Nanoparticles for Therapeutic Use and Targeted Drug Delivery Applications

MICHAEL ADENIYI[1], PECULIAR LAWRENCE[2]
[1]*Department of Mechanical Engineering, Georgia Southern University, Statesboro Georgia, USA,*
[2]*Biomedical Engineering Department, Cornell University, USA.*

Abstract- ***This review offers a comprehensive analysis of biodegradable nanoparticles, emphasizing their biocompatibility, adaptability, and customizable characteristics, which render them ideal for drug delivery applications. It discusses various preparation techniques for biodegradable nanoparticles, through the polymerization of monomers and dispersion of preformed polymers, including solvent evaporation, solvent diffusion, nanoprecipitation, and electros praying methods, highlighting their utility in targeted drug delivery applications. The review also examines therapeutic nanoparticles and different classes of therapeutic nanoparticles, including polymer-based nanoparticles, non-polymeric nanoparticles and lipid-based nanoparticles, detailing their unique properties and significant role in optimizing drug delivery systems. It further explores strategies for drug incorporation into nanoparticles—encompassing encapsulation, surface adsorption, and chemical conjugation techniques—and investigates their release mechanisms and applications in targeted drug delivery.***

Indexed Terms- ***Nanotechnology, Therapeutic nanoparticles, Drug Delivery Systems, Encapsulation, Electrospray***

I. INTRODUCTION

Nanotechnology has seen rapid advancements in recent years due to breakthroughs in material science and nano-engineering. These developments have unlocked new possibilities for using nanoparticles, which are structures ranging from 1-100 nanometers, in cutting-edge biomedical applications. The unique size and structural properties of these materials enable innovative solutions across various domains, including healthcare. [1]In modern medicine, nanomaterials are transforming approaches to treatment and diagnostics [2]. They play a pivotal role in applications such as tissue engineering, precision drug delivery, cancer therapies, and bioanalytical diagnostics. Nanoparticles, in particular, have shown immense potential in delivering therapeutic agents, including small-molecule drugs and larger biological molecules like proteins and genes, with remarkable precision and efficiency. Recent breakthroughs have also enabled the formulation of biocompatible and biodegradable nanocomposites, such as nanoparticles, nanocapsules, and micellar systems. These technologies are pushing the boundaries of medical science, offering targeted and localized therapeutic delivery systems that promise to revolutionize patient care. This discussion emphasizes the preparation of polymer-based nanoparticles and their growing impact on medical innovation.

Nanoparticles represent a highly adaptable platform for the delivery of diverse therapeutic agents, including both hydrophilic and hydrophobic drugs, proteins, vaccines, and macromolecules. They can be precisely tailored to target specific tissues, such as the brain,tumor sites, arterial walls, lungs, liver, or spleen, while also being engineered for prolonged systemic circulation. Moreover, nanoparticles conjugated with imaging agents expand their utility beyond drug delivery, offering capabilities for advanced diagnostics, such as Magnetic Resonance Imaging (MRI) and optical imaging, as well as guided interventions like hyperthermia therapy, particularly in the context of cancer treatment. [3]

There are several methods available to synthesize nanoparticles, tailored to the type of drugs being used, the targeted organ, and the chosen delivery mechanism. The synthesis parameters can be adjusted based on the selected method, allowing for the optimization of the nanoparticle characteristics. This

article offers an in-depth review of biodegradable nanoparticles, focusing on their characteristics, method of preparation, types of therapeutic nanoparticles, and drug encapsulation strategies. It further examines the specific applications of various nanoparticle types, emphasizing their role in advancing targeted drug delivery technologies.

Preparation of Nanoparticles

Biodegradable nanoparticles are synthesized using various materials, including natural proteins, polysaccharides, and synthetic polymers, chosen based on the intended application and desired properties. Critical factors influencing the material choice include the required size of the nanoparticles, compatibility with the drug being delivered, desired surface features, biodegradability, and the release profile needed for therapeutic effectiveness. Depending upon selection of desired criteria for the preparation of the nanoparticles, the methods can be classified into, dispersion of preformed polymers and polymerization of a monomer. These methodologies enable the customization of nanoparticles to suit specific biomedical uses, such as targeted drug delivery or advanced therapeutic systems.

Nanoparticles obtained from preformed polymers

This method is one of the most widely employed approaches for creating biodegradable nanoparticles using polymers such as poly-lactic acid (PLA), poly-D-L-glycolide (PLG), poly-D-L-lactide-co-glycolide (PLGA), and poly-cyanoacrylate (PCA). The technique can be implemented in various forms, as detailed in the following procedures.

(a) Emulsification/solvent evaporation

In this process, the polymer is initially dissolved in a volatile organic solvent, such as dichloromethane or chloroform. The drug is then integrated into this polymer solution, which is emulsified into an oil-in-water (o/w) system with the aid of emulsifying agents like gelatin or polyvinyl alcohol. Once the emulsion is stabilized, the solvent is removed through evaporation, typically under heat or reduced pressure, while continuous stirring ensures uniformity. The final particle size is determined by key factors such as stabilizer and polymer concentrations and the stirring speed during emulsification [4].Figure 1 shows a schematic illustration of the solvent evaporation technique

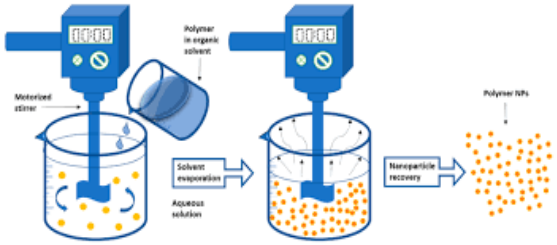

Figure 1. Schematic representation of the solvent evaporation technique (Adapted from Wang et al. 2016)

(b) Emulsification/solvent diffusion

The Emulsification/Solvent Diffusion (ESD) method involves dissolving the polymer in a partially water-soluble solvent, such as propylene carbonate, which is then saturated with water to establish a thermodynamic equilibrium. To facilitate nanoparticle formation, the solvent is diffused by dilution with excess water or another organic solvent, causing the polymer to precipitate. This phase is then emulsified in an aqueous solution containing a stabilizer, which leads to the formation of nanospheres or nanocapsules, depending on the oil-to-polymer ratio. The solvent is eventually removed through evaporation or filtration, depending on its boiling point. This approach allows for controlled nanoparticle synthesis, with characteristics that can be tailored based on the solvent, stabilizers, and other formulation variables used[5].This procedure is illustrated in Figure 2.

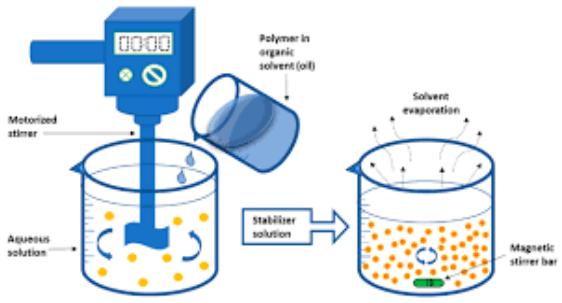

Figure 2. Schematic illustration of the solvent diffusion technique(Adapted from Wang et al. 2016)

(c) Nanoprecipitation method

This technique, originally optimized for encapsulating hydrophobic drugs, has been refined to accommodate hydrophilic compounds as well. The process involves dissolving the active compound and polymer in a water-miscible polar solvent like acetone or methanol. The prepared solution is then systematically added

into an aqueous medium containing surfactant, triggering the immediate formation of nanoparticles through solvent diffusion dynamics. The final step involves the controlled removal of the solvent under vacuum conditions, resulting in stable nanoparticles. This method showcases an advanced and versatile approach for producing nanoparticles suitable for diverse pharmaceutical applications [6]. The schematic representation of solvent evaporation is shown in Figure 3.

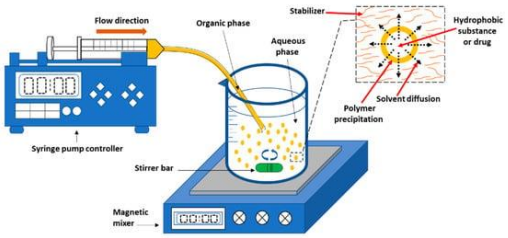

Figure 3. Diagrammatic representation of the solvent evaporation technique

(d) Salting out with synthetic polymers

The salting-out technique is a refined method for nanoparticle production that employs the selective exclusion of a water-miscible solvent from an aqueous phase using salting-out agents. This strategy builds upon emulsification/solvent diffusion principles, enhancing nanoparticle synthesis and encapsulation precision. The process begins with dissolving the polymer and therapeutic compound in a solvent like acetone, followed by emulsification into an aqueous gel containing electrolytes (e.g., magnesium or calcium chloride) or non-electrolytes (e.g., sucrose), combined with stabilizers like polyvinylpyrrolidone. The introduction of additional water facilitates the solvent's diffusion into the aqueous phase, prompting nanoparticle formation. The careful selection of salting-out agents is essential, as these directly influence drug encapsulation efficiency and particle properties. Final purification is achieved through cross-flow filtration, removing residual agents and solvents. This technique ensures controlled particle synthesis and high encapsulation efficiency, proving indispensable in advanced drug delivery systems and precision medicine [7].

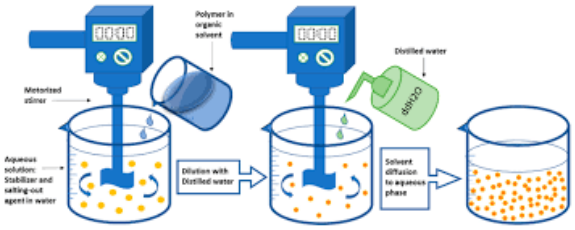

Figure 4. Schematic of the solvent evaporation technique

(e) Electrospray Method:

Electrospray is an advanced and highly precise method for generating biodegradable nanoparticles, offering unparalleled precision in tailoring particle size, shape, and drug incorporation. The technique leverages the application of a high-intensity electric field to a polymer solution, producing a Taylor cone—a dynamic structure that facilitates the emission of charged microdroplets. As these droplets migrate toward a collection electrode, the solvent evaporates, yielding uniform, solid nanoparticles. This advanced methodology offers unparalleled consistency and customization, making it particularly promising for targeted drug delivery systems and innovative biomedical applications [8].

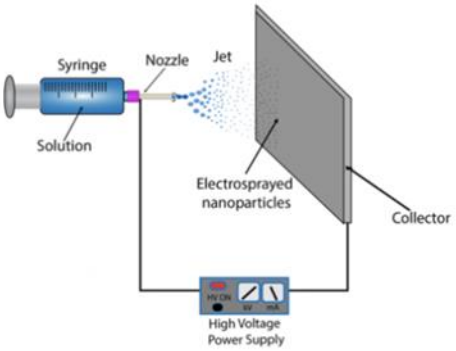

Figure 5. Schematic of Electrospraying (Huang, Koutsos, &Radacsi, 2020)

Nanoparticles obtained by polymerization of a monomer

Nanoparticles (NPs) are synthesized by polymerizing monomers in aqueous solutions, resulting in the formation of the nanoparticles. Therapeutic agents such as drugs or vaccines can be incorporated into these NPs by either dissolving the drug within the polymerization medium or attaching it to the surface of the formed NPs. After the NPs are produced, they

are purified by removing stabilizers, and surfactants can be reused for subsequent synthesis processes. This technique is commonly employed to prepare polybutylcyanoacrylate or poly-alkyl-cyanoacrylate NPs. The concentration of surfactants and stabilizers during synthesis directly impacts the final size of the nanoparticles. [9]

Biodegradable Nanoparticles

Biodegradable nanoparticles are engineered from materials capable of being broken down by natural biological processes into harmless by-products, which can then be metabolized or expelled from the body. These nanoparticles are increasingly recognized for their potential in drug delivery, owing to their unique characteristics such as biocompatibility, tunable degradation rates, and the ability to encapsulate a variety of therapeutic agents. The synthesis of biodegradable nanoparticles relies on the careful selection of materials that can balance stability, degradation, and functionality. This chapter will discuss the key properties of such materials, focusing on their role in advancing sustainable drug delivery systems that are not only effective but also environmentally friendly. The choice of biodegradable materials significantly influences the design of nanoparticles for controlled drug release, enabling precision in therapy while minimizing side effects.

Biocompatibility: It is essential that the materials used for nanoparticles are well-tolerated by biological systems, minimizing the likelihood of adverse reactions. Materials like poly(lactic-co-glycolic acid) (PLGA), polylactic acid (PLA), and chitosan are frequently selected for their proven compatibility and regulatory approval for medical applications (Danhier et al., 2012). These materials ensure that the nanoparticles interact safely with biological tissues, avoiding toxicity and enhancing patient safety. [10]

Degradability: An important characteristic of biodegradable nanoparticles is their ability to break down in physiological conditions. This degradation results in the generation of non-toxic byproducts that the body can metabolize or eliminate, thus preventing the accumulation of nanoparticles in tissues over time. This reduces the risks associated with long-term exposure, such as inflammation or tissue damage. Effective biodegradation also ensures that the nanoparticles do not persist in the body, contributing to their safety profile.(Mura et al., 2013)[11]

Tunable Properties: One of the major advantages of using biodegradable materials is the ability to modify the properties of the nanoparticles. By adjusting factors such as particle size, shape, surface charge, and degradation rates, these materials can be tailored to create nanoparticles that provide optimal drug release profiles, target specific tissues, and improve therapeutic outcomes. This customization capability is key to the design of efficient drug delivery systems that meet the precise needs of different therapies. (Alexis et al., 2008) [12]

Composition: Biodegradable nanoparticles typically consist of biocompatible materials like polymers or lipid-based compounds. Among the commonly used polymers are poly(lactic-co-glycolic acid) (PLGA), polylactic acid (PLA), poly(caprolactone) (PCL), and chitosan, which are favored for their biocompatibility and biodegradability. Lipid-based nanoparticles such as liposomes, solid lipid nanoparticles (SLNs), and nanostructured lipid carriers (NLCs) also play a significant role in drug delivery systems due to their unique properties, including improved stability and bioavailability. (Tran et al., 2019) [13]

Synthesis Methods: The synthesis of biodegradable nanoparticles involves various methods like emulsification, nanoprecipitation, solvent evaporation, and self-assembly. These techniques offer precise control over the size, shape, surface properties, and drug-loading capabilities of nanoparticles, ensuring the desired characteristics for efficient and targeted drug delivery. (Tran et al., 2019) [13]

Drug Encapsulation: Biodegradable nanoparticles are highly effective in encapsulating a wide range of therapeutic agents, including small molecules, proteins, nucleic acids, and peptides. This encapsulation protects the drugs from premature degradation, enhances their solubility, prolongs their circulation time in the body, and allows for targeted delivery to specific tissues or cells, improving therapeutic outcomes and reducing side effects (Tran et al., 2019) [13]

Controlled Release: One of the significant advantages of biodegradable nanoparticles is their capacity for controlled and sustained drug release. This is achieved through the degradation of the nanoparticle matrix or the diffusion of the drug through the nanoparticle pores. The controlled release of drugs ensures that therapeutic agents are delivered over an extended period, which not only optimizes the desired therapeutic effects but also reduces the likelihood of side effects associated with drug peaks and valleys in concentration (Hua et al., 2018). The degradation rate of the polymer matrix or the structural properties of the nanoparticles can be tailored to provide a precise drug release profile, thereby enhancing the treatment's efficacy while minimizing the impact on healthy tissues. [14]

Targeted Delivery: Biodegradable nanoparticles can be further enhanced through surface modifications, where targeting ligands—such as antibodies, peptides, or aptamers—are attached. This modification allows the nanoparticles to specifically recognize and bind to targeted cells or tissues, improving the precision of drug delivery. This targeted approach leads to a higher accumulation of the nanoparticles at the desired site of action, enhancing the therapeutic outcome. By focusing on specific areas, targeted delivery reduces off-target effects, making treatments more effective while decreasing potential harm to surrounding healthy tissues (Danhier et al., 2012). [10]

Types of Therapeutic Nanoparticles

Nanomaterials are divided into Nano-structured and nanocrystalline materials. Nano-structured materials are classified into three primary types: polymer-based, non-polymeric, and lipid-based nanoparticles, each offering unique characteristics and applications. Polymer-based nanoparticles, include dendrimers, micelles, nanogels, protein carriers and drug conjugates. Polymeric nanoparticles, provide a flexible platform for drug delivery and therapeutic applications due to their customizable properties. Non-polymeric nanoparticles includes advanced materials like carbon nanotubes, nanodiamonds, metallic nanoparticles, quantum dots, and silica-based nanoparticles, they are valued for their distinct structural and functional features, including optical and electronic properties. Lipid-based nanoparticles, comprising liposomes and solid lipid nanoparticles, have gained prominence in drug delivery systems for their biocompatibility and efficacy.

Among these, polymer-based and lipid-based nanoparticles dominate clinical applications, forming the majority of nanoparticles approved for therapeutic use. Their superior biocompatibility, adaptability, and established safety profiles underscore their prominence in advancing nanomedicine. Here, we outline the different classes of clinically used nanoparticles, their specific roles in treatment, as well as the current strategies developed to deliver them in challenging medical conditions.

Polymer-Based Particles

Nanoparticles

Polymer-based nanoparticles, derived from both synthetic and natural materials, are emerging as highly adaptable platforms for therapeutic delivery due to their intrinsic properties such as biocompatibility, biodegradability, and low immunogenicity. [15]. Synthetic polymers, like polycaprolactone (PCL) and polylactic acid (PLA), are often employed in their polyester derivatives to reduce potential immunogenicity and toxicity, while natural polymers such as chitosan, gelatin, albumin, and alginate demonstrate inherent biocompatibility and superior therapeutic efficiency compared to conventional delivery methods.

These nanoparticles function as a matrix system, either forming nanocapsules, where the drug is encased within a polymeric shell, or nanospheres, where the drug is homogeneously integrated into the polymer matrix [16]. Advanced fabrication techniques enable precise modulation of drug release profiles, ensuring controlled and sustained delivery to target sites. Furthermore, their surfaces can be engineered with specific recognition ligands, enhancing targeting accuracy and therapeutic specificity, thus aligning with precision medicine goals for improved clinical outcomes.

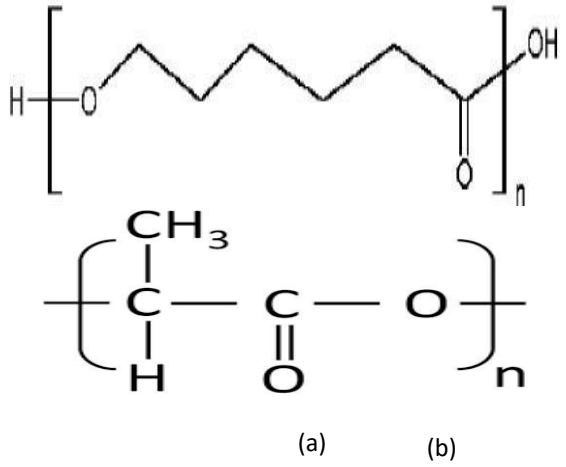

Figure 6. Chemical structure of (a)Poly-caprolactone (PCL) and (b) Poly lactic acid (PLA)

Dendrimers

Dendrimers are a distinguished class of polymeric nanoparticles utilized in clinical applications, notable for their highly branched, compartmentalized structure and remarkable monodispersity. The precise control over the branching of dendrimer molecules allows for the synthesis of particles within the range of 1-5 nm, making them ideal for therapeutic purposes. These polymers are typically fabricated into spherical shapes, creating internal cavities that enhance encapsulation efficiency, particularly in high-generation dendrimers that feature a large number of surface functional groups (e.g., over 64 surface groups). This high-generation design enhances their capability for drug delivery, offering a significant advantage in therapeutic applications.Moreover, dendrimers possess terminal functional groups that can be easily modified, enabling conjugation with biocompatible molecules to improve biocompatibility, bio-permeability, and minimize cytotoxicity. Such surface modifications also facilitate targeted delivery, enhancing the precision with which therapeutic agents are directed to specific sites. Their unique structural versatility allows for the encapsulation or complexation of biologically active substances, such as drugs, vaccines, and genes, improving their delivery efficiency. Currently, commonly used dendrimer platforms are synthesized from various mono- and copolymers, including polyethyleneimine, polyamidoamine, poly(propyleneimine), and chitin, each contributing to the dendrimer's functionality and effectiveness in therapeutic applications [17].

Micelles

Polymeric micelles are advanced nanostructures utilized primarily for the systemic delivery of hydrophobic drugs that are poorly soluble in water. These nanoparticles, typically under 100 nm, form aggregates in solution where their amphiphilic molecules arrange into a spherical configuration. The hydrophilic exterior provides a protective barrier that shields the micelles from nonspecific uptake by the reticuloendothelial system, ensuring enhanced circulation stability. Simultaneously, the hydrophobic core is capable of encapsulating insoluble therapeutic agents, either via physical encapsulation or covalent linkage. This dynamic structure allows polymeric micelles to offer a versatile drug delivery platform with high loading capacity, targeted ligand conjugation capabilities, and controlled release, making them particularly effective for precise and sustained therapeutic applications [18].

Drug Conjugates

Polymer-drug conjugation is a widely adopted strategy in cancer therapy, particularly for enhancing the therapeutic efficacy of low molecular weight drugs. This technique increases the molecular weight of the drug, which modifies its pharmacokinetics, facilitating improved cellular uptake and promoting sustained drug release. These conjugates function as effective carriers by improving solubility, stability, and enhancing the enhanced permeability and retention (EPR) effect, which is particularly beneficial for targeting tumor cells. Furthermore, pH-sensitive conjugates leverage the acidic microenvironment of tumors to enable controlled drug release through the use of pH-responsive bonds. This method has shown significant promise in enhancing the bioavailability of drugs, as exemplified by combination therapies like paclitaxel and doxorubicin [19].

Protein Nanoparticles

Viruses are inherently efficient in transferring their genetic material, encapsulated by capsid proteins, and this natural process has been harnessed to create Virus-like Particles (VLPs). These VLPs mimic the structure of viruses but are devoid of their genetic content, making them highly useful as nanocarriers for therapeutic purposes. Additionally, Caged Proteins (CPs) are self-assembled protein nanostructures that resemble viral particles, yet are not derived from

actual viruses, thus offering another platform for drug delivery applications. Both VLPs and CPs are especially promising for cancer vaccine development due to their ability to evoke targeted immune responses against malignant cells. Furthermore, self-assembling protein-based nanoparticles, derived from natural sources such as collagen, albumin, or silk, can be engineered through genetic manipulation to form functional carriers. This approach not only mirrors the benefits of traditional polymeric nanoparticles but also opens the door to more sophisticated systems. Abraxane®, an FDA-approved drug, exemplifies this potential, using albumin-coated nanoparticles to effectively deliver paclitaxel. Additionally, the success of VLP-based HIV vaccines has spurred advancements in protein nanoparticle research, accelerating their clinical application for diverse therapeutic purposes. [20]

Non-Polymeric Nanoparticles

Carbon Nanotubes

Carbon nanotubes (CNTs), including single-walled nanotubes (SWNTs), multi-walled nanotubes (MWNTs), and C60 fullerenes, are nanoscale cylindrical structures formed by rolling graphene sheets into seamless tubes. With diameters as small as 1–2 nm and lengths up to 100 nm, CNTs exhibit exceptional dimensional precision and stability, making them ideal carriers for therapeutic agents. They can penetrate cells via endocytosis or membrane insertion, enabling efficient intracellular delivery. Fullerenes, with their unique spherical arrangement and conjugated double bonds, further enhance drug delivery capabilities by scavenging free radicals and protecting damaged mitochondria, enabling tissue-specific targeting. CNTs have shown promise in delivering antibiotics, antivirals, anticancer drugs, and other therapeutics, positioning them as cutting-edge tools for precision medicine. [21].

Nanodiamonds (NDs)

Nanodiamonds (NDs), a distinct subset of carbon-based nanomaterials, exhibit nanoscale dimensions under 100 nm, with intricate faceted geometries arising from synthesis techniques such as detonation, chemical vapor deposition (CVD), and high-pressure/high-temperature processes. Among these, the detonation method, the most established, involves inducing controlled explosions of carbon-rich precursors within sealed chambers, yielding NDs characterized by sp^2 carbon surface layers and shape-dependent electrostatic potential. Alternatively, the CVD approach is optimal for producing defect-free ND thin films, making it advantageous for substrate coatings. [22].

Metallic Nanoparticles

Metallic nanoparticles, generally measuring between 1 and 100 nanometers, are composed primarily of metals such as cobalt, nickel, iron, gold, and their respective oxides, including magnetite and maghemite. Their versatility stems from their ability to be synthesized and modified with a wide range of functional chemical groups, enabling the attachment of various biomolecules, including therapeutic agents, peptides, proteins, and nucleic acids. These nanoparticles stand out not only for their stability and biocompatibility but also for their unique magnetic properties, making them valuable tools in the medical field. [23]

Gold nanoparticles (AuNPs) have garnered considerable attention in the medical field, especially in cancer detection and treatment, thanks to their distinctive optical properties, including localized surface plasmon resonance (LSPR). This unique characteristic enables AuNPs to interact with light in such a way that they significantly enhance imaging contrast, making them invaluable for diagnostic applications. Their inert nature results in minimal cytotoxicity, adding a layer of safety for in vivo use. A key feature of AuNPs in cancer therapy is their ability to convert light energy into heat, triggering localized hyperthermia. This photothermal conversion, activated by specific light wavelengths, facilitates the destruction of cancerous cells in targeted tumor regions without affecting surrounding healthy tissues. Furthermore, the capacity to precisely control the release of drugs upon light exposure enhances the specificity of therapeutic interventions, ensuring that drugs are delivered directly to the tumor site. Beyond their applications in therapy and diagnostics, the tunable optical properties of AuNPs make them versatile tools in various other medical technologies, such as biosensing, imaging, and electrochemical detection. Their ability to provide targeted treatments and enhance diagnostic imaging positions AuNPs as a powerful platform for advancing personalized medicine. [24].

Quantum Dots

Quantum dots (QDs) are nanoscale semiconducting particles, typically ranging from 2 to 10 nanometers in diameter composed of a semiconducting core like cadmium selenide (CdSe) and an outer shell, such as zinc sulfide (ZnS), that provides water solubility. The emission color of QDs is determined by their core material, and this emission is characterized by narrow, bright fluorescence. Their high surface-to-volume ratio leads to unique optical properties, including the ability to emit different colors depending on their size. Furthermore, their outer organic shell can be modified to allow for the conjugation of biomolecules like peptides, proteins, or DNA, enabling targeted therapeutic or diagnostic applications. [25]

Lipid-Based Nanoparticles

Liposomes

Liposomes are versatile nanostructures synthesized by the hydration of phospholipids, which can be precisely engineered to vary in size, structure, composition, and flexibility by adjusting lipid molecules and applying surface modifications. A notable characteristic of liposomes is their ability to fuse with cellular membranes, enabling the efficient release of encapsulated substances directly into the cytoplasm, which is a key feature for targeted drug delivery systems. Typically, liposomes consist of a lipid bilayer surrounding an aqueous core, with diameters ranging from 50 to 1000 nm [26].Depending on the bilayer configuration, liposomes can be classified into three primary categories: multilamellar vesicles (MLVs), containing multiple lipid bilayers separated by aqueous spaces; small unilamellar vesicles (SUVs), which are composed of a single lipid bilayer enclosing the aqueous core; and large unilamellar vesicles (LUVs). This structural versatility allows liposomes to accommodate both hydrophilic and hydrophobic drugs, with hydrophilic compounds being enclosed within the aqueous interior and hydrophobic agents being incorporated into the lipid bilayer [27].

Exosomes

Exosomes are small extracellular vesicles, typically ranging from 30 to 150 nm in size, secreted by a variety of cell types. These vesicles, which are derived from endosomes and encased in a lipid bilayer similar to that of the cell membrane, are present in numerous biological fluids such as blood, saliva, urine, and breast milk. Exosomes are loaded with a diverse array of molecular cargo, including RNA, DNA, proteins, and lipids, and play a crucial role in intercellular communication. Their functions extend to key physiological processes such as immune modulation, antigen presentation, and neural communication, impacting the pathogenesis of diseases like cancer, cardiovascular disorders, diabetes, and inflammation. A significant advantage of exosomes lies in their natural occurrence in bodily fluids, which enhances their potential as drug delivery vehicles. Their inherent ability to evade immune detection enables them to deliver therapeutic agents directly to targeted sites with reduced clearance, positioning exosomes as a promising tool for drug delivery, disease diagnosis, and tissue regeneration [28] [29].

Solid lipid nanoparticles

Solid lipid nanoparticles (SLNs) are colloidal systems that maintain a solid lipid core at both ambient and physiological temperatures. Ranging from 10 to 1000 nm in size, they are stabilized by surfactants and can encapsulate both lipophilic and hydrophilic substances, including drugs and nucleic acids. SLNs offer versatile drug delivery applications, including targeted and stimuli-responsive systems. Modifications, such as functionalizing with antibodies or magnetic nanoparticles, enhance their ability for controlled drug release and targeted delivery. These characteristics make SLNs valuable in treating cancer, pulmonary diseases, and for oral drug delivery [30][31].

Drug Loading and Encapsulationinto therapeutic nanoparticles

Drug loading into nanoparticles plays a pivotal role in optimizing the efficiency and therapeutic impact of drug delivery systems. Various strategies are employed to incorporate drugs into nanoparticles, each offering distinct benefits based on the drug's characteristics and desired release profile. The commonly employed techniques for loading drugs into therapeutic nanoparticles includephysical entrapment, adsorption and chemical conjugation. Details on each of these techniques are outlined below.

Physical Entrapment

The method of physical entrapment involves incorporating drugs into nanoparticles during their

formation [32]. The process typically starts with preparing nanoparticles via techniques such as emulsion, solvent evaporation, or nanoprecipitation, wherein the polymer material is dissolved in a suitable solvent. The drug is either mixed with the polymer solution before or simultaneously with nanoparticle formation, allowing it to integrate within the forming matrix.Once the nanoparticles are structured, the solvent is removed through evaporation or washing, leading to solidification with the drug securely embedded within the matrix. Key performance indicators for this method include drug loading (DL), which represents the ratio of the drug to the total weight of the drug-loaded nanoparticles, and entrapment efficiency (EE), which measures the proportion of the drug successfully encapsulated compared to the initial amount used. These metrics are crucial for optimizing nanoparticle formulations for targeted and efficient drug delivery. [33]

Adsorption

The adsorption technique for drug loading is a surface-based method where drug molecules bind to the surface of pre-formed nanoparticles. This approach is particularly advantageous for incorