecule and shield it from environmental interference and degradation, and become increasingly popular and have led to an increase in clinical trials.

4.3. Enhanced BBB penetration

Being a fragile and sensitive tissue, brain is supplied by metabolic fuels nutrients, gases for maintaining its homeostasis and carrying out vital functions. But a complex vasculature system called Blood Brain Barrier (BBB) inhibits the passage of over 98% of the small molecules and other conventional therapeutic drugs and obstructs neuropeptides and antineoplastic agents, antibiotics to nervous system (Bharadwaj et al., 2025; Upadhyay, 2014). He further stated the use of various transport systems like lipid carrier or liposomes micelles, colloidal drug carriers, chimeric peptide technology intranasal route and nanoparticles to transport the therapeutic agents to the brain across Blood Brain Barrier has been proved to be safe and better method. He et al. (2018)reported the molecules having structures that resemble the endogenous substrates of different carrier proteins have been transported using carrier-mediated transport (CMT). This pathway is used for the transport of Levodopa and gabapentin across Blood Brain Barrier (BBB). However CMT are used for the transportation of stereospecific and smaller cargoes as they are difficult to modify for the delivery of large molecule therapeutics (Jones & Shusta, 2007). A range of polymers, and methods can be used to create solid colloidal particles called nanoparticles (Jones & Shusta, 2007; Soppimath et al., 2001). Drugs can be adhered to the surface of a nanoparticle, encased in the core or trapped in the matrix(Koziara et al., 2006; Soppimath et al., 2001). Poly (butyl cyanoacrylate) nanoparticles are the most widely utilized formulation for delivery of therapeutics to brain across Blood Brain Barrier (Alyautdin et al., 1997; Gao & Jiang, 2006; Kreuter et al., 2002). Due to their more drug loading and bioavailability, greater stability, better biodegradability and biocompatibility, fewer adverse effects and lesser invasiveness, nanoparticles provide better option for therapeutics benefits (Lai et al., 2010; Lei, 2013). Nanoparticles delivery carriers are prepared for the encapsulation of drugs or coupling on their surfaces and are very specific for carrying the therapeutic drugs for particular diseases (Adeel et al., 2020; Han et al., 2023; Joudeh & Linke, 2022). Although Nanomaterials are effective safe drug delivery carriers across BBB for therapeutic and diagnostic use, yet there are numerous limitations to be resolved like inorganic nanoparticles including iron and gold nanoparticles can be neurotoxic to brain after their accumulation in brain (Behera et al., 2023; Kostka et al., 2024; Liu et al., 2025) The advancement of CNS disease diagnosis and treatment depends on improving drug delivery to the brain by exploiting this substance to cross the blood-brain barrier. It is a significant challenge in contemporary nanomedicine as well.

4.4. Reduced toxicity

Carrier based drug delivery system encapsulates the therapeutic drug inside the vehicles such as nanoparticles and liposomes to reduce toxicity and protect the healthy tissues from the adverse effects of the toxic doses. Carrier-based drug delivery system prevent systemic accumulation and localize the drug precisely at the particular diseased site (Etter et al., 2021; Rekha & Sharma, 2011). Nanoscale carrier system delivers the therapeutic drug so efficiently at the target site that a smaller dose is required for the same therapeutic effect leading to lower the risk of dose dependent toxicity (Pandita et al., 2023; Rekha & Sharma, 2011). All these factors enable the carrier-based drug delivery system to reduce the systemic toxicity.

5. Lipid-Based Carrier Systems

Although hydrophilic medications are commonly used and effective therapeutic agents, yet they exhibit poor pharmacokinetic profiles, low intracellular absorption, quick enzymatic breakdown and clearance, moderate distribution, low therapeutic index, and poor permeability (Mirchandani et al., 2021). Therefore Lipid-Based Carrier Systems (LBCSs) colloidal vehicles formulated from biocompatible, biodegradable fats and oils are engineered to protect delicate therapeutic payloads, enhance the bioavailability of poorly water-soluble drugs, and enable targeted and controlled drug release (Antonara et al., 2025; Dharanguttikar et al., 2026). Lipid-based nanoparticles are a perfect way to distribute poorly soluble medications because many of the newest chemicals being created in the pharmaceutical sector are poorly soluble in water, enable the pharmaceutical drug to reach the target site efficiently without compromising with its efficacy (Dharanguttikar et al., 2026). There are numerous such vehicles discussed ahead in this review.

