International Journal of Applied Pharmaceutics

ISSN- 0975-7058 Vol 16, Issue 5, 2024

Review Article

THERAPEUTIC IMPACT OF NANOMEDICINE FOR THE TREATMENT OF NEUROPATHIC PAIN: PRINCIPLE, PROSPECTIVE AND FUTURE

INDU MELKANI, BIMLESH KUMAR*, NARENDRA KUMAR PANDEY, SAURABH SINGH, DILEEP SINGH BAGHEL, KAVATALA SUDHAKAR

School of Pharmaceutical Sciences, Lovely Professional University, Phagwara-144411, Punjab, India
***Corresponding author: Bimlesh Kumar; *Email: bimlesh1pharm@gmail.com**

Received: 09 Feb 2024, Revised and Accepted: 03 Jul 2024

ABSTRACT

Researchers in medicine and pharmacology are working to develop more effective and focused painkillers as a result of growing public awareness of chronic pain brought on by disease and injury. On the other hand, overreliance on medically prescribed painkillers has resulted in several unfavorable outcomes, including drug addiction, tolerance, and other severe side effects that can worsen pain and reduce their efficacy. Drug delivery has benefited from the use of nanotechnology in reducing adverse effects, increasing therapeutic efficacy, and delaying tolerance development. Neuropathic pain is pain that develops as a result of nerve malfunction as well as damage to the somatosensory nervous system. The exact cause of neuropathic pain is not specifically clear. However, many factors, including spinal cord damage, Chronic Constriction Injury (CCI), diabetes, cancer, alcoholism, and trauma, can cause neuropathic pain. There is no doubt that we have many options for conventional treatment, yet either very few patients receive pain relief, or their pain relief is only momentary. Numerous nanocarrier varieties and the accompanying neuropathic pain treatment modalities were also examined. These forms included those based on nonpolymeric nanoparticles, polymeric micelles, lipids, and emulsions. Comparing nanomaterials to other forms of therapy for chronic pain, there are several benefits: reduced side effects, regulated release, and prolonged circulation. Alongside nanotechnology, approaches to treating chronic pain are surface-modification-based and employ a variety of nanoparticles. The current state of the pain-relieving effect of nanomaterial design is covered in the present review article.

Keywords: Neuropathic pain, Bioavailability, Nanomedicine, Nanocarrier

DOI: https://dx.doi.org/10.22159/ijap.2024v16i5.50457 Journal homepage: https://innovareacademics.in/journals/index.php/ijap

INTRODUCTION

Now-a-day Neuropathic Pain (NP) is becoming a global burden of disease as it measures the degree of disability, unbearable pain, and premature death [1]. In several systemic reviews and various meta-analyses, it was found that the patient with the NP has a lower quality of life. Depression, anxiety, and low sleep were found in people suffering from NP. This led to an unsolved argument about whether pain causes these diseases or whether these diseases are the signs of developing a risk of pain [2]. Hence NP is a major health problem in today's society and needs proper attention to provide sufficient relief. NP is defined as pain due to nerve damage and these damages are associated with the damage of sensory nerves as well as motor nerves. These damages are involved in the signaling pathway [3]. It directly affects the somatosensory system. About 3-17 % of the population is affected all over the world [4]. This is further sub-categorized into peripheral and central NP. As the name suggests "peripheral neuropathic pain" is the pain that occurs due to damage of the nerves except the brain and spinal cord. The damage to nerves caused by people suffering from diabetes mellitus is an example of peripheral neuropathy [5]. Central neuropathic pain is the pain caused by damaged nerves of the Central Nervous System (CNS-brain and spinal cord). An example of this type of pain is stroke, which is caused due to injury in the spinal cord, brain injury, multiple sclerosis, cardiovascular diseases, etc [6]. Four routes are involved in the NP process. When a stimuli attack, sometimes referred to as a noxious stimulus (which might include a mechanical, thermal, or chemical stimulus), it first becomes a nociceptive signal. Transduction is the term for this action. It is followed by transmission, which involves the transport of noxious signals from the spinal cord to the brain [7]. The following route is transduction. It is a method by which the central nervous system and synapses modify nociceptive signals. Perception, the final channel, is where the emotional response is noticed. Although it is unclear exactly how the brain produces pain.

Mechanism of development of neuropathic pain

The pain from neuropathy is further divided into central and peripheral pain and their distinct mechanism of development are indicated in the fig. 1. Peripheral neuropathy develops when pathologic active or sensitized nociceptors can induce secondary changes in central processing, nociceptor function may be selectively impaired within the allodynic skin, persistent inflammatory reactions affect the nerve trunk and after nerve lesion, the sympathetic nervous system might interact with afferent neurons. These all contributing events cause damage to Aβ-fibers and C fibers. RAS pathway is also one of the major factors. Dorsal Root Ganglia (DRG) and dorsal horn activation of the Mitogen-Activated Protein Kinase (MAPK) family is a result of peripheral nerve damage, along with neuropathic pain. Following nerve damage, wounded big DRG neurons, microglia, astrocytes, and neurons in the dorsal horn and gracile nucleus phosphorylate Extracellular Signal-Regulated Protein Kinase (ERK), an important member of this family [8]. Substance P and calcitonin gene-related peptides, as well as excitatory neurotransmitters like glutamate, are released from primary afferents in a markedly increased amount after peripheral nerve injury. Furthermore, it has been shown that nerve damage increases the expression of Brain-Derived Neurotrophic Factors (BDNF) in DRG neurons. Nociceptive sensory inputs and NMDA-evoked responses are linked to increased BDNF release in the dorsal horn. There is evidence that BDNF has a role in the emergence of neuropathic pain.

When a peripheral nerve is damaged, NP can manifest in many ways. Numerous chemical compounds, including substance P, globulin, arachidonic acid, and histamine, are released when a nerve is damaged. The threshold of sensory fibers decreases as a result of the release of numerous chemicals, which leads to peripheral sensitization. It is followed by hyperexcitability and axonopathy, which cause aberrant distributions as well as the expression of the sodium ion channel [8, 6]. The damage that occurs in the nerve present in the CNS causes pain even after the injury has healed [9]. In addition to peripheral sensitization, neural sensitization, which results in cell death, was discovered at the spinal level. A shift in calcium permeability results from an increase in sensitivity. Numerous recent investigations have shown that interactions between microglial cells and neurons can lead to a variety of pathogenic diseases. Microglial cells will be activated, releasing many pain-promoting chemicals. Chronic pain was created as a result of altered plasticity [10].

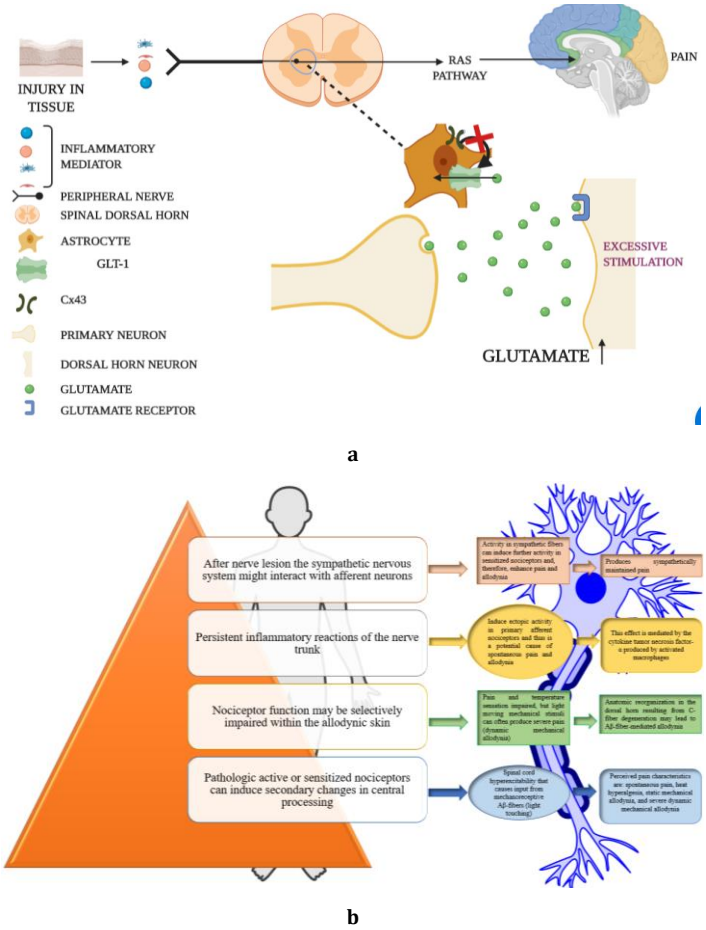

Fig. 1: a. Mechanism of neuropathic pain b. Neuropathic pain development and its symptoms

It is commonly assumed that a single etiological factor causes NP in a uniform way [11–13]. But it is important to note that various environmental and genotype factors, also contribute to the development of NP, which follows different pathophysiology and results in the neuropathy syndrome as shown in fig. 2. The nervous system's maladaptive reaction to injury is neuropathic pain. Allodynia (pain in response to a harmless stimulus), hyperalgesia (increased pain reaction to a noxious stimulus), spontaneous pain (electric shock-like or shooting pain), and, sporadically, causalgia or constant searing pain are among the warning signs and symptoms [14–16]. Due to neurogenic inflammation and/or pathologic cross-talk between the sympathetic and sensory systems, neuropathic pain is also present in complicated regional pain syndromes I and II [17]. For any of the aforementioned causes, neuropathic pain is frequently referred to as the "disease of pain." Changes in regular sensory signaling that take place over weeks or months at the level of the peripheral nervous system, spinal cord, and brain (thalamus and cortex) are indicative of neuropathic pain. These result in different cortical architectures and changes to genetic expression [18].

As a result, neuropathic pain's pathophysiological modifications at its inception are different from those that cause it to manifest as chronic pain. When seeking to connect research from animal models with how pain manifests in the clinic, the distinction between the onset phase and the maintenance phase of neuropathic pain becomes very important. The long-term persistence of pain, which is more relevant to the clinical condition, is not addressed in many animal research; instead, they focus on the beginning of pain [19, 20].

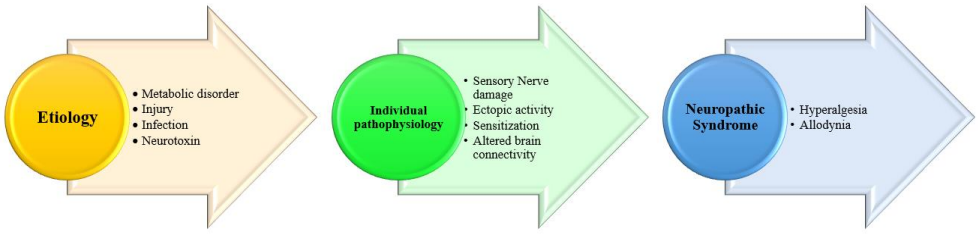

Fig. 2: Schematic representation from various etiology to neuropathy syndrome

A few of the several illnesses connected to this pain include diabetic neuropathy, vitamin deficiency-induced neuropathy, traumatic nerve injury, post-hepatic neuralgia, and alcohol-induced neuropathy. These illnesses are the result of numerous environmental and genetic factors, such as food and lifestyle selections [21]. The NP signs and symptoms might vary greatly. It has three distinct characteristics: tingling, burning, and shooting. The terms "tingling" and "shooting" both refer to pricking

sensations. Numerous articles have been published, and multiple screening instruments have been developed, including the Michigan Neuropathy Screening Instrument, the Neuropathic Pain Scale, and the Neuropathic Pain Questionnaire [7]. The permeability of the blood-brain barrier has been discovered to vary as a result of neuropathic pain. This is due to the activation of the astrocyte and microglial cells as well as the overexpression of certain biomarkers [22-24].

Despite the benefits of employing nanomaterials to encase medications for the treatment of chronic pain, their insufficient efficacy has highlighted the urgent need to create more effective alternatives. Since there are numerous potential causes of chronic pain, different therapy interventions call for different drug types and dosages [25]. One strategy to boost treatment effectiveness and reduce side effects off-target is to increase the drug's concentration at the targeted site of action. To achieve this site-specific targeting, targeting agents like peptides and antibodies can be used to modify nanomaterials [26]. For the use of these targeted substances in the relevant chronic pain models, the route of delivery is also a crucial factor. For instance, exposed locations of chronic pain on the skin can be topically treated with a smear or spray, whereas chronic spinal nerve pain is better treated with an injection via the dorsal root ganglion [27]. Depending on the cause and location of the pain, internal injuries or diseases may benefit from oral, intranasal, intramuscular, or intravenous injections. Due to this, the nanoformulation of drug delivery shows a positive response in the treatment of NP [28, 29].

Roadbacks in conventional treatment approach

Health practitioners frequently employ traditional therapy. The use of these therapies in NP is constrained by their numerous negative effects. There is currently no accepted protocol for treating NP. The existing treatments had some negative effects and had moderate efficacy. To manage NP, analgesics, the installation of an intrathecal pump, and occasionally physical therapy are indicated [30]. The first line of treatment for the NP is a Tricyclic Antidepressant Drug (TCA) (Amitriptyline) and Serotonin reuptake norepinephrine inhibitor (Duloxetine, venlafaxine). It was found that TCA can develop a cardiotoxic effect in the neuropathic pain patient [31]. Anticonvulsant drugs like gabapentin and pregabalin were also considered the first-line drug of choice [32]. This anticonvulsant drug may enhance the suicidal risk if given in an NP [33]. Urinary retention, arrhythmia, and anticholinergic effects are some of the common adverse effects that were observed. Opioids (tramadol) and topical drug (lidocaine), which is the second line of treatment, also possess adverse effects like a seizure, ataxia, local erythema, and itching [34]. The last treatment, which is the third-line therapy, was a neurotoxin (botulinum toxin) and strong opioid (morphine) that causes constipation, lethargy, and dizziness. Some common adverse effects like nausea, vomiting, lethargy, and vertigo which was mild and observed in almost all therapy. The uptake of serotonin reuptake inhibitors may also cause side effects if used for a longer period. There was also an Intrathecal Drug Delivery System (IDDS) that was used to treat the NP. But this system also possesses side effects like injury in the nerve, anticoagulation, and respiratory depression. At the site of surgery, local infection was also found [35]. These substantial shortcomings of currently existing medications have caused drug development to shift its attention to enhancing drug targeting, minimizing side effects, and extending the release of active ingredients. Hence, to enhance the treatment efficacy and to increase the duration of pain relief Nanomedicine emerged. It also served as a novel way for the treatment of NP.

Requisite for novel nanomedicine-based therapeutic strategy

Even so, treating NPs effectively and appropriately presents a significant medical problem. Modern formulations are difficult to make consistently due to their quick metabolism, and the necessary dosage can have poorly tolerated physical adverse effects. A significant step in developing more potent medications for chronic pain with fewer side effects has been the integration of pharmacological sciences with nanotechnology. Nanomaterials are designed to be a. highly biocompatible [36] b. loaded with drugs more effectively than conventional formulations [37], c. can preserve the stability of protein-based drugs [38], and can sustain controlled release with prolonged circulation time [39]. The nano drug delivery technology has many advantages over traditional medication delivery. It was starting to emerge as a new area for scientific investigation and technological growth. It is a form of technology that makes use of diverse objects and materials on a nanoscale. These had numerous applications in a variety of industries. [40]. Nanomedicine is one of the branches of nanotechnology. The best application of its use was in biotechnology and health. It serves a wide range of applications to serve a good quality of health for future society. It was formulated and then encapsulated by the nanocarrier (10-200 nm). Nanotechnology and medicine were joined and brought together to develop a novel therapy and also to improve the already existing treatment [41]. In Nanomedicine the atom and the molecule are used and manipulated and nanostructure is formed. This nanostructure is about the same size as the biomolecule present in human cells for interaction [42]. Nanomaterials have been created specifically for the targeted delivery and release of painkillers in the field of treating chronic pain. Doxil, the first nano drug approved by the Food and Drug Administration (FDA), served as an inspiration for the development of numerous other biomedical applications, but with a limited focus on the treatment of chronic pain [43–45]. One of the most diverse areas of research is drug delivery. Additionally, it is changed as necessary. The development of a drug delivery system is the result of several different circumstances. These results were acquired *in vivo* using a traditional drug delivery method. Poor solubility and absorption, an increase in metabolism, and an increase in dry plasma level volatility are a few examples. Due to the usage of lipids as a carrier, medicine delivery has changed during the past few decades [46]. The nanoscale-based delivery approach is starting to have a significant impact on pharmaceutical marketing and planning on a worldwide basis. The word "nanocarrier" refers to a broad spectrum of nanoparticles that are utilized in delivery systems as a means of transport. Based on their constituent parts, nanomaterials can be classified as organic, inorganic, or metal-organic [47, 48]. To reduce side effects and increase the effectiveness of pain medication treatments, all three types of nanomaterials have been employed as controlled-release delivery systems [49]. Both free molecules and protein-based medications can be enclosed in nanomaterials to enhance blood circulation time with sustained, regulated release, leading to long-lasting pain alleviation with few adverse effects. The biocompatibility of the suggested nanomaterial should be a primary issue before putting it into a clinical application. Consequently, researchers typically start by looking at nanomaterials that have previously received FDA approval [48, 50, 51].

BBB (blood brain barrier) and nanoformulation

As we've just discussed, NP alters how permeable the BBB barrier is. Opioids were frequently prescribed as traditional neuropathic pain medications. The ability of an opioid to cross the BBB determines how it reacts to pain. In the BBB, a p glycoprotein receptor can be found. This receptor controls the flow of opioids from the brain into the blood. Tolerance to opioids is caused by a rise in the quantity of the p glycoprotein receptor during prolonged use [52]. BBB thus creates a barrier to the delivery of CNS drugs. Approximately 95% of CNS medication delivery was ineffective at penetrating the BBB [53]. There have been several attempts to solve this issue. either through a surgical procedure or a nonsurgical one. But each step had a particular obstacle. Due to the admission of non-specific substrates in non-surgical processes and the possibility of brain toxicity, maintaining an accurate dose was crucial in surgical processes [54, 55].

A more contemporary method was developed by using nanomedicine, which, if properly built, will increase the capacity to enter the BBB and release the drug to demonstrate its pharmacological reaction. The unique features of nanoparticles are their small size and biocompatibility [56]. Three different types of nanoparticles pass through the BBB in three different transport mechanisms shown in fig. 3. These transport mechanisms are caveolin-mediated endocytosis, receptor, and cell-mediated.

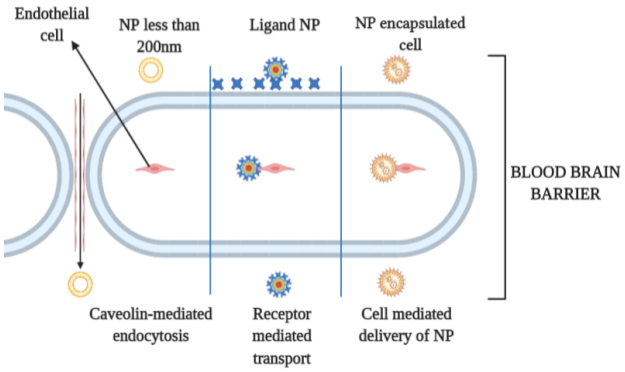

Fig. 3: Different properties of NP crossing the BBB by different transport mechanisms

Nanocarrier for NP

Drug delivery systems using colloidal particles smaller than 500 nm are known as nanocarriers. To deliver the medicine to the target site with reduced systemic toxicity, these carriers are frequently utilized. The properties of the nanocarrier include an improvement in pharmacokinetics, biodistribution, solubility, and stability [57]. Delivering a therapeutic material to a specific location with regulated release is a key characteristic of nanocarriers. Due to the numerous functional components on the nanocarrier's surface, the medicine is transported to the desired location (fig. 4) [58].

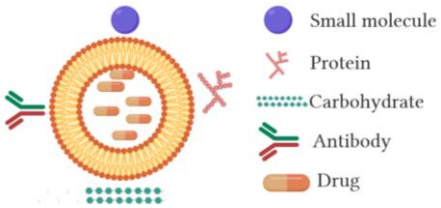

Fig. 4: Structure of multifunctional nanocarrier

To get the drug molecule to the site of action, they include proteins, tiny molecules, carbohydrates, antibodies, and many more substances. The main objective of this is to treat any disease or NP with minimal or no side effects and for a longer time [59]. Various nanocarrier-based products, such as lipid-based nanocarriers, polymeric nanoparticles, and emulsion-based carriers, were used to alleviate neuropathic pain. A variety of research studies were also conducted using various types of drugs that become trapped in nanocarriers, and successful pharmacotherapy outcomes were reached. Every study using nanocarriers sought to increase the bioavailability of the medicine as well as transport it to the target region with little harm. The adverse reaction that was discovered to be connected with this will also be managed since by enhancing this property, the dose quantity required will also decrease [60].

The drug delivery carriers commonly used for NP

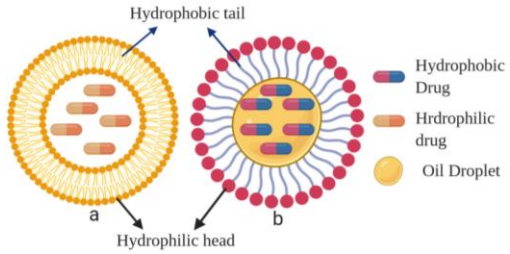

Fig. 5: (a): Structure of liposome, (b): Structure of oil in water nanoemulsion

Lipid-based carrier

Lipids are the fundamental component of biological membranes, as is well known. The potential of lipid to increase the bioavailability of drugs that are weakly water soluble and lipophilic is what distinguishes it from other substances. As a result, it is frequently utilized as a drug carrier for both hydrophobic and hydrophilic drugs. The drug carrier in the biological system made use of the massive protein structure. The spherical shape of a liposome comprises an aqueous pore that is encircled by a lipid bilayer (fig. 5a).

Liposomes were discovered in 1965 by Alec. D. Bangham for the treatment of neuropathic pain in cancer therapy [61]. The hydrophilic drug is found to be present in the lipid membrane as well as the hydrophilic drug, which is loaded in the aqueous layer of the liposome [62]. They are one of the greatest therapeutic carriers due to their composition, which is non-toxic, biodegradable, and biocompatible. Since it shares characteristics with human cell membranes, the contact between liposomes and cell membranes is successful [63]. There was a wide application of liposomes in the formulation of biomedicine. Mostly the liposome was prepared by the process of sonication of the amphiphilic lipid in water [64]. In this process, some of the biological molecules get destroyed [65]. There is a wide use of the liposome as a nanocarrier for the treatment of NP [66, 67]. The next generation of nanomaterials is concentrated on a variety of tunable features, including size, surface properties, responsiveness, controlled circulation time, high loading efficiency, and the ability to target particular tissues. Although liposomes have many benefits and profit from established synthesis techniques, they lack many of the features that distinguish the next generation from current nanomaterials. For their capacity to transport cannabinoids orally, [68] contrasted PEG-modified lipid nanoparticles with chitosan-modified lipid nanomaterials and PLGA nanomaterials. The three biocompatible nanoparticles had varying performance, which served as design requirements for the creation of nanomaterials for the transport of painkilling drugs [68].

Some of the NP treated by the use of liposomes were discussed in table 1. In one study, the mouse model of CDI had the medication zoledronic acid encapsulated in a liposome with a size range of 240 nm. It was discovered that, despite the drug's concentration remaining the same, mechanical allodynia was eased for a longer period than it was with free zoledronic acid. This is primarily because medication encapsulation on lipids lengthens the duration of action by increasing bioavailability [48]. Numerous other medications, including Clodronate, dexamethasone, and morphine, were also encapsulated in liposomes of various sizes, and each one demonstrated an efficient pharmacological response. In addition to all of these benefits, these liposome formulations improve medication circulation in the blood. Additionally, it was utilized in gene therapy. One study demonstrates that the administration of carbon monoxide prevents the production of cytokines mediated by Lipopolysaccharide (LPS). Both cytoprotective and anti-inflammatory properties are present. The CORM-2 molecule, which is produced by carbon monoxide and reduces neuropathic pain, exists. The lipid nanoparticle included CORM-2, which proved successful in reducing the neuropathic pain brought on by CCI [69].

