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Review Article

Nano-Engineered Carriers for Advanced Analgesic Drug Delivery:Targeting Pain Pathways with Biocompatible Nanobiotechnology.

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ABSTRACT

Pain is one of the most frequently observed conditions in clinical practice, and analgesic drugs are commonly used to provide relief. However, conventional dosage forms, such as tablets and capsules, have certain limitations, including poor bioavailability, shorter therapeutic duration, frequent administration, and adverse effects such as gastric irritation and peptic ulcers. To overcome these challenges, nanobiotechnology-based drug delivery systems have emerged as promising alternatives. Nanobiotechnology utilizes nanosized carriers, generally ranging from 1–100 nm, to deliver drugs in a controlled and targeted manner. This review highlights different nanocarriers used for analgesic drug delivery, including liposomes, polymeric nanoparticles (chitosan and PLGA), solid lipid nanoparticles (SLNs), nanogels, and transdermal nanopatches. These systems can enhance drug solubility, provide sustained drug release, decrease dosing frequency, and reduce unwanted side effects. Diclofenac-loaded liposomal gels and ibuprofenloaded polymeric nanoparticles are discussed as important examples. The review also covers targeted drug delivery mechanisms, various administration routes, including oral, transdermal, and intranasal pathways, and evaluation parameters such as particle size, entrapment efficiency, and drug release. Overall, nanocarrier-based systems offer promising possibilities for improving pain management through enhanced therapeutic effectiveness, reduced drug dosage, and better patient compliance. Nanotechnology may contribute significantly to the development of safer and more efficient analgesic therapies in the future.

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INTRODUCTION:

Pain is a protective response of the body to harmful stimuli and is a common manifestation of various diseases. It occurs when harmful stimuli activate or irritate the free nerve endings of nociceptors (pain receptors). This process involves several chemical mediators, including histamine, leukotrienes, substance P, acetylcholine, bradykinin, and prostaglandins. These mediators also contribute to changes in blood vessel diameter, including vasodilation and vasoconstriction, as well as alterations in capillary permeability at the site of injury.

Clinically, pain is classified into two categories: acute and chronic pain. Inadequate pain management can result in significant complications. Poorly controlled acute pain may increase the risk of conditions such as deep vein thrombosis and pneumonia and may eventually develop into chronic pain. Similarly, inadequately managed chronic pain can interfere with daily activities and negatively affect a patient's overall quality of life.Based on its underlying pathophysiology, pain is broadly classified as nociceptive or neuropathic. Prolonged exposure to harmful stimuli or persistent tissue injury can continuously activate nociceptors, potentially contributing to tissue damage. However, pain originating in peripheral regions is not always nociceptive in a nature. Neuropathic pain, on the other hand, develops due to abnormal processing or transmission of pain signals within the peripheral or central nervous systems.[1]

Pain relief has been a major health concern throughout human history, leading to the development of various traditional remedies, including creams, ointments, pastes, powders, and plant- or animal-derived extracts. In recent years, transdermal drug delivery systems have gained considerable research interest because they provide a minimally invasive alternative with several advantages over oral administration and injections.[2] More than 40% of patients receiving treatment for primary pain experience insufficient pain relief.[3] Many pain medications are associated with serious adverse effects, including liver toxicity, depression, respiratory suppression, and addiction. The opioid crisis further emphasizes the need for safer chronic pain treatments, particularly as chronic pain affects over 20% of adults in the United States.[4,5] Chronic pain is associated with conditions such as cancer, diabetes, cystic fibrosis, inflammation, and physical injuries or surgery. It also increases the risk of anxiety, depression, sleep disturbances, addiction, and disability.[6]

Chronic pain significantly affects quality of life, social relationships, work productivity, and healthcare costs, making it a major public health concern and a leading cause of long-term disability. Despite the need for effective treatment, managing chronic pain without adverse effects remains challenging.

Nanotechnology has emerged as a promising approach to pain management through the development of targeted drug delivery systems, stimuli-responsive nanocarriers, and paindetecting nanodevices. Nanoparticles can improve drug effectiveness, reduce required doses, and provide prolonged pain relief. Other emerging approaches include nanoparticle-based gene therapy, CRISPR technology, and anti-inflammatory scavengers that target pain-related molecules and reduce neuronal sensitization. Overall, nanotechnology offers new opportunities for developing safer and more effective treatments by targeting the underlying mechanisms of chronic pain.[7].

Chronic pain negatively affects quality of life and increases healthcare and socioeconomic burdens. Nanotechnology offers promising treatment strategies through targeted drug delivery, nanoparticle-based gene therapy, CRISPR technology, and anti-inflammatory approaches. These innovations may provide longer-lasting pain relief with fewer side effects by targeting the underlying causes of pain.[8].

Several FDA-approved nano-based analgesics are available, including Exparel, a liposomal bupivacaine formulation, and DepoDur, an extended-release liposomal morphine used for postoperative pain relief. However, these formulations may cause adverse effects such as vomiting, constipation, itching, and reduced oxygen saturation. Despite the potential of nanomedicine to improve drug delivery, stability, and bioavailability while reducing toxicity, its development remains expensive and time-consuming, and the search for an ideal nanoparticle continues. [10-11]

2. Physiology and pathways of pain:

Pain is a fundamental physiological process that has evolved to protect the body and support survival. It involves complex interactions among various biological systems. As a common medical complaint, pain can provide important clues about underlying diseases. Understanding its mechanisms is essential for assessing its impact on health and developing effective treatment strategies. [12]

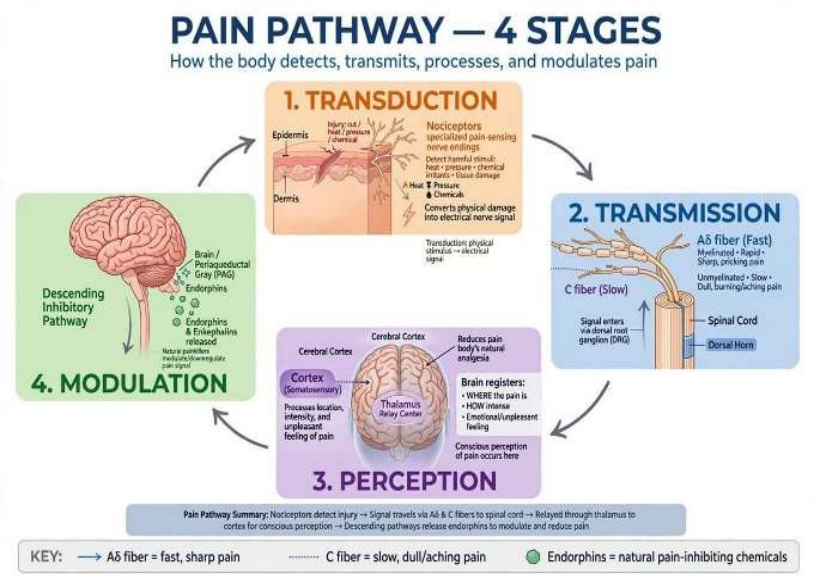


Figure 1: Physiology of Pain.

2.1. Transduction**:** Specialized sensory nerve endings, known as nociceptors, detect potentially harmful stimuli, including extreme temperatures, mechanical pressure, and chemical signals released from damaged tissues. These receptors convert the detected harmful stimuli into electrical impulses, which are then transmitted through the nervous system to the brain for processing and interpretation as pain.

2.2. Transmission: The generated electrical impulses are transmitted through sensory nerve fibers, with fast A-delta fibers carrying sharp, immediate pain signals and slower C fibers transmitting dull, aching pain. These signals enter the spinal cord and travel upward to the thalamus in the brain, which acts as a relay center for further processing of pain information.

2.3. Perception: The pain signals are processed by the thalamus and cerebral cortex, enabling the brain to identify the pain's location, intensity, and unpleasant sensory experience.

2.4. Modulation: The brain and spinal cord release endogenous pain-relieving substances, such as endorphins, to inhibit or reduce the transmission of pain signals. [13]

3. Need for Advanced Drug Delivery Systems**:**

Despite their widespread use, conventional drug delivery methods have several limitations, including low bioavailability, rapid drug elimination, poor targeted delivery, and unwanted side effects. Oral drugs may degrade in the gastrointestinal tract, reducing their effectiveness, while intravenous administration can cause widespread drug distribution and toxicity in non-target tissues. These drawbacks highlight the need for advanced drug delivery systems that offer safer, more effective, and patient-friendly treatment options. [14] The limitations of conventional drug delivery methods have encouraged the development of Advanced Drug Delivery Systems (DDS). These systems utilize innovative technologies, including nanoparticles, liposomes, and biodegradable polymers, to enhance drug delivery, therapeutic effectiveness, and treatment outcomes. Advanced DDS can selectively target specific tissues or cells, provide controlled and sustained drug release, and reduce the frequency of drug administration. For instance, targeted drug delivery systems can selectively transport therapeutic agents to diseased

cells while minimizing their exposure to healthy tissues, thereby reducing adverse effects and improving treatment efficacy. [15] Furthermore, controlled-release drug formulations help maintain consistent therapeutic drug concentrations in the body for prolonged periods, thereby enhancing patient compliance and improving overall treatment effectiveness. These technological advancements play a significant role in the treatment and management of diseases that require accurate and sustained drug delivery, including cancer, diabetes, and neurological disorders. [16]

4.What is Nanobiotechnology?

Nature serves as a major source of inspiration for scientific research, particularly because many biological processes and structures function at the nanoscale. By combining knowledge and techniques from various disciplines, including biology, chemistry, physics, nanotechnology, and engineering, researchers can develop, analyze, and formulate biological molecules and devices at the nanoscale under laboratory conditions. This multidisciplinary integration has contributed to the development of an emerging scientific field known as nanobiotechnology. [17] Nanobiotechnology refers to the integration of biotechnology and nanotechnology, combining conventional microtechnology with techniques derived from molecular biology. Biotechnology has wide-ranging applications in various sectors, particularly agriculture and medicine, where genetic, molecular, and cellular processes are manipulated to develop useful products and services. The integration of these two advanced technologies offers significant opportunities, particularly in the field of life sciences, where it has the potential to contribute to numerous biomedical applications. Nanobiotechnology is expected to play an important role in advancing drug delivery systems, gene therapy, biomarker development, molecular imaging, and biosensor technologies. Among its major research applications are targeted drug delivery and the development of early diagnostic methods for detecting pathological conditions. In the coming years, pharmaceutical research and drug development are anticipated to become some of the most significant clinical applications of nanotechnology. [18]

Research in the field of drug delivery has increasingly shifted its focus from the microscale to the nanoscale. The application of nanoparticles (NPs) as pharmaceutical carriers or therapeutic agents represents an innovative approach to targeted drug delivery, controlled drug release, and improved drug bioavailability. Nanosized polymeric capsules offer several advantages, including enhanced drug absorption, regulated release profiles, and the ability to release their contents at specific target sites [19]. Currently, researchers worldwide are focusing on the development of novel polymers and investigating the effectiveness of different drug–polymer combinations. For instance, nanocapsules can be fabricated using monomer-based polymerization techniques or through relatively simple polymer nanodeposition methods. [20]

Currently, nanocapsules are being developed using materials such as liposomes and albumin. Implantable drug delivery systems may also incorporate nanoporous structures to achieve controlled and sustained drug release. In addition, nanomaterials have diverse applications in medical science, particularly in the field of nanomedicine, owing to their distinctive physical properties and unique characteristics. These materials play an important role in disease diagnosis and treatment at the molecular level. They can be specifically designed to interact with biological molecules, detect molecular changes, and facilitate the targeted transport of diagnostic and therapeutic agents. Furthermore, nanomaterials can be engineered with customized sizes, shapes, surface properties, compositions, and structural characteristics to meet the specific requirements of various biomedical applications. [21]

Nanomaterials can be broadly categorized into three major groups: metallic nanoparticles, organic nanoparticles, and hybrid particles consisting of combinations of metallic and nonmetallic components, including semiconducting materials. To improve targeting efficiency and enhance drug bioavailability, the surfaces of nanoparticles (NPs) can be modified with natural, synthetic, or biologically recognizable molecules. The development and formulation of an effective drug delivery system require a thorough understanding of its synthesis, drug delivery mechanisms, and potential applications in diagnostic devices. Several

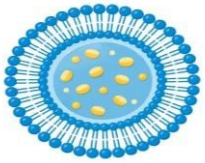
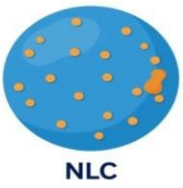
important physicochemical characteristics must be considered during formulation, including the surfacearea-to-volume ratio, particle size, and shape, as these properties influence the ability of nanoparticles to cross biological barriers and reach specific target sites. [22]

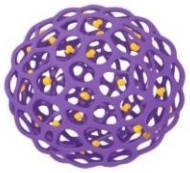
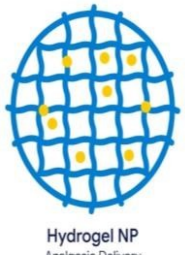
Commonly utilized nanoparticles (NPs) include iron oxide nanoparticles, colloidal gold nanoparticles, and semiconductor quantum dots. Gold nanoparticles have been widely employed as fluorescence quenchers in fluorescence resonance energy transfer (FRET)-based studies [23]. Iron oxide nanoparticles have several diagnostic applications due to their superparamagnetic properties, making them useful as contrast agents in magnetic resonance imaging (MRI). They are also utilized for monitoring gene expression and identifying various pathological conditions, including brain inflammation, cancer, atherosclerotic plaques, and arthritis. Quantum dots, on the other hand, can be used for the detection and visualization of biological systems both in vitro and in vivo through optical and electrical techniques. Recent studies have demonstrated their potential in tracking metastatic tumour cells. Moreover, their high surface-area-to-volume ratio makes quantum dots promising candidates for the development of multifunctional nanosystems with diverse biomedical applications. [24]

5.Types of Nanocarriers for Analgesic Drug Delivery System :

Over the past few decades, nanostructures with diverse shapes, sizes, and compositions have been successfully developed and utilized for the delivery of various therapeutic drugs. This section provides an overview of different types of nanostructures fabricated from a range of materials, highlighting their characteristics and applications in drug delivery systems. [25] The primary objective of developing nanoscale drug carriers is to improve therapeutic effectiveness while ensuring greater safety and efficacy. Nanocarrier-based delivery systems can enhance drug administration and biodistribution while minimizing immunogenic responses and unwanted side effects. These systems transport therapeutic agents to diseased sites through either active or passive targeting mechanisms. By enabling precise drug delivery, controlled release, and effective administration at lower doses, nanocarriers help reduce treatment-related adverse effects. Furthermore, they address several major limitations of conventional drug delivery approaches, such as nonspecific drug distribution, rapid elimination from the body, uncontrolled drug release, and poor bioavailability. [26]

Table 1: [27]

Nanocarrier type	Main composition	Size (nm)	Loaded molecules/ Examples	Common use	Duration of effect	Illustrative scheme
Liposomes	Closed vesicles with a phospholipid bilayer and cholesterol core.	50-900 nm	Hydrophilic , hydrophobic. E,g.exparel, Devour.	Local anaesthetics, opioids.	Hours to days (e.g., 24–72 hours).	
Solid Lipid Nanoparticles (SLNs)	Composed of a solid lipid core stabilized by surfactants.	100500nm	Hydrophobic drugs. E,g.Triglyceride.	NSAIDs, antiinflammatory agents.	Up to several days.	

Nanocarrier type	Main composition	Size (nm)	Loaded molecules/ Examples	Common use	Duration of effect	Illustrative scheme
Polymeric nanoparticles.	Natural or synthetic biodegradable polymers (e.g., PLGA, chitosan)	100900nm	Hydrophilic. E,g.(chitosan /PLGA)Fentanyl, Buprenorphine, Ibuprofen	Analgesics, hydrophobic small molecules.	48 hours to 30 days.	
Dendrimers	Highly branched, monodisperse nanoscale synthetic polymers.	3-20nm	Hydrophilic, Hydrophobic. E,g.Ketorolac, Morphine, Indomethacin.	Targeted delivery of analgesics and anti-inflammatory agents to inflamed joints or nerves.	24 to 48 hours.	
Polymeric micelles	Amphiphilic block copolymers self-assembled into tiny spheres (<100 nm)	5-50nm	Hydrophilic, Hydrophobic. E,g.paclitaxel, doxorubicin, amphotericin B	To encapsulate poorly watersoluble drugs, improve bioavailability, and enable targeted, controlled drug delivery.	12 to 36 hours.	
Nanohydrogel	Threedimensional, crosslinked hydrophilic polymer networks	20200nm	Hydrophilic, Hydrophobic. E,g.Curcumin, Ibuprofen, Cannabidiol (CBD).	as a smart delivery system for medicines, vaccines, and diagnostic agents in modern medicine.	24 hours to multiple weeks.	
Inorganic/ metallic nanoparticles	Gold, silica, or iron oxide cores	1-100mn	Hydrophilic, Hydrophobic. E,g. CYT6091	Targeted Drug Delivery, Medical Imaging and Diagnostics, Antimicrobial Coating, Catalysis in Organic Synthesis, Chemical and Biological Sensin.		

5.1 Lyposomes:

Liposomes were first described in 1961 by Alec D. Bangham, and remain among the most widely used nano-sized drug carrier aggregates. Liposomal structures are artificial vesicles composed of one or several lamellae of phospholipids which surround an inner aqueous core.[28]

Structure and Composition :

Liposomal bupivacaine is an innovative formulation in which bupivacaine is encapsulated within lipid-based vesicles known as liposomes. These liposomes are composed of phospholipid bilayers that encapsulate aqueous compartments, providing structural integrity and protecting the active pharmaceutical ingredient. [29]

Main components:

- Phospholipids: Phosphatidylcholine (PC) is most abundant, egg PC, dipalmitoylphosphatidylcholine, phosphatidylethanolamine - represent >50% of lipid weight.
- Cholesterol: Added up to 1:1 molar ratio, stabilizes bilayer, prevents protein interaction.Cholesterol increases fluidity in core and stabilizes carriers by protecting them from proteins like albumin, transferrin.
- Charge modifiers: phosphatidic acid, stearylamine - to make anionic, cationic, neutral.[30,31]

Diagram None:

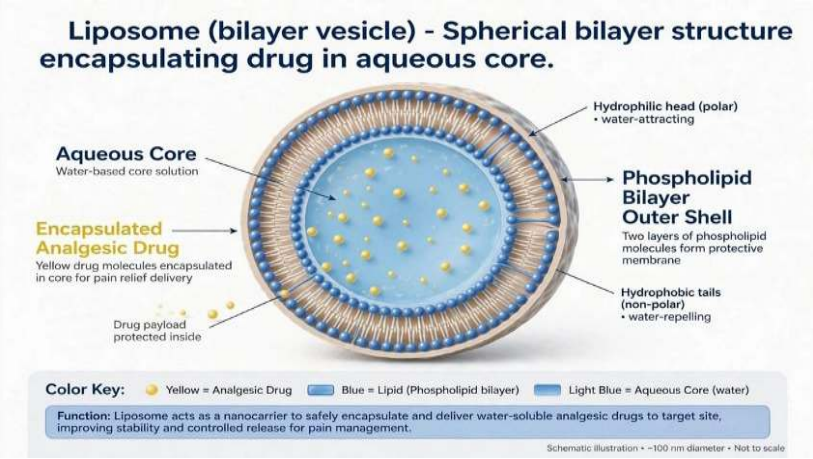


Figure 2: Liposomes.

Classification by lamellarity:

- SUV (Small Unilamellar Vesicles): 25 nm, single bilayer, diameter ~ 75 nm for ideal encapsulation. ~
- LUV (Large Unilamellar Vesicles): 1 µm, single large aqueous compartment.
- MLV (Multilamellar Vesicles): heterogeneous size up to several microns.[30]

Properties relevant to analgesia:

- Liposomes are generally considered non-toxic, biodegradable, and non-immunogenic, as they are typically composed of naturally occurring lipids.
- Association with liposomes prolongs circulation half-life, reduces volume of distribution, and lowers systemic toxicity. Drug is protected from early degradation.
- The lipid bilayers act as physical barriers, gradually releasing bupivacaine through liposomal degradation, diffusion, interaction with tissue fluids, significantly prolonging therapeutic effects.
- Elastic nature allows liposomes to penetrate more deeply into skin when compared to conventional non-elastic liposomes - useful for transdermal NSAIDs. [29,32,33]

Mechanism in Pain Management:

- Penetrate epidermis and carry drug into skin, where MLV could lose external bilayer during penetration.
- Loosening lipid structure of stratum corneum and promoting increased skin partitioning.
- Localized retention, minimizing rapid systemic absorption and extending duration at injection site. [29,31,32]

Clinically, liposomal bupivacaine (Exparel) shows analgesic duration 6 times higher than plain bupivacaine in rat model and newer unsaturated phospholipid multilamellarmultivesicular liposomes show 2-3 weeks numbing vs 4-8 hours commercial. [35,36]

Advantages:

- Can carry both hydrophilic (aqueous core) and hydrophobic (bilayer) drugs.
- Controlled, zero-order release.
- No biotoxicity, biocompatible .

Disadvantages:

- Low stability, drug leakage due to unsaturation.
- Fast clearance by RES unless PEGylated.
- Expensive manufacturing.[8,37]

5.2.Solid Lipid Nanoparticles (SLNs) :

Definition:

SLNs are first-generation lipid nanocarriers, introduced in 1991 as an alternative to emulsions, liposomes and polymeric nanoparticles.[38]

- Submicron colloidal carriers (50-1000 nm) composed of physiological lipids that remain solid at both room and body temperature, dispersed in aqueous surfactant solution.
- They are typically spherical with a solid lipid core matrix that can solubilize lipophilic molecules, stabilized by surfactants.
- Core lipids: fatty acids, triglycerides (tristearin, glyceryl monostearate), waxes, steroids. Stabilizers: phospholipids, bile salts, cholesterol, Poloxamer 188, Tween 80.[39]

Structure & Drug Incorporation Models:

Structure: Solid hydrophobic core with monolayer of phospholipids coating, drug dissolved/dispersed in solid fat matrix.

Diagram None:

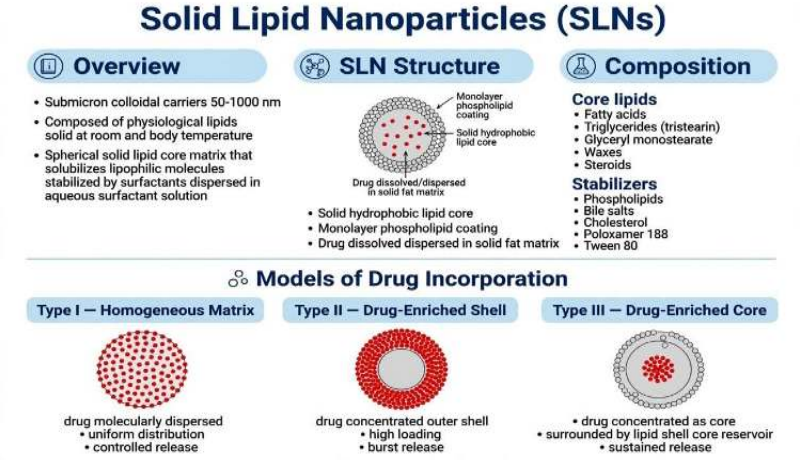


Figure 3: Solid Lipid Nanoparticles.

- 3 models:
  - Type I - Homogeneous matrix: Drug molecularly dispersed in lipid.
  - Type II - Drug-enriched shell: Drug concentrated in outer shell (burst release).
  - Type III—Drug-enriched core: Drug core surrounded by lipid shell (sustained release).

Preparation Methods:

High-pressure homogenization (hot & cold) - most scalable.

- Microemulsion technique.
- Solvent evaporation / emulsification.
- Ultrasonication.
- Ethanol injection.

Characterization:

- Particle size, PDI by Photon Correlation Spectroscopy / DLS.
- Zeta potential, DSC for crystallinity, X-ray scattering, IR.
- Drug entrapment efficiency and in vitro release. [39]

Advantages :

- Excellent biocompatibility, biodegradability, low toxicity (physiological lipids).
- Avoidance of organic solvents, easy scale-up and sterilization.
- Protects labile drugs, enhances bioavailability, controlled release.
- Can deliver both hydrophilic and lipophilic drugs.
- Crosses BBB due to lipophilic nature - useful for neuro-analgesia.[41]

Disadvantages:

- Low drug loading capacity and drug expulsion during storage due to polymorphic transition and highly ordered crystalline structure.
- Particle growth, unpredictable gelation, burst release.
- High water content (70-99.9%), poor hydrophilic drug loading.
- Stability issues due to lipid crystallization.[40]

Application in Analgesic Delivery:

- Topical: Diclofenac, Ibuprofen, Celecoxib SLN for arthritis pain - improved skin retention, reduced inflammation.
- Oral: Tramadol SLN - improved oral bioavailability of BCS Class II drugs.
- Parenteral & CNS: Nitrendipine, buprenorphine SLN show improved pharmacokinetics and BBB crossing.
- Wound therapy: combines sustained release, antimicrobial effects.[41]

Note: NLCs (2nd generation) were developed to overcome SLN limitations by mixing solid + liquid lipids, creating imperfect matrix for higher loading and less expulsion.[39]

5.3 Polymeric Nanoparticles (PNPs) :

Definition:

Polymer-based nanoparticles are a colloidal system made from natural or synthetic polymers.

Polymeric nanoparticles are nanoscale particles composed of natural or synthetic polymers, typically ranging in size from 10 to 1000 nanometers.

Polymeric nanoparticles based on biodegradable polymers such as poly (lactide-co-glycolid) (PLGA) polymers are the most widely used.

PLGA-based nanoparticles (10–1000 nm) or microparticles (1–100 μm) have been employed for controlled release.[42]

Types - Natural vs Synthetic

A. *Natural Polymers:* Natural polymer which has been produced naturally from plant origin or animal origin that dissolves in water is named natural hydrophilic polymer. For examples- starch, algin, pectin, xanthan gum, insulin, agarose etc. are natural hydrophilic polymers.

Other natural: chitosan, alginate, gelatin, albumin.

B. *Synthetic Polymers:* Poly (lactic acid) (PLA), poly (lactic-co-glycolic acid) (PLGA), poly (εcaprolactone) (PCL), poly (ethylene glycol) (PEG).

Key Polymers - PLGA & Chitosan:

I) *PLGA:* Among the polymeric materials widely used to fabricate biodegradable nanoparticles are poly (D,L-lactide-co-glycolide) (PLGA) and chitosan (CS). PLGA is a polymer that undergoes degradation to form lactic and glycolic acid monomers.

Poly (lactic-co-glycolic acid) (PLGA) is a polymer randomly polymerized from lactic and glycolic acids.

Different proportions of monomers can produce different PLGAs, and their degradation degrees are different.

PLGA has attracted attention due to its unique characteristics of simple preparation, biodegradability, and high drug-loading capacity.

II) *Chitosan:* CS is a linear polysaccharide and positively charged at pH 6.5. Depending on degree of deacetylation, CS contains different numbers of acetyl groups and is regarded as biocompatible, nontoxic and biodegradable.

Chitosan nanoparticles are nanoparticles that contain chitosan or its derivative (s). Like chitosan, they are biocompatible, biodegradable, and cationic in nature. They are relatively non-toxic.

Chitosan is a non-toxic, biodegradable polymer that also shows high biocompatibility, a low level of immune reactions, and both mucoadhesive and absorption-enhancing properties.

Structure:

Nanosphere vs Nanocapsule Diagram illustrating the structure of polymeric nanoparticles, showcasing the difference between a nanosphere with its entangled polymer matrix and a nanocapsule with a distinct core-shell structure.

Polymeric nanoparticles have much of their internal volume available for carriage of drug cargo, either within a hollow polymer shell or mixed in with a porous low-density polymer structure throughout the particle[43]

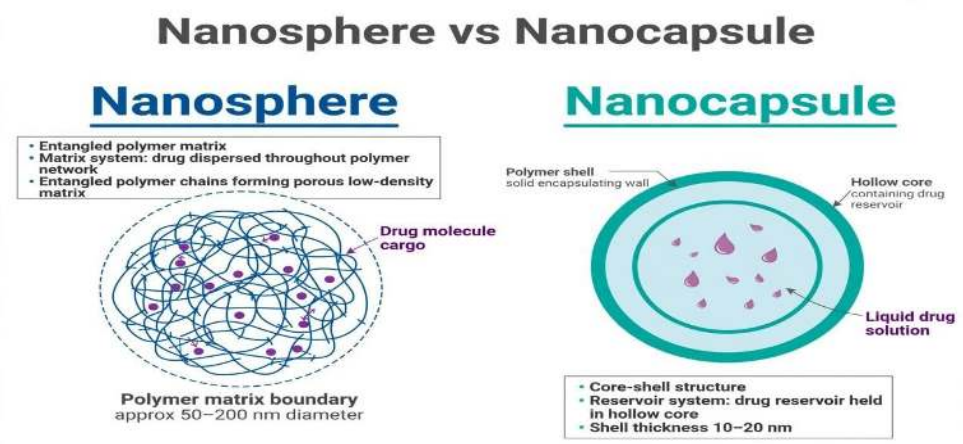


Diagram None:

Figure 4: Polymeric Nanoparticles.

Advantages:

- Potential advantages include their reduced toxicity and avoidance of accumulation in the cells after repeated administration.
- They retain significant advantages over other nanocarriers like micelles, liposomes, and inorganic nanosystems.
- Polymers such as PEG are commonly utilized as biocompatible coatings; thus, polymeric nanoparticles avoid early elimination by circulating phagocytotic cells while being easily degraded once within lysosomal compartments.
- The slow release of drugs encapsulated in PLGA can reduce routine dosing, enhance patient compliance, reduce discomfort, and avoid side effects.

Disadvantages:

- The main disadvantage is the preparation process's usage of organic solvents, which can damage physiological systems and the environment, and ruin some pharmaceutical drug molecules.
- Another disadvantage of PLGA NPs is presence of drug burst release, which could result in side effects.
- Chitosan insoluble at neutral and alkaline pH values.

Application in Analgesic Delivery:

A. General Pain Management.

B. BBB Crossing & Neuropathic Pain.

C. Sustained Analgesia.

D. Drugs Used: Ketorolac, Oxycodone, Curcumin, Loperamide, Ketamine, Tramadol, Morphine derivatives.[42]

5.4. Dendrimers:

Definition: Word from Greek *dendron* = tree + *meros* = part. Dendrimers are nanoparticles (1 nm to 100 nm diameter), highly branched, three-dimensional, monodisperse structures containing a central core surrounded by peripheral groups. Also called Starburst dendritic macromolecules / nanocascade spheres, first reported in 1985. Also called arborols.

Structure:

1. *Core:* An atom or group of atoms, with branches of carbon added through sequence of reactions producing spherical structure
2. *Branches / Interior Layer:* Repeating units radially attached to core, organized in radially concentric layers called "generations"
3. *Terminal Groups / Exterior:* Functional groups attached to outermost generation, determine physicochemical properties.

Diagram None:

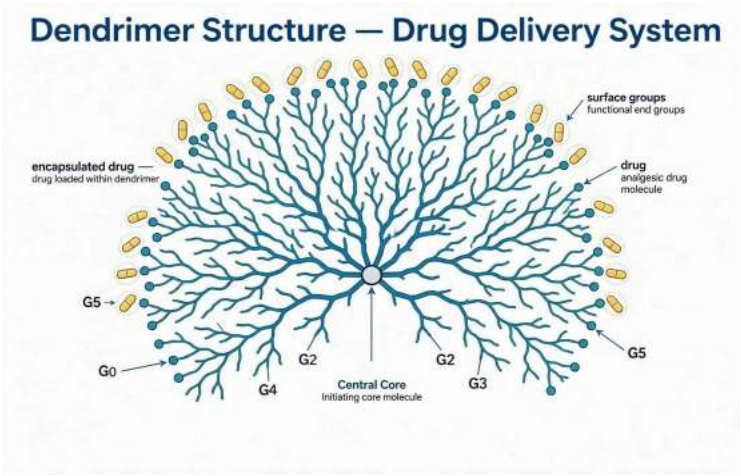


Figure 5: Dendrimers.

Types:

1.PAMAM Dendrimer (Poly Amido Amine) - Most common, spheroidal, synthesized by divergent method using ammonia/ethylenediamine core, commercially available as methanol solutions, Starburst is trademark name

2.PPI (Poly Propylene Imine), Chiral, Multilingual, Tecto, Hybrid, Amphiphilic, Frechettype, Peptide, PAMAMOS.

Synthesis:

Divergent Approach: Starts from core, arms attached by adding building blocks

stepwise.*Convergent Approach:* Starts from exterior, beginning with surface, introduced by Fréchet in 1989 for greater purity.Drug Loading Mechanisms: Simple encapsulation, electrostatic interaction, and covalent bonds.

- Non-covalent interactions (ionic, hydrophobic, hydrogen-bond).
- Covalent bindings and spacer-mediated conjugates.
- Drug release dependent on cleavage of dendrimer-drug linkage.

In Drug Delivery:

- Increase drug solubility and improve bioavailability.
- Reduce therapeutic dosage by increasing time of exposure.

- Targeted to cancer cells via molecular hooks (active targeting) and accumulate via EPR effect (passive targeting)
- Determine toxicity by surface charge; higher generation and cationic most toxic, lower generation anionic at low concentrations showed no toxicity.
- Properties:
- Highly branched, symmetric, homogeneous, monodisperse, low polydispersity index, globular structure occupies smaller hydrodynamic volume than linear polymers.
- Very dense surface surrounding relatively hollow core.
- Surface can be easily modified.[44]

5.5. Polymeric Micelles:

Definition:Polymeric micelles (PMs) are nanoscale drug-delivery systems, normally between 10 and 100 nm, self-assembled nanostructures formed from amphiphilic block copolymers with hydrophilic (A) and hydrophobic (B) blocks self-assembled in aqueous solutions. They are defined as organized auto-assemblies formed in a liquid, composed of amphiphilic macromolecules, in general amphiphilic di- or tri-block copolymers made of solvophilic and solvophobic blocks.Can exceed 100 nm and still be regarded as micelles, usually <50 nm diameter but polymeric micelles can be more stable.

Structure - Core-Shell: Special biphilic core-shell structure. Two-phase structure, commonly spherical, characterized by hydrophobic inner core and hydrophilic outer shell.

- *Core = Hydrophobic:* Encapsulates hydrophobic drugs, binds micelles together and wraps around insoluble molecules, formed by self-assembly of hydrophobic blocks
- *Shell = Hydrophilic:* Carries hydrophilic drugs, prevents aggregating and settling, protects therapeutic drugs, provides steric protection, reduces protein adsorption that leads to systemic clearance.

Nonpolar drugs on the core, polar drugs on the shell and drugs with intermediate polarity encapsulated between core and shell.

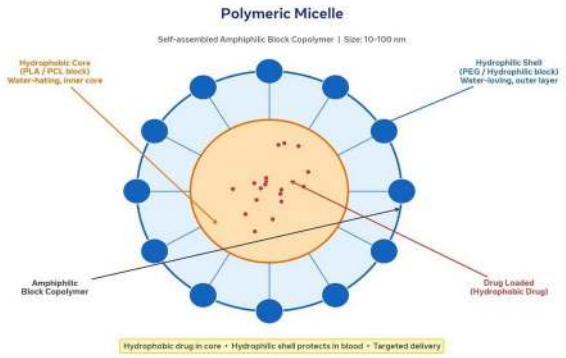


Diagram None:

Figure 6: Polymeric Miicelle.

Composition:

- Di-block (A-B) or tri-block (A-B-A) copolymers such as poloxamers and poloxamines, graft copolymers (G-chitosan) or ionic copolymers (PEG-PCL-g-PEI)
- Hydrophilic units: PEG (poly ethylene glycol), PEO, PVP
- Hydrophobic units: Polypropylene, polystyrene, poly amino-acid, PCL (poly εcaprolactone), PDLLA, PGA.

Mechanism -

CMC: Self-assembling is reversible process dependent on critical micelle concentration (CMC) - minimum concentration leading to micelles formation. Micelles stable above CMC, disassemble when diluted below CMC. Polymer concentration at which association first takes place known as CAC, lower by several orders than surfactant CMC values, thus more stable toward dilution in biological fluids.

Types:

- Based on intermolecular force: hydrophobically assembled amphiphilic micelles, polyion complex micelles, micelles from metal complexation.
- Morphology wise: Spherical (<100 nm most common), Cylindrical/worm-like, Vesicular/hollow, plus regular, snowman, dumbbell, reverse shape, multicompartment disc-like, raspberry-like.

Preparation Methods:

- Direct Dissolution: Copolymers with high aqueous solubility mixed with drugs in aqueous solvents with stirring, sonication, heating.
- Dialysis, Solvent Evaporation, Film Formation.

Advantages:

- Ability to solubilize poorly water-soluble drugs within core, enhancing bioavailability.
- Small size favors blood circulation, tissue penetration, cell uptake - preferred 40-50 nm.
- Prolonged circulation, control of drug release, targeted ligands for site-specific release, biocompatible, high diversity of polymers.
- Protects drugs from metabolism/oxidation, increases half-life.

Limitations:

- Lack of stability in PMs and slow release of drugs, sensitive to inner environment causing early release
- Disassemble below CMC after IV dilution.[45]

5.6. Nanohydrogel :

Definition: Nanohydrogels are submicron hydrogel particles, also called Nanogels / Hydrogel nanoparticles. Hydrogels are three-dimensional hydrophilic polymer chain networks that are crosslinked. These networks consist of natural or synthetic polymers and display swelling behavior when introduced to water or physiological fluids, able to revert to initial state when removed. Nanohydrogels are the nanoscale version (20-200 nm typical, systemic carriers 10100 nm, kidney clearable <10 nm) made to overcome high viscosity of macro hydrogels.

First term "NanoGel" used when PEG and PEI were chemically crosslinked for antisense oligonucleotide delivery.

Structure:

- Three-dimensional structure formed by chemically or physically crosslinked polymers with hydrophilic or amphiphilic chains, able to swell holding large amount of water without dissolving, maintaining structure intact
- Physical linkage: hydrogen bonding, hydrophobic, ionic interactions. Chemical crosslinking: covalent bonds - very strong
- Highly porous network, water content >90% w/w, fluid-like transport for drugs smaller than pore size
- Mesh size: 5 to 100 nm, through which drug releases to tissue/organs
- Posses attributes of both hydrogels and nanoparticles - polymer nanoparticles.

Diagram None:

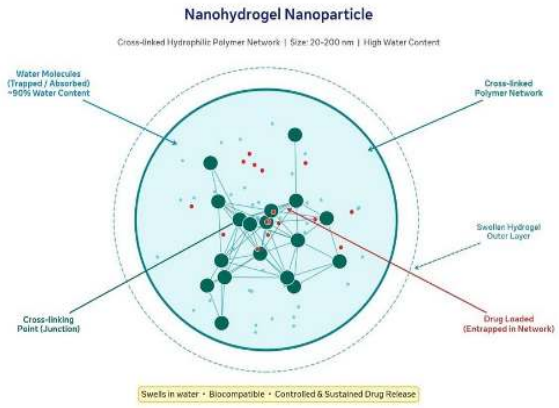


Figure 7: Nanohydrogel

Types:

- Based on polymer: Natural (alginate, chitosan, dextran, pullulan) and Synthetic (PEG, PVA, PNIPAM)

- Based on crosslinking: Physically crosslinked and Chemically crosslinked
- Based on stimuli response: pH-sensitive, temperature-sensitive (smart hydrogels), ionic strength, light
- Morphologically: Nanocomposite, Hybrid hydrogels, Polymeric nanogels, Nanoorganogels (holds oily substances)

Synthesis / Preparation:

Free radical polymerization, chemical and physical crosslinking, heterogeneous atom polymerization, inverse emulsion method, W/O heterogeneous emulsion, precipitation polymerization, heterogeneous controlled/living radical polymerization, dispersion polymerization, electrospinning, microfluidics, stereolithography.

Drug Loading: Methods: dissolution, entrapment, adsorption, attachment, encapsulation. The hydrogel's porous network allows encapsulation of both hydrophilic and hydrophobic drugs. Though hydrophilic nature limits hydrophobic encapsulation, structure engineering permits high encapsulation of poorly soluble anticancer drugs.

Drug Release Mechanism:

1. Diffusion through meshes - controlled by crosslink-controlled pore structure
2. Swelling controlled - as swelling continues, mesh sizes increase and gradually release encapsulated drug
3. Stimuli-responsive - mesh sizes change with stimuli (temperature/pH) according to crosslink bond concentration that forms or breaks, regulating breakage will provide control of drug release acceleration.

Advantages:

- Physiochemically very similar to extracellular matrix + very high water content = very high biocompatibility
- Can be extruded through injector needle (submicron), escape renal clearance and prolonged serum half-life due to size 20-200 nm
- Thermodynamic stability, high solubilization capacity, relatively low viscosity, can undergo vigorous sterilization
- High drug loading, biocompatibility, controlled drug release, ability to carry variety of drugs, responsiveness to environmental stimuli
- Increased surface area provides further bioconjugation, easily modified with targeting ligands for targeted delivery.

Disadvantages:

- Hydrophilic nature may limit hydrophobic drug loading without modification
- Stability issues

Applications: Drug delivery, vaccine design, cancer therapeutics, wound healing (moist environment), diagnostic biosensors, contact lenses, protein and gene delivery, ocular, transdermal, CNS therapies.[46]

5.7. Inorganic /metallic nanoparticles:

Definition:

Inorganic nanoparticles are non-toxic, hydrophilic, biocompatible and highly stable compared to organic materials. Divided into non-metallic (silicon, carbon) and metallic. Metallic nanoparticles (MNPs) are metallic nanostructures with dimensions 1-100 nm, with high surface area, optical characteristics, tunable size/shape. Given their fundamental chemical and physical characteristics, low cost and excellent biocompatibility, they stand out for manufacturing of nanocarriers.

Properties

- Small size, can exhibit magnetic characteristics. Beneficial when developing systems that respond to magnetic fields. By adding magnetic components, researchers can use external magnetic fields to control movement and localization within body. Precision of delivering drugs to particular tissues/organs is improved.

Diagram None:

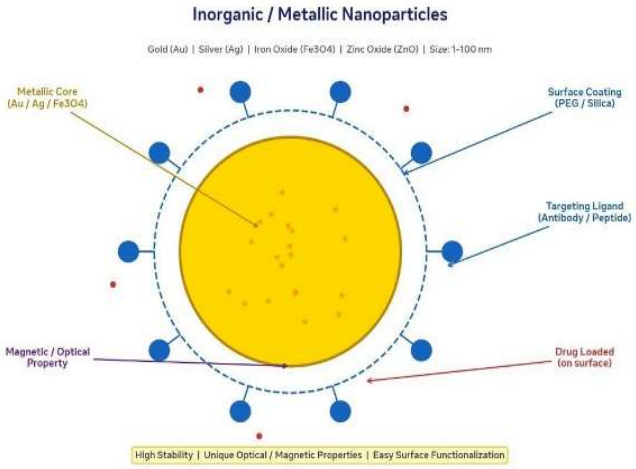


Figure 8: Inorganic/Metallic NPS

Types of MNPs and Applications in Medicine:

1)Gold NPs.

2)Silver NPs.

3)Iron oxide NPs.

4)Copper NPs.

5)Titanium dioxide, Zinc oxide,Aluminum oxide.

Gold and Silver NPs:

- AuNPs and AgNPs have attracted significant attention due to remarkable optical properties. Can display SPR behaviour, when light excites electrons at interface between conductor and insulator. Optical properties are mainly shape and sizedependent.
- When light absorbed, electrons undergo collective oscillation, generates local heat usable in biomedical applications. Enables photothermal therapy (PTT) – utilization of light energy to kill cancer cells.

Advantages as Drug Carriers:

1. Optical/Electronic: Tunable by changing size, shape, surface chemistry. Absorb light and convert to heat for PTT.
2. Drug Delivery: AuNPs can be functionalized with ligands, antibodies, peptides, or drugs to achieve targeted delivery and controlled release. Surface modification enables selective binding to cancer cells, enhancing efficacy and reducing systemic toxicity.
3. Controlled Release: Can be designed as controlled drug-release systems relying on photothermal effect (PTE), which induces release of encapsulated payloads through outer layer phase change due to localized temperature increase.
4. High Stability: Gold and silver nanoparticles are most stable in physiological media compared to ZnO, Fe2O3. 20 nm particles least stable possibly due to surface curvature.
5. Antimicrobial Co-delivery: AgNPs explored for co-delivery with antibiotics to improve effectiveness and reduce resistance.

Limitations:

- Expensive, limited biodegradation (Au), potential toxicity (Ag due to ion release), agglomeration and synthesis complexity (Fe oxide), tendency to aggregate in biological fluids – overcome by organic coatings like chitosan, PEG, thiols, dextran, citrate.
- Need electrostatic attractive forces between polysaccharide (amino groups of chitosan) and metallic nanoparticle to stabilize.

Synthesis Methods:

Physico-chemical methods: laser ablation, chemical reduction, green synthesis. Size and shape highly dependent on production technique.

Market Significance:

Metal NPs particularly Au and Ag represent 28.7% of inorganic nanoparticles market with CAGR 13.2%

through 2034. Over 18 clinical trials investigating gold-based treatments targeting solid tumors.[47]

6.Mechanism of action:**[12]**

Nanoparticles act as tiny carriers for analgesic drug delivery, helping transport pain-relieving drugs to the targeted site in the body. The drug is encapsulated within or attached to nanoparticles, which protect it from degradation and improve its absorption and bioavailability. Due to their small size, nanoparticles can enhance drug penetration into tissues and facilitate cellular uptake. They release the drug in a controlled and sustained manner through diffusion or degradation, helping reduce inflammation and block pain signals. Thus, nanoparticle-based drug delivery can improve analgesic effectiveness, prolong pain relief, reduce dosing frequency, and minimize unwanted side effects.

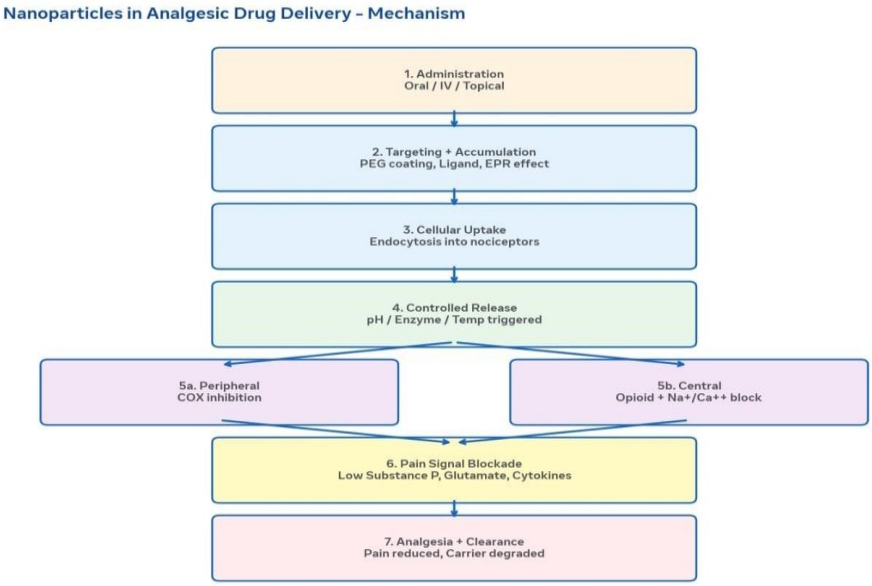


Figure 9: Mechanism of Action

7. Route of administration:

- Oral route: Nanoparticles shield drugs from degradation by gastric acids and digestive enzymes while enhancing their absorption through the intestinal wall.

Example: Ibuprofen-PLGA Nanoparticles.

Advantages: Easy,patient friendly, sustained release.

- Transdermal route: Nanogels, nanopatches, and liposomal gels are applied topically, allowing the drug to penetrate through the skin and reach the targeted site of pain.

Example: Diclofenac liposomal gel.

Advantages: No gastric ulcer, local pain relief, no first pass metabolism.

- Intranasal route: Nanoparticles administered through nasal sprays can deliver drugs directly to the brain via the olfactory pathway, potentially bypassing the blood–brain barrier (BBB).

Example: Tramadol-chitosan NPs.

Advantages: Fast action, brain targetting, use full in migrane.

- Intra venous (IV) route: Nanoparticles injected directly into vain target to inflamed tissue.

Example: Morphine liposomes.

Advantages: 100% bioavailability, immediate action.

- Intramuscular/subcutaneous route: Nanoparticles injected into muscle /under skin ,slow release for long time.

Example: Bupivacaine Liposomes.

Advantages: Long duration analgesia, 24-72 hrs relief.

- Local/Intrarticular route: Nanoparticles injected directly into joint or painful areas.

Example: Diclofenac nanoparticles in knee joint.

Advantages: High local concentration, very low systemic side effect. [1]

8. Evaluations: Table No.2

Parameter	Method Used	Ideal Value	Importance
Particle size	Dynamic light Scattering (DLS)	10-200nm	Small size =Better absorption, crosses BBB and skin.
PDI-Polydispersity Index	DLS	Less than 0.3	Show uniformity. Low PDI =All particles are the same size.
Zeta Potential	Zeta Sizer	+30mv to -30mv	Show stability. High value =Particles will not aggregate.
Shape/ Morphology	SEM/TEM	Spherical, smooth	Spherical particles give better drug releases.
Entrapment Efficacy %	Centrifugation + UV/HPLC	70-95%	How much drug is inside nanoparticles. High= Less wastage.
Drug loading%	UV/HPLC	10-30%	How much drug per weight of nanoparticles.

9.Advantages and disadvantages:

Advantages:

- Targeted delivery: Nanoparticles can be designed by size, shape and surface charge to target specific tissue, nerve, or inflamed sites; this reduces systemic exposure.
- Prolonged and sustained release: Liposomal and dendrimer-based formulations allow extended release and more prolonged and stable analgesia. PLGA nanoparticles showed sustained release up to 21 days in vitro for ketamine.
- Improved solubility and bioavailability: Nano formulations increase solubility of poorly soluble analgesics and improve pharmacokinetics and biodistribution.
- Reduced side effects and toxicity: By targeting delivery, off-target toxicity is reduced, and bioavailability is improved.
- Reduced dose and frequency: Controlled release reduces routine dosing, enhances patient compliance, and avoids side effects.
- Protection of drug: Encapsulation protects drug from degradation in GI tract and from enzymes and improves stability via encapsulation of free molecules.

Disadvantages:

- Toxicity concerns: Toxicity of nanoparticles, especially metal-based and inorganic nanoparticles, is not fully known. Less than 8% of publications on nanotechnologies report their toxicity.
- Lack of clinical trials: Most data are preclinical. Several barriers include lack of clinical trials, difficulties in mass production, toxicity concerns and regulatory issues.
- Scale-up and manufacturing difficulty: Difficulties in mass production of several nanoparticles, poor reproducibility, and need for specialized equipment.
- Stability and storage problems: Aggregation, drug leakage, burst release, and physical instability on long storage.
- High cost: Complex formulation, characterization and quality control increase cost compared to conventional tablets.[8]

CONCLUSION:

Conventional analgesic drugs such as Diclofenac, Ibuprofen, and Paracetamol are commonly used to relieve pain and inflammation. However, their effectiveness may be limited by poor bioavailability, a short duration of action, and the need for frequent administration, which can increase the risk of adverse effects such as gastric ulcers, liver damage, and kidney

toxicity. To overcome these limitations, nanobiotechnology has emerged as an innovative approach to analgesic drug delivery.

Various nanocarriers, including Liposomes, Polymeric Nanoparticles (PLGA and Chitosan), Solid Lipid Nanoparticles (SLNs), and Nanogels, help improve drug absorption, stability, and targeted delivery to painful or inflamed tissues. Their nanoscale size facilitates better drug penetration and controlled release, providing prolonged pain relief with lower doses and potentially reducing side effects. Additionally, advanced approaches such as transdermal nanopatches and intranasal drug delivery offer alternative and effective methods for managing localized and severe pain, thereby improving treatment outcomes and patient compliance

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