



Nanomaterial-Based ON Drug Delivery Systems For Pain Relief

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ABSTRACT

The use of nanomaterials in drug delivery for medical purposes is becoming increasingly common. The review aims to summarize nanomaterial based drug that can be used to treat and reduce pain through a single drug or a combination of several treatments. The use of nanoparticles can provide controlled release and targeted delivery of drug while increasing the compatibility of antibiotics. These not only improve the pharmacokinetics and biodistribution of analgesia but also improved the analgesic effect while reducing side effects. In addition the combination is often used for anesthesia. Coencapsulation of multiple therapeutics agent into a single nano formulation for synergistic drug delivery has received great attention. Various system used a combination of several goals to provide longterm physical activity and reduce the frequency of medication use. However it is worth noting that these nanomaterial-based treatments are still in the research phase and more research is needed before they can be effectively translated into clinical practice.

KEYWORD:- Nanomedicine, drug delivery, pain treatment, combination therapy, Nanoformulation.

INTRODUCTION

The disease is a global disease that affects people's lives and has significant impacts on health and society. Approximately 20% of adults worldwide are injured. Currently opioids are used mainly to control and reduce pain. It should not be forgotten the single drug therapy has many disadvantages such as side effects of many antibiotics sedation high toxicity depression respiratory depression and addiction. These disadvantage are difficult to eliminate affect treatment and cause many problems in society Therefore better treatment must be developed. The Rapid development of nanotechnology in medicine and other industries has become the focus of researches in recent years. Nanoparticles generally refer to particles between 1 and 100 nm in size. They have unique physical and chemical properties due to their high surface to volume ratio. They can be divided into two groups according to their composition inorganic nanocarriers (mostly carbon nanotubes) mesoporous micelles dendrimers polymer conjugates and polymer nanoparticles. As drug carriers nanoparticles have good biocompatibility and can effectively deliver drugs to tissues.

Nanocarriers can improve drug safety, reduce side effects control release change pharmacokinetics, improve effects and treat diseases with fewer side effects. Additionally nanotechnology tools can improve medical imaging by providing better representation and higher resolution. Nanosensors and nanodevices can monitor many abnormalities in the body providing important information for diagnosis and disease management. The nanomedicine industry is constantly evolving and with continued research and advancements has the potential to change the way we diagnose treat and manage diseases including controlling pain. NP-based drug delivery for clinical and therapeutic applications has been the subject of many preclinical studies providing competing strategies for effective pain management (Figure 1.). They can also better heal pain. This study examines the therapeutic effects of a single drug or multiple drug combinations focusing on the progress and challenges of therapeutic nanoformulation from single drug delivery to multidrug delivery.

