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Current progress and challenges of nanoparticle-based therapeutics in pain management

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ABSTRACT

Pain is a widespread and growing health problem worldwide that exerts a considerable social and economic impact on both patients and healthcare systems and, therefore, on society in general. Although current treatment modalities include a wide variety of pharmacological and non-pharmacological approaches, due to the complexity of pain and individual differences in clinical response these options are not always effective in mitigating and relieving pain. In addition, some pain drugs such as non-steroidal anti-inflammatory drugs (NSAIDs), local anesthetics and opioids show several unfavorable side effects. Therefore, current research advances in this medical field are based on the development of potential treatments to address many of the unmet needs and to overcome the existing limitations in pain management. Nanoparticle drug delivery systems present an exciting opportunity as alternative platforms to improve efficacy and safety of medications currently in use. Herein, we review a broad range of nanoparticle formulations (organic nanostructures and inorganic nanoparticles), which have been developed to encapsulate an array of painkillers, paying special attention to the key advantages that these systems offer, (compared to the use of the free drug), as well as to the more relevant results of preclinical studies in animal models. Additionally, we will briefly discuss the impact of some of these nanoformulations in clinical trials.

KEYWORDS: pain; local anesthetics; opioids; NSAIDs; nanoparticles; clinical trials.

1. PAIN: DEFINITION AND TYPES

The current established definition of pain, "an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage", established by the Subcommittee on Taxonomy of the International Association for the Study of Pain in 1994, suggests the complexity of this phenomenon[1]. This definition implies that pain is a subjective experience and, therefore, each individual interprets it based on unique early life experiences related to injury, consequently yielding a high inter-individual variability in pain perception. Also, culture heritage, gender, ethnicity and environmental, genetic and personality-related factors play a substantial role in tolerance and response to pain. The integration of these psychological and social factors into clinical practice is not easy and these individual differences in pain sensitivity often hinder the correct diagnosis and proper treatment of pain, making it an enormous public health problem[2].

In addition, over the years, the lack of recognition of this condition as a priority health problem has caused major deficits in understanding the mechanisms and management of pain and has impeded the development and implementation of new therapies. At present, great efforts are being made to change the paradigmatic view of pain, aiming to have it recognized as a unique medical disease instead of a symptom of disease[3].

From a clinical perspective, the use of a classification system for pain could be helpful to give an initial approximation to guide assessment and proper diagnosis of those patients suffering pain as well as to select a suitable treatment. Generally, pain can be categorized according to specific characteristics (Figure 1A): anatomic location (muscles, viscera, joints, tendons, and bones), pain physiology (nociceptive, neuropathic and inflammatory), pain duration (acute, chronic and breakthrough pain), intensity (mild, moderate or severe) and etiology (malignant or non-malignant).

However, the pathophysiological classification of pain is one of the most used in the framework for clinical management of pain considering that treatment approaches for nociceptive, inflammatory or neuropathic pain are different (Figure 1B).

Nociceptive pain is produced by the stimulation of the particular pain receptors called nociceptors, which are sensitive to potentially harmful stimuli. In that case, pain operates as an early-warning physiological protective system to avoid any contact with the noxious stimuli[4]. According to the location of activated nociceptors, nociceptive pain can be either somatic (superficial and deep) or visceral pain. Somatic nociceptive pain arises from injury into superficial or deep tissues. It is usually characterized by being well-defined, clearly located, constant or intermittent and normally movement dependent. However, visceral nociceptive pain, which is typically diffuse, difficult to localize, usually constant, and sometimes attributed to a far body part , is produced by the stimulation of nociceptors located in the internal organs or viscera.

After an unavoidable injury to tissues or nerves, an inflammatory response is triggered by activation of the immune system to aid in the healing of the damaged region. The main objective of this process is the elimination of potential pathogens, the clearance of damaged tissue, the restoration of the homeostasis and the anatomic and physiologic re-establishment of the affected area. In addition, as a consequence of this inflammatory response and the temporary sensitization of the nociceptive system, a situation of tenderness or pain hypersensitivity is created in the damaged area and non-swollen surrounding tissues, preventing additional damage and promoting the protection of the injured area. Thus, the abnormal sensory processing implies that any innocuous stimuli that would normally not produce pain may now do so and noxious stimuli may cause an increased pain response. This kind of pain, named inflammatory pain, is protective, adaptive and beneficial for a successful recovery. Generally, this pain disappears at the

same time the injury state is resolved. However, under certain physiological or pathophysiological circumstances, nociceptive signaling can operate abnormally, causing pain with no discernable protective or reparative role. In these cases, pain becomes persistent and can last for months or years, as long as inflammation continues[5].

Finally, neuropathic pain, which is generated by lesion or dysfunction of the nervous system, is a maladaptive and multifactorial pain. In 2008, the concept of neuropathic pain was redefined by a group of experts in the fields of neurology and pain as pain caused by a lesion or disease of the somatosensory system[6]. Although a clear distinction is not easy, there are two subtypes of this disorder, peripheral and central neuropathic pain. Neuropathic pain disorders have common clinical characteristics, and, are frequently described as burning or stabbing pain. Also, it is often associated with the appearance of symptoms, such as allodynia, hyperalgesia, dysesthesia (tingling and numbness) and lancinating pain.

2. PREVALENCE OF PAIN

The published data of several population-based surveys carried out in Europe and the U.S. showed large differences between pain prevalence rates, which could likely be attributed to differences in the selected methodology such as the definition of chronic pain, the pain scale included in the survey and the selection of surveyed subjects. Thus, although a general prevalence of moderate to severe chronic pain of 19 % in the adult population was estimated in a large-scale telephone survey carried out in Europe and Israel, large variations were observed between participant countries[7]. More recently, an age-standardized analysis of 18 surveys revealed that 37 % of surveyed people in developed countries and 41 % in developing countries reported suffering a chronic pain condition in the last 12 months. In this study, considerable international modification in

chronic pain prevalence rates was also observed[8]. Published data about an internet-based survey conducted in the U.S. were similar; showing that the overall crude point prevalence of pain lasting at least 6 months was 34.5 %[9]. Hence, these data provide evidence that although the prevalence rates may vary substantially between different geographic regions, chronic pain is a habitual condition in the general population worldwide. This high prevalence across the globe is one of the many reasons why pain should be conceptualized as a public health priority. Despite the substantial variation in the country-specific prevalence rates, several findings were consistent globally. For instance, the overall prevalence of chronic pain is consistently higher in females than males and increases with age. Although the reasons for the sex bias are still not clear, possible mechanisms underlying gender-related differences include biological and psychosocial factors[10]. And in spite of several population-based studies having documented that population ageing influences the prevalence of the chronic pain condition, to date, there is no consensus concerning the existing association between these two factors. Some studies reported that this relationship appears to be lineal; others indicated that it steadily rises with increasing age up to approximately 65 years and, then, it declines slowly in the older age-groups. Regarding the psychosocial or bio-behavioral factors, a relevant connection between pain and mental illness has been observed in both developed and developing countries[10].

3. PAIN-ASSOCIATED COSTS

Pain is considered an important clinical and social problem worldwide, having a significant economic burden on patients and their relatives, health systems and society in general. In addition, the extended life expectancy, increased levels of obesity and the sedentary lifestyle are likely to cause an increase in the prevalence of this condition and, therefore, on the impact of chronic pain in society. Chronic pain affects the physical and

psychological health of the sufferers, reducing their quality of life and interfering on their daily activities, autonomy, employment and social and economic well-being. Thus, the economic costs of pain are generally evaluated at two levels: direct cost associated with physician's visits, diagnostics, treatments, hospitalizations and medications and indirect costs due to the increased probability of having to leave the labor market as a consequence of the scarce productivity and high rates of absenteeism found in patients. According to a study carried out in the U.S. in 2010, the pain cost at national level ranged from $560 to $635 billion annually[11]. The comparison of these data with those published by the National Institutes of Health (NIH) demonstrated that the economic impact of persistent pain exceeded the economic costs of the 6 most costly diagnosed diseases. An economic analysis of costs attributable to chronic pain in various European countries indicated that direct healthcare costs and indirect costs reached billions annually as well, representing between 1.5 % and 3 % of the European gross domestic product[12]. The economic impact of chronic pain and related conditions in different European countries can vary substantially because those studies have been focused mainly on specific pain subgroups such as back pain, musculoskeletal disorders and others. For example, in Ireland, the published cost of chronic pain was estimated at 5.34 € billion or 2.86% of Irish Gross Domestic Product per year in 2008[13]. While several other international studies determined that the socioeconomic impact of back pain exceeds 1.18 € billion in Belgium[14], 1.86 € billion in Sweden[15] and 48.9 € billion in Germany[16] annually.

4. CURRENT STATUS OF PAIN TREATMENT

There is a need to improve chronic pain management to improve clinical outcomes and to generate tangible savings in the economy of patient and in health-care systems in general.

The goal of pain management is to reduce sensitisation, decrease pain amplification and restore normal pain thresholds, relieving pain completely and improving the quality of life of those people living with distress associated to this condition. The first key step to plan effective and individualized pharmacologic therapy is an adequate and comprehensive clinical assessment, involving not only the search for the physical source of the pain but also the documentation of pain history and the screening for psychosocial comorbidities that could contribute to a more complex pain condition. However, the multifactorial and subjective nature of chronic pain makes a standardized evaluation difficult to produce. Therefore, clinicians should use a variety of screening and assessment tools to predict prognosis and to search for risk factors or morbidities. This kind of evaluation, usually based on the use of scales, would allow health care providers to integrate pain intensity, pain affect and pain-related disability and to assess a multitude of patient-specific factors with the goal of determining individualized treatment. In addition, a therapeutic plan must be multidisciplinary, not only aiming at pain relief but also solving psychosocial factors associated with the disease outcome[17] (Figure 2).

A variety of medications such as nonsteroidal anti-inflammatory drugs (NSAIDs), local anesthetics, antiepileptic drugs, antidepressants, topical agents (capsaicin, doxepin, topical NSAIDs, anesthetic patch), skeletal muscle relaxants, and opioids are currently available and their use individually or in combination seems to be effective in the treatment of chronic pain disorders[18]. Furthermore, the combination of pharmacotherapy with nonpharmacologic therapies can play a key role in mitigating pain. Nonpharmacologic strategies including interventional pain management, physiotherapy, and psychotherapy as well, pain rehabilitation can decrease fear, reduce

distress, pain and anxiety, minimize adverse effects and allow patients to have an active role in self-managing their symptoms[19].

However, current pain pharmacotherapies present dose-related adverse side effects and insufficient efficacy in several kinds of pain disorders[20]. For example, NSAIDs and steroids, amongst the most habitually prescribed drug groups, potentially present severe side effects in the gastrointestinal tract (ulcers, bleeding, myocardial infarction, stroke and infections)[21,22]. Regarding local anesthetics, some of them are linked with a short action period which is inadequate at the clinical level, being often necessary to administer them in combination with neural blockade enhancers. In addition, the use of potent local anesthetic drugs such as bupivacaine can involve serious side effects on the heart and peripheral blood vessels (cardiotoxicity) and on the central nervous system (neurotoxicity)[23]. Likewise, the widespread use of opioid therapy for patients suffering pain continues being a controversial issue due to the reduction of their analgesic efficacy through the course of treatment and their limited clinical utility as a consequence of induced side effects. Most commonly reported opioid-induced side effects happen at gastrointestinal, cutaneous , neurologic and autonomic levels[24,25]. As a consequence, medication adherence is negatively affected, leading to discontinuation of the treatment and, so, non-effective pain control, inadequate relief and reduced responsiveness to the treatment. Also, unpleasant side effects can affect the quality of life of patients according to the willingness of these patients to adapt to a new lifestyle. Recently, the implementation of different approaches has been recommended to attempt to reduce the resulting side effects of conventional opioids both before and during opioid treatment in elderly patients[26]. Some of these strategies include dose reduction, opioid rotation, altering the route of opioid administration, and symptomatic management of adverse effects[26]. However, efforts to overcome these adverse effects

have met with limited success. In addition, several studies have associated high rates of opioid prescription with an increased risk of abuse, addition, overdose and death[27,28].

To date, treatment methods for chronic pain are limited and many patients continue to receive ineffective treatments. In 2010, the Institute of Medicine (IOM) on pain in the U.S. reported that the strategy to address this problem is based not only on the development of new drugs but also on educating health care specialists in the complex etiology, prevention, assessment, and safe and efficacious treatment of pain[29]. Thus, the development of new treatments for chronic pain is a high-priority in the medical field.