5.1. Liposomes

Sustained delivery of analgesic compounds to the targeted tissue is a critical issue for effective pain management. Numerous carriers are used to facilitate the drug to the targeted tissue. Liposomal carriers deliver the therapeutic compounds at the target site due to its biodegradability and flexible physicochemical properties. Liposomal association with cargo drugs are shielded against inactivation, dilution and degradation in circulation reduces the volume of dosage, increases the half life ultimately reduce the systemic toxicity (Hua & Wu, 2013). There are numerous limitations that need to be rectify to increase the liposome circulation times like stabilizing the vesicles to prevent leakage of cargo drug,

avoiding opsonization and minimizing the removal by reticuloendothelial system (Nsairat et al., 2022; Ulrich, 2002). High electrostatic surface charges promotes liposomes to interact with cells and biomolecules that may function as opsonins (Laverman et al., 1999; Mall et al., 2025). Generally speaking, small, neutral, or positively charged liposomes are eliminated more slowly than modified big liposomes (Nsairat et al., 2022; Ulrich, 2002)

5.2. Solid Lipid Nanoparticles (SLNs)

Solid Lipid Nanoparticles (SLNs) are submicron (10–1000 nm) colloidal carriers composed of physiological lipids (e.g., stearic acid, glyceryl monostearate) that are solid at both room and body temperature (Ghasemiyeh & Mohammadi-Samani, 2018; Loira-Pastoriza et al., 2014). Because SLNs may encapsulate both hydrophilic and lipophilic medications, enhance oral bioavailability, and penetrate physiological barriers (such as the blood-brain barrier) to target central nervous system pathways, they represent a significant development in the treatment of neuropathic pain (Mishra et al., 2018; Satapathy et al., 2021). The biphasic release profile that SLNs offer—an initial burst followed by regulated release—helps sustain steady, long-lasting therapeutic doses of analgesics (Pandey et al., 2022; Yu et al., 2018). Moreover, SLNs provide efficient oral or transdermal delivery by shielding therapeutic drugs from hepatic metabolism and enzymatic or proteolytic destruction. SLNs can be surface-modified (e.g., PEGylation) to target certain tissues, like the central nervous system or the dorsal root ganglia, which are the main locations for neuropathic pain modulation,. SLNs are typically non-toxic and biodegradable since they are made from physiological lipids and surfactants that are generally recognized as safe (GRAS), such as Pluronic F-68 or Tween 80 (Bhandari et al., 2022; Mishra et al., 2018; Üner & Yener, 2007; Yu et al., 2018).

5.3. Nanostructured Lipid Carriers (NLCs)

Nanostructured Lipid Carriers (NLCs) are nanoscale colloidal systems composed of solid and liquid lipids, surfactants, and water. They provide a non-toxic, highly biocompatible way to encapsulate and administer lipophilic medications. NLCs improve medication penetration and shield delicate therapeutic molecules from premature degradation for neuropathic pain, offering controlled, sustained release for long-lasting comfort (Beloqui et al., 2016; Khan et al., 2023; Khosa et al., 2018). NLCs increase the bioavailability of analgesics by passing through physiological barriers like the skin for topical application or mucosal layers for nasal delivery. They make it possible to distribute drugs gradually and under control, which lessens the need for frequent doses and aids in maintaining a steady therapeutic window. Because of their tiny size, systemic side effects are reduced by focused administration to pain receptors or the central nervous system. (Kumari et al., 2026; Masoomzadeh et al., 2022; Tripathi et al., 2025)Keeping these points in attributes Nanostructured Lipid Carriers (NLCs) are considered as one of the best carriers to deliver the therapeutics to the target tissue specially in case of Neuropathic pain.

5.4. Nanoemulsions

Nanoemulsions are submicron drug carriers which deliver the analgesics like gabapentin or NSAIDs through targeted and sustained release. By allowing for direct localized or intravenous administration, they get around conventional drug limitations including low solubility and serious systemic side effects (Golmakani et al., 2026; Janjic et al., 2018; Shinde et al., 2024). Nanoemulsions penetrate the biological barriers easily, (such the skin for transdermal gels or mucosal membranes). Targeted and intravenous administration methods accumulate the therapeutic drug perfectly at the location of nerve damage by packing them into immune cells like monocytes. Hence, such carriers can reduce the necessary dosage by up to 2000 times by delivering the medication precisely where it is needed, minimizing harmful systemic side effects (Golmakani et al., 2026; Shinde et al., 2024; Taherianrad et al., 2025).