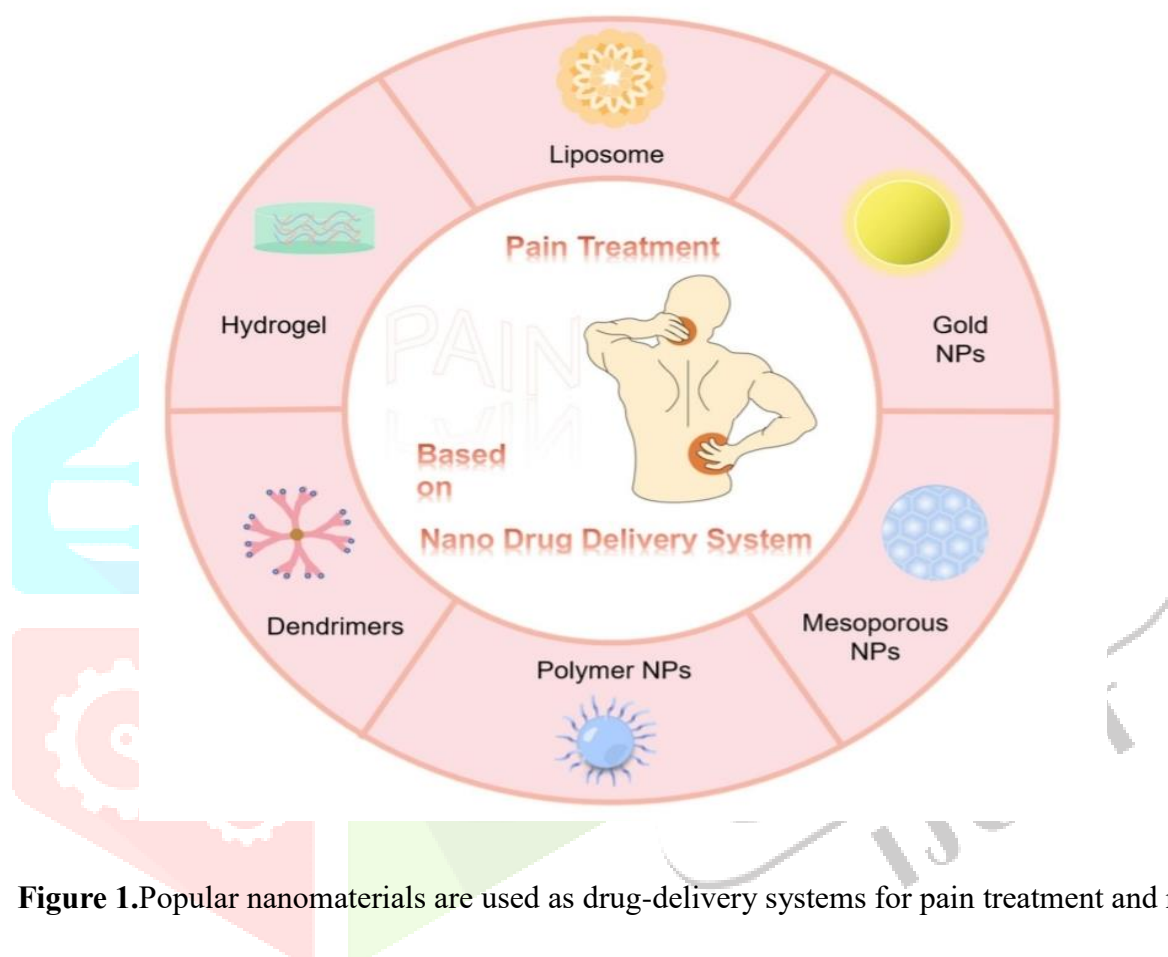
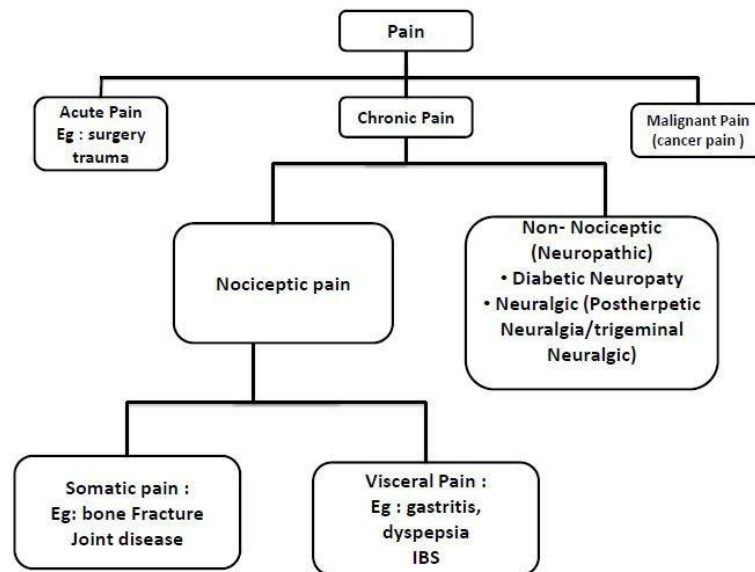


Figure 1. Popular nanomaterials are used as drug-delivery systems for pain treatment and relief.

DEFINITION OF PAIN :-

Pain is a physical and psychological activity defined by the International Association for the Study of Pain (IASP) (2023) as negative feelings and emotions associated with or similar to tissue damage.

CLASSIFICATION OF PAIN :-

I) Acute Pain :- Pain usually results from injury or disease and follows a three neuron sensory pathway in which peripheral nervous travel to the spinal cord via receptors in the dorsal root ganglia and synapse with gelatinous spinal cord neurons into the dorsal horn of the spinal cord. Spinal cord and the travel to the somatosensory cortex causing the sensation of pain. Its duration is short usually not exceeding 3 months. Acute pain can be divided into nociceptive pain and neuropathic pain.

II) Chronic Pain:-

Approximately 8% of the population developed pain that lasts for a long time and occurs without tissue damage. Primary pain including migraine is generally considered pain. Chronic inflammatory diseases are caused by other diseases such as rheumatoid arthritis (RA). Chronic pain is a complex problem there are many problems it is generally believed that peripheral and central nervous system pain are important in such chronic pain disease. On the other hand in the peripheral nervous system there are many non-neuronal calls as immune cells and glial cells that are activated at the time of pain and cause local pain in the peripheral nerves. On the other hand central sensitivity plasticity in central pain pathways increased neuronal reactivity due to pain cause I of the central nervous system.

III) Malignant Pain:-

The multi dimensional pain experience is associated with various neuro physiological changes and is cognitive emotional and behavioral. As new treatment improves survival rates cancer patients will live longer through the pain of the disease and their treatment. Therefore the problem of analgesia in patients with malignant tumors needs to be solved. It is difficult to calculate the life expectancy of a cancer patients because there are many factors that affect the cancer patients life by working with pain

3] MANAGEMENT OF PAIN . Pain can be managed through:

- I) Pharmacological interventions
- II) Nonpharmacological interventions

I) Pharmacological interventions:-

- i) Pharmacological therapy is given by using Analgesics.
- ii) The analgesics may be OPIOIDS (NSAIDS) OR OPIOIDS OR ADJUVANTS
- iii) NSAIDS: Nonsteroidal anti-inflammatory drugs
- iv) Opioids: Opioids are medications that relieve pain. Derived from opium.
- v) Adjuvants: Adjuvants are drugs originally developed to treat conditions other than pain but also have analgesic properties.

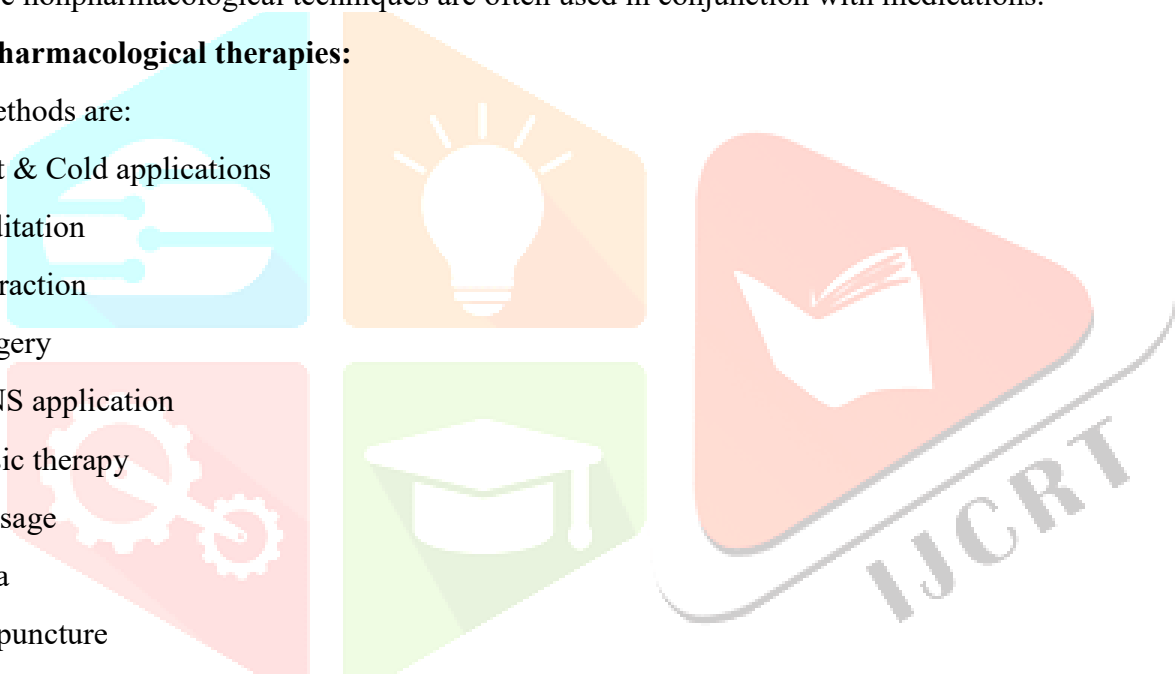
II) Non-Pharmacological Pain Management

- i) For many people treatments can be provided with non-drug methods.
- ii) These nonpharmacological techniques are often used in conjunction with medications.

Non-Pharmacological therapies:

The methods are:

- 1) Heat & Cold applications
- 2) Meditation
- 3) Distraction
- 4) Imagery
- 5) TENS application
- 6) Music therapy
- 7) Massage
- 8) Yoga
- 9) Acupuncture
- 10) Herbal therapy Garlic Echinacea Ginseng.



4] COMMON DRUGS USED TO TREAT PAIN

Opioid analgesics have been used to treat moderate to severe pain and chronic pain recent centuries and are known for their beneficial effects. Opiate receptors are found throughout the body in the central nervous system and peripheral tissues and their analgesic properties are primarily due to the mucus opiate receptor gene encoding the receptors. Commonly used opioid analgesics include morphine tramadol fentanyl sufentanil oxycodone cannabidiol crayoned enkephalin and other. Meperidine, methadone codeine pentazocine etc. Local anesthetics which usually target sodium ion channels for nerve block are also used medically to reduce pain. Local anesthetics procaine lidocaine meperidine bupivacaine hydrochloride procaine etc. It is divided into amide local anesthetics such as esters of local anesthetics include procaine and benzocaine. Nonsteroidal anti-inflammatory drugs (NSAIDs) produce anti inflammatory drugs mainly by inhibiting the activity of cyclooxygenase isoenzymes and inhibiting prostaglandin synthesis. Common NSAIDs include aspirin acetaminophen ketoprofen ibuprofen naproxen diflunira nimesuride indomethacin diclofenac leucophenol meloxicam celecoxib and other. Compared to opioid analgesics NSAIDs have a weak analgesic effect. Dexamethasone is a glucocorticoid that inhibit inflammatory cells and has anti-inflammatory properties. Other antibiotics include calcium channels blocker ziconotide sodium channel blocker tetrodotoxin, potassium

channel opener, nicotine and flupirtine, tizanidine, a competitive antagonists of the capsaicin acetate related. Antineoplastic drug temozolomide selective serotonin and serotonin Norepinephrine reuptake inhibitor duloxetine antihistamine promethazine and fexofenadine anti-osteoporosis drug zoledronic acid and anticonvulsant drug carbamazepine.

5] COMBINATION DRUGS FOR TREATMENT

Disadvantages of a single antibiotic include poor clinical efficacy, serious side effects, and biocompatibility issues. Therefore, using two or more drugs in combination can often achieve better therapeutic results and has the potential to improve quality. In recent years, combination therapy has begun to attract more attention in the treatment of pain. An early 2014 study reported that the combination of morphine and clonidine had synergistic effects in rats. Although there is no relationship between sedation and cardiac arrest, treatment with the combination of the two drugs has been successful. (such as musculoskeletal pain and postoperative pain), but also affects conditions such as osteoarthritis (OA). The analgic effects and negative effects of flupirtine, a Kv7 potassium channel opener, along with the antihistamines promethazine and fexofenadine, on acute and chronic pain in rats were investigated. This study established models of acetic acid induced writhing pain, carrageenan induced inflammatory pain, and paclitaxel induced neuropathic pain.

Antihistamines use drugs to activate Kv7/M channels. CBD and beryophyllene (BCP) are nonpsychoactive components of cannabis that have more benign effects than other cannabis components and may reduce neuropathic and inflammatory conditions. The powerful combination of CBD and BCP was evaluated in a mouse model of chronic pain due to spinal cord injury. A reduction in dose occurred when CBD and BCP were combined in the same ratio; Synergy was observed in men and women, with additional benefits in contact hypersensitivity seen for men. These findings suggest that coadministration of CBD/BCP may provide a safe and effective treatment for chronic spine pain. The above studies show that the integrated medical model changes the medical model. Interaction between the hypoglycemic drug metformin and duloxetine/oxycodone/eslicarbazepine acetate/vitamin B12 in the treatment of hypersensitivity in patients with diabetes. Metformin, when used with antibiotics or vitamin B12, may reduce inflammation and reduce vitamin B12 deficiency caused by metformin.