It is very interesting to note that Reactive Oxygen Species (ROS) that are produced in excess at inflammatory locations can lead to chronic pain; as a result, nanomaterials that absorb ROS are a viable method for relieving pain [70, 71]. To protect inflammatory regions and alleviate pain, used fullerol nanoparticles, which are known to consume ROS [72, 73].

Emulsion based carrier

A single phage solution is created by combining two insoluble, immiscible liquids into a nanoemulsion with the aid of an emulsifying agent. A surfactant or emulsifying agent aids in maintaining the stability of the emulsion [42]. In this the dispersed phage (vesicle) gets itself, surrounded by the continuous phage [74]. Fig. 5b's depiction of an oil-in-water emulsion shows how the oil behaves as a scattered phage and the water as a continuous phage. Many emulsion formulations were used in drug delivery systems where the particle size requirement was less than 200 nm. The medicine was delivered via a non-aqueous phage in this example [75, 76]. In a recent study, it was found that one of the plant components *Bauhinia variegata,* was loaded under nanoemulsion. The use of the ultrasonic emulsion method was done to incorporate the component. The hyperalgesia and allodynia were evaluated by the radiant heat planter and Ven frey test simultaneously. The result obtained was effective and also satisfying. It results in lower blood glucose levels and also prevents any progress for diabetic neuropathy. Hence the BVN was proven as an effective formulation for diabetic neuropathy [77]. Numerous medications can be packaged as nanoemulsions and exhibit their pharmacological effects. Table 1 lists some of the recently examined medications. The nanoemulsion also underwent vitro research, which indicates that it can alleviate NP. In one such study, phenytoin was used as a medicine that was encapsulated in a nanoemulsion formulation and showed an instant response as well as a sustained action. Since free phenytoin has a solubility issue, it was avoided [78]. Lidocaine@PLGA, a microcapsule made of polylactic acid and glycolic acid that responds to ultrasound, is used to treat sciatica nerve pain [79]. According to studies, applying ultrasound as a trigger switch could encourage the quick release of lidocaine from the microcapsules, achieving the dual effects of long-term sustained release and short-term ultrasound-triggered rapid release. This could allow the use of ultrasound-responsive Lidocaine@PLGA microcapsules for nerve root block and postoperative pain relief [80, 81].

Table 1: Nanocarrier for treatment of NP

Nanocarrier system	Drug	Model used (Animal)	Molecular mechanism	Pharmacological response	Size (nm)	Ref.
Liposome	Clodronate	STZ (Wistar rat)	Decreasing the peripheral monocyte or macrophage	Decreases mechanical allodynia	-	[82]
Liposome	Clodronate	SNL (Wistar Rat)	• Decrease the microglia • Reversely block the antinociception of the GLP-1 agonist	Reduces the starting of the pain	300 nm	[83]
Liposome	Capsaicin	SD Rat	Desensitizes the nociceptive sensory nerve-ending	Improve oral bioavailability	52.2	[84]
Liposome	Dexamethasone and sexitoxin	SNL (CDI mice)	Blocks the site 1 of the sodium channel	Delay the onset of allodynia for one month	5. 4µm	[85]
Liposome	Morphine or Oxymorphone	SNL (SD rats)	Hydrolyzed easily to 6-hydroxy metabolites of hydromorphone	Restricts hyperalgesia up to a 7 d	29µm	[86]
Liposome	Bupivacaine	-	Decreases inflammation, block pain receptor	Prevent NP and central sensitization	-	[87]
Liposome	Hepatocyte growth factor gene	CCI (Wistar Rat)	Reduces level of P2X3, P2X4, and P2Y1 receptor mRNAs, interleukin-6 (IL-6)	Transfer of the HGF gene in the nervous system with less damage to sensory nerve	300 nm	[88]
Liposome	Verbascoside	CCI (SD rat)	Inhibiting the protein kinase inhibitor.	Prolong antihyperalgesic effect	120.15	[89]
Liposome	BDNF Binding domain of TrkB (e TrkB protein)	SNL (Wistar Rat)	• TrkB and BDNF binding causes the activation of PI3K, ERK, and PLCY. • Nanoformulation suppresses BDNF-TrkB pathway	Treat mechanical allodynia and hyperalgesia	-	[90]
Nanoemulsion	celecoxib	SNL (Wistar rat)	Decreases mast cell and macrophage Decreases COX-2 and prostaglandin E2.	Relieved pain with 24 h of surgery, which last for 6 days	-	[91]
Nanoemulsion	celecoxib	CCI (SD rat)	Reversal of gene in NP	Decrease in Inflammation and mechanical allodynia		[92]
Nanoemulsion (SNEDDS)	Curcumin	Diabetic neuropathic model (SD rat)	Decreases COX-2, TNF-alpha and IL-6	Longer duration of action of drug due to increase in bioavailability and treat the symptoms of NP		[93]
Nanoemulsion	Pyrazoloquinolinone (DK-I-56-1)	CCI (Wister albino rat)	Acts on GABA receptors and reduces inflammation	Reduced trigeminal NP Reduction in NP symptoms	10-300 nm	[94]
Nanoemulsion	Capsaicin (Topical cream formulation)	Wistar rat and male rabbit	Decreasing the substance P	Enhanced analgesic as well as anti-inflammatory response.	13-14	[95]
Nanoemulsion	Doxepin	Sprague Dawley Rat	Bind to histamine H1	Potent analgesic property	6.1	[96]

Polymeric nanoparticle (PNP)

The size range of Polymeric Nanoparticle **(**PNP) colloidal particles is 10-1000 nm. There are two components to it. The hydrophobic character of the core contrasts with the hydrophilic nature of the surroundings. The stability of nanoparticles in an aqueous environment is aided by this outer layer. These are the containers in which the medicinal substances are dispersed and trapped in the polymer matrix (fig. 5a) [97, 98]. These are produced using many materials, including natural, synthetic, and semi-synthetic ones. Different techniques were employed to create polymeric nanoparticles. Some of these techniques, such as double emulsion, emulsification, and emulsification-solvent evaporation, were often employed. Additionally, it was prepared to utilize two methods: Technology involving supercritical fluids and nanoprecipitation [99, 66]. Because of its biocompatibility, target site of action, biodegradability, and ability to release drugs in a controlled and sustained manner, PNP is a good and useful nanocarrier in the field of medicine [100]. The medication is essentially trapped by two processes: chemical conjugation and physical entrapment. The drug molecules will be trapped in the matrix by this carrier, preventing further enzymatic breakdown. The most widely used polymer is PLGA, which was given the go-ahead for parenteral administration by a drug and medical organization. It enables the medicine to cross the blood-brain barrier, which is an efficient method of treating CNS diseases [101]. Bupivacaine was entrapped in the PLGA nanocarrier

by the L3 and L4 DRG injection in one of the studies. It has been discovered that this lessens the impact of neuronal hyperexcitability. Numerous additional medications were capsuled and produced great results [102]. Due to its biocompatibility, and low toxicity, they are used as a carrier. It also has the capacity to load a combination of hydrophilic and macro-molecular drugs (protein, antibodies, growth factor, etc.). They possess the potential to deliver the drug to various target organs [103].

Types of polymer

Polymers used in nanoformulation are of three types. They are natural, semi-synthetic, and synthetic [104].

Natural polymer: When an organism was going through its growth cycle, this polymer was created. Two different types of reactions are used in the creation of natural polymers, which are created inside of cells through intricate metabolism. A chain growth reaction and an enzyme-catalyzed reaction are the two types of reactions. Corn, cellulose, potatoes, and other natural resources were used to create the natural polymer. The source can also be created synthetically from a bacterial microbe that produces polyhydroxy butyrate from butyric acid. Animal sources, in addition to natural and microbiological sources, also contribute. the chitin, protein, and other components of animal sources [105]. The nature of this polymer is hydrophilic.

Semisynthetic polymer: A suitable reagent is used to transform the natural polymer into a semi-synthetic polymer. In biomedical devices and pharmaceutical technology, semi-synthetic polymers like cyclodextrin, modified dextrin, and chiton are employed [106]. The hydrogen group in the CD was changed to customize the natural cyclodextrin. This alteration improves solubility and stability and reduces toxicity [105].

Synthetic polymer: Using a combination of biomass, oil, and petroleum, this polymer was created. This has a hydrophobic nature to it. There are two further subcategories inside it: biodegradable and non-biodegradable. Polycaprolactone, a petroleum-based synthetic polymer, was the most widely used biodegradable material. However, numerous different polymers are utilized in the medical industry. Polylactic acid, polyglycolic acid, polylactic glycolic acid, and poly-e caprolactone are among them [105].

Type of polymeric nanoparticle based on structure

The structure of polymeric nanoparticles is another category used to group them. Nanosphere and nanocapsule are two examples (fig. 6b and 6c) [107]. Both their origins and their inclinations are different from one another. The polymer matrix used to create the nanospheres allows the polymer to either soak onto the surface or become stuck within the matrix. It is constructed of a dense matrix polymer, in which the medicament is evenly distributed. The medication molecule is trapped inside the nanocapsule's vascular system, which creates an internal reservoir. The outside shell is covered with solid, and the core is comprised of liquid water or oil. The thin layer of polymeric membrane covers the core of the nanocapsule. Both types of polymeric nanoparticles are used in medicine. However, nanocapsules have an edge over nanospheres. The medicine is integrated into nanocapsules in both solid and liquid form as a molecular dispersion. Less toxicity is there when there is less polymer [105].

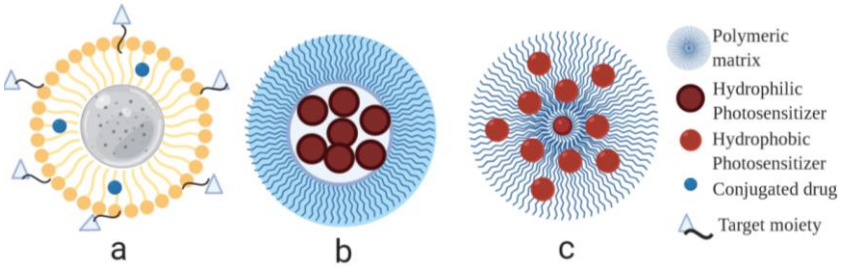

Fig. 6: (a): Structure of polymeric nanoparticle, (b): Structure of polymeric nanocapsule, (c): Structure of polymeric nanosphere

Nefopam hydrochloride loaded nanosphere.

Nanospheres were used in only a few formulations hence, their application is very restricted. One of the studies involved the medication Nefopam Hydrochloride (NFH), which was first made into nanospheres and used [108]. The free medication from NFH was also used to treat post-operative shivering and NP. It works by preventing the reuptake of dopamine, serotonin, and noradrenaline, which also has an analgesic effect. The unfavorable reaction includes nausea, vomiting, and dizziness. However, the main issue is patient non-compliance because it is administered so frequently (almost 3–4 times per day). The quasi-solvent diffusion approach was used to create the NFH-loaded nanosphere. Following that, the box-Behnken design optimized this. This design of the experiment provides a piece of precise information about the development of nanoformulations [109, 110]. The Wistar rat chronic constriction injury model was then given NFH-NS, and a sustained releasing action was seen. The limited oral bioavailability of NFH is one of the main issues it encounters.

Nanocapsule

In comparison to nanosphere, nanocapsule offers a wider range of applications. The Organoselenium Molecule [(OMePhSe)2] known as p, p'-methoxyl-diphenyl diselenide, exhibits an antinociceptive effect. But when this is contained in a nanocapsule, the compound's potency is increased. The purpose of the study was to determine if free (OMePhSe)2 administration or encapsulated (OMePhSe)2 administration may lessen the discomfort associated with sciatic nerve ligation surgery. (OMePhSe)2 was administered to mice in the Partial Sciatic Nerve Ligation (PSNL) paradigm both free and in nanocapsule form. Both treatments were shown to attenuate PSNL-related hyper nociception, while the nanocapsule (OMePhSe)2 was found to boost antinociception by a factor of two over the free (OMePhSe)2 [111]. Another study found that paclitaxel, a chemotherapy medication that causes peripheral neuropathy, can treat neuropathic pain syndrome when it is encapsulated. In a recently completed study, paclitaxel nanoparticle-encapsulated medication was given to a model of peripheral neuropathy brought on by paclitaxel. PTX and nPTX were intraperitoneally injected, and neuropathic pain and any neuronal damage were observed by an immunohistochemistry investigation of its behavior. It was discovered that nPTX has a lower threshold for nociceptive pressure. Dorsal root ganglion degeneration was lessened. Consequently, the paclitaxel nanoparticle's encapsulation aids in the treatment of PTX-induced peripheral neuropathy [112].

Polymeric self-assembled carrier

Self-assembly is defined as the spontaneous molecular arrangement in a properly ordered structure. The process of self-assembly plays an important role in the designing, and synthesis of new nanomaterial. This self-assembled carrier was designed such that the inner core is hydrophobic and the outer shell is hydrophilic. Due to this amphiphilic characteristic, it has the potential to carry a drug molecule also. It also has a good distribution property [113]. This carrier was efficiently used for drug delivery systems and diagnosis purposes. They are termed the bioactive molecule in the

pharmaceutical industry. A drug is said to have an ideal drug delivery system if it possesses biocompatible, biodegradable scaffolding properties, and low toxicity. The self-assembled polymer possesses all the above features [114].

Polymeric micelles

Polymeric micelles were a novel drug carrier system. Polymeric micelles are used for the delivery of poorly soluble drugs. As compared to the other drug nanocarriers the polymeric micelles have a benefit of a very small size range of 10-100 nm [115]. This micelle is of three types based on the intermolecular driving force. They are hydrophobically assembled amphiphilic micelles, micelles stemming from metal complexation, and polyion-complex micelles [116]. They contain different shapes, such as rods, vesicles, spheres, etc. Their shape depends on the hydrophobic and hydrophilic block and also the environment of the solvent. Poly Ethylene Glycol (PEG) was the most commonly hydrophilic micelles, which were used for drug delivery. This PEG has a molecular weight of 2-15 kDa and is water soluble. It is charged naturally and also nontoxic. It also increases the circulation time by forming a hydrophilic layer on the surface of the micelle. Not only PEG, but other polymers like Poly (N-vinyl pyrrolidone) (PVP) were also in use for the same hydrophilic part of the micelles. The polymer was used as the hydrophobic domain, such as polylactic acid, which is a polyester, and poly (l-lysine), which is a polyamide. In polyester and polyamide, the enzyme catalyzes hydrolysis, and they are considered biodegradable. Lipid was also in use in the hydrophobic core [116].

Polymeric micelles were also helpful in the treatment of neuropathic pain, which is a major clinical challenge nowadays. We know that the agonist of the cannabinoid receptor was effective in reducing neuropathic pain. A Styrene Maleic Acid (SMA) is encapsulated with the cannabinoid WIN 55,212-2 (WIN) and forms micelles known as SMA-WIN micelles. When this formulation was injected into the chronic construction injury model of sciatic neuropathy, it was found that there was a decrease in the neuropathic pain for a prolonged duration as compared to the control, which is only WIN; hence, prolonged drug release was observed. Another recent study was done, which showed that one of the micelles, named phospholipase A_2 inhibitor-loaded phospholipid micelles, decreases neuropathic pain. In general, the secretory phospholipase A_2 is an inflammatory mediator enzyme that tends to increase in the spinal cord when there is compression in the root of the nerve. However, a micelle was formed by loading the phospholipid with the Secretory Phospholipase A_2 ($sPLA_2$) inhibitor. The phospholipid micelles will help by releasing their payload in the presence of $sPLA_2$. A rodent model of neuropathic pain was used and these formed micelles were injected intravenously or locally at the site of injury. It was observed that after administration of micelles formulation, which was given immediately after the compression, the pain was relieved for 7 days which was less in the case of delayed administration. Hence it was concluded that the secretory has anti-inflammatory properties for neuropathic pain treatment [117]. There is a wide range of drugs which was formulated into Nanoformulation to show effective results. A small glisp of some polymeric nanoformulations which are used to treat and alleviate neuropathic pain are listed in table 2.

Table 2: Polymer-based nanocarrier for treatment of neuropathic pain

Nanocarrier system	Drug	Models used (Animal)	Molecular mechanism	Pharmacological response	Size (nm)	Ref.
PLGA nanocarrier	Cannabinoid	CCI in SD rats	Stimulates the lymphatic transport and enhances the bioavailability	Maintain analgesic activity up to 7 d	200 nm	[118]
Double Emulsion (W/O/W)	P38 Si RNA	SNL in SD rats	Inhibiting the microglia activation in the dorsal spinal horn	Reduce mechanical allodynia	153.1	[119]
PLGA Nanocarrier	Bupivacaine	CCI C57BL/6 mice	Reduces neural excitability	Prevent the development of allodynia and hyperalgesia	150	[102]
PLGA Nanoparticle	Baclofen Nanoprecipitation method	Cytotoxic assay, Gamma scintigraphy	Suppresses excitatory neurotransmitter	Drugs remain in the brain for a longer duration	124.8	[120]
PLGA Nanoparticle	Lamotrigine Nanoprecipitation method	PSNL Swiss albino mice	Sodium and calcium channel blocker	Increases duration of action, and bioavailability and decreases the accumulation of drug	141. 1-158	[121]
PLGA Nanoparticle	Foxp 3 plasmid	SNL in SD rats	Up-regulation of anti-nociceptive gene and down-regulation of pro-nociceptive gene in spinal dorsal horn	Alleviate the NP	224	[122]
Polymeric Nanoparticle	p,p′-methoxyl diphenyl diselenide Solvent displacement	PSNL Swiss mice	Decrease inflammatory protein content.	Prominent antinociception	N/A	[111]
Polyester Nanoparticle	Paclitaxel	PIPN Sprague–Dawley rats	Improves density of neuronal maker, Decreases the TUNEL positive cell	At low concentrations treat NP	262	[112]
poly-pegmadmaema-mao	Curcumin	Type 2 diabetic mellitus	It acts by decreasing the IL-1β, Cx43. There is also up-regulation of P_2Y_{12} which activates the SGC	Reduces the mechanical and thermal hyperalgesia	N/A	[123]
Porous polymersome	Superoxide dismutase	Nerve root compression	Improve the antioxidant nature	Enhances the therapeutic efficacy for longer duration	108	[124]
PLGA Nanoparticle	Amitriptyline Doxepin Imipramine	Sprague Dawley rat	Blocking the pain pathway	Increase in duration of anti-allodynia and antinociceptive action	373-480	[125]
CH-PCL	Ropivacaine Dexamethasone			.	190	[126]

Non-polymeric nanoparticle

Till now we have studied some of the polymer which was used for the treatment of NP. Some polymer gets incorporated with the drug molecule and forms a new formulation, whereas in some cases the nanocapsule formulation was adapted to treat and increase the efficacy of the free drug. But apart from polymers, many nonpolymers get trapped or incorporated into the drug and show their effectiveness for the treatment of NP. The nonpolymer is like metal, gold, silver, magnesium oxide. This nonpolymer was in use as a carrier for different drug molecules for the treatment of NP. In one of the studies, the silver was used as a carrier named as silver nanoparticle which was incorporated under the drug basalin in the animal model of oxaliplatin-induced neuropathic pain to alleviate the pain for a longer period. The mechanism involved here is the reduction of the level of aluminum in the DRG by chelation of

BAgNPs [127]. The intrathecal drug delivery system was also used to treat neuropathic pain effectively [128]. Gold-coated Fe_3O_4 nanoparticle of size range 20-25 nm was administered through the intrathecal route in the human spinal cord [129]. There was a gold-coated in the outer layer because it protects the Fe_3O_4 from being oxidized and targets a wide variety of substances which decrease the pain. It was concluded from a study that the Nanoformulation here increases the target-specific capacity and response efficacy by nine-fold time. The response was observed within 15 min of administration there are many other formulations of nonpolymeric which was used in neuropathic pain. Some of the recent studies related to this are given in table 3.

Table 3: Non-polymer-based nanocarrier for treatment of neuropathic pain

Nanocarrier system	Method used	Drug	Model used (Animal)	Molecular mechanism	Pharmacological response	Ref.
Manganese oxide nano enzymes	Hydrothermal	Manganese oxide	PSNT Male Wistar rats	Superoxide dismutase reduces ROS formation	• Reduce the mechanical allodynia • Decrease the expression of CoX 2 enzymes	[130]
PLGA Coated magnetic nanoparticle	Solvent Evaporation and Coprecipitation	Capsaicin	Carrageenan-induced inflammatory pain male C57BL/6 mice	• Desentize the TRPV1 (Capsaicin receptor) • Inhibit inflammation and pain	Release of the drug is in a sustained release manner Which increases the drug solubility to prevent NP	[131]
Liposome @MSN	Surfactant self-assembly method	Interleukin-10 transgene	CCI Sprague–Dawley rats	Protecting DNA cargo, which is highly biocompatible in the CNS	Suppresses the pain	[132]
Gold Nano rods (TNF Nanoplexes)		SiRNA and target the TNF mRNA	CCI Harlan Sprague–Dawley rats	Down-regulation of the TNF	Alleviation of NP	[133]
Iron Oxide Nanoparticle	Chemical coprecipitation method	Magnetite (Fe_3O_4)	CDI	Reduce the inflammatory cell, pro-inflammatory marker, and ROS formation	Analgesic effect	[134]
USPIO-MRI	-	Minocycline	SNI (Sprague-Dawley Rat)	Monocyte act by retarding the movement of macrophages	Decrease in the development of allodynia and hyperalgesia.	[135]
Basalin@silver NP	Green method	Basalin	oxaliplatin-induced neuropathic pain C57BL6J mice	Reducing the aluminum in the drug response curve	Alleviate the NP	[127]

A clinical trial of nanoformulation in the treatment of NP

Different Nanoformulations treat the NP in different ways. After the preclinical research, some clinical research was done to see how the nanoformulation affected neuropathic pain in people [136]. The opioid, local anesthetic, NSAID, was incorporated in the liposome nanocarrier in human beings and a positive result was found [137]. In one of the clinical trials, the local anesthetic was encased in a liposome. To determine the strength and duration of the action, as well as whether the liposome formulation exhibits superior pharmacological reference or not, this liposome formulation is being compared in this experiment to bupivacaine given as a single dosage with a placebo. 184 patients who underwent hemorrhoidectomy were chosen. The trial was randomized, multicentric, and double-blinded. It was noted that the pain did not return for 72 h, and the patient did not require any additional opioid medication [138]. Another clinical research that examined the duration of pain alleviation between the liposomal and free versions of the medication bupivacaine was carried out. In contrast to free medicine, which acts only for 4 h, liposomal bupivacaine provides pain relief for 11 h [139]. In the Liposome topical capsaine study, a Post-Herpetic Neuralgia (PHN) patient was selected for this trial. A formulation of Liposomal Capasaine (LC) was prepared. This was a placebo-controlled cross-sectional study. As an inclusion criterion for the trial, patients with any symptoms following first-and second-line therapy were chosen. The LC topical application was done. At weeks 2, 4, and 6, the baseline was reached. It was discovered that LC was both safe to use and well tolerated by the patient. LC concentration was previously only negligible [140]. NSAID and liposome were both enclosed within the clinical research. When compared to free medication, an indomethacin-encapsulated liposome that was placed into a hydrogel demonstrated an effective, sustained release of activity. The subject chosen for the study was UVB-induced erythema. The liposome bupivacaine was found to have a good anti-inflammatory effect concerning the free formulation [141, 142]. Till now only the conventional liposome clinical study was done in which passive targeting was permitted. If in the case of passive targeting, there can be use of active targeting for neuropathic pain which will increase the efficacy as well as decrease any side effects.

Application of nanocarrier in NP

There is a wide range of applications of Nanomedicine in the treatment of NP. In this review, we have discussed the various nanocarriers with their property to cure or alleviate neuropathic pain. Apart from the treatment of neuropathic pain, this technology is also used for the diagnosis of pain behavior. One quick and sensitive device was found that detects the presence of opioids or other substances present in urine. This device's name was given as point-of-care urine drug monitoring [143]. One more device found is an ultrasensitive nanosensor which is used to detect the biomarkers that are pain-related and initiated by blood. For example, in the case of osteoarthritis, there is an increase in the level of IL-6 which was detected by this nanosensor [144, 145]. There are many studies conducted to detect the presence of biomarkers in blood. By this nanotechnology, we can achieve a novel drug delivery system in controlling pain with effective response and no side effects. Various literature research was searched and concluded that Nanomedicine was developed for targeting, and alleviating neuropathic pain. In the case of neuropathic pain, these nanoformulations mainly act by increasing the duration of action from the free drug, or by decreasing the mechanical allodynia or hyperalgesia symptom. Sometimes the initiation of pain was also prolonged so that the sensation of pain occurs after some time.

Toxicity aspects of various nanocarriers

A coin has two sides. Everything in this universe has a useful effect at some point and also has a toxic effect. Till now we have shown a huge advantage of Nanomedicine and its use. We have discussed the benefit of the nanoparticle over the conventional approach. But this approach also possesses some toxicity [146]. Although the organic nanoparticle-like lipid-based, polymer-based possesses no cytotoxic effect and shows tolerability even at high doses [147, 148]. It is a challenge to analyze the toxic effect of inorganic polymeric nanoparticles. One of the studies shows that the metal nanoparticle has a high chance of neurotoxicity because of the release of ROS, which ultimately leads to cell death. Nanoparticles like gold nanoparticles, silver nanoparticles, carbon nanotubes, and many inorganic nanoparticles imposed toxicity on the environment as well as on various bacteria, fish, rats, mice, and human cell lines [148]. As safety is important for us, being aware of toxicity is also a concern in this field. Hence the *in vivo* and *in vitro* assessment was conducted by the nanoparticle on the organism. These methods are assays of oxidative stress, proliferation, apoptosis, and DNA damage [149, 150]. The *in vivo* assessment test is clearance, biodistribution, serum chemistry, and hematology. By the use of radiolabel, the

nanoparticle was also detected in living or sacrificed animals [151]. The clearance and the biodistribution test were performed by observing the excretion and metabolism at a point in time after the nanoparticle was administered [152]. Similarly, other tests like histopathology study of tissue like the eye, brain, liver, heart, spleen, and kidney were also evaluated after the nanoparticle was administered [153]. In various research studies, it was found that nanoparticle also has an impact on the respiratory tract, which can cause asthma, lung cancer, and bronchitis. It leads to Crohn's disease, colon cancer, clotting in the blood, and heart disease [154].

CONCLUSION

Life quality suffers as a result of NP. In the recently developed and quickly expanding field of nanomedicine, scientists alter the drug or encapsulate it in a nanoparticle using various alterations. It serves as a diagnostic tool as well as a method of drug delivery to the intended location of action. The drug's solubility, stability, bioavailability, and biodistribution are all improved by the nanoformulation. Most importantly, it lessens the drug's toxicity. Here, the medication delivery to the site of action is significantly aided by the nanocarrier. In NP, the nanoformulation lengthens the time that pain alleviation lasts, causing the discomfort to only last briefly. By reducing allodynia and mechanical hyperalgesia, it also lessens NP.

ACKNOWLEDGMENT

The authors would like to thank the School of Pharmaceutical Sciences, Lovely Professional University, Punjab for organizing 3rd International Conference of Pharmacy (ICP-2022).

FUNDING

School of Pharmaceutical Sciences, Lovely Professional University, Punjab for organizing 3rd International Conference of Pharmacy (ICP-2022)

ABBREVIATION

SNL; Spinal nerve ligation, CCI; Chronic constructive injury, LEC: Liposome encapsulated Clodronate, GLP-: Glucagon like peptide-1, IL; Interleukin, mRNA; Messenger RNA, HGF; Hepatocyte growth factor, PSNL: Partial spinal Nerve ligation, ROS: Reactive oxygen species, Si RNA: Small interfering RNA, CDI: Chronic inflammatory pain model, Cx43: Gap junction alpha 1 protein, P2Y12:Purini receptor 2, STZ: Steptozosin induced diabetes model, Trkβ: tyrosine kinase receptor, PIP3: phosphoinositide 3-kinase, ERK: extracellular signal regulated, PLCγ: phosphoinositide phospholipase C, TNF-α: Tumor necrosis factor, SNEDDS: Self nanoemmulsion drug delivery syste, USPIO-MRI: ultra small superparamagnetic iron oxide-magnetic resonance imaging, CH PCL: Chitosan coated poly (ε-caprolactone)

AUTHORS CONTRIBUTIONS

All authors have contributed equally. All authors have contributed equally. Bimlesh Kumar devised the project, the main conceptual ideas, and wrote the article and the proof outline. Indu Melkani worked out almost all of the technical details and wrote the manuscript. Narendra Kumar Pandey developed the theoretical framework. Saurabh Singh discussed the results and commented on the manuscript. Dileep Singh Baghel and Kavatala Sudhakar contributed to the design and implementation of the research.

CONFLICTS OF INTERESTS

The authors have declared no conflict of interest.

REFERENCES

1. Blyth FM. Global burden of neuropathic pain. Pain. 2018;159(3):614-7. doi: 10.1097/j.pain.0000000000001127, PMID 29447139.
2. Doth AH, Hansson PT, Jensen MP, Taylor RS. The burden of neuropathic pain: a systematic review and meta-analysis of health utilities. Pain. 2010;149(2):338-44. doi: 10.1016/j.pain.2010.02.034, PMID 20227832.
3. Gutierrez J, Raju S, Riley JP, Boulis NM. Introduction to neuropathic pain syndromes. Neurosurg Clin N Am. 2014;25(4):639-62. doi: 10.1016/j.nec.2014.06.002, PMID 25240654.
4. Van Hecke O, Austin SK, Khan RA, Smith BH, Torrance N. Neuropathic pain in the general population: a systematic review of epidemiological studies. Pain. 2014;155(4):654-62. doi: 10.1016/j.pain.2013.11.013, PMID 24291734.
5. Baron R, Maier C, Attal N, Binder A, Bouhassira D, Cruccu G. Peripheral neuropathic pain: a mechanism-related organizing principle based on sensory profiles. Pain. 2017;158(2):261-72. doi: 10.1097/j.pain.0000000000000753, PMID 27893485.
6. Meacham K, Shepherd A, Mohapatra DP, Haroutounian S. Neuropathic pain: central vs. peripheral mechanisms. Curr Pain Headache Rep. 2017;21(6):28. doi: 10.1007/s11916-017-0629-5, PMID 28432601.
7. Cavalli E, Mammana S, Nicoletti F, Bramanti P, Mazzon E. The neuropathic pain: an overview of the current treatment and future therapeutic approaches. Int J Immunopathol Pharmacol. 2019;33:2058738419838383. doi: 10.1177/2058738419838383, PMID 30900486.
8. Sommer C, Leinders M, Uceyler N. Inflammation in the pathophysiology of neuropathic pain. Pain. 2018;159(3):595-602. doi: 10.1097/j.pain.0000000000001122, PMID 29447138.
9. Navarro X, Vivo M, Valero Cabre A. Neural plasticity after peripheral nerve injury and regeneration. Prog Neurobiol. 2007;82(4):163-201. doi: 10.1016/j.pneurobio.2007.06.005, PMID 17643733.
10. Apkarian AV, Sosa Y, Sonty S, Levy RM, Harden RN, Parrish TB. Chronic back pain is associated with decreased prefrontal and thalamic gray matter density. J Neurosci. 2004;24(46):10410-5. doi: 10.1523/JNEUROSCI.2541-04.2004, PMID 15548656.
11. Alles SR, Smith PA. Etiology and pharmacology of neuropathic pain. Pharmacol Rev. 2018;70(2):315-47. doi: 10.1124/pr.117.014399, PMID 29500312.
12. Barthas F, Humo M, Gilsbach R, Waltisperger E, Karatas M, Leman S. Cingulate overexpression of mitogen-activated protein kinase phosphatase-1 as a key factor for depression. Biol Psychiatry. 2017;82(5):370-9. doi: 10.1016/j.biopsych.2017.01.019, PMID 28359564.
13. Costigan M, Scholz J, Woolf CJ. NIH public access; 2010. p. 1-32.
14. Baron R, Binder A, Wasner G. Neuropathic pain: diagnosis, pathophysiological mechanisms, and treatment. Lancet Neurol. 2010;9(8):807-19. doi: 10.1016/S1474-4422(10)70143-5, PMID 20650402.
15. Cohen SP, Mao J. Neuropathic pain: mechanisms and their clinical implications. BMJ. 2014;348:f7656. doi: 10.1136/bmj.f7656, PMID 24500412.
16. Ji RR, Xu ZZ, Gao YJ. Emerging targets in neuroinflammation-driven chronic pain. Nat Rev Drug Discov. 2014;13(7):533-48. doi: 10.1038/nrd4334, PMID 24948120.
17. Knudsen LF, Terkelsen AJ, Drummond PD, Birklein F. Complex regional pain syndrome: a focus on the autonomic nervous system. Clin Auton Res. 2019;29(4):457-67. doi: 10.1007/s10286-019-00612-0, PMID 31104164.
18. Belmonte C, Nichols JJ, Cox SM, Brock JA, Begley CG, Bereiter DA. TFOS DEWS II pain and sensation report. Ocul Surf. 2017;15(3):404-37. doi: 10.1016/j.jtos.2017.05.002, PMID 28736339.
19. Robertson SA, Lascelles BD. Long-term pain in cats: how much do we know about this important welfare issue? J Feline Med Surg. 2010;12(3):188-99. doi: 10.1016/j.jfms.2010.01.002, PMID 20193910.
20. Chapman CR, Vierck CJ. The transition of acute postoperative pain to chronic pain: an integrative overview of research on mechanisms. J Pain. 2017;18(4):359.e1-359.e38. doi: 10.1016/j.jpain.2016.11.004, PMID 27908839.
21. Xu L, Zhang Y, Huang Y. Advances in the treatment of neuropathic pain. Adv Exp Med Biol. 2016;904:117-29. doi: 10.1007/978-94-017-7537-3_9, PMID 26900067.
22. Shigemoto Mogami Y, Hoshikawa K, Sato K. Activated microglia disrupt the blood-brain barrier and induce chemokines and cytokines in a rat *in vitro* model. Front Cell Neurosci. 2018;12:494. doi: 10.3389/fncel.2018.00494, PMID 30618641.
23. Richner M, Ferreira N, Dudele A, Jensen TS, Vaegter CB, Gonçalves NP. Functional and structural changes of the blood-nerve-barrier in diabetic neuropathy. Front Neurosci. 2018;12:1038. doi: 10.3389/fnins.2018.01038, PMID 30692907.