6. Polymeric Carrier Systems

polymeric carrier systems are advanced drug delivery systems made to carry analgesics (such gabapentin, pregabalin, and lidocaine) straight to specific pain pathways. These carriers offer controlled release, shield medications from premature breakdown, and greatly increase localized bioavailability by encasing therapeutic compounds in biodegradable and biocompatible polymers like PLGA and hydrogels (Chelladurai et al., 2026a; Phm & Kim, 2020; Pușcașu et al., 2023; Xue et al., 2026).

6.1. Polymeric Nanoparticles (e.g., PLGA):

Xue et al. (2026) suggested that PLGA can penetrate physiological barriers (such the blood-brain barrier) and promote cellular absorption into the nervous system thanks to their nanoscale size. They provide sustained release and protect medications from quick physiological clearance, extending the analgesic impact for days. Polymeric Micelles are self-assembling amphiphilic copolymers forming a core-shell structures which significantly boost the water solubility and stability of lipophilic (hydrophobic) drugs, allowing for easier systemic administration (Gavit et al., n.d.; Xue et al., 2026). Nanogels are perfect for transdermal or localized drug delivery as they are three-dimensional, hydrophilic polymeric networks that expand in water. They enable transdermal penetration of medications like lidocaine or gabapentin with less systemic side effects, have good biocompatibility, and avoid hepatic first-pass metabolism (Chelladurai et al., 2026b; R. Sun et al., 2025). Nanogels

play pivotal role in the treatment and management of pain as they are topical therapeutics and not released into blood stream, therefore they manage the impacted site without showing any adverse effect on systemic organs.

6.2. Hydrogel-Based Drug Delivery Systems

One kind of pharmaceutical device that has seen a lot of research and development in recent years is novel drug delivery systems (NDDS). Hydrogel formulations can be used to create a variety of physical forms, including slabs, microparticles, nanoparticles, coatings, and films (Fariba and Ebrahim 2010). Because of their distinctive three-dimensional networks of hydrophilic polymers, hydrogels have become a key component in the development of biomaterial science, transforming applications in a wide range of biological domains. (Dreiss 2020**,** Kesharwani et al., 2021, Patel et al., 2023). These networks stand out for their amazing capacity to enlarge without dissolving, preserving structural integrity through chemical or physical cross-linking mechanisms. They can absorb and hold significant amounts of water. (Qiu and Park 2001). Hydrogels are especially well-suited for use in drug delivery systems, tissue engineering, wound healing, and other fields because of their inherent ability to replicate the physicochemical characteristics of the natural extracellular matrix (Thang et al., 2023 & Shan and Wo 2024). Hydrogel research's beginnings and growth into the biomedical sciences are prime examples of an innovative trajectory, demonstrating the materials' adaptability in resolving challenging biological problems and their contribution to the advancement of biomedical solutions. In the 1960s, Wichterle and Lim created poly(hydroxyethylmethacrylate) (pHEMA) hydrogel, which marked the beginning of hydrogels as biomaterials and provided the groundwork for hydrogel technology (Wichterle and Lim 1960). Since then, developments in polymer science and a growing comprehension of biological interactions have propelled the field's exponential growth (Soon-Shiong et al., 1994). Theoretical frameworks and computational modeling have been crucial in illuminating the structural dynamics of hydrogels, in addition to the extensive experimental study of hydrogels in biological applications, especially in drug delivery (Vernerey et al., 2021, Jia and Muthukumar 2021).