5. NANOPARTICLE-BASED FORMULATIONS IN PAIN TREATMENT

Researchers have been focused on the manufacturing of both organic and inorganic nanoparticle formulations intended for the delivery of a variety of pain drugs including local anesthetics, NSAIDs or opioids (Figure 3). Herein, the current progress and challenges in synthesizing nanoparticulated drug delivery systems for pain management are reviewed.

5.1. ORGANIC NANOPARTICLE FORMULATIONS

Among all types of drug carriers, organic nanoparticle formulations, including liposomes, polymeric nanoparticles, niosomes, solid-lipid nanoparticles, dendrimers and polymeric micelles, are offering unique advantages for their applications in the nanoparticle-mediated drug delivery field. The design of nanoparticles, their physicochemical properties of bioavailability, biocompatibility and biodegradability as well as the ease of using them for drug encapsulation, the precise control of the drug release at the desired site and pharmacokinetic properties are important parameters which are going to dictate their therapeutic outcome. In this section, we will review

specific examples of applications of organic nanoparticles as drug delivery systems for pain relief.

LIPIDS BASED SYSTEMS

Vesicle based

Among the numerous nanoparticle formulations employed, liposomes, spherical vesicles made up of one or more phospholipid bilayers, have been studied profoundly as suitable candidates for chronic pain treatment (Table 1). Several studies demonstrated prolonged duration of anesthetic effect of some of the most commonly used local anesthetic after their encapsulation into liposomes. Thus, different liposomal formulations encapsulating intermediate-duration local anesthetics (prilocaine, lidocaine or mepivacaine) increased the duration and the intensity of anesthetic effect compared to plain solutions of each of these three local anesthetics[30]. For example, the duration of infraorbital nerve blocking was significantly prolonged in rats using liposomal prilocaine in comparison to free prilocaine, demonstrating an example of their effectiveness as an alternative to replace the local anesthetics in clinical practice[31]. In a later study, physicochemical stability after a sterilization process and local toxicity of this liposomal formulation were evaluated as a previous step to consider its possible use in future clinical trials. Studied liposomal formulation did not cause inflammatory response on rat paws, corroborating their safety as long acting local anesthetic carrier[32]. A similar *in vivo* study also demonstrated that encapsulation of ropivacaine into unilamellar vesicles substantially improved the intensity of their anesthetic effect and, thereby, prolonged the duration of sciatic and infraorbital nerve blockades in mice and rats, respectively[33]. In addition, this ropivacaine liposomal formulation did not induce toxicity *in vitro* or *in vivo*, indicating that liposomes have a cellular protective effect avoiding the usual cytotoxic effects of plain ropivacaine. The evaluation of the

local toxicity of liposomal mepivacaine formulations administered intra-orally in rats showed similar results. The authors demonstrated that this oral injection did not evoke a greater inflammatory reaction than that produced by a 0.9 % NaCl solution[34]. Taking into account these results, it could be said that the development of sustained release liposomal formulations containing local anesthetics improves their bioavailability and, thereby, enhances their pharmacological actions and reduces the local and systemic toxicity of these drugs compared to in their free form, and as such they are gaining popularity as promising candidates to alleviate pain in the dentistry field.

On the other hand, liposomes are already being used as carriers of NSAIDs, non-specific inhibitors of the cycloxygenase pathway thus suppressing the generation of inflammation mediators such as prostaglandins. Encapsulation plays a pivotal role in improving the efficacy, safety and tolerability of these active molecules[35]. For example, the significantly greater antinociceptive response exhibited by diclofenac loaded liposomes with respect to the nonencapsulated form, has been attributed to an enhanced drug solubility and more effective delivery of the loaded diclofenac to the targeted area[36]. The evaluation of the antinociceptive activity of this liposomal diclofenac was carried out in Sprague Dawley rats and male Balb/C mice using well-established nociceptive assay models half an hour after ingestion of the drug, exhibiting a significantly higher antinociceptive response, better inflammatory pain inhibition and a greater tolerance for mechanical and thermal hyperalgesia in comparison to the non-encapsulated form of diclofenac. Elron-Gross et al.[37] reported high encapsulation efficiency of diclofenac in two different types of bioadhesive liposomes covered with either hyaluronan or collagen, reaching therapeutically-relevant doses (13 mg /ml drug). Both liposomal formulations behaved as controlled release diclofenac depots with half-lives of biologically active ingredient in a period of few days. These liposomes had a

great affinity for specific sites binding to recognition sites and moleculesin CT-26 cell lines, resulting in an increased retention of the liposomes in the targeted area where diclofenac needed to exert its action. In a later study, the same authors demonstrated that drugs retained their biological activity after encapsulation in this novel drug-carrier formulation based on liposomes. These results were confirmed in a rat osteoarthritis model, demonstrating substantially reduced inflammation levels over time, in comparison to control animals after a single intra-articular injection[38]. Also, these authors carried out the co-encapsulation of sodium diclofenac and dexamethasone, a hydrophilic and a hydrophobic drug respectively, in the same liposome in an effective manner.

Regarding dermal topical anesthetic agents, Paavola et al.[39] studied the sustained ibuprofen release and *in vitro* dural permeation of liposomal gels of ibuprofen, showing a prolonged release and a marked increment of dural ibuprofen permeation compared with the control gel formulations.

The transdermal administration of conventional liposomes to provide successful delivery of drug molecules into systemic circulation is a controversial issue. Although some reports suggest that liposomes are suitable carriers for skin drug delivery, many studies have shown that these carriers are not very effective due to their limited ability to go across the stratum corneum before reaching their cellular target[40]. For this reason, efforts are being made to design a new generation of liposomes with increased elasticity and flexibility, with the intent of overcoming the existing drawbacks. For example, Duangjit et al.[41] compared the capability of ultradeformable, deformable and conventional liposomes to deliver meloxicam, demonstrating that the first two formulations were the most efficient vehicles for transdermal drug delivery of this NSAID.

Liposome encapsulation of opioids is one of the alternative approaches used in the field of pain management in order to avoid the serious central side effects of opioids. Significant differences in the encapsulation efficiency and in the release kinetics were observed when the most commonly used opioids (morphine, alfentanil, fentanyl, and sufentanil) were encapsulated into D-α-dipalmitoyl phosphatidylcholine multilamellar liposomes compared to the use of the drug in free form[42]. Similarly, a method based on the hydration-rehydration technique was used to efficiently encapsulate the agonist opioid drugs oxymorphone and hydromorphone into liposomes. When liposome-encapsulated oxymorphone was administrated subcutaneously in a single dose in a neuropathic pain rat model, it prevented the development of thermal hyperalgesia for up to seven days[43]. Similar studies have shown prolonged analgesic effects of liposome-encapsulated hydromorphone after subcutaneous administration in chronic constriction injury model rats. It is worth mentioning that the analgesic effectiveness took place at both a pre-emptive level as well as once the neuropathic pain had developed due to the ability of this novel formulation for reversing thermal hyperalgesia for an extended period of time compared to non-loaded hydromorphone[44].

Several ligands have been incorporated across the nanoparticle surfaces to increase their binding affinity to targeted sites. Thus, loperamide HCl loaded immunoliposomes conjugated with the anti-intercellular adhesion molecule-1, (ICAM-1), antibody were designed to provide prolonged analgesic and anti-inflammatory effects by delivering the encapsulated opioid directly at the site of inflammation[45]. After intravenous administration in rat models with chemically-induced inflammatory pain, these targeted nanoparticles exerted a localized response at the peripheral inflammatory site, improving the therapeutic potency of this pharmaceutical formulation. In a similar way, the RGD targeting peptide was incorporated to the surface of tramadol encapsulated

liposomes in an attempt to increase the permanence of this formulation at targeted cells, raising the overall effectiveness of the opioid drug. In fact, the intranasal administration of a liposome-containing aerosol resulted in a greater analgesic effect as well as in a slower therapeutic onset in comparison with the non-loaded drug formulation. Hoekman et al[46] hypothesized that RGD peptide anchored in the liposome surface may facilitate its binding to integrin proteins on olfactory epithelial cells, resulting in retention of fentanyl for an extended time period.

More recently, new efforts directed toward the development of an external stimuli-responsive liposomal drug delivery have been made with the objective of providing on demand adjustable control over drug release that allows patients to adjust the duration and intensity of local anesthesia in parts of the body where pain occurs according to patient's needs. For instance, a proof of concept carried out by Rwei et al.[47] showed that a temporal control of sciatic nerve blockade could be achieved in response to near-infrared light irradiation using phototriggerable liposomal nanoparticles containing tetrodotoxin (TTX). Only a mild inflammatory response was observed at the site of nanoparticle injection. Similarly, gold nanorods attached to temperature sensitive liposomes produced repeatable and adjustable on-demand anesthesia infiltration or sciatic nerve blockade with minimal toxicity upon NIR irradiation[48].

In addition to the aforementioned systems, ethosomes are a new class of vesicular nanocarriers whose use has evolved as non-invasive drug delivery systems over the past several years (Table 2). Ethosomes, unilamellar or multilamellar vesicles made up mainly of phospholipids, ethanol as a permeation enhancer, and water, were developed in the late 90s to resolve the problems associated with the incapacity of liposomes to cross the intercellular channels of the stratum corneum, that act as a rate limiting factor during drug permeation. Ethanol aids in the fluidization of the intercellular lipids

through the stratum corneum. In addition, the development of these ethanol-based vesicular carriers for transdermal delivery has become an interesting research area because this route of administration has many advantages over others, including the avoidance of gastrointestinal tract problems and hepatic first pass effects as well as improvement in patient compliance. A few studies have evaluated the potential use of ethosomes to deliver different local anesthetics transdermally. Different ethosomal formulations containing ropivacaine[49], lidocaine[50,51] or benzocaine[52] were synthetized and characterized in terms of particle size and superficial charge, morphology, encapsulation efficiency and vesicles stability with the objective to establish the most appropriate synthesis parameters in each case. In addition, different preclinical studies were employed in these research efforts to evaluate the potential of various local anesthetic loaded ethosomal formulations showing an enhanced penetration into the skin layers in all cases. The only histopathological study proved that ethosomal formulations significantly modified the structure of the stratum corneum, observing swelling and increment of total thickness[49].

Similarly, ethosomal formulations have been proposed as potentially useful carriers for transdermal delivery of NSAIDs such as ketoprofen and sodium diclofenac[53,54]. In this scenario, aceclofenac loaded ethosomes were prepared, optimized and characterized by measuring different physicochemical properties and entrapment efficiency, demonstrating that they offer more vesicle density, drug loading, and deformability index as compared with that of other elastic membrane-based vesicles[55]. It has also been proven that formulations and physicochemical properties (vesicle size, elasticity and zeta potential) of diclofenac loaded ethosomes play a considerable role in the skin permeability enhancement and, thereby, in the therapeutic results[56].

For ease of their application and storage stability, ethosomal systems have been successfully incorporated in proper carriers such as gels, achieving the required viscosity and bioadhesive properties for an efficient adhesion to the skin. Optimized formulations of ibuprofen, indomethacin, aceclofenac, lorxicam or piroxicam loaded ethosomal vesicles were dispersed in a gel using carbopol, one of the most commonly used gel-forming agents, achieving pharmaceutically acceptable formulations [57–61]. In general, *in vivo* pharmacodynamic studies of these nanoethosomal gels showed improved skin permeation and enhanced anti-inflammatory activity compared with control formulations. For example, a more effective anti-inflammatory activity was observed when meloxicam nanoethosomes added into carbopol-based gels were evaluated in a rat paw edema model induced by carrageenan [62]. Thus, the inhibition of swelling of the edema by this formulation was higher than that observed with oral administration of meloxicam.

Particle based

Solid lipid nanoparticles (SLNs) are nanocolloidal drug delivery systems that have emerged as alternative systems to the existing traditional carriers (i.e., polymeric nanoparticles, liposomes and others) to overcome limitations such as poor physicochemical stability and low encapsulation efficiency for hydrophobic drugs (Table 3). These nanosized particles, which have a solid lipid matrix made of physiologically well-tolerated, biocompatible, and biodegradable lipid components, present several benefits such as low acute and chronic toxicity, improved physical stability, low cost, free organic solvent synthesis, ease of scale-up and sterilization. Only a few studies have been published concerning the encapsulation of local anesthetics by SLNs. In one study, lidocaine loaded solid lipid nanoparticles prepared with solid lipids of different melting points were synthetized for the purpose of

prolonging the short duration of the epidural analgesia of this local anesthetic. Although all formulations showed a sustained release profile, which depended on the nature of the selected solid lipid, glyceryl palmitostearate-based SLNs demonstrated the longest extended-effect[63]. Although no sign of local anesthetic toxicity or irreversible functional impairment was observed, the authors pointed out that more extensive toxicity testing is required to establish the specific adverse effects, if any, of this investigational formulation. Some studies have also reported the incorporation of SLN dispersions into hydrogel-based formulations suitable for topical applications. For example, the intensity and duration of anesthesia using benzocaine significantly improved when benzocaine loaded SLN-based hydrogels were used compared to just benzocaine hydrogels[64]. SLN-based hydrogels with lidocaine were also prepared, characterized and successfully used in preclinical studies. As well, *in vivo* efficacy results of the nanoparticulate systems on guinea pigs showed a prolonged anesthetic effect with lidocaine loaded SLNs acting as depots from which the local anesthetic was slowly released [65].

Recently, a variety of topical systems based on SLNs has been used for administration of active substances and have shown success in preclinical studies. This method of administration is the most preferred route for management of ocular inflammations. In fact, ocular drug delivery has become a major challenge because most of the topical ophthalmic formulations commercially available reach the inner ocular tissues with difficulty and therefore are associated with poor bioavailability. NSAIDs such as indomethacin have been successfully incorporated in SLNs significantly improving ocular bioavailability possibly because of improved pre-corneal retention and enhanced drug corneal permeability[66]. Furthermore, a cationic polymer, chitosan, was used to coat the surface of indomethacin loaded SLNs to obtain an enhanced ocular penetration

of the encapsulated therapeutic agent and, thereby, higher drug levels in inner ocular tissues due to the adhesive properties of chitosan[67].

Regarding topical delivery to the skin, SLNs could be used as potential vehicles for prolonged and targeted delivery and, therefore, successfully resolve the problems related to the systemic toxicity of these anti-inflammatory drugs. For example, an enhanced concentration of the naproxen remained retained locally in the skin, increasing the anti-inflammatory response of the encapsulated drug in an *in vitro* skin permeation study carried out with naproxen loaded SLNs[68]. Recently, Peng et al.[69] observed high encapsulation efficacy of piroxicam in SLNs accompanied by an *in vitro* sustained release of the entrapped drug compared to formulations containing the free NSAID. One of the strategies used to enhance drug delivery through skin is the introduction of structural modifications within the skin by adding chemical enhancers. Thus, these authors added oleic acid, a chemical permeation enhancer, to topically administrate piroxicam-SLNs solutions, achieving a substantial improvement in skin penetration. The anti-inflammatory response of different platforms was evaluated in a rat paw edema model induced by carrageenan. The highest inhibition rates were achieved when SLNs were used as carriers of piroxicam together with oleic acid as a permeation enhancer. However, similar results in reducing carrageenan-induced injuries were observed with piroxicam-SLNs with or without added oleic acid groups. Kaur et al.[70] recently evaluated the use of diflunisal loaded SLNs gel formulations for topical/dermal application. *Ex vivo* skin permeation/retention assays and preclinical investigations in various animal models for therapeutic efficacy evaluation revealed the potential of these formulations to effectively treat local inflammatory conditions associated with various pain disorders. Thus, better skin permeation and retention were observed in comparison to conventional cream formulations (oil-in-water (o/w) cream). Several mechanisms

have been used to explain the mode of action of these carriers. In general, SLNs promote skin permeation owing to their occlusive and adhesive properties. Thus, they adhere to the skin surface forming a hydrophobic monolayer that combines with the skin lipidic film, providing an occlusive effect. The formation of an occlusive layer reduces the loss of moisture, maintaining sufficient skin hydration which ultimately facilitates drug penetration into deeper layers of skin. In addition, SLNs may interact with lipids in the outermost skin layer, resulting in a modified stratum corneum morphology and increased drug penetration across the skin. On the other hand, good skin retention has been assigned to better contact of the incorporated drug with the outermost layer of the epidermis thanks to elevated surface area offered by the nano-scaled SLNs.

Similar results were observed after intra-articular administration of celecoxib loaded SLNs, exhibiting sustained release properties, enhanced retention of the NSAID in the joints and lower distribution in the reticuloendothelial organs than free celecoxib[71]. Regardless of the via of administration, the histopathological studies carried out in the above cited reports established the biosafety of SLN-based systems on mice skin and on rat joints, respectively[70,71].

The search of more efficient, safer and innovative opioid-based controlled release formulations has driven researchers towards the encapsulation of these chemicals in SLNs. In this context, a high entrapment rate of buprenorphine hydrochloride and its methylated prodrugs into SLNs was achieved by Wang et al.[72] The buprenorphine-loaded SLN-based formulation presented a moderate release profile of the drug, prolonged antinociceptive effect, and reduced toxicity. Küchler et al.[73] developed morphine-loaded SLNs as a new and innovative approach to topically apply opioids and, thereby, to reduce pain in severe skin wounds. Although these authors described

the influence of the unloaded and morphine loaded nanoformulations in different processes of wound healing such as keratinocyte migration and re-epithelization, drug release profiles of morphine-loaded SLN was not reported.

A second generation of lipid nanoparticles, called nanostructured lipid carriers (NLCs), has appeared in an attempt to overcome limitations of SLNs such as low drug payload capacity and risk of drug loss during the solidifying step of the synthesis process and upon storage[74] (Table 4). In fact, the encapsulation of benzocaine and lidocaine in NLC dispersions was evaluated by Puglia et al.[75], exhibiting better results in terms of encapsulation efficiencies for both local anesthetics than those formulations based only on SNLs. In addition, the authors corroborated the influence of the lipid phases of these nanoparticulated systems in the *in vitro* drug release rate, as previously described[76]. In this case, both the drug partition between oil compartments and solid lipid and a progressive interface between solid lipid and water seem to be responsible for a sustained drug release. These authors reported a prolonged antinociceptive effect achieved when lidocaine or benzocaine loaded NLCs were topically applied on the rat-tail, most likely due to the creation of a depot of therapeutic agent into the upper skin layers.

Ribeiro et al.[77] optimized a process for the synthesis of NLCs based on cetyl palmitate and capric/caprylic triglycerides for delivery of the local anesthetics lidocaine and prilocaine applied in dentistry. The optimal formulation, which was physicochemically stable during 14 months in storage at room temperature, presented desirable structure-dependent properties, high encapsulation efficiency of the eutectic mixture of both local anesthetics and satisfactory sustained release profile, confirming the potential of this formulation for use during and after the dental procedures.

As in other formulations, the objective of the encapsulation of NSAIDs in NLCs is to improve their pharmacokinetic and pharmacodynamic properties and avoid the adverse effects produced at the gastrointestinal level. For example, oxaprozin loaded NLCs functionalized with folic acid were designed to overcome the side effects that this NSAID produces when it is administrated orally [78]. Also, flurbiprofen or indomethacin-loaded NLCs [67,79] and flurbiprofen or lornoxicam loaded NLCs[80–82] have been designed, optimized and proposed as delivery systems suitable for ocular and transdermal delivery, respectively. These topical formulations were used and were shown to enhance efficiency in *in vitro* or in preclinical studies. Similarly, in order to ameliorate the bioavailability of ocular medications, the viscosity and mucoadhesive properties of ibuprofen-loaded NCLs were modified by means of the combination of these lipid nanocarriers with the thermoresponsive polymer Pluronic F-127 to extend the precorneal residence time and to improve the drug availability. These new ophthalmic formulations based on NLCs, which turned into a gel at corporal temperature, presented high encapsulation efficiency and a prolonged ibuprofen release profile[83]. Although the data obtained in *in vitro* biocompatibility studies did not show cytotoxic effects of optimized formulations in Y-79 human retinoblastoma cells, the authors pointed out that others preclinical studies have to be carried out to corroborate the biosafety of the developed NLCs for ocular drug delivery.

NSAID loaded NCL carriers have also been investigated for topical treatment of skin diseases. For example, celecoxib[84], meloxicam[85,86], indomethacin[87], ketoprophen and naproxen[88], and valdecoxib[89] have been incorporated into NCL-based gels to improve current topical drug therapy. Once more, authors hypothesized that the small size and the high specific surface area of these nanocarriers ensure close contact with the stratum corneum, thus provoking a reduced burst drug release. Instead,

the formation of a drug depot using those vectors guarantees the increase in the residence time and the release of the active ingredient in a sustained mode toward deeper skin layers. Generally, this dermal location of the carriers allows for a skin targeting effect, reducing drug side effects by means of lower systemic uptake of the drug. In addition, it is worth mentioning that Khurana et al.[86] observed that the application of meloxicam-NLC gel induced a significant reduction of the total lipid content of the stratum corneum, leading to the disruption of the barrier properties and facilitating drug permeation into the skin. In addition, toxicity screening of meloxicam loaded NLC gel showed suitable skin tolerability and safety for transdermal delivery. In the only previous study concerning the encapsulation of opioids in NCLs, several lipid nanocarriers with different liquid oil/solid lipid ratios were used to encapsulate buprenorphine and its ester prodrugs (buprenorphine propionate, valerate and enanthate) with the main purpose of modifying its pharmacokinetics and, thereby, overcoming the current limitations of the clinical use of this drug for treating chronic pain[72]. In spite of having a moderate drug release profile among all tested carriers, loading buprenorphine propionate into NLCs prolonged the duration of the antinociceptive effect up to 10 hours, being the most potent carrier tested in this study. The utilization of the prodrug approach together with the design of delivery systems based on lipids seems to be a good strategy to achieve a prolonged efficacy of opioid agents.

POLYMER BASED SYSTEMS

Polymeric nanoparticles, composed of natural, semi-synthetic, and/or synthetic polymers, have been extensively studied as promising organic nanoparticle systems for pain treatment (Table 5). Major advances have been registered in the synthesis, formulation, processing, and characterization of new polymer-based nanoformulations to improve the therapeutic outcome of various pain killers. One of the current

approaches consists of the development of sustained delivery drug systems to provide long-lasting therapeutic alternatives with reduced toxicity. Biodegradable polymers such as polylactic acid (PLA), poly(lactic-co-glycolic acid) (PLGA) and polycaprolactone (PCL) used in a multitude of FDA approved therapeutic devices have also been widely used to synthesize local anesthetics loaded nanoparticulated carriers, providing a base for future applications in pain management. In this regard, PLGA nanocarriers containing bupivacaine, ropivacaine or benzocaine [90–94], lidocaine encapsulated PCL nanospheres[95], and benzocaine-loaded PLA or PCL nanocapsules[96] have been proposed as interesting candidates to overcome the drawbacks of local anesthetic. De Mello et al.[94] pointed out the importance of the composition of the core not only in parameters such as toxicity, good physicochemical stability and others but also in boosting the efficiency of analgesia. In regard to sciatic nerve blockade by local anesthetics encapsulated in polymeric nanoparticles, similar findings have been reported in several studies, indicating that local anesthetic loaded formulations significantly enhanced the intensity and duration of analgesia in comparison to non-loaded drug[94,95,97].

Both natural and synthetic polymers can be blended for developing new polymeric materials with improved physical and mechanical properties and biocompatibility in comparison with those made of just synthetic polymers. In order to improve the pharmacological properties of bupivacaine, alginate/bis(2-ethylhexyl) sulfosuccinate (AOT) and alginate/chitosan nanoparticles loading this local anesthetic were developed and characterized, obtaining a slower and sustained drug release profile in comparison with free bupivacaine. These potential pharmaceutical carriers, were physicochemically stable and presented a significantly reduced toxicity with respect to just bupivacaine[97]. In another similar study, two hydrophilic nanocarriers with different

structures, alginate/chitosan nanospheres and polietilenglicol (PEG)-PCL nanocapsules, were used to encapsulate arcaine, a dental, amide-type local anesthetic. Overall, higher encapsulation efficiency, a slower release profile, and a lower toxicity were observed in the case of PEG-PCL nanocapsules in comparison to the other formulations and unloaded drug[98].

In relation to NSAIDs, numerous reports concerning the application of formulations based on polymers have been published: piroxicam-loaded nanoparticles consisting of PLGA and Eudragit® RL[99], ibuprofen-loaded Eudragit® S100 nanoparticles[100], diclofenac sodium loaded Eudragit® L100 and Eudragit® L100-(PLGA) nanoparticles containing [101], celecoxib-loaded PCL-, PLA-, or PLGA-nanoparticles based topical ophthalmic formulations[102], N-trimethyl chitosan nanoparticles containing sodium diclofenac [103], meloxicam loaded PCL nanoparticles[104], ibuprofen-sodium loaded PEGylated gelatin nanoparticles[105], indomethacin-loaded Eudragit L 100 nanocapsules[106], piroxicam-loaded ethyl cellulose-based nanoparticles[107], and dexibuprofen-loaded PEGylated PLGA nanospheres[108] have been proposed as potential candidates to provide controlled release properties, enhancing the therapeutic efficacy of these drugs and reducing the severity of their gastrointestinal side effects. As mentioned in the liposomes section, recently, smart nanoparticles have been designed to react to external factors, such as pH, light, and temperature[109]. For instance, the release of the charged NSAIDs into indomethacin loaded smart nanoparticles based on pullulan-g-poly(N-isopropylacrylamide) (PNIPAM) and piroxicam-loaded polypyrrole nanoparticles was triggered by changes in temperature/pH and pH, respectively[110,111].

Several opioids have been encapsulated in polymer based pharmaceutical formulations with the purpose of protecting and delivering them at a desirable site, avoiding their

undesirable side-effects. For example, to facilitate the transport of nanoparticles containing molecules with therapeutic value through the blood-brain barrier, Lalani et al.[112] conjugated different ligands (transferrin and lactoferrin) to tramadol hydrochloride-loaded PLGA nanoparticles, achieving an enhanced brain uptake due to receptor mediated intracellular endocytosis. The most pronounced nociceptive effect was achieved after intravenous injection of tramadol-loaded PLGA nanoparticles surface modified with lactoferrin. Similarly, an efficient transport of loperamide to the central nervous system was achieved when loperamide-loaded PLGA nanoparticles were functionalized with an antibody against the transferring receptor, overexpressed in the blood-brain barrier[113]. Formulated nanoparticles crossed the blood-brain barrier and produce central analgesia at levels similar to those of the positive morphine control. The surface of the loperamide loaded-PLGA nanoparticles was also modified with octa-arginine 8 (cell-penetrating peptide) to improve blood-brain barrier delivery[114]. In fact, a rapid nanoparticle uptake was observed in an *in vitro* blood-brain barrier cell model, probably due to specific receptor-mediated transport[114]. In addition, although R8-PLGA NPs administered intranasally as well as intravenously showed the highest rates and extent of loperamide delivery, the profile of antinociceptive effect was different over time in both cases. In the same way, Kreuter et al.[115] demonstrated that only dalargin preadsorbed to polysorbate 80 coated polybutylcyanoacrylate, (PBCA), nanoparticles was able to enter the brain to cause antinociceptive effects.

The ability of chitosan nanoparticles to deliver the D-ala2-D-leu5-enkephalin synthetic opioid (DADLE) to neuronal cells in a sustained manner, protecting the loaded opioid from degradation and extending its analgesic response[116], was also reported. In addition, the encapsulation of tapentadol in stable polysorbate 80 coated chitosan nanoparticles has been proposed to prevent hepatic first pass metabolism, improving the

delivery of this opioid to the brain, and, thereby, improving its antinociceptive efficacy[117].

Nanogels, multifunctional polymer-based materials, are currently being explored as a strategy to create innovative targeted drug delivery systems. High drug encapsulation capacity, excellent thermodynamic stability, low viscosity, tunable size, ease of preparation and minimal toxicity are some of the potential advantages attributed to these hydrophilic three dimensional polymeric networks. For instance, a controlled release of piroxicam for more than 21 days was achieved when piroxicam-loaded polypyrrole nanoparticles were dispersed in a calcium alginate hydrogel, highlighting the importance of this extended delivery particularly for patients with chronic pain[110]. Hydrogels containing pranoprofen-loaded PLGA nanoparticles and chitosan–ibuprofen-gellan ternary nanogels have been also proposed as novel formulations with potential topical application[118,119].

The same as with the previously described nanoparticulated vectors, in recent years, research has also focused on the synthesis of smart nanogels sensitive to subtle change by environmental stimuli like the pH or temperature[120]. As such, nanogels based on thermoresponsive polymers have been designed with the objective of obtaining on demand drug delivery. For example, acid-functionalized nanogels based on PNIPAM were loaded with effectively high amounts of bupivacaine principally owing to the ionic interactions that take place between the anionic charges of the nanogels and cationic nature of this local anesthetic at physiological pH[121]. Regarding *in vitro* cytotoxicity assays and *in vivo* biocompatibility studies, nanogels exhibited minimal cytotoxic effects in a wide range of concentrations over several cell lines and, in general, they showed proper biocompatibility after peritoneal administration in model animals. Also, biodegradable nanoparticles in hydrogels were specifically used for encapsulating

lidocaine and prolonging infiltration anaesthesia without causing severe toxicity[122]. Foley et al.[123] synthetized ropivacaine-chitosan thermogel-based controlled release systems (with and without dexamethasone) to minimize the toxicity of the local anesthetic without loss of anesthetic effectiveness. The gel formulation made up of chitosan, ropivacaine and dexamethasone prolonged neural blockade activity in comparison with its counterparts after directly applying it on the sciatic nerve. Also, an inflammatory effect associated with the treatment was observed in all cases except for in the case of thermogels containing dexamethasone and having a low ropivacaine concentration (75 mg/Kg), postulating that the inflammation is likely an effect dependent of the dose of this local anesthetic. It is worth mentioning that adding dexamethasone to thermogels was able to ameliorate the observed inflammatory response[123]. Finally, a sustained release profile and a prolonged ocular residence time of ketorolac were obtained with a thermosensitive gel including ketorolac tromethamine loaded Eudragit® RL100 nanodispersions, improving the ocular availability of this NSAIDs in targeting without causing irritation to eye[124].

Dendrimers, are highly branched three-dimensional macromolecules with unique molecular architectures that provide them with improved physical and chemical properties when compared to traditional linear polymers (Table 6). Dendrimers have received a great amount of attention in recent years as drug delivery systems due to the presence of cavities in their structure, which are used to improve the solubility and provide protection against degradation of therapeutic agents. Also, the external surface of the dendrimers can be functionalized with the therapeutic molecule of interest. For example, Lamanna et al.[125] reported the successful coupling of ibuprofen moieties at the periphery of the different generations of adamantane-based dendrons. A greater availability associated with the multivalent nature of ibuprofen-dendron conjugates may

be the underlying reason for the enhanced anti-inflammatory effect of this drug compared to the free formulation. Some reports have been focused on the use of dendrimers as solubilizing agents of NSAIDs in water in order to enhance the drug bioavailability. For example, several reports showed a significant enhancement of the solubility of different NSAIDs (ibuprofen, ketoprofen, indomethacin and diflunisal) when they were associated with different types of dendrimers such as polyamidoamine dendrimers[126–128], triazine based dendrimers[129], ethylenediamine or polypropyleneoxide cored polyamidoamine (PAMAM)[130] and cationic carbosilane dendrimers[131]. Several types of drug-dendrimer interactions involved in both the entrapment of the active pharmaceutical ingredient inside the dendritic structure and the interaction of the drug with the periphery of the dendrimer seem to be implicated in the dendrimer-mediated solubility enhancement[132].

MICELLES

Micelles are formed by amphiphilic molecules, which self-assemble into nanosized core–shell structures at a level above that of the critical micellar concentration. During the past few decades, micelles have received growing scientific attention as drug delivery formulations due to their ability for solubilizing and stabilizing hydrophobic drugs in their inner core. In addition, their small size reduces the typically fast recognition by the mononuclear phagocytic system (Table 7). Scherlund et al.[133] demonstrated that a eutectic mixture of lidocaine and prilocaine loaded within mixed micelles possessed the required characteristics (proper gelation temperature, an adequate release profile and excellent long-term stability) for acting as a potential drug delivery formulation of anesthetics in the field of dentistry. A thermoresponsive mixed micellar nanogel system composed of lidocaine and prilocaine was also developed for topical delivery, attempting to improve pain relief therapy through localized delivery to

the site of action[134]. In this same manner, poloxamer (PL)-based binary hydrogels containing ropivacaine were prepared and characterized in order to prolong the duration of action of the local anesthetic ropivacaine and ameliorate the outcome during post-operative pain relief application, obtaining regular release profiles and lower drug release percentages in comparison with free drug used for the same amount of time[135]. The synthesis of novel mPEG-PLA/Solutol® HS15 mixed micelles were optimized to achieve the efficient solubilization of anesthetic agent propofol and, thereby, solve some the drawbacks of other developed propofol formulations[136]. Aforementioned, the poor solubility and the relatively short plasma half-life of NSAIDs as well as the side effects associated with their use make these kinds of drugs ideal candidates to be encapsulated within micelles. For example, Bhat et al.[137] studied the solubilization of naproxen in micellar solutions composed of single, binary, and ternary surfactant combinations. In general, the solubilization capacity of mixed surfactant systems was better than those of single-surfactant. Kulthe et al.[138] encapsulated another NSAID, aceclofenac in Pluronic L81/P123 mixed micelles, obtaining high drug entrapment efficiency and a sustained release profile. Also, several strategies were used to load indomethacin in poly(ethylene oxide)-poly(β-benzyl L-aspartate) block copolymer micelles as an alternative approach to reduce the side effects of this NSAID. The finding of this study showed that the indomethacin release pattern from the synthetized micelles was pH-dependent, controlled probably by the partition coefficient of the drug and the interaction between indomethacin and the hydrophobic portion of the carrier system[139]. Wu et al.[140] reported the synthesis of ibuprofen loaded complex micelles made of a biodegradable PLA-based core and a mixed PEG/PNIPAM shell. At temperatures above the lower critical solution temperature of PNIPAM, the chains of this thermoresponsive polymer collapsed onto the PLA core, acting as barriers

for the diffusion of the drugs into and out of the micelle. Simultaneously, the PEG chains stretched through the collapsed PNIPAM shell, leading to the creation of hydrophilic conduits around them, which act as a passageway for drug release. Therefore, the ibuprofen diffused in a slow manner through the channels and its release rate could be controlled by modifying the size and permeability of the channels by varying the PEG/ PNIPAM chains ratio in the corona.

SURFACTANT BASED SYSTEMS: NIOSOMES

Niosomes are biodegradable, biocompatible, and non-immunogenic closed bilayer structures created by self-association of non-ionic surfactants and cholesterol in an aqueous phase (Table 8). Their special structure makes it possible for them to entrap both hydrophilic and lipophilic drugs into the aqueous core and the membrane bilayer of the niosome, respectively. Thanks to this and other outstanding characteristics such as biodegradability, biocompatibility, non-toxicity and non-immunogenicity, enhanced drug penetration and sustained drug release profile, niosomes are broadly used in topical drug delivery.

Carafa et al.[141] studied the influence of different parameters such as vesicle composition and environmental pH condition in the encapsulation efficiency of lidocaine (free base form or hydrochloride) in different Tween20/Cholesterol vesicles. In addition, to analyze the influence of vesicle charge on therapeutic agent loading, dicetylphosphate and N-cetylpyridinium chloride were utilized to fabricate vesicles with negative and positive charge, respectively. Fluorescence quenching analyses showed that at pH similar to that of the skin (pH 5.5) the entrapment efficiency of lidocaine in positive and negative charged vesicles was negligible in compared to neutral vesicles. The obtained findings in diffusion experiments of drug loaded niosomal or liposomal

formulations through mouse abdominal skin exhibited the importance of non-ionic surfactant vesicles in dermal delivery of charged therapeutic agents[141]. Polysorbate-20 derivatized by glycine was used to prepare pH-sensitive niosomes for delivering ibuprofen or lidocaine. A remarkable reduction in vesicle dimensions was observed after drug encapsulation without modification of the corresponding ζ-potential values when compared to empty ones. Loaded vesicles were stable for 1 month at 25ºC and their stability was not modified by the addition of serum at pH 7.4. Lidocaine interactions with the hydrophobic moiety of tween and the existence of electrostatic repulsive forces between the carboxyl group of ibuprofen and the polar niosome surface were noted as reasons to explain greater and reduced entrapment efficiency for lidocaine and ibuprofen, respectively[142]. Diclofenac sodium and aceclofenac have been also loaded in niosomes in an attempt to improve poor skin penetration as well as enhance skin drug retention, achieving high efficiency as topical anti-inflammatory formulations[143,144]. Moreover, aceclofenac, lornoxicam, meloxicam, nimesulide, rofecoxib and, diclofenac diethylammonium loaded niosomal dispersions were incorporated into gel matrixes to create topical formulations with increased skin permeation as a promising alternative to treat pain associated to various inflammatory conditions[145–151]. In general, anti-inflammatory activity of the cited niosomal gel formulation was significantly higher than that achieved with the free drug or other non-niosomal gel formulation containing the free drugs.

5.2. INORGANIC NANOPARTICLE FORMULATIONS

In spite of the non-biodegradability, inorganic materials have widely emerged as good candidates for the delivery of an extensive range of drugs, providing several advantages in drug delivery applications due to their unique physicochemical properties such as

facile preparation, versatility, good storage stability and biocompatibility. Among these, structured porous inorganic materials have been outlined in this field owing to their well-known intrinsic properties such as mechanical and chemical stability under physiological conditions, large inner surface areas and high surface to volume ratios, colloidal stability, tailorable pore sizes and possibility of specific functionalization of their pore walls. In the developing research field toward the use of these materials to adsorb or encapsulate a wide variety of drugs and modify their release kinetics, few research studies have addressed the development of silica-based nanocarriers as hosts for local anesthetics, nonsteroidal anti-inflammatory and opioid drugs for pain management (Table 9). In one study, Abd-Elrahman et al. [152] reported high ketoprofen loading on SBA-15 and a reduction of the loading time combining two commonly accepted for that purpose, which are immersion and rotavapor-based method. Although no significant differences in the anti-inflammatory response and central analgesic properties of the drug loaded SBA15 and the commercial product, Ketofan, were found after 120 minutes of administration, their onset of action was very different, obtaining therapeutic benefit more rapidly in the case of the encapsulated ketofan. Also, several studies reported the inclusion of NSAIDs such as piroxicam, ibuprofen and indomethacin in MCM-41 and SBA-15 mesoporous silicas with the objective of enhancing the bioavailability and pharmacokinetic profile of these poorly water-soluble drugs[153–156]. Overall, these *in vitro* studies demonstrated the ability of mesoporous silicas to improve the dissolution rate of the drug loaded, most likely overcoming the low oral availability problem of these poorly water-soluble drugs. However, little is known about the potential *in vivo* absorption improvement of these new formulations. A multifunctional drug delivery system using MCM-41 mesoporous silica nanoparticles loaded with a cannabinoid (Δ9- tetrahydrocannabinol) and an erythropoietin-derived

polypeptide with tissue-protective actions (ARA29) was designed as a therapeutic strategy for suppressing chronic neuropathic pain. The findings showed that those nanoparticles significantly attenuated the inflammatory response at *in vitro* and *in vivo* levels. Additionally, the authors described a more potent effect in cells treated with nanocomplexes in comparison with the corresponding single drug controls, suggesting the existence of an additive or synergistic pharmacological effect of both drugs[157].

Other nanoparticle drug-delivery vehicles that have been widely explored for their application in the biomedical field include metal nanoparticles such as gold, silver, platinum, palladium, and hybrid organic/inorganic NPs. Despite their important role in the biomedical field, to our knowledge there are no reports in the literature about the utilization of metal nanoparticles for pain relief, suggesting that this topic remains largely unexplored.

Magnetic nanoparticles exhibit a wide variety of attributes, such as the intrinsic properties of their magnetic cores and their drug loading capability, which make them attractive platforms for targeted drug delivery. In particular, in the field of pain relief, magnetic nanocarriers functionalized with oleic acid and chitosan and diclofenac sodium-loaded Fe/ethylcellulose (core/shell) nanoparticles were developed as controlled diclofenac delivery systems for the treatment of inflammatory diseases[158,159]. Also, as drug carriers, they provide significant opportunities in locally targeted therapy (Table 9). Magnetic carriers associated with drugs can be directed or guided by means of an external magnet towards certain organs or tissues. This approach was used as a proof of concept by Mantha et al.[160] to produce anesthetic ankle block in rats using magnetic nanoparticles and ropivacaine complexes driven by a magnet. Thirty minutes after the magnet application at the ankle of the animals intravenously injected with the optimized complexed, an increased thermal antinociceptive response was observed. Also, it is

important to mention that an enhancement of the safe dose of ropivacaine was achieved after its combination with magnetic nanoparticles. This same strategy was used by Nadri et al.[161] to design bupivacaine-loaded magnetic hydrogel-based nanocomposites in order to induce rat ankle block. Neither of the studies previously cited completed formal toxicity studies, indicating the necessity of carrying out further research to address questions indispensable for its translation to clinical practice.

In the only previous study concerning the use of inorganic NPs without drugs as payload for pain relief, there was clear evidence that ultrasmall Fe_3O_4 NPs produce anti-allodynia and anti-hyperthermia effects in a dose dependent manner in a chronic inflammatory pain model in mice. This analgesic response probably happens via attenuation of inflammatory cell infiltration and reduction of ROS production[162].

6. CLINICAL STUDIES

Although nanoparticles present an exciting opportunity to obtain medical breakthroughs in the management of painful conditions, few clinical trials have been carried out and their current clinical use is limited.

To date, the majority of cited clinical trials have been carried out to evaluate the efficacy of liposomal formulations loaded with local anesthetics in the dentistry field. A systematic meta-analysis of the literature including clinical trials using liposomal formulations loaded with local anesthetic reported varied results. For instance, infiltration of mepivacaine liposomal (3%) at maxillary level resulted in more prolonged pulpal and soft-tissue anesthesia than the unloaded mepivacaine at the same concentration[34]. However, a randomized, double-blind, crossover design clinical study involving 40 healthy volunteers carried out to analize the efficiency of ropivacaine liposomal (0.5%) in dental anesthesia compared to three other local anesthetic combinations showed liposome encapsulation did not improve the anesthetic

effectiveness of ropivacaine for this anesthetic technique in humans[163]. Another comparative clinical trial was conducted in 40 volunteers to analyze the influence of liposome-encapsulated 2% ropivacaine on pulpal response in comparison with those observed with other topical formulations. The study concluded that although the dose of liposomal ropivacaine was effective to promote soft tissue anesthesia and to reduce pain during needle insertion, it was insufficient in inducing pulpal anesthesia[164]. A similar study carried out previously by the same authors showed equivalent results in relation to inducing pulpal anesthesia after topical application of liposome-encapsulated ropivacaine (1%)[165]. However, it is worth indicating that none of the studied topical formulations in both studies were able to induce pulpal anesthesia either. No significant differences were observed either between prilocaine loaded liposomes (3%) and free prilocaine or free prilocaine plus a vasoconstrictor[166]. The comparison of results obtained from different formulations in clinical trials remains difficult due to wide range of tested local anesthetics and selected doses in human trials.

Among the various routes of administration used, topical anesthesia plays a pivotal role in the control of pain and, therefore, in the comfort and safety of patients during clinical and diagnostic procedures. Several studies have also demonstrated that the encapsulation of local anesthetics in liposomes provides significant benefits for prevention of procedural pain. For example, the efficacy of liposomal lidocaine was evaluated during the dermal procedure of intravenous cannulation in children showing successful clinical benefits such as higher intravenous cannulation rate, less pain, shorter total procedure time and minor dermal changes[167]. Also, Franz-Montan et al.[168] showed in healthy volunteers that a topical gel composed of liposome-encapsulated (5%) lidocaine effectively increased the duration of tissue anesthesia and reduced pain during needle insertion with the same efficacy than commercially

available formulation EMLA®, making is a good candidate for efficient and effective topical anesthetic in dentistry.

The efficacy of NSAID skin-delivery systems based on liposomal based formulations was also demonstrated on healthy volunteers with UVB-induced erythema [169]. For example, the cutaneous application of indomethacin-loaded liposomes incorporated into hydrogels provided a more extended anti-inflammatory response compared to system composed of gel and the free drug, probably associated to a controlled release rate of the active ingredient to deeper skin layers in consequence of the interaction of loaded liposomes with the stratum corneum.

Similar results were observed in two independent studies after the indirect evaluation of ketopren or naproxen and indomethacin percutaneous absorption from NLC by monitoring the effect on on healthy human volunteers with UVB-induced erythema. In both cases, an extended and targeted anti-inflammatory response was observed, reflecting the grand potential of NLC as vehicles for dermal delivery[87,88].

Finally, it is noteworthy to mention that two drug delivery nanocarriers are already on the market. Diprivan®, an injectable emulsion formulation of propofol, was approved by FDA in 1989 for its utilization in the induction and maintenance of anesthesia or sedation in adults. Also, DepoDur®, an extended-release injectable formulation of morphine, was approved by the FDA in 2004 for the treatment of pain following major surgery. The efficacy of DepoDur® was demonstrated in different clinical trials performed in 876 patients undergoing surgical procedures such as hip arthroplasty, prostatectomy, colon resection and cesarean section. NKTR-119 is an investigational drug candidate based on the combination of Movantik® (naloxegol) and an opioid analgesic for pain relief without the gastrointestinal side effects associated with habitual opioid treatments.

Over the past few decades, the research on drug formulations has been aimed primarily at the design of drug delivery systems, which are capable of delaying and sustaining drug release and achieving selective delivery to specific physiological sites. Particulate drug-delivery formulations based on micro- and nanoparticles have become prominent in research as an alternative to overcome most of the shortcomings associated with traditional pharmaceuticals (instability, unfavorable pharmacokinetics, high toxicity, poor solubility and low cellular uptake). Particulate drug-delivery systems offer many advantages, including high drug stability, feasibility of incorporating hydrophilic and hydrophobic active principles, drug protection from degradation, modification of pharmacokinetics and drug tissue distribution profiles, improved efficacy, reduced toxicity, increase of drug circulation time (when intravenously administered), and a decrease of nonspecific uptake. Also, nanostructured materials show exceptional physicochemical properties such as small and controllable size, large surface area to volume ratio, high reactivity, and functionalizable structure. A number of micro- and nanoparticle-based therapies have been approved by the FDA for clinical use, highlighting the benefit of these drug formulations in the development of health care products for the area of pharmacology [170,171]. Specifically, in 2011, a bupivacaine liposomal injectable suspension, commercially named Exparel™, was approved by the FDA for single-dose administration into the surgical site to produce postsurgical analgesia in adults. The FDA approval of Exparel™ was based on two multicenter, randomized, double-blind clinical trials that evaluated their efficacy versus placebo in the treatment of patients undergoing two different surgeries, hemorrhoidectomy and bunionectomy. The use of bupivacaine loaded liposomes has proved to be a highly effective and safe treatment with adequate pharmacokinetics and pharmacodynamics reducing the risk of systemic toxicity[172,173]. Although Exparel™ was approved by

FDA exclusively for postsurgical analgesia in adults, several studies about their use in peripheral nerve blockade have been carried out in recent years. In the absence of published animal data about Exparel™'s biocompatibility in proximity to major nerves and muscles, McAlvin et al.[174] decided to determine the efficacy of this new bupivacaine liposomal formulation in sciatic nerve in rat models and evaluate their biocompatibility in near nerve tissues, comparing its effects with those of two different concentrations of bupivacaine HCl in its free form (0.5 and 1.3 % (w/v), a concentration of bupivacaine used in clinical practice and a concentration of bupivacaine equal to that in Exparel™, respectively). Histological evaluation at four days post-injection reported that both Exparel™ and bupivacaine hydrochloride 0.5% (w/v) produced a similar degree of myotoxicity and local tissue inflammation, consisting of a mixed inflammatory infiltrate in the soft tissues surrounding the muscle. However, in the case of Exparel™, the macrophages had a foamy cytoplasm; likely reflecting uptake of the lipid-rich particles and, in addition, inflammation lasted much longer. The histological findings also showed that inflammation and myotoxicity degrees were more severe in the case of bupivacaine HCl compared to that of encapsulated in Exparel™ when using equal concentrations. No neurotoxicity was observed in any of the treatment groups. In another preclinical study, conducted in rabbits and dogs to evaluate the potential safety of Exparel™, no local signs of toxicity were observed. The minimal to mild granulomatous inflammation of adipose tissue seen around nerve roots was associated with a nonspecific foreign-body type reaction[175]. In spite of the successful results obtained in preclinical studies, the data collected from 6 prospective and controlled clinical studies for the use liposomal bupivacaine in peripheral nerve blockade did not render sufficient data to obtain a final conclusion about their safety profile when utilized

in distinct classes of nerves in heterogeneous patient populations[176] and, thus, a more exhaustive evaluation has to be conducted.