24. Zhao H, Alam A, Chen Q, A Eusman MA, Pal A, Eguchi S. The role of microglia in the pathobiology of neuropathic pain development: what do we know? Br J Anaesth. 2017;118(4):504-16. doi: 10.1093/bja/aex006, PMID 28403399.
25. Asplin BR, Magid DJ, Rhodes KV, Solberg LI, Lurie N, Camargo Jr CA. A conceptual model of emergency department crowding. Ann Emerg Med. 2003;42(2):173-80. doi: 10.1067/mem.2003.302, PMID 12883504.
26. Vargason AM, Anselmo AC, Mitragotri S. The evolution of commercial drug delivery technologies. Nat Biomed Eng. 2021;5(9):951-67. doi: 10.1038/s41551-021-00698-w, PMID 33795852.
27. Flynn GL. Cutaneous and transdermal delivery-processes and systems of delivery. Mod Pharm. 2002;72:293-363.
28. Saraiva C, Praça C, Ferreira R, Santos T, Ferreira L, Bernardino L. Nanoparticle-mediated brain drug delivery: overcoming blood-brain barrier to treat neurodegenerative diseases. J Control Release. 2016;235:34-47. doi: 10.1016/j.jconrel.2016.05.044, PMID 27208862.
29. Hoekman JD, Srivastava P, Ho RJ. Aerosol-stable peptide-coated liposome nanoparticles: a proof-of-concept study with opioid fentanyl in enhancing analgesic effects and reducing plasma drug exposure. J Pharm Sci. 2014;103(8):2231-9. doi: 10.1002/jps.24022, PMID 24909764.
30. Bates D, Schultheis BC, Hanes MC, Jolly SM, Chakravarthy KV, Deer TR. A comprehensive algorithm for management of neuropathic pain. Pain Med. 2019;20Suppl 1:S2-S12. doi: 10.1093/pm/pnz075, PMID 31152178.
31. Glassman AH. Cardiovascular effects of tricyclic antidepressants. Annu Rev Med. 1984;35:503-11. doi: 10.1146/annurev.me.35.020184.002443, PMID 6372670.
32. Macone A, Otis JA. Neuropathic pain. Semin Neurol. 2018;38(6):644-53. doi: 10.1055/s-0038-1673679, PMID 30522140.
33. Dreier JW, Pedersen CB, Gasse C, Christensen J. Antiepileptic drugs and suicide: role of prior suicidal behavior and parental psychiatric disorder. Ann Neurol. 2019;86(6):951-61. doi: 10.1002/ana.25623, PMID 31621936.
34. James DL, Jowza M. Treating opioid dependence: pain medicine physiology of tolerance and addiction. Clin Obstet Gynecol. 2019;62(1):87-97. doi: 10.1097/GRF.0000000000000422, PMID 30614846.
35. Saulino MF, Patel T, Fisher SP. The application of failure modes and effects analysis methodology to intrathecal drug delivery for pain management. Neuromodulation. 2017;20(2):177-86. doi: 10.1111/ner.12475, PMID 27477689.
36. Nystrom AM, Fadeel B. Safety assessment of nanomaterials: implications for nanomedicine. J Control Release. 2012;161(2):403-8. doi: 10.1016/j.jconrel.2012.01.027, PMID 22306428.
37. Farokhzad OC, Langer R. Impact of nanotechnology on drug delivery. ACS Nano. 2009;3(1):16-20. doi: 10.1021/nn900002m, PMID 19206243.
38. Xu C, Lei C, Yu C. Mesoporous silica nanoparticles for protein protection and delivery. Front Chem. 2019;7:290. doi: 10.3389/fchem.2019.00290, PMID 31119124.
39. Etheridge ML, Campbell SA, Erdman AG, Haynes CL, Wolf SM, McCullough J. The big picture on nanomedicine: the state of investigational and approved nanomedicine products. Nanomedicine. 2013;9(1):1-14. doi: 10.1016/j.nano.2012.05.013, PMID 22684017.
40. Hughes GA. Nanostructure-mediated drug delivery. Nanomedicine. 2005;1(1):22-30. doi: 10.1016/j.nano.2004.11.009, PMID 17292054.
41. Boisseau P, Loubaton B. Nanomedicine, nanotechnology in medicine. C R Phys. 2011;12(7):620-36. doi: 10.1016/j.crhy.2011.06.001.
42. Boulaiz H, Alvarez PJ, Ramirez A, Marchal JA, Prados J, Rodriguez Serrano F. Nanomedicine: application areas and development prospects. Int J Mol Sci. 2011;12(5):3303-21. doi: 10.3390/ijms12053303, PMID 21686186.
43. Li C, Wang J, Wang Y, Gao H, Wei G, Huang Y. Recent progress in drug delivery. Acta Pharm Sin B. 2019;9(6):1145-62. doi: 10.1016/j.apsb.2019.08.003, PMID 31867161.
44. Barenholz YC. Doxil®-the first FDA-approved nano-drug: lessons learned. J Control Release. 2012;160(2):117-34. doi: 10.1016/j.jconrel.2012.03.020, PMID 22484195.
45. Kaushik S, Hord AH, Denson DD, McAllister DV, Smitra S, Allen MG. Lack of pain associated with microfabricated microneedles. Anesth Analg. 2001;92(2):502-4. doi: 10.1097/00000539-200102000-00041, PMID 11159258.
46. Mehanna M, Motawaa A, Samaha M. Pharmaceutical particulate carriers: lipid-based carriers. Natl J Physiol Pharm Pharmacol. 2012;2(1):10-22.
47. Lismont M, Dreesen L, Wuttke S. Metal-organic framework nanoparticles in photodynamic therapy: current status and perspectives. Adv Funct Materials. 2017;27(14):1606314. doi: 10.1002/adfm.201606314.
48. Caraglia M, Luongo L, Salzano G, Zappavigna S, Marra M, Guida F. Stealth liposomes encapsulating zoledronic acid: a new opportunity to treat neuropathic pain. Mol Pharm. 2013;10(3):1111-8. doi: 10.1021/mp3006215, PMID 23327778.
49. Pradhan M, Singh D, Singh MR. Novel colloidal carriers for psoriasis: current issues, mechanistic insight and novel delivery approaches. J Control Release. 2013;170(3):380-95. doi: 10.1016/j.jconrel.2013.05.020, PMID 23770117.
50. Chen J, Jin T, Zhang H. Nanotechnology in chronic pain relief. Front Bioeng Biotechnol. 2020;8:682. doi: 10.3389/fbioe.2020.00682, PMID 32637406.
51. Qiao B, Song X, Zhang W, Xu M, Zhuang B, Li W. Intensity-adjustable pain management with prolonged duration based on phase-transitional nanoparticles-assisted ultrasound imaging-guided nerve blockade. J Nanobiotechnology. 2022;20(1):498. doi: 10.1186/s12951-022-01707-z, PMID 36424657.
52. Chaves C, Remiao F, Cisternino S, Decleves X. Opioids and the blood-brain barrier: a dynamic interaction with consequences on drug disposition in brain. Curr Neuropharmacol. 2017;15(8):1156-73. doi: 10.2174/1570159X15666170504095823, PMID 28474563.
53. Bors LA, Erdo F. Overcoming the blood-brain barrier. Challenges and tricks for CNS drug delivery. Sci Pharm. 2019;87(1). doi: 10.3390/scipharm87010006.
54. Burgess A, Hynynen K. Microbubble-assisted ultrasound for drug delivery in the brain and central nervous system. Adv Exp Med Biol. 2016;880:293-308. doi: 10.1007/978-3-319-22536-4_16, PMID 26486344.
55. Vega RA, Zhang Y, Curley C, Price RL, Abounader R. 370 Magnetic resonance-guided focused ultrasound delivery of polymeric brain-penetrating nanoparticle microRNA conjugates in glioblastoma. Neurosurgery. 2016;63Suppl 1:370. doi: 10.1227/01.neu.0000489858.08559.c8.
56. Hua S, de Matos MB, Metselaar JM, Storm G. Current trends and challenges in the clinical translation of nanoparticulate nanomedicines: pathways for translational development and commercialization. Front Pharmacol. 2018;9:790. doi: 10.3389/fphar.2018.00790, PMID 30065653.
57. Mishra B, Patel BB, Tiwari S. Colloidal nanocarriers: a review on formulation technology, types and applications toward targeted drug delivery. Nanomed Nanotechnol Biol Med. 2010;6(1):9-24. doi: 10.1016/j.nano.2009.04.008.
58. Patra JK, Das G, Fraceto LF, Campos EV, Rodriguez Torres MD, Acosta Torres LS. Nano based drug delivery systems: recent developments and future prospects. J Nanobiotechnology. 2018;16(1):71. doi: 10.1186/s12951-018-0392-8, PMID 30231877.
59. Bidve P, Prajapati N, Kalia K, Tekade R, Tiwari V. Emerging role of nanomedicine in the treatment of neuropathic pain. J Drug Target. 2020;28(1):11-22. doi: 10.1080/1061186X.2019.1587444, PMID 30798636.
60. Vizirianakis IS. Nanomedicine and personalized medicine toward the application of pharmacotyping in clinical practice to improve drug-delivery outcomes. Nanomedicine. 2011;7(1):11-7. doi: 10.1016/j.nano.2010.11.002, PMID 21094279.
61. Allen TM, Cullis PR. Liposomal drug delivery systems: from concept to clinical applications. Adv Drug Deliv Rev. 2013;65(1):36-48. doi: 10.1016/j.addr.2012.09.037, PMID 23036225.