6.3. Injectable Hydrogel-Based Drug Delivery

A state-of-the-art medication delivery method that makes administration easier using less invasive methods is injectable hydrogels. These hydrogels are ideal for targeted treatments for a wide range of medical problems because they provide exact control over the kinetics and location of drug release (Yu and Ding 2008). For injectable hydrogels to be administered easily and function well, their rheological characteristics must be customized. In order to provide both easy passage through needles and instant stability within the target region, they must exhibit shear thinning behavior, decreasing in viscosity under the shear stress of injection but rapidly rebounding once injected (Alonso et al., 2021). Because injectable hydrogels may load components and be injected into the lesion region, they are employed in clinics for a variety of purposes, such as drug administration and tissue regeneration. According to research, CHA gel greatly aided in tissue regeneration following spinal cord injury. Furthermore, an 8:2 gel formulation showed full disintegration in 28 days, while a 9:1 (gC: oHA) CHA gel broke down in 14 days (Daye Lee et al., 2025). ZL006, a small-molecular molecule, offers fresh promise for neuropathic pain treatment by suppressing N-Methyl-d-aspartate receptor (NMDAR)-mediated neuropathic pain behaviors without impairing vital NMDAR function. Neuropathic pain requires long-term care due to its chronic nature. However, ZL006 has a brief duration of action, just like other analgesics now on the market. The stability of ZL006 in aqueous solutions is examined, and a thermoresponsive injectable hydrogel based on P407 is created in order to fully realize the therapeutic potential of ZL006. To help realize the intended ZL006-loaded hydrogel system and clarify the gelation mechanism, computational analysis is carried out. Without the need for expensive specialist equipment or an organic solvent, ZL006 can be put into the hydrogel matrix in an aqueous phase at room temperature, where the sol is created and injectable (Zeng et al., 2022).

6.4. Stimulus Responsive Hydrogels

A) Thermoresponsive Hydrogels

Thermoresponsive hydrogels, commonly called thermogels, are a class of polymer that swells in water to produce gels. There are several mechanisms that cause thermogelation in aqueous solutions, some of which are still up for discussion for certain polymers. A common feature of many thermoresponsive polymers is a change in solubility brought on by variations in the overall hydrophilicity of polymer chains in reaction to temperature changes (Klouda and Mikos 2008). Because thermogels may undergo sol–gel transitions in response to temperature changes, they are used in a variety of applications, including medication delivery, where they are used to construct controlled and sustained release systems. Thermogels offer a supporting scaffold that resembles the extracellular matrix in 3D cell culture, promoting tissue development and cell proliferation. Furthermore, these hydrogels are essential for in situ tissue repair and regeneration in tissue engineering because they offer a biocompatible and injectable medium that promotes cell proliferation and tissue regeneration. Their promise in these biomedical applications is further enhanced by their non-toxic nature and programmable characteristics. Furthermore, thermoresponsive hydrogels have been thoroughly studied for application in biosensing and spectroscopy (Toma et al., 2013).

B) pH-Responsive Hydrogels

A number of factors affect the swelling and deswelling behavior of pH-sensitive hydrogels, which are under intense development. Ionic charge, the degree of ionization, the surrounding medium's pH, the kind of monomer, the concentration of polymers, and the networks' hydrophilicity are some of these variables. Weakly acidic functional groups (including phosphate −PO42−, sulfonate −SO3−, and carboxylic −COO−) ionize at higher pH levels in anionic hydrogels, causing the network to swell. On the other hand, cationic hydrogels swell at lower pH levels because basic functional groups like amines are ionized (Protsak and Morozov 2025).

Combining biocompatibility, biodegradability, mechanical integrity, and stimulus responsiveness, smart-responsive hydrogels are adaptable scaffolds for neural tissue healing. Important developments include injectable systems that enable minimally invasive CNS and PNS regeneration, composite designs that combine artificial strength with natural ECM-like bioactivity, and conductive hydrogels that facilitate electrical communication. Axonal development, neuronal differentiation, and functional recovery are all improved by these characteristics.

C) Sustained drug delivery

Scaffolds made of thermoplastics, and especially hydrogel, are appealing for controlled drug administration because their characteristics may be adjusted during production and they can be implanted, released, and degraded safely. Highly hydrated mesh networks known as hydrogels are created by physically or covalently crosslinking natural, synthetic, or semi-synthetic polymers. Because of their great biocompatibility, drug protection, spatiotemporal control of the drug release, and physicochemical tailorability, this class of materials is employed for local drug delivery (Nairon et al., 2020, Li and Mooney 2016).

7. Biological and Biometric Carriers

7.1. Exosomes and Extracellular Vesicles have garnered a lot of attention due to their mechanical and structural characteristics that are similar to those of many tissues and the extracellular matrix (ECM). Considerable progress has been made in the design, synthesis, and use of these materials for numerous biological and biomedical applications (Rosales and Anseth 2016). Exosomes are tiny, secreted extracellular vesicles (EVs) with a single membrane that are rich in specific proteins, lipids, and nucleic acids. They are created to alter the extracellular matrix (ECM) and transfer signals and useful macromolecules to neighboring cells. They bud at the plasma and endosomal membranes of every mammalian cell type that has been investigated to date. Exosomes' many surface molecules allow recipient cells to absorb them by endocytosis, which is crucial for controlling cell-to-cell communication (Pegtel and Gould 2019). As a result, research on exosomes in the pathophysiology of many diseases is ongoing, and the investigation of therapeutic exosomes as delivery vesicles has provided fresh perspectives for clinical applications in recent years.