More recently, the Company Heron Therapeutics, Inc. has developed an extended release biochronomer-based delivery system (HTX-011) that contains bupivacaine and meloxicam, as a preventative treatment for post-operative pain. Biochronomer™ technology consists of bioerodible polymers designed to release drug over long periods of time. Data from four phase II clinical trials evaluating HTX-011 as a preventative treatment for post-operative pain in several types of surgeries, including bunionectomy, hernia repair, and abdominoplasty, showed significant improvements in pain and reductions in opioid use. HTX-011 can be administrated by both injection and instillation. The evaluation of its efficacy and safety in an ongoing phase 2 randomized, controlled, multicenter study shows that the treatment with HTX-011 by injection or instillation is tolerated similarly well by patients undergoing elective open inguinal hernia repair [177]. In light of the obtained positive outcomes, a phase III clinical trial has been recently initiated by Heron Therapeutics, Inc. Company.

7. CONCLUSIONS

Over the last few decades, nanomedicine is enabling the development of numerous biocompatible nanoparticule drug carriers for their use in therapeutic applications, contributing significantly to the progress of medical science. Scientific evidence demonstrates that the nanoencapsulation of different painkillers in nanostructured carriers shows clear advantages compared to the administration of the drugs in their free form including the improvement of the drugs bioavailability and pharmacokinetic profiles and minimized side-effects. To translate these advances into clinical practice, it is necessary to perform an initial evaluation of novel nanotechnology-derived

pharmaceutical platforms in extensive *in vivo* clinical studies to achieve detailed information about the pharmacologic effects of administered materials in terms of efficacy and to determinedosing and toxicity levels with the objective of predicting possible adverse effects. Some of those nanostructured formulations have already reached the market highlighting the potential of the field to fulfill the unmet needs and to overcome the existing limitations in pain management.

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Table 1. Liposomal formulations for pain management described in the literature.

Nanoparticle Type	**Drug**	***In vitro* evaluation**	***In vivo* evaluation**	**Administration Route**	**Outcomes**	**Reference**
Liposomes						
	Local anesthetic					
Liposomes	Prilocaine, lidocaine or mepivacaine	-	Infraorbital nerve blockade test in rats	-	Increased analgesic duration and intensity for the three local anesthetics after their encapsulation	[30]
Liposomes	Prilocaine	-	Infraorbital nerve blockade test in rats	-	Prolonged anesthesia duration	[31]
Liposomes	Prilocaine	-	Local Toxicity Evaluation (paw edema test) Histological Analysis after administration in the oral mucosa of the right-upper first molar	Intraplantar	No inflammatory effects Less inflammatory reaction in the rat oral mucosa than that achieved by a commercial vasoconstrictor-containing	[32]

					formulation	
Liposomes	Ropivacaine	Cytotoxicity assay in sciatic nerve Schwann cells	Infraorbital nerve blockade test in rats Sciatic nerve blockade test in mice	Injection into the mouse sciatic nerve	Improved analgesic effect Decreased cytotoxicity of drug in comparison with the free drug	[33]
Liposomes	Mepivacaine	-	Local toxicity study in rats	Intra-oral	Liposomal drug might protect the tissue against local inflammation	[34]
Liposomal gel	Lidocaine	-	*Ex vivo* permeation study across pig palatal mucosa	-	The highest permeation compared to other formulations	[167]
	NSAIDs					
Liposomes	Diclofenac		Mechanical and thermal hyperalgesia evaluation in rats	Oral	Enhanced antinociceptive effects	[36]
Liposomes carrying hyaluronan or collagen on their surface	Diclofenac	Liposome-cell binding study in different cell lines	-	-	Increased retention of the liposomes in the targeted area	[37]
Liposomes carrying	Diclofenac and/or	-	Evaluation of anti-	Intra-	Reduced inflammati	[38]

hyaluronan or collagen on their surface	dexametason e		inflammatory activity in osteoarthritis model rat	articular	on volume compared to the untreated animals	
Liposomal gel	Ibuprofen	-	Ex vivo permeation accross pig dural membrane	-	Increased dural permeation of ibuprofen compared with the gel control	[39]
Ultradeforma ble, deformable and conventional liposomes	Meloxicam	Skin Permeat ion Study across excised skin of hairless mice	-	-	An efficient carrier for transderma l drug delivery	[41]
	Opioids					
Multilamellar liposomes	Morphine, fentanyl, alfentanil and sufentanil	-	Microdialysis experiments		Different parameters such as drug hydrophobi city and lipid content of the liposomes modulate drug distribution *in vivo*	[42]

Liposomes	Oxymorphone		*In vivo* pharmacokinetic assays. Thermal hyperalgesia analysis in neuropathic pain rat model	Subcutaneous	Long-term analgesia	[43]
Liposomes	Hydromorphone	-	Thermal hyperalgesia analysis in neuropathic pain rat model	Subcutaneous	Prolonged relief	[44]
Immunoliposomes	Loperamide	Cellular Uptake of Liposomes in primary high endothelial venule cells	Antinociceptive and inflammatory testing in acute inflammatory pain rat model	Intravenous	Analgesic and anti-inflammatory effects exclusively in peripheral painful inflamed tissue	[45]
RGD peptide anchored liposomes	Fentanyl	-	Pharmacokinetic study and analgesic pharmacodynamic effect analysis in rats	Intranasal (POD device)	More gradual, long-lasting analgesic effect in comparison with the free drug	[46]
Phototriggerable liposomal device	Tetrodotoxin	Cytotoxicity studies C2C12 and PC12	Neurobehavioral testing and histological studies in rats	Intramuscular	Not cytotoxic formulations *in vitro* and *in vivo* Light-sensitive	[47]

		cells			liposomes induced sensory and motor nerve block	
Gold nanorods attached to low temperature sensitive liposomes	Tetrodotoxin and dexmedetomidine	Cytotoxicity studies C2C12 and PC12 cells	Nociceptive behavioral testing in rats	Intraplantar	On-demand infiltration anesthesia or sciatic nerve blockade with minimal toxicity	[48]

Table 2. Ethosomal formulations for pain management described in the literature.

Nanoparticle Type	Drug	*In vitro* evaluation	*In vivo* evaluation	Administration Route	Outcomes	Reference
Ethosomes						
	Local anesthetic					
Ethosomes	Ropivacaine	-	Ex vivo permeation study in dorsal skin mice Vesicle-skin interaction histopathological study	-	Increased transdermal drug flux Modified the stratum corneum structure by the interaction ethosomes-skin	[49]
Ethosomes	Lidocaine	*In vitro* rat skin permeation and drug deposition studies	-	-	Skin penetration of drug and deposition of nanoethosomes in deep skin layers	[50]
Ethosomes	Lidocaine	*In vitro* Percutaneous Penetration across rat abdominal skin	*In vivo* Cutaneous Irritancy study	Topical	Excellent percutaneous drug penetration from ethosomes No evidence of skin erythema or swelling	[51]

Ethosomal gel	Benzocaine	*In vitro* permeation studies using artificial membranes simulating epidermal barrier	Anesthetic activity study in rabbit	Topical	Increased intensity and duration of anesthetic effect	[52]
	NSAIDs					
Ethosomes	Ketopren	*In vitro* permeation studies through adult Chinese female skin	-	-	Improved drug permeation and higher transdermal flux	[53]
Ethosomal gel	Diclofenac sodium	Skin permeation and drug deposition studies in rat skin	-	-	Ethosomal formulations can act as drug reservoir in skin and extend the pharmacologic effects	[54]
Ethosomes	Aceclofenac	-	*Ex vivo* permeation studies through mice abdominal skin Anti-inflammatory activity study in carrageenan-induced rat paw edema	Topical	Superior drug permeation and retention in comparison with conventional drug-containing products	[55]

			model			
Ethosomes	Diclofenac sodium	*In vitro* skin permeation study through rat abdominal skin	Anti-inflammatory activity study in carrageenan-induced rat paw edema model	Topical	Increased permeation and anti-inflammatory activity compared to control formulations	[56]
Ethosomal gel	Piroxicam	*In vitro* permeation study	-	-	Significant amount of drug transported across the skin when entrapped in ethosomes	[57]
Ethosomal gel	ibuprofen	-	Analgesic effect study in mice. Skin histological examination.	Trandermal	Drug ethosomal gel is safe Systemic antinociceptive effect in rats	[58]
Ethosomal gel	Aceclofenac	*In vitro* skin permeation study through rat skin	Anti-inflammatory activity study in carrageenan induced rat paw edema model	Topical	Improved anti-inflammatory activity in comparison with other control formulations	[59]
Ethosomal gel	Lornoxicam	*In vitro* diffusion study using cellophane	Anti-inflammatory activity study in carrageenan induced rat	Topical	Enhanced anti-inflammatory activity of	[60]

		membrane	paw edema model		ethosomal gel	
Ethosomal gel	Indomethacin	-	-	-	Higher entrapment efficiency for ethosomes than liposomes Increased viscosity and stability of the gel formulation	[61]
Ethosomal gel	Meloxicam	*In vitro* skin permeation study	Anti-inflammatory activity study in carrageenan induced rat paw edema model	Topical	Higher inhibition of swelling of rat paw edema by drug ethosomal gel compared with other formulations	[62]

Table 3. Solid lipid nanoparticles (SLNs) for pain management described in the literature.

Nanoparticle Type	Drug	*In vitro* evaluation	*In vivo* evaluation	Administration Route	Outcomes	Reference
Solid Lipid Nanoparticles (SLNs)						
	Local anesthetic					
SLNs	Lidocaine	-	Neurobehavioral testing and histological studies in rats	Epidural	Extended anesthetic effect with all tested formulations	[63]
SLNs gel formulation	Benzocaine	-	*Ex vivo* permeation studies in rat skin Analgesic effect analysis in rats	Topical	Higher drug permeation compared to free drug Improved intensity and duration of anesthetic effect	[64]
SLNs gel formulation	Lidocaine	Skin permeation studies using hairless abdominal guinea pig skin	Efficacy evaluation of gel formulations on pigs	Topical	Sustained release from SLNs and increased anesthesia duration	[65]
SLNs	Indomethacin	*In vitro* corneal	-	-	Improved corneal drug	[66]

		permeation studies and histological studies			permeability after encapsulation No major structural damage to the corneal epithelium	
SLNs and Chitosan-SLNs	Indomethacin	*In vitro* corneal and sclera-choroid-RPE permeation studies	*In vivo* bioavailability studies in rabbits	Topical application	Increased ocular drug penetration after surface modification with chitosan Superior transmembrane drug permeation compared to SLNs	[67]
	NSAIDs					
SLNs	Naproxen	*In vitro* skin permeation study in rat abdominal skin	-	-	Increased drug concentration at the top layers of the skin	[68]
SLNs and oleic acid-SLNs	Piroxicam	*In vitro* transdermal efficiency of the piroxicam from SLNs	Anti-inflammatory effect study in a carrageenan-induced rat paw edema model	Topical administration	Decreased inflammatory responses in the edema site and reduced secretion of inflammatory cytokines	[69]

					Oleic acid-SLNs significantly promoted the skin drug penetration	
SLNs gel formulations	Diflunisal	-	*Ex vivo* permeation studies across mice skin. Pharmacodynamic evaluation in three different animal models	Topical administration	Better permeation as well as skin retention compared to conventional formulations High-efficacy therapeutic effects	[70]
SLNs	Celecoxib	-	Biodistribution, pharmacokinetic and histological studies in Sprague Dawley rats	Intra-articular	Enhanced retention in the joint and reduced uncontrolled distribution to other organs Reduced toxicity of the drug and prolongation of their effects Assured biocompatibility	[71]
	Opioids					
SLNs	Buprenorphine and its prodrugs	-	Evaluation of analgesic effect in Sprague-	Intravenous	Moderate release, prolonged antinocicepti on and low	[72]

			Dawley rats		toxicity	
SLNs	Morphine	Evaluation of effect in 3D-wound healing model	-	-	Unloaded and drug-loaded SLN promoted wound reepithelialization	[73]

Table 4. Nanostructured lipid carriers (NCLs) for pain management described in the literature.

Nanoparticle Type	**Drug**	***In vitro* evaluation**	***In vivo* evaluation**	**Administration Route**	**Outcomes**	**Reference**
Nanostructured lipid carriers (NLCs)						
	Local anesthetic					
NLC	Benzocaine or Lidocaine	*In vitro* Skin Permeation Experiments	Antinociception test in mice	Topical	Decreased drug permeation through the skin and prolonged antinociceptive effect	[75]
Folate functionalized NLC	Lidocaine and Prilocaine	-	-	-	-	[77]
	NSAIDs					
NLC	Oxaprozin	Cell viability assay and cell uptake in RAW264.7 cells and cell permeability studies in Caco2 cells	-	-	NLC are not toxic Enhanced cell uptake over time Encapsulation did not interfer with oxaprozin permeability	[78]
NLC	Flurbiprofen	-	*In vivo* Draize test (irritation	Topical	Minimal irritation	[79]

			test) in rabbits			
NLC	Indomethacin	*In vitro* corneal and sclera-choroid-RPE permeation studies	*In vivo* bioavailability studies in rabbits	Topical	Higher drug concentrations in all ocular tissues tested	[67]
NLC	Flurbiprofen	*In vitro* permeation studies through rat abdominal skin	-	-	Improved permeated drug amount	[80]
NLC	Flurbiprofen	*In vitro* rat skin permeation studies	Anti-inflammatory activity evaluation in rats and pharmacokinetic studies	Topical	Increased drug bioavailability, sustained drug release and better therapeutic effect up to 24 h compared with the commercial gel	[81]
NLC	Lornoxicam	Drug penetration through rat skin	-	-	Increased skin penetration rate of the drug compared to a traditional gel formulation	[82]
NLC	Ibuprofen	Biocompatibility	-	-	The formulations	[83]

		studies in Y-79 cells			were safe at the concentrations tested	
NLC based gel formulation	Celecoxib	*In vitro* rat abdominal skin permeation studies	Pharmacodynamic efficacy	Topical	Rapid onset of action of the NLC gel	[84]
NLC based gel formulation	Meloxicam	Toxicity screening	*Ex vivo* rat abdominal skin permeation and skin deposition. Pharmacodynamic activity study in a carrageenan induced rat paw edema volume model	Topical	Hemocompatible, non-irritant and nontoxic gel formulation Improved skin permeation and deposition NLC based gel showed higher anti-inflammatory effect than the drug gel	[85]
NLC based gel formulation	Meloxicam	-	*In vivo* visualization of skin penetration Pharmacokinetic study in rat Toxicity study in mice and skin irritation study in rabbit	Topical	Good skin tolerability and biosafety Improved skin drug penetration Pronounced analgesic effect of the NCL-based gel	[86]

NLC	Indomethacin	Human skin membrane permeation study	Anti-Inflammatory activity in humans	Topical	Delayed and sustained activity of drug loaded NLC formulation	[87]
NLC	Ketoprophen and naproxen	*In vitro* skin permeation experiment	Anti-Inflammatory activity in humans	Topical	Extended anti-inflammatory effect of loaded active molecules, providing prolonged release in the epidermis	[88]
NLC based gel formulation	Valdecoxib	-	Skin irritation studies. Pharmacodynamic efficacy in aerosil-induced rat paw edema method		No signs of skin irritation Faster onset and prolonged anti-inflammatory activity with NLC formulations	[89]
	Opioids					
SLNs	Buprenorphine and its prodrugs	-	Analgesic effect evaluation in Sprague–Dawley rats	Intravenous	Moderate release, prolonged antinociception and low toxicity	[72]

Table 5. Polymeric nanocarriers for pain management described in the literature.

Nanoparticle Type	**Drug**	***In vitro* evaluation**	***In vivo* evaluation**	**Administration Route**	**Outcomes**	**Reference**
Polymer NPs						
	Local anesthetic					
PLGA nanospheres (NS)	Ropivacaine	Cytotoxic Assays in Balb/c mouse fibroblasts	-	-	PLGA-NS had no effect on cell viability.	[90]
PLGA nanocapsules	Benzocaine	Cytotoxic Assays in Balb/c mouse fibroblasts	-	-	No cytotoxic effect at tested concentrations	[91]
PLGA nanocapsules	Bupivacaine	-	-	-	Good physicochemical stability	[92]
PLGA NPs	Bupivacaine	-	Analgesic effect analysis in rats and and anti-allodynic effect analysis chronic constriction injury rat model	Subplantar region	Longer and higher analgesic and anti-allodynic activity in comparison to non-encapsulated drug	[93]
PLGA nanocapsules	Benzocaine	-	Sciatic nerve blockade evaluation	Intramuscular	Increased duration of motor blockade	[94]

			in mice		Increased duration and intensity of the antinociceptive effect in comparison to the free drug	
PCL nanospheres	Lidocaine	Cell viability assay in Balb-c mouse 3T3 fibroblasts	Sciatic nerve blockade evaluation in mice		Reduced toxicity Motor blockade were not affected Intense and prolonged analgesic effect of the optimized nanoformulation	[95]
PLA or PCL nanocapsules	Benzocaine	-	Sciatic nerve blockade evaluation in mice	Intramuscular	Enhanced anesthetic effect of benzocaine after its encapsulation	[96]
Alginate/chitosan NPs and alginate/bis(2-ethylhexyl) sulfosuccinate NPs	Benzocaine	Cytotoxicity assays in Balb-c mouse 3T3 fibroblasts	Sciatic nerve blockade evaluation in mice	Intramuscular	Increased duration and intensity of the anti-nociceptive effect in comparison to the non-encapsulated drug	[97]

Alginate/chitosan nanospheres and PEG-PCL nanocapsules	Articaine	Cytotoxicity assays in Balb-c mouse 3T3 fibroblasts	-	-	Drug encapsulation reduced its cytotoxicity	[98]
	NSAIDs					
Eudragit® RL and PLGA NPs	Piroxicam		Rats	Intra-articular	Prolonged drug retention in the joint	[99]
Eudragit-S100 NPs	Ibuprofen	-	-	-	Good stability, maximum entrapment efficiency and sustained drug release	[100]
Eudragit® L100 and Eudragit® L100/PLGA NPs	Diclofenac Sodium	-	-	-	The amount of Eudragit in the blend influenced in the encapsulation efficiency and the drug release profile	[101]
PCL-, PLA-, or PLGA-NPs	Celecoxib	Cytotoxicity assay in HEK293 cells	-	-	Excellent biocompatibility	[102]
N-Trimethyl/Chitosan NPs	Diclofenac Sodium	Eye Irritation test in rabbit corneal cell line cells	Eye irritation test and drug absorption study in albino rabbits	Ophthalmic	Drug -loaded nanoparticles were safe for ophthalmic use. Improved ophthalmic drug	[103]

					bioavailability	
PCL NPs	Meloxicam	-	Anti-inflammatory activity evaluation in carrageenan-induced paw edema model (Sprague-Dawley rats) Ulcerogenic study in the ulcer model	Oral	Higher activity anti-inflammatory effect for a longer duration Lower ulceration index than a free drug suspension	[104]
PEGylated gelatin nanoparticles	Ibuprofen Sodium	Hemocompatibility, plasma coagulation, platelet activation and aggregation, inflammatory response and cytokine induction lymphocyte proliferation, suppression and toxicity studies	Cytokine induction studies, pharmacokinetic analysis and histological analysis in Sprague Dawley rats	Intravenous	Non-toxic, hemocompatible and nonimmunogenic NPs Sustained drug release for 4 days with improved bioavailability and pharmacokinetics	[105]
Eudragit® L 100 nanocapsules	Indomethacin	Cytotoxicity study in HepG2 cells Genotoxicity study and	-	-	Nanocapsules were not cytotoxic to lymphocytes and HepG2	[106]

		cytokinesis-block micronucleus cytome assay in HepG2 cells and Human peripheral blood lymphocytes			cells Only the highest concentration tested caused a small increase in micronucleated cells, indicating a clastogenic/aneugenic effect	
Ethyl cellulose-based NPs	Piroxicam	-	Drug profile in blood samples, pharmacokinetic study, histological examination and gastric irritation test in Wistar rats	Oral	Time to reach maximum plasma concentration was significantly higher than that of commercial capsules Drug encapsulation into NPs suppressed significantly gastric ulceration potential in rats	[107]
PEGylated PLGA nanospheres	Dexibuprofen	Short-term stability Cytotoxicity assay human retinoblasto	*Ex vivo* corneal and scleral permeation experiments in rabbits	Ophthalmic	Significantly reduced cell viability Increased tropism to the cornea	[108]

		ma cell line. Ocular tolerance assays: HET-CAM	Ocular tolerance assays: Draize irritation test Inflammatory activity assay Ocular drug bioavailability		enhancing drug retention and permeation Good ocular tolerance Nanospheres were effective both preventing and treating inflammation	
Polypyrrole nanoparticles	Piroxicam	-	-	-	Sustained drug release profile	[110]
Pullulan-g-poly(N-isopropylacrylamide) NPs	Indomethacin	-	-	-	Drug loaded polymeric particles prepared by different methods High drug entrapment efficiency In vitro drug release depended on different parameters	[111]
	Opioids					
Lactoferrin or transferrin anchored PLGA nanoparticles	Tramadol hydrochloride	-	Antinociceptive test in mice	Intravenous	Extended antinociceptive effect	[112]
8D3-PLGA nanoparticles	Loperamide	Cell viability assay in HeLa and MDR-MDCK	Antinociceptive test in mice	Intravenous	Non cytotoxic Higher analgesia than negative	[113]

		cells			controls	
PLGA NPs surface modified with octa-arginine	Loperamide	Cell viability assay in Caco cells	Antinociceptive testing in mice	Intranasal and intravenous	No toxic at tested concentrations Highest rate and extent of drug delivery	[114]
Polysorbate-80-coated poly(Butylcyanoacrylate) nanoparticles	Dalarguin	Transendothelial permeability studies in an *in vitro* blood-brain barrier model	Antinociceptive testing in mice	Intravenous	A significant analgesic effect was produced by drug delivered to the CNS from formulated NPs	[115]
Chitosan nanoparticles	Delta opioid peptide (DADLE)	B50 rat neuronal cells	-	-	Prolonged intracellular effects of DADLE	[116]
Polysorbate 80 coated chitosan nanoparticles	Tapentadol	-	Pharmacodynamic studies in Wistar rats model of acute pain: Antinociceptive test	Intravenous	Central antinociceptive activity over a period of 24 h	[117]
Polymeric Nanogels						
	NSAIDs					
Ternary chitosan–ibuprofen–gellan nanogel	Ibuprofen	-	*Ex vivo* pig skin permeation and pig skin	-	Enhanced permeability	[118]

			retention studies			
Hydrogels containing pranoprofen-loaded PLGA nanoparticles	Pranoprofen	-	*Ex vivo* skin human permeation and *in vivo* anti-inflammatory efficacy studies in mice Draize irritation test in rabbits	Topical	No signs of skin irritancy One of the optimized semi-solid formulation prolonged drug contact on the skin and improved its skin retention, being more effective	[119]
PNIPAM nanogels	Bupivacaine	Cytotoxicity assays in different cell lines	Histological analysis to assay *in vivo* nanogels biocompatibility	Peritoneal	Minimal cytotoxicity to multiple cell types Well tolerated *in vivo*	[121]
Poly(e-caprolactone)–poly(ethylene glycol)–poly(e-caprolactone) nanoparticles in Pluronic F-127 hydrogel	Lidocaine	-	Antinociceptive testing in rats	Subcutaneous	Prolonged duration of anesthesia and long-lasting sensory blockade Non systemic toxicity or skin irritation/damage	[122]
Chitosan thermogels	Ropivacaine and dexamethasone	-	Neurobehavioral monitoring in rats: sensory	Direct application to the sciatic	Extended neural blockade activity with gel system	[123]

			and motor blockade	nerve	composed of chitosan, ropivacaine and dexamethasone	
Thermosensitive gel including Ketorolac tromethamine loaded Eudragit® RL100 nanodispersions	Ketorolac tromethamine	-	*Ex vivo* transcorneal permeation on excised bovine cornea and i*n vivo* pharmacokinetic study in rabbits	Ophthalmic	Improved corneal drug permeation High relative ocular availability	[124]

Table 6. Dendrimers and dendritic polymers for pain management described in the literature.

Nanoparticle Type	Drug	*In vitro* evaluation	*In vivo* evaluation	Administration Route	Outcomes	Reference
Dendrimers						
	NSAIDs					
Adamantane based dendrons	Ibuprofen	Cytotoxicity evaluation in murine RAW 264.7 macrophages Anti-inflammatory activity	-	-	The coupling of ibuprofen to a dendritic structure increased its cytotoxicity Enhanced anti-inflammatory activity of the drug	[125]
Polyamidoamine dendrimers	Ketoprofen	-	-	-	Enhanced drug solubility	[126]
Polyamidoamine dendrimers	Indomethacin	*In vitro* skin permeation studies in rat dorsal skin	*In vivo* transdermal permeation evaluation Pharmacokinetic study and pharmacodynamic evaluation in carrageenan-induced rat paw	Transdermal patches	Increased drug flux across the skin *in vitro* as well as *in vivo*	[128]

			edema model			
Triazine based dendrimers	Ketoprofen	-	-	-	Enhanced drug solubility	[129]
Polypropylene oxide cored PAMAM dendrimers	Ketoprofen, Ibuprofen and Diflunisal	-	-	-	Dendrimers are highly effective solubility enhancer for NSAIDs	[130]
Cationic carbosilane dendrimers	Ibuprofen	Viability assay and inflammatory response analysis in macrophages	-	-	One formulation reduced inflammatory responses in a better way than that achieved by the free drug	[131]

Table 7. Micelles used for pain management described in the literature.

Nanoparticle Type	Drug	*In vitro* evaluation	*In vivo* evaluation	Administration Route	Outcomes	Reference
Micelles						
	Local anesthetic					
Polyethylene oxide and polypropylene oxide micelles	Lidocaine and prilocaine	-	-	-	Suitable gelation temperature, good release profile and excellent long-term stability of micellar formulation	[133]
Thermoresponsive Mixed Micellar Nanogel	Lidocaine and prilocaine	*Ex Vivo* permeation and retention studies on mice excised abdominal skin Pharmacodynamic evaluation	-	-	Enhanced intensity of anaesthetic effect in an *invivo* rabbit model and mice tail flick model Well tolerated formulations by skin	[134]
PL407-PL188 mixed micelles hydrogels	Ropivacaine	*In vitro* citotoxicity assays in 3T3-fibroblasts cells	*In vivo* local toxicity and pharmacological evaluation in rats	-	Reduced cytotoxic effects No inflammation signs	[135]

					Increased analgesic effects for the micellar formulation	
mPEG-PLA/Solutol® HS15 mixed micelles	Propofol	Stability of mixed micelles under storage condition	Sleep/recovery studies in rats	Intravenous route (caudal vein)	Drug-loaded micelles were stable at room temperature Pharmacological effect of mixed micelles was comparable to commercial lipidic emulsions	[136]
	NSAIDs					
Micellar solutions composed of single, binary, and ternary surfactant systems	Naproxen	-	-	-	Solubilization capacity of mixed surfactant systems was better than those of single-surfactant Cationic surfactants exhibited higher solubilization capacity	[137]

					than nonionics and anionics	
Pluronic L81/P123 mixed micelles	Aceclofenac	-	-	-	High drug entrapment efficiency, sustained release profile and good stability	[138]
Poly(ethylene oxide)-Poly(β-benzyl L-aspartate) Block Copolymer Micelles	Indomethacin	-	-	-	Drug delivery controlled by the medium pH and interaction between drug and the hydrophobic core of the micelles	[139]
Complex Micelles	Ibuprofen	-	-	-	Drug release rate could be controlled by modifying the size and permeability of the channels	[140]

Table 8. Niosomes used for pain management described in the literature.

Nanoparticle Type	**Drug**	***In vitro* evaluation**	***In vivo* evaluation**	**Administration Route**	**Outcomes**	**Reference**
Niosomes						
	Local anesthetic					
Neutrally, positively and negatively charged Tween20/Cholesterol vesicles	Lidocaine or lidocaine hydrochloride	Diffusion experiments in abdominal skin of male nude mice	-	-	Drug permeation rate was quite similar for niosomes and liposomes A higher permeation flux and a shorter lag time of niosomes with respect to classical liposomes	[141]
Polysorbate-20 derivatized by glycine niosomes	Lidocaine	Cytotoxicity studies in immortalized HaCaT cells and immortalized mouse fibroblasts Balb/3T3	*In vivo* efficacy study of the drug-loaded niosomes in murine pain and inflammation models	Subcutaneous	Not cytotoxic. Enhanced therapeutic effects of optimized formulations in *in vivo* pain and inflammation models	[142]
	NSAIDs					

Polysorbate-20 derivatized by glycine niosomes	Ibuprofen	Cytotoxicity studies in immortalized HaCaT cells and immortalized mouse fibroblasts	*In vivo* efficacy study of the drug-loaded niosomes in murine pain and inflammation	Subcutaneous	Not cytotoxic Enhanced therapeutic effects of optimized formulations in *in vivo* pain and inflammation models	[142]
Span 60/F127 and Tween 60/F127 niosomes	Diclofenac sodium	-	*Ex vivo* permeation studies in rabbit ear skin	-	Higher drug flux through ear membrane after its nanoencapsulation	[143]
Phosphatidylcholine (PC): Cholestherol (CH), PC:CH: stearylamine or PC:CH: dicetylphosphate niosomes	Aceclofenac	-	Anti-inflammatory activity in rat paw oedema model	Topical	Prolonged anti-inflammatory effect	[144]
Niosomal hydrogels						
	NSAIDs					
Niosomal gel	Lornoxicam	*In vitro* skin permeation studies in rat skin	Anti-inflammatory effects of the prepared niosomal gels in rat inflammatory model and	Topical	Enhanced anti-inflammatory effect of drug niosomal gel No signs of	[145]

			skin irritation test		irritation	
Niosomal hydrogels	Meloxicam	*In vitro* skin permeation studies in rat skin	Anti-inflammatory effects of the prepared niosomal gels in rat inflammatory model	Topical	All niosomal gel formulations had significant anti-inflammatory effect	[146]
Niosomal Gel	Lornoxicam	*In vitro* occlusivity study	Primary skin irritation study in rabbits and pharmacodynamic evaluation using rat paw edema model	Topical	No signs of irritation. Higher occlusivity properties Improved anti-inflammatory activity of drug after its encapsulation in niosomal system.	[147]
Vesicular hydrogel	Meloxicam	-	Acute anti-inflammatory activity analysis of hydrogels in rat paw edema model	Topical	Anti-inflammatory activity enhancement of meloxicam	[148]
Elastic and conventional Tween 61 niosomes incorporated into a	Diclofenac diethylammonium	*In vitro* skin permeation study in rat skin	*In vivo* anti-inflammatory assay in rat ear edema model	Topical	High fluxes of drug entrapped in niosomes through rat skin and high	[149]

Carbopol gel					anti-inflammatory activity of formulations in rat ear edema assay	
Tween20:cholesterol Niosomal gel formulation	Nimesulide	In vitro skin permeation study in human cadaver skin	*In vivo* anti-inflammatory assay in rat paw edema model	Topical	Higher drug retention and increased permeation across the skin after niosomal drug encapsulation Prolonged and enhanced anti-inflammatory activity	[150]
Span 60:cholesterol Niosomal gel formulations	Aceclofenac	*In vitro* rat skin permeation study	*In vivo* anti-inflammatory activity effects of niosomal gels in rat paw edema model	Topical	Improved anti-inflammatory activity of niosomal gel formulations	[151]

Table 9. Inorganic nanoparticles used in pain management described in the literature.

Nanoparticle Type	**Drug**	***In vitro* evaluation**	***In vivo* evaluation**	**Administration Route**	**Outcomes**	**Reference**
Silica mesoporous materials						
	NSAIDs					
SBA-15	Ketoprofen	-	The analgesic and anti-inflammatory activity studies in carrageenan-induced edema in paw rat model	Oral	Enhanced drug bioavailability after encapsulation	[152]
MCM-41	Piroxicam	-	-	-	Good matrix to prepare a rapid onset therapeutic formulation with poorly water-soluble drug	[153]
MCM-41	Ibuprofen	-	-	-	Drug was homogenously loaded into MCM-41 without adversely affecting its activity	[154]

SBA-15	Indomethacin	-	-	-	Enhanced dissolution of poorly soluble drugs after encapsulation in SBA-15	[155]
SBA-15	Indomethacin	-	-	-	Immediate and complete drug release from SBA-15 happened in simulated intestinal fluid	[156]
	Others					
MCM-41	Δ9-tetrahydrocannabinol and ARA29	Cell viability studies in murine brain microglia cells	Thermal hyperalgesia and mechanical allodynia evaluation in chronic constriction injury mice model	Intraperitoneal	Attenuation of *in vitro* and *in vivo* inflammation and a sustained relief of neuropathic pain in injured animals	[157]
Magnetic nanoparticles						
	NSAIDs					

Magnetic nanocarriers functionalized with oleic acid and/or chitosan	Diclofenac sodium	-	-	-	Controlled drug release from novel magnetic nanocarrier	[158]
Fe/ethylcellulose (core/shell) nanoparticles	Diclofenac sodium	-	-	-	High drug loading, enhanced magnetic susceptibility and prolonged drug release	[159]
	Local anesthetic					
Magnetic nanoparticles nanocomplexes	Ropivacaine	-	Assessment of ankle block and pharmacokinetics experiments in rats	Intravenous	Ankle block after injection of nanocomplexes and magnet application at the ankle	[160]
Magnetic Nanogel	Bupivacaine	-	Assessment of ankle block and paw withdrawal latency testing	Intravenous	Ankle block after injection of nanocomplexes and magnet application at the	[161]

					ankle	
Fe_3O_4 NPs	-	-	Mechanical and thermal response analysis in mice chronic inflammatory pain model and immunohistochemistry analysis in paw skin sections	Injection into the paw	Dose-dependent analgesic effect	[162]

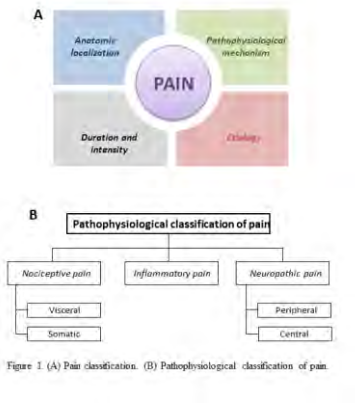


Figure 1. (A) Pain classification. (B) Pathophysiological classification of pain.

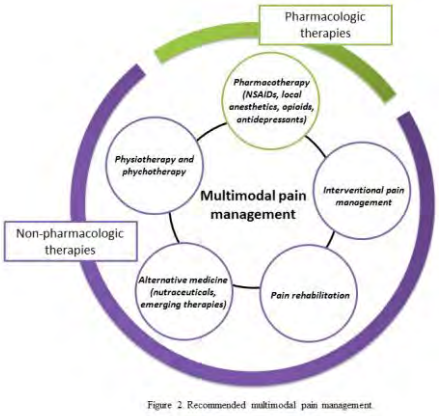


Figure 2 Recommended multimodal pain management

Figure 2. Recommended multimodal pain management.

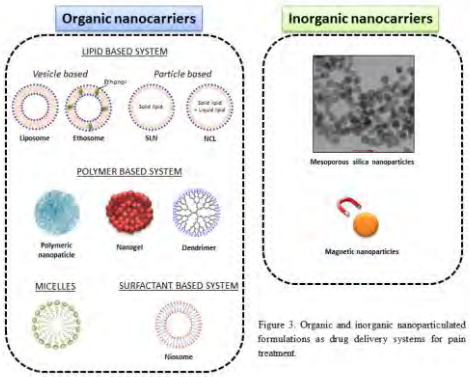
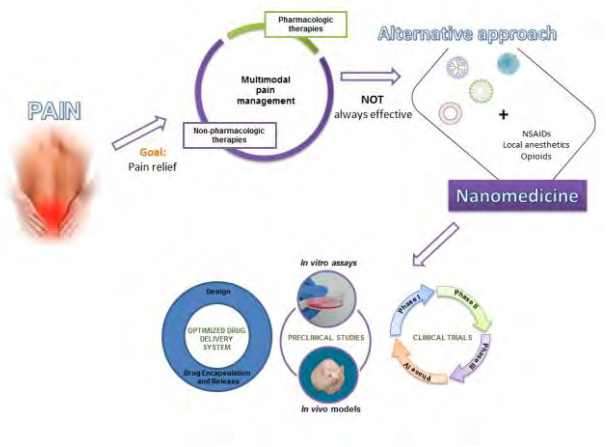


Figure 3. Organic and inorganic nanoparticulated formulations as drug delivery systems for pain treatment.



Graphical abstract