TARGETED NANOMATERIALS FOR PAIN RELIEF

Despite the benefits of using nanomaterials to encapsulate drugs to reduce chronic pain, their limited clinical use has led to an urgent need to develop better solutions. Because the causes of chronic pain vary, the type and amount of medication needed varies depending on the treatment program. Increasing the concentration of the drug at the point of action is one way to improve performance and reduce side effects. Use the target to modify nanomaterials substances such as peptides and antibodies can help achieve this site-specific targeting. Additionally.

The application method is important when using these devices in acute cases. For example, chronically painful areas of the skin can be treated with spots or sprays, while injections from the dorsal root ganglion are better for spine pain. Depending on the location and location of the pain, internal injury or disease may benefit from oral, intranasal, intramuscular, or intravenous administration. In the next section, we focus on research for strategies to support longterm treatment. Surface modification of nanomaterials is a simple and effective method to improve sitespecific absorption of drugs. So far, target nanomaterial design has focused on the modification of target ligands, but other target,directed strategies have not yet been explored, which will be demonstrated in the theoretical part.

NON-TARGETED NANOMATERIALS FOR PAIN RELIEF

Nanomaterials can be divided into organic/inorganic nanomaterials and metalorganic nanomaterials according to their properties. All three classes of nanomaterials were used for controlled release to reduce side effects and increase the effectiveness of antibiotics. Nanomaterials can be used to encapsulate free molecules and protein drugs to increase blood circulation time and provide controlled release, providing longterm pain relief with minimal side effects. In this chapter, we describe the development of organic and inorganic offtarget nanomaterials that are widely used in various analgesic drugs. When nanomaterials are incorporated into medical applications, the main concern is the biocompatibility of these nanomaterials. Liposomes are particularly attractive because they are derived from cellular lipidoids, making them less biocompatible and something that has not been well studied. Various liposomal formulations have become the focus of clinical trials. For example, PEGylated liposomes have been used to encapsulate and enhance the accumulation of zoledronic acid (ZOL), an inhibitor of addiction-mediated pathways used to treat neuropathic pain. This liposome,based delivery system was found to promote the ability to cross the blood brain barrier. The products of these three biocompatible nanomaterials are different and provide a design for the production of nanomaterials for pain medication delivery. Overproduction of reactive oxygen species (ROS) at the site of inflammation can lead to chronic pain, so ROS,depleting nanomaterials are a promising approach to alleviate pain. In this regard, many functional nanomaterials are known to use reactive oxygen species, protect the inflammation site and reduce inflammation. Nanomaterials can be divided into organic inorganic nanomaterials and metalorganic nanomaterials according to their properties.

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DRUG COMBINATION-BASED DRUG DELIVERY SYSTEMS FOR PAIN TREATMENT

Nanocarrier based drug combination technology combines two drugs in a modified drug delivery system to achieve effective drug delivery. Coloadng of nanocarriers has many advantages compared to direct coloadng of free drugs. In these systems, coencapsulated drugs are loaded into different parts of the nanostructure (e.g. different layers of the core or shell, inner or outer) without affecting each other, and the dosage of different drugs can also be easily adjusted. , reduces side effects and has joints. Additionally many drug delivery system

can control the duration of action of various drugs to achieve the effect of the drug. Multidrug delivery systems based on nanomaterials can be successfully integrated into multiple pathways and multiple targets.

i) Liposomes:-

Liposomes, the first material used in nanomedicine, were used in two treatments in 2009. It is given to the body in the form of liposomes carrying hyaluronic acid as a surfacebound ligand, such as dexamethasone and diclofenac. Lesion sites in OA rats. This study found that two different drug packages in the same liposome did not interfere with each other and maintained biological activity. This preparation has a stable formula and can be stored for 14 months at 25°C. These studies provide new information for the development of better local anesthetics for medical and other applications.