One of the most deadly conditions affecting the central nervous system is spinal cord injury (SCI), which causes a temporary or permanent loss of feeling, strength, movement, and bodily functions (Ahuja et al., 2017). The local injection of exosomes shielded by hydrogels is a promising therapeutic approach to address the reduced cell survival caused by the inhibitory environment at the lesion site. Li et al. successfully encouraged spinal cord regeneration and the restoration of hindlimb motor function in vivo by increasing the affinity of HA hydrogels and MSC-derived exosomes by a laminin modification (Li et al., 2020). Remarkably, it has been shown that plant-derived exosomes, such as those generated from ginseng, can stimulate the neural development of BMSCs and can be loaded in GelMA to fill the irregular forms of damage defects (Li et al., 2020). After SCI, angiogenesis is beneficial for the regeneration of neural networks. Motivated by this, Luo et al. immobilized exosomes from M2 macrophages using a hybrid hydrogel system that included GelMA, HA-NB, and a photoinitiator (LAP). The exosomes were shielded from extreme oxidative stress and inflammation by the hydrogel-mediated release mechanism (Shi et al., 2017).

7.2. Cell Membrane-Coated Nanoparticles

Neurological diseases like Alzheimer's, Parkinson's, brain tumors present great challenges to drug delivery. The presence of the blood-brain barrier (BBB) makes most of the drugs very difficult to enter the brain tissue. Traditional drug delivery system often cannot deliver drugs into CNS in the adequate concentration. Cell membrane coated nanoparticle provides an excellent choice to overcome the BBB. Cell membrane derived from specific cells that can transport across BBB is chosen, for example, macrophage cell or stem cell which can interact with brain endothelial cells. Drug loaded nanoparticle with cell membrane coating can be transported across BBB (Hu et al., 2025 and Cheng et al., 2025). Drug can be delivered to the brain target and treat the neurological disease effectively. Furthermore, biomimetic nanoparticle has other benefit such as minimizing neuro inflammation and oxidative stress which are important contributors in neurodegenerative diseases. The drug can be sustainably released which is beneficial for the chronic neurological disease treatment.

7.3. Biometric Nanocarriers

Because molecular hydrogen (H_2) has strong antioxidant, anti-inflammatory, and anti-apoptotic qualities, hydrogen-based medication delivery devices have become a promising

therapeutic approach for the treatment of neuropathy. Molecular hydrogen selectively scavenges dangerous reactive oxygen species (ROS), shielding neurons from oxidative damage. Peripheral neuropathy and neurodegenerative diseases are largely caused by excessive oxidative stress and chronic inflammation. However, hydrogen's short biological half-life and quick dispersion restrict its direct medicinal use. In order to get around these restrictions, scientists have created sophisticated delivery systems that allow for regulated and prolonged hydrogen release at the target region, including hydrogen-loaded liposomes, polymeric nanoparticles, hydrogels, nanobubbles, and metal hydride-based carriers. These administration methods improve bioavailability, increase hydrogen stability, extend circulation duration, and enable targeted delivery to damaged brain areas. In models of diabetic neuropathy, spinal cord injury, and other neurological disorders, preclinical research has shown that hydrogen-based nanocarriers reduce neuroinflammation, inhibit neuronal apoptosis, promote nerve regeneration, and improve functional recovery, indicating significant potential for future clinical applications. By imitating the biological and structural traits of normal cells, biomimetic nanocarriers offer yet another cutting-edge method for targeted medication administration in neuropathy. Usually, natural cell membranes from red blood cells, platelets, macrophages, stem cells, or naturally released extracellular vesicles like exosomes are applied to synthetic nanoparticles to create these nanocarriers. The nanoparticles can engage specifically with sick tissues, prolong systemic circulation, and avoid immune identification thanks to the biomimetic membrane coating. Crucially, these carriers are especially useful for treating neurological conditions because of their improved capacity to pass biological barriers, such as the blood–brain barrier. Neuroprotective medications, antioxidants, anti-inflammatory medicines, growth factors, or nucleic acids can all be encapsulated in biomimetic nanocarriers and delivered with great specificity to injured neurons while reducing off-target toxicity. According to experimental research, these systems improve nerve function in diseases like diabetic neuropathy, peripheral nerve injury, Alzheimer's disease, Parkinson's disease, and spinal cord injury by reducing oxidative stress and neuroinflammation, promoting axonal regeneration, and improving remyelination. Despite the fact that the majority of biomimetic nanocarriers are still in the preclinical stage, they are among the most promising next-generation drug delivery platforms for the treatment of neuropathy and other neurological disorders due to their superior biocompatibility, targeted delivery capability, and therapeutic efficacy.

8. Intranasal and Nose-to-Brain Carrier Approaches for Neuropathic Pain

Intranasal administration offers a unique alternative by enabling direct transport of drugs from the nasal cavity to the brain. The nasal route provides a large surface area, rich vascularization, rapid absorption, and avoidance of hepatic first-pass metabolism (Lofts et al. 2022). Importantly, drugs can reach the CNS through neuronal pathways associated with the olfactory and trigeminal nerves, thereby circumventing the BBB (Wu et al. 2023). Recent advances in nanotechnology have facilitated the development of sophisticated carrier systems that improve drug stability, prolong nasal residence time, enhance mucosal permeation, and achieve targeted brain delivery. Consequently, intranasal nose-to-brain delivery has gained considerable attention for neuropathic pain treatment (Gao et al. 2026).

8.1. Mechanisms of Nose-to-Brain Transport

The nasal cavity serves as a direct interface between the external environment and the CNS. Anatomically, it is divided into vestibular, respiratory, and olfactory regions. The **olfactory region**, situated in the upper posterior part of the nasal cavity, occupies approximately 10% of the human nasal surface and plays a crucial role in direct brain targeting. Several pathways contribute to nose-to-brain drug transport (Xu et al 2024).

A) Olfactory Pathway

The olfactory epithelium contains olfactory sensory neurons whose dendrites extend into the nasal cavity and whose axons project directly into the olfactory bulb. Drugs administered intranasally can enter the CNS through following:

B) Intracellular Transport

Therapeutic molecules are internalized by olfactory neurons via endocytosis or pinocytosis. The compounds are subsequently transported along axons through axonal transport mechanisms toward the olfactory bulb (Minn et al. 2002). Although highly specific, intracellular transport is relatively slow, requiring several hours to days (Liu et al. 2023).

C) Extracellular or Paracellular Transport

Drug molecules diffuse through intercellular junctions surrounding olfactory neurons and supporting cells. They then migrate into the subarachnoid space and brain tissue. This pathway is considerably faster and is responsible for rapid CNS delivery observed with many intra-nasally administered drugs (Cheng et al. 2025)

D) Trigeminal Nerve Pathway

The trigeminal nerve innervates both respiratory and olfactory regions of the nasal cavity. It provides another direct route to various brain regions, including: Brainstem, Spinal cord, Pons and Midbrain. Transport along trigeminal nerve branches may occur via intracellular axonal transport or extracellular diffusion. This pathway is particularly relevant for drugs intended to modulate pain processing within central nociceptive circuits (Lu et al. 2025).

E) Systemic Absorption Followed by BBB Crossing

Some fraction of intranasally administered drugs enters systemic circulation through the highly vascularized respiratory epithelium. Subsequently, these molecules may cross the BBB and access the CNS (Yang et al. 2026). Although indirect, this pathway contributes to overall brain drug concentrations.

F) Lymphatic and Perivascular Transport

Emerging evidence suggests that drugs can move through nasal lymphatic channels and perivascular spaces connected with cerebrospinal fluid (CSF) (Ghosh et al. 2024). This "glymphatic" transport system may facilitate widespread distribution of therapeutics within the brain.

9. Carrier Approaches for Intranasal Delivery in Neuropathic Pain

Many advanced and effective approaches to brain delivery of drugs have emerged in recent years. Intranasal drug delivery is one of the important delivery options for brain targeting, as the brain and nose compartments are connected to each other via the olfactory/trigeminal route and via peripheral circulation. Realization of nose to brain transport and the therapeutic viability of this route can be traced from the ancient times and has been investigated for rapid and effective transport in the last two decades (Misra et al. 2008). Numerous nanocarrier systems have been designed to improve nose-to-brain drug delivery.

9.1. Polymeric Nanoparticles

Polymeric nanoparticles are colloidal carriers ranging from 10–1000 nm in size. They protect drugs from enzymatic degradation and enable sustained release. Polymeric nanoparticles are among the most extensively investigated carrier systems for nose-to-brain delivery. These colloidal systems generally prepared using biodegradable and biocompatible polymers (Nigam et al. 2019, Meher et al. 2023). Drugs may either be entrapped within the polymeric matrix (nanospheres) or enclosed within a polymeric shell surrounding a liquid core (nanocapsules). Commonly employed polymers include chitosan, poly(lactic-co-glycolic acid) (PLGA), alginate, gelatin, polycaprolactone (PCL), and polyvinyl alcohol (Omidian et al. 2024, Nango et al. 2025). Some of the highlighted advantages of using polymeric nanoparticles are enhanced muco-adhesion, prolonged nasal residence, controlled release and improved brain targeting. Chitosan nanoparticles are especially attractive because chitosan transiently opens tight junctions in nasal epithelium, enhancing paracellular transport (Gulati et al. 2013, Omidian et al. 2024).

9.2. Liposomes

Liposomes are spherical vesicular carriers composed of one or more phospholipid bilayers enclosing an aqueous core. Their structural similarity to biological membranes makes them highly suitable for intranasal brain targeting. Liposomes can encapsulate both hydrophilic and lipophilic therapeutic agents. Hydrophilic drugs are entrapped within the aqueous core, whereas lipophilic compounds are incorporated into the phospholipid bilayer. Liposomes are phospholipid vesicles capable of encapsulating both hydrophilic and lipophilic drugs. Their structural similarity to biological membranes facilitates such as, improved membrane penetration, reduced toxicity and enhanced CNS uptake (Assadpour et al. 2022). Intranasal liposomal formulations of analgesics and anti-inflammatory agents have demonstrated significant antinociceptive effects in preclinical neuropathic pain models (Mura et al. 2018).

9.3. Solid Lipid Nanoparticles (SLNs)

Solid lipid nanoparticles are submicron colloidal carriers composed of physiologically acceptable lipids that remain solid at both room and body temperatures. Typical lipid components include glyceryl monostearate, stearic acid, tristearin, and cetyl palmitate. SLNs consist of physiological lipids that remain solid at body temperature. Intranasal SLNs have been developed for several neuropathic pain therapeutics, including anticonvulsants and anti-inflammatory drugs. Enhanced brain targeting and prolonged analgesic responses have been demonstrated. They demonstrated excellent biocompatibility, controlled drug release, improved drug stability and feasibility for large-scale manufacturing. SLNs have been investigated for delivering anticonvulsants such as gabapentin and pregabalin used in neuropathic pain management (Zheng et al. 2024).

9.4. Nanoemulsions

Nanoemulsions are kinetically stable dispersions consisting of oil droplets dispersed within an aqueous phase and stabilized by surfactants. Their droplet size usually ranges between 20 and 200 nm.

Depending on composition, nano-emulsions can be:

- Oil-in-water (O/W).
- Water-in-oil (W/O).

- Bicontinuous systems.

They improve intranasal transport by increasing solubility of lipophilic drugs, enhancing membrane permeation, increasing surface area for absorption and facilitating rapid drug diffusion. Certain surfactants also act as permeation enhancers by altering epithelial membrane fluidity. Intranasal nanoemulsions of opioids, cannabinoids, and anti-inflammatory drugs have demonstrated significant efficacy in neuropathic pain models (Lalani et al. 2015, Chatzidaki and Mitsou 2025).

Conclusion

Neuropathic pain remains a major therapeutic challenge due to inadequate efficacy of conventional treatments and restricted CNS drug delivery. Intranasal nose-to-brain delivery provides a non-invasive, rapid, and efficient means of bypassing the blood-brain barrier and directly targeting the CNS. Multiple transport mechanisms, including olfactory, trigeminal, and extracellular pathways, facilitate brain delivery following intranasal administration. Advanced carrier systems such as nanoparticles, liposomes, nanoemulsions and in situ gels have significantly improved therapeutic outcomes in preclinical models of neuropathic pain. Recent innovations involving surface-modified nanocarriers, exosomes, and smart delivery systems further enhance the potential of this approach. Although substantial challenges remain regarding clinical translation, intranasal nose-to-brain delivery represents a promising frontier in the development of safer and more effective therapies for neuropathic pain.

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