62. Torchilin VP. Recent advances with liposomes as pharmaceutical carriers. Nat Rev Drug Discov. 2005;4(2):145-60. doi: 10.1038/nrd1632, PMID 15688077.
63. Gonda A, Zhao N, Shah JV, Calvelli HR, Kantamneni H, Francis NL. Engineering tumor-targeting nanoparticles as vehicles for precision nanomedicine. Med One. 2019;4. doi: 10.20900/mo.20190021, PMID 31592196.
64. Stathopulos PB, Scholz GA, Hwang YM, Rumfeldt JA, Lepock JR, Meiering EM. Sonication of proteins causes formation of aggregates that resemble amyloid. Protein Sci. 2004;13(11):3017-27. doi: 10.1110/ps.04831804, PMID 15459333.
65. Mozafari MR. Liposomes: an overview of manufacturing techniques. Cell Mol Biol Lett. 2005;10(4):711-9. PMID 16341279.
66. Kuthati Y, Navakanth Rao V, Busa P, Tummala S, Davuluri Venkata Naga G, Wong CS. Scope and applications of nanomedicines for the management of neuropathic pain. Mol Pharm. 2020;17(4):1015-27. doi: 10.1021/acs.molpharmaceut.9b01027, PMID 32142287.
67. Koudelka S, Turanek J. Liposomal paclitaxel formulations. J Control Release. 2012;163(3):322-34. doi: 10.1016/j.jconrel.2012.09.006, PMID 22989535.
68. Duran Lobato M, Martin Banderas L, Gonçalves LM, Fernandez Arevalo M, Almeida AJ. Comparative study of chitosan- and PEG-coated lipid and PLGA nanoparticles as oral delivery systems for cannabinoids. J Nanopart Res. 2015;17:1-17.
69. Joshi HP, Kim SB, Kim S, Kumar H, Jo MJ, Choi H. Nanocarrier-mediated delivery of CORM-2 enhances anti-allodynic and anti-hyperalgesic effects of CORM-2. Mol Neurobiol. 2019.
70. Zhang T, Wang Y, Li R, Xin J, Zheng Z, Zhang X. ROS-responsive magnesium-containing microspheres for antioxidative treatment of intervertebral disc degeneration. Acta Biomater. 2023;158:475-92. doi: 10.1016/j.actbio.2023.01.020, PMID 36640954.
71. Gwak YS, Hassler SE, Hulsebosch CE. Reactive oxygen species contribute to neuropathic pain and locomotor dysfunction via activation of CamKII in remote segments following spinal cord contusion injury in rats. Pain. 2013;154(9):1699-708. doi: 10.1016/j.pain.2013.05.018, PMID 23707296.
72. Wei B, Zhao Y, Li W, Zhang S, Yan M, Hu Z. Innovative immune mechanisms and antioxidative therapies of intervertebral disc degeneration. Front Bioeng Biotechnol. 2022;10:1023877. doi: 10.3389/fbioe.2022.1023877, PMID 36299288.
73. Liu Q, Jin L, Mahon BH, Chordia MD, Shen FH, Li X. Novel treatment of neuroinflammation against low back pain by soluble fullerol nanoparticles. Spine. 2013;38(17):1443-51. doi: 10.1097/BRS.0b013e31828fc6b7, PMID 23466506.
74. Singh Y, Meher JG, Raval K, Khan FA, Chaurasia M, Jain NK. Nanoemulsion: concepts, development and applications in drug delivery. J Control Release. 2017;252:28-49. doi: 10.1016/j.jconrel.2017.03.008.
75. Sarker DK. Engineering of nanoemulsions for drug delivery. Curr Drug Deliv. 2005;2(4):297-310. doi: 10.2174/156720105774370267, PMID 16305433.
76. Janjic JM, Vasudeva K, Saleem M, Stevens A, Liu L, Patel S. Low-dose NSAIDs reduce pain via macrophage targeted nanoemulsion delivery to neuroinflammation of the sciatic nerve in rat. J Neuroimmunol. 2018;318:72-9. doi: 10.1016/j.jneuroim.2018.02.010, PMID 29519721.
77. Gupta PS, Singh SK, Tripathi AK. Pharmacopuncture of bauhinia variegata nanoemulsion formulation against diabetic peripheral neuropathic pain. J Pharmacopuncture. 2020 Mar;23(1):30-6. doi: 10.3831/KPI.2020.23.005, PMID 32322433.
78. Pires PC, Peixoto D, Teixeira I, Rodrigues M, Alves G, Santos AO. Nanoemulsions and thermosensitive nanoemulgels of phenytoin and fosphenytoin for intranasal administration: formulation development and *in vitro* characterization. Eur J Pharm Sci. 2020;141:105099. doi: 10.1016/j.ejps.2019.105099, PMID 31672614.
79. Xu X, Chang S, Zhang X, Hou T, Yao H, Zhang S. Fabrication of a controlled-release delivery system for relieving sciatica nerve pain using an ultrasound-responsive microcapsule. Front Bioeng Biotechnol. 2022;10:1072205. doi: 10.3389/fbioe.2022.1072205, PMID 36507268.
80. Chen Y, An Q, Teng K, Zhang Y, Zhao Y. Latest development and versatile applications of highly integrating drug delivery patch. Eur Polym J. 2022;170:111164. doi: 10.1016/j.eurpolymj.2022.111164.
81. Shen H, Hu X, Szymusiak M, Wang ZJ, Liu Y. Orally administered nanocurcumin to attenuate morphine tolerance: comparison between negatively charged PLGA and partially and fully pegylated nanoparticles. Mol Pharm. 2013;10(12):4546-51. doi: 10.1021/mp400358z, PMID 24195658.
82. Mert T, Gunay I, Ocal I, Guzel AI, Inal TC, Sencar L. Macrophage depletion delays progression of neuropathic pain in diabetic animals. Naunyn Schmiedebergs Arch Pharmacol. 2009;379(5):445-52. doi: 10.1007/s00210-008-0387-3, PMID 19139849.
83. Wang YR, Mao XF, Wu HY, Wang YX. Liposome-encapsulated clodronate specifically depletes spinal microglia and reduces initial neuropathic pain. Biochem Biophys Res Commun. 2018;499(3):499-505. doi: 10.1016/j.bbrc.2018.03.177, PMID 29596830.
84. Zhu Y, Wang M, Zhang J, Peng W, Firempong CK, Deng W. Improved oral bioavailability of capsaicin via liposomal nanoformulation: preparation, *in vitro* drug release and pharmacokinetics in rats. Arch Pharm Res. 2015;38(4):512-21. doi: 10.1007/s12272-014-0481-7, PMID 25231341.
85. Shankarappa SA, Tsui JH, Kim KN, Reznor G, Dohlman JC, Langer R. Prolonged nerve blockade delays the onset of neuropathic pain. Proc Natl Acad Sci USA. 2012;109(43):17555-60. doi: 10.1073/pnas.1214634109, PMID 23045676.
86. Smith LJ, Valenzuela JR, Krugner Higby LA, Brown C, Heath TD. A single dose of liposome-encapsulated hydromorphone provides extended analgesia in a rat model of neuropathic pain. Comp Med. 2006;56(6):487-92. PMID 17219779.
87. Surdam JW, Licini DJ, Baynes NT, Arce BR. The use of exparel (liposomal bupivacaine) to manage postoperative pain in unilateral total knee arthroplasty patients. J Arthroplasty. 2015;30(2):325-9. doi: 10.1016/j.arth.2014.09.004, PMID 25282071.
88. Tsuchihara T, Ogata S, Nemoto K, Okabayashi T, Nakanishi K, Kato N. Nonviral retrograde gene transfer of human hepatocyte growth factor improves neuropathic pain-related phenomena in rats. Mol Ther. 2009;17(1):42-50. doi: 10.1038/mt.2008.214, PMID 18941443.
89. Isacchi B, Bergonzi MC, Iacopi R, Ghelardini C, Galeotti N, Bilia AR. Liposomal formulation to increase stability and prolong antineuropathic activity of verbascoside. Planta Med. 2017;83(5):412-9. doi: 10.1055/s-0042-106650, PMID 27191581.
90. Masatsugu T, Keita H, Hirotaka K, Yoshitarou I, Kyoichiro M, Mamoru O. Development of a novel analgesic for cancer pain targeting brain-derived neurotrophic factor. Kawasaki Medical Journal. 2017;43(2):107-20. doi: 10.11482/KMJ-E43(2)107.
91. Saleem M, Deal B, Nehl E, Janjic JM, Pollock JA. Nanomedicine-driven neuropathic pain relief in a rat model is associated with macrophage polarity and mast cell activation. Acta Neuropathol Commun. 2019;7(1):108. doi: 10.1186/s40478-019-0762-y, PMID 31277709.
92. Stevens AM, Liu L, Bertovich D, Janjic JM, Pollock JA. Differential expression of neuroinflammatory mrnas in the rat sciatic nerve following chronic constriction injury and pain-relieving nanoemulsion NSAID delivery to infiltrating macrophages. Int J Mol Sci. 2019;20(21):1-24. doi: 10.3390/ijms20215269, PMID 31652890.
93. Joshi RP, Negi G, Kumar A, Pawar YB, Munjal B, Bansal AK. SNEDDS curcumin formulation leads to enhanced protection from pain and functional deficits associated with diabetic neuropathy: an insight into its mechanism for neuroprotection. Nanomedicine. 2013;9(6):776-85. doi: 10.1016/j.nano.2013.01.001, PMID 23347896.
94. Vasovic D, Divovic B, Treven M, Knutson DE, Steudle F, Scholze P. Trigeminal neuropathic pain development and maintenance in rats are suppressed by a positive modulator of α6 GABAA receptors. Eur J Pain. 2019;23(5):973-84. doi: 10.1002/ejp.1365, PMID 30633839.

95. Ghiasi Z, Esmaeli F, Aghajani M, Ghazi Khansari M, Faramarzi MA, Amani A. Enhancing analgesic and anti-inflammatory effects of capsaicin when loaded into olive oil nanoemulsion: an *in vivo* study. Int J Pharm. 2019;559:341-7. doi: 10.1016/j.ijpharm.2019.01.043, PMID 30710660.
96. Sandig AG, Campmany AC, Campos FF, Villena MJ, Naveros BC. Transdermal delivery of imipramine and doxepin from newly oil-in-water nanoemulsions for an analgesic and anti-allodynic activity: development, characterization and *in vivo* evaluation. Colloids Surf B Biointerfaces. 2013;103:558-65. doi: 10.1016/j.colsurfb.2012.10.061, PMID 23261580.
97. Akpan EI, Shen X, Wetzel B, Friedrich K. Design and synthesis of polymer nanocomposites. Polym Compos Functionalized Nanoparticles Synth Prop Appl. 2018.
98. Din FU, Aman W, Ullah I, Qureshi OS, Mustapha O, Shafique S. Effective use of nanocarriers as drug delivery systems for the treatment of selected tumors. Int J Nanomedicine. 2017;12:7291-309. doi: 10.2147/IJN.S146315, PMID 29042776.
99. Papa S, Ferrari R, De Paola M, Rossi F, Mariani A, Caron I. Polymeric nanoparticle system to target activated microglia/macrophages in spinal cord injury. J Control Release. 2014;174(1):15-26. doi: 10.1016/j.jconrel.2013.11.001, PMID 24225226.
100. Hanemann T, Szabo DV. Polymer-nanoparticle composites: from synthesis to modern applications. Materials. 2010;3(6):3468-517. doi: 10.3390/ma3063468.
101. Phạm TL, Kim DW. Poly(lactic-co-glycolic acid) nanomaterial-based treatment options for pain management: a review. Nanomedicine (Lond). 2020. doi: 10.2217/nnm-2020-0114, PMID 32757701.
102. Wang T, Hurwitz O, Shimada SG, Tian D, Dai F, Zhou J. Anti-nociceptive effects of bupivacaine-encapsulated PLGA nanoparticles applied to the compressed dorsal root ganglion in mice. Neurosci Lett. 2018;668:154-8. doi: 10.1016/j.neulet.2018.01.031, PMID 29355697.
103. Singh R, Lillard Jr JW. Nanoparticle-based targeted drug delivery. Exp Mol Pathol. 2009;86(3):215-23. doi: 10.1016/j.yexmp.2008.12.004, PMID 19186176.
104. Alves TF, Morsink M, Batain F, Chaud MV, Almeida T, Fernandes DA. Applications of natural, semi-synthetic, and synthetic polymers in cosmetic formulations. Cosmetics. 2020;7(4):75. doi: 10.3390/cosmetics7040075.
105. Ribeiro AM, Veiga F, Figueiras A. Biodegradable polymeric nanostructures: design and advances in oral drug delivery for neurodegenerative disorders. Nanostructures for oral medicine. Elsevier Inc.; 2017. p. 61-86.
106. Zhao D, Zhuo RX, Cheng SX. Alginate modified nanostructured calcium carbonate with enhanced delivery efficiency for gene and drug delivery. Mol Biosyst. 2012;8(3):753-9. doi: 10.1039/c1mb05337j, PMID 22159070.
107. Gundloori RV, Singam A, Killi N. Nanobased intravenous and transdermal drug delivery systems. Appl Target Nano Drugs Deliv Syst; 2019. p. 551-94.
108. Sukhbir S, Yashpal S, Sandeep A. Development and statistical optimization of nefopam hydrochloride loaded nanospheres for neuropathic pain using box-behnken design. Saudi Pharm J. 2016;24(5):588-99. doi: 10.1016/j.jsps.2015.03.020, PMID 27752232.
109. Kumar B, Garg V, Singh A, Pandey NK, Singh S, Panchal S. Investigation and optimization of formulation parameters for self-nanoemulsifying delivery system of two lipophilic and gastrointestinal labile drugs using box-behnken design. Asian J Pharm Clin Res. 2018;11(14)Special Issue 2:12-8. doi: 10.22159/ajpcr.2018.v11s2.28585.
110. Kaur J, Bawa P, Rajesh SY, Sharma P, Ghai D, Jyoti J. Formulation of curcumin nanosuspension using box-behnken design and study of impact of drying techniques on its powder characteristics. Asian J Pharm Clin Res. 2017;10(16)Special Issue:43-51. doi: 10.22159/ajpcr.2017.v10s4.21335.
111. Marcondes Sari MH, Zborowski VA, Ferreira LM, Jardim ND, Araujo PC, Brüning CA. Enhanced pharmacological actions of p,p'-methoxyl-diphenyl diselenide-loaded polymeric nanocapsules in a mouse model of neuropathic pain: behavioral and molecular insights. J Trace Elem Med Biol. 2018;46:17-25. doi: 10.1016/j.jtemb.2017.11.002, PMID 29413106.
112. Ganugula R, Deng M, Arora M, Pan HL, Kumar MN. Polyester nanoparticle encapsulation mitigates paclitaxel-induced peripheral neuropathy. ACS Chem Neurosci. 2019;10(3):1801-12. doi: 10.1021/acschemneuro.8b00703, PMID 30609902.
113. Jung SW, Jeong YI, Kim YH, Kim SH. Self-assembled polymeric nanoparticles of poly(ethylene glycol) grafted pullulan acetate as a novel drug carrier. Arch Pharm Res. 2004;27(5):562-9. doi: 10.1007/BF02980132, PMID 15202564.
114. Pippa N, Pispas S, Demetzos C. Polymer self-assembled nanostructures as innovative drug nanocarrier platforms. Curr Pharm Des. 2016;22(19):2788-95. doi: 10.2174/1381612822666160217141232, PMID 26898736.
115. Miyata K, Christie RJ, Kataoka K. Polymeric micelles for nano-scale drug delivery. React Funct Polym. 2011;71(3):227-34. doi: 10.1016/j.reactfunctpolym.2010.10.009.
116. Zhang Y, Huang Y, Li S. Polymeric micelles: nanocarriers for cancer-targeted drug delivery. AAPS PharmSciTech. 2014;15(4):862-71. doi: 10.1208/s12249-014-0113-z, PMID 24700296.
117. Kartha S, Yan L, Ita ME, Amirshaghaghi A, Luo L, Wei Y. Phospholipase A2 inhibitor-loaded phospholipid micelles abolish neuropathic pain. ACS Nano. 2020;14(7):8103-15. doi: 10.1021/acsnano.0c00999, PMID 32484651.
118. Berrocoso E, Rey Brea R, Fernandez Arevalo M, Mico JA, Martin Banderas L. Single oral dose of cannabinoid derivate loaded PLGA nanocarriers relieves neuropathic pain for eleven days. Nanomedicine. 2017;13(8):2623-32. doi: 10.1016/j.nano.2017.07.010, PMID 28756090.
119. Shin J, Yin Y, Park H, Park S, Triantafillu UL, Kim Y. P38 siRNA-encapsulated PLGA nanoparticles alleviate neuropathic pain behavior in rats by inhibiting microglia activation. Nanomedicine (Lond). 2018;13(13):1607-21. doi: 10.2217/nnm-2018-0054, PMID 30028250.
120. Nigam K, Kaur A, Tyagi A, Manda K, Gabrani R, Dang S. Baclofen-loaded poly (D,L-lactide-Co-glycolic acid) nanoparticles for neuropathic pain management: *in vitro* and *in vivo* evaluation. Rejuvenation Res. 2019;22(3):235-45. doi: 10.1089/rej.2018.2119, PMID 30175946.
121. Lalani J, Patil S, Kolate A, Lalani R, Misra A. Protein-functionalized PLGA nanoparticles of lamotrigine for neuropathic pain management. AAPS PharmSciTech. 2015;16(2):413-27. doi: 10.1208/s12249-014-0235-3, PMID 25354788.
122. Shin J, Yin Y, Kim DK, Lee SY, Lee W, Kang JW. Foxp3 plasmid-encapsulated PLGA nanoparticles attenuate pain behavior in rats with spinal nerve ligation. Nanomedicine. 2019;18:90-100. doi: 10.1016/j.nano.2019.02.023, PMID 30858084.
123. Jia T, Rao J, Zou L, Zhao S, Yi Z, Wu B. Nanoparticle-encapsulated curcumin inhibits diabetic neuropathic pain involving the P2Y12 receptor in the dorsal root ganglia. Front Neurosci. 2017;11:755. doi: 10.3389/fnins.2017.00755, PMID 29422835.
124. Kartha S, Yan L, Weisshaar CL, Ita ME, Shuvaev VV, Muzykantov VR. Superoxide dismutase-loaded porous polymersomes as highly efficient antioxidants for treating neuropathic pain. Adv Healthc Mater. 2017;6(17):1-6. doi: 10.1002/adhm.201700500, PMID 28671302.
125. Garcia X, Escribano E, Colom H, Domenech J, Queralt J. Tricyclic antidepressants-loaded biodegradable PLGA nanoparticles: *in vitro* characterization and *in vivo* analgesic and anti-allodynic effect. Curr Nanosci. 2011;7(3):345-53. doi: 10.2174/157341311795542336.
126. Zhang Y, Yue Y, Chang M. Local anaesthetic pain relief therapy: *in vitro* and *in vivo* evaluation of a nanotechnological formulation co-loaded with ropivacaine and dexamethasone. Biomed Pharmacother. 2017;96:443-9. doi: 10.1016/j.biopha.2017.09.124, PMID 29031203.
127. Gao L, Zheng Y, Zhao C, Teng H. Investigation on effect of basalin coated silver nanoparticles as antioxidant for alleviating peripheral neuropathy in mice treated with oxaliplatin. J Photochem Photobiol B. 2017;177:56-61. doi: 10.1016/j.jphotobiol.2017.10.003, PMID 29069632.

128. Pope JE, Deer TR. Intrathecal drug delivery for pain: a clinical guide and future directions. Pain Manag. 2015;5(3):175-83. doi: 10.2217/pmt.15.12, PMID 25971641.
129. Lueshen E, Venugopal I, Kanikunnel J, Soni T, Alaraj A, Linninger A. Intrathecal magnetic drug targeting using gold-coated magnetite nanoparticles in a human spine model. Nanomedicine (Lond). 2014;9(8):1155-69. doi: 10.2217/nnm.13.69, PMID 23862614.
130. Kuthati Y, Busa P, Goutham Davuluri VN, Wong CS. Manganese oxide nanozymes ameliorate mechanical allodynia in a rat model of partial sciatic nerve-transection induced neuropathic pain. Int J Nanomedicine. 2019;14:10105-17. doi: 10.2147/IJN.S225594, PMID 31920306.
131. Baskaran M, Baskaran P, Arulsamy N, Thyagarajan B. Preparation and evaluation of PLGA-coated capsaicin magnetic nanoparticles. Pharm Res. 2017;34(6):1255-63. doi: 10.1007/s11095-017-2142-2, PMID 28326459.
132. Dengler EC, Liu J, Kerwin A, Torres S, Olcott CM, Bowman BN. Mesoporous silica-supported lipid bilayers (protocells) for DNA cargo delivery to the spinal cord. J Control Release. 2013;168(2):209-24. doi: 10.1016/j.jconrel.2013.03.009, PMID 23517784.
133. Gerard E, Spengler RN, Bonoiu AC, Mahajan SD, Davidson BA, Ding H. Chronic constriction injury-induced nociception is relieved by nanomedicine-mediated decrease of rat hippocampal tumor necrosis factor. Pain. 2015;156(7):1320-33. doi: 10.1097/j.pain.0000000000000181, PMID 25851457.
134. Wu PC, Hsiao HT, Lin YC, Shieh DB, Liu YC. The analgesia efficiency of ultrasmall magnetic iron oxide nanoparticles in mice chronic inflammatory pain model. Nanomedicine. 2017;13(6):1975-81. doi: 10.1016/j.nano.2017.05.005. PMID 28539274.
135. Ghanouni P, Behera D, Xie J, Chen X, Moseley M, Biswal S. *In vivo* USPIO magnetic resonance imaging shows that minocycline mitigates macrophage recruitment to a peripheral nerve injury. Mol Pain. 2012;8:49. doi: 10.1186/1744-8069-8-49, PMID 22742763.
136. Beltran Gracia E, Lopez Camacho A, Higuera Ciapara I, Velazquez Fernandez JB, Vallejo Cardona AA. Nanomedicine review: clinical developments in liposomal applications. Cancer Nano. 2019;10(1). doi: 10.1186/s12645-019-0055-y.
137. Hua S, Wu SY. The use of lipid-based nanocarriers for targeted pain therapies. Front Pharmacol. 2013;4:143. doi: 10.3389/fphar.2013.00143, PMID 24319430.
138. Gorfine SR, Onel E, Patou G, Krivokapic ZV. Bupivacaine extended-release liposome injection for prolonged postsurgical analgesia in patients undergoing hemorrhoidectomy: a multicenter, randomized, double-blind, placebo-controlled trial. Dis Colon Rectum. 2011;54(12):1552-9. doi: 10.1097/DCR.0b013e318232d4c1, PMID 22067185.
139. Lafont ND, Legros FJ, Boogaerts JG. Use of liposome-associated bupivacaine in a cancer pain syndrome. Anaesthesia. 1996;51(6):578-9. doi: 10.1111/j.1365-2044.1996.tb12569.x, PMID 8694214.
140. Teixeira MJ, Menezes LM, Silva V, Galhardoni R, Sasson J, Okada M. Liposomal topical capsaicin in post-herpetic neuralgia: a safety pilot study. Arq Neuropsiquiatr. 2015;73(3):237-40. doi: 10.1590/0004-282X20140232, PMID 25807130.
141. Puglia C, Tirendi GG, Bonina F. Emerging role of colloidal drug delivery systems (CDDS) in NSAID topical administration. Curr Med Chem. 2013;20(14):1847-57. doi: 10.2174/0929867311320140004, PMID 23410154.
142. Puglia C, Trombetta D, Venuti V, Saija A, Bonina F. Evaluation of *in vivo* topical anti-inflammatory activity of indometacin from liposomal vesicles. J Pharm Pharmacol. 2004;56(10):1225-32. doi: 10.1211/0022357044445, PMID 15482636.
143. Chakravarthy KV, Boehm FJ, Christo PJ. Nanotechnology: a promising new paradigm for the control of pain. Pain Med. 2018;19(2):232-43. doi: 10.1093/pm/pnx131, PMID 29036629.
144. Bäckryd E. Pain in the blood? Envisioning mech-based diagnoses biomark clin pain med diagn; 2015.
145. Arendt Nielsen L, Eskehave TN, Egsgaard LL, Petersen KK, Graven Nielsen T, Hoeck HC. Association between experimental pain biomarkers and serologic markers in patients with different degrees of painful knee osteoarthritis. Arthritis Rheumatol. 2014;66(12):3317-26. doi: 10.1002/art.38856, PMID 25168637.
146. De Jong WH, Borm PJ. Drug delivery and nanoparticles: applications and hazards. Int J Nanomedicine. 2008;3(2):133-49. doi: 10.2147/ijn.s596, PMID 18686775.
147. Li X, Wang L, Fan Y, Feng Q, Cui FZ. Biocompatibility and toxicity of nanoparticles and nanotubes. J Nanomater. 2012;2012:1-19. doi: 10.1155/2012/548389.
148. Kumar V, Sharma N, Maitra SS. *In vitro* and *in vivo* toxicity assessment of nanoparticles. Int Nano Lett. 2017;7(4):243-56. doi: 10.1007/s40089-017-0221-3.
149. Sayes CM, Reed KL, Warheit DB. Assessing toxicity of fine and nanoparticles: comparing *in vitro* measurements to *in vivo* pulmonary toxicity profiles. Toxicol Sci. 2007;97(1):163-80. doi: 10.1093/toxsci/kfm018.
150. Voigt N, Henrich Noack P, Kockentiedt S, Hintz W, Tomas J, Sabel BA. Toxicity of polymeric nanoparticles *in vivo* and *in vitro*. J Nanopart Res. 2014;16(6):2379. doi: 10.1007/s11051-014-2379-1, PMID 26420981.
151. Kim SC, Kim DW, Shim YH, Bang JS, Oh HS, Wan Kim SW. *In vivo* evaluation of polymeric micellar paclitaxel formulation: toxicity and efficacy. J Control Release. 2001;72(1-3):191-202. doi: 10.1016/s0168-3659(01)00275-9, PMID 11389998.
152. Li YP, Pei YY, Zhang XY, Gu ZH, Zhou ZH, Yuan WF. Pegylated PLGA nanoparticles as protein carriers: synthesis, preparation and biodistribution in rats. J Control Release. 2001;71(2):203-11. doi: 10.1016/s0168-3659(01)00218-8, PMID 11274752.
153. Lei R, Wu C, Yang B, Ma H, Shi C, Wang Q. Integrated metabolomic analysis of the nano-sized copper particle-induced hepatotoxicity and nephrotoxicity in rats: A rapid *in vivo* screening method for nanotoxicity. Toxicol Appl Pharmacol. 2008;232(2):292-301. doi: 10.1016/j.taap.2008.06.026, PMID 18706438.
154. Muller J, Huaux F, Moreau N, Misson P, Heilier JF, Delos M. Respiratory toxicity of multi-wall carbon nanotubes. Toxicol Appl Pharmacol. 2005;207(3):221-31. doi: 10.1016/j.taap.2005.01.008, PMID 16129115.