ii) NLCs:-

In dental practice local anesthesia is used to reduce discomfort from injection and reduce symptoms of injury to the oral mucosa but there are no proven commercial formulations. Some studies have improved the preparation of NLC with lidocaine (59%) and prilocaine (66%) . Coencapsulated in the carrier and confirmed that the lipid structure is not altered by encapsulation of the anesthetic. Alright. willing to release. Display features. It provides an effective and easy way to prepare this nanosystem, which is expected to become a combined system

iii) PLGA NPs:-

Using electrospinning technology, PLGA nanofibers can continue to elute hemostatic and analgesic drugs in the wound area, indicating that they are good hemostatic and promote analgesic effects and can be used in the treatment of mouth wounds on the palate. PLGA nanofiber membranes for surgical wounds were fabricated using electrospinning technology, loaded with sheathlike structures of the anesthetic lidocaine and human epidermal growth factor, and their good work in promoting healing and treatment was evaluated. Celecoxib not only reduces the allergic potential but also regulates the release of dexamethasone, showing significant effects in the treatment of OA with different functions and mechanisms.

iv) Hydrogels:-

In recent years, nerve analgesia administered with local anesthesia has become a way to reduce postoperative pain. However local anesthetics always have disadvantages such as short lifespan and strong toxicity. Some studies suggest that local anesthetics should be combined with antiinflammatory drugs such as dexamethasone to increase the effectiveness of local anesthetics. However the local anesthetic ropivacaine which does not contain nanocarrier often causes pain in the body. Solubility studies showed that the nanocomposite hydrogel system increased the solubility of the two drugs to $73.13 \pm 8.86\%$ ($29.25 \pm 3.55 \mu\text{g/mL}$). In addition, the mouse ankle joint model showed that the use of this second drug reduced controlled the expression of inflammatory diseases and almost completely got rid of factors affecting the morphological characteristics of rats joints. He has done great work on the prevention of disease and has high scientific value.

v) MSNs:-

Two regions of MSNs allow the delivery of different drugs at different stages; This would be ideal for longterm treatment. A team created a mesoporous silicone material containing both the cannabinoid Δ^9 tetrahydrocannabinol (Δ^9 THC) and the erythropoietin derived peptide cybinide. THC spontaneously distributes into the pathway and cybinide peptides are released as glutathione induced disulfide bond cleavage. Both have analgesic and antiinflammatory properties. Preliminary studies show that this drug can release analgesic molecules, is very safe, and can prevent neuropathic pain. This provides evidence for the feasibility of its application in the treatment of neuropathic pain and may contribute to the development of effective treatments for chronic pain.

vi) Other Nanoformulations:-

Meloxicam is a medication used to treat RA and postoperative surgical pain. However poor oral administration low bioavailability and serious gastrointestinal damage. Tizanidine not only has a pronounced analgesic and anti-inflammatory effect, but also enhances the analgesic and anti inflammatory effects of meloxicam and improves bowel function. Research shows that this drug has the potential to treat many conditions. Additionally, polymer sheets containing

ketorolac/lidocaine have been developed to reduce pain and discomfort and promote healing after gum surgery.

CONCLUSION

Pain management is one of the most important medical problems. Although the use of antibiotics and vaccines has reduced poverty over the past few decades, many limitations remain. With the development of nanomedicine, nanomedicine delivery technology has also gradually matured. Whether it is a single drug carrier or a combination of various drugs, it has great clinical benefits in terms of bioavailability, biosafety and pharmacokinetic properties. Although nanodrug delivery systems offer new hopes for medical treatment, they still suffer from insurmountable limitations.

1) Nanoformulation reduces the side effects of analgesics and increases their therapeutic effect. However, the biosafety of nanomaterials used in nanoformulations, especially inorganic nanomaterials, has not been fully evaluated. Longterm toxicity studies and primate toxicity studies are required.

(2) Improved bioavailability, pharmacokinetics and clinical efficacy require further validation using beagles or primates.

(3) Lack of data support for the stability and large scale preparation of nanoformulations which may also limit their clinical application.

●Future perspective

The great potential of nanotechnology offers a great opportunity to solve many unsolved problems in pain management. In addition to these resources, joint efforts are also required to ensure maximum progress in the field. Therefore, concerted efforts should be made to advance research on the effects of nanoparticles on different disease processes, develop biomarker discovery technologies, expand tissue engineering research to reduce the pain sensation associated with nerve damage, and introduce new and cutting-edge research. details. Gene therapy and CRISPR in disease treatment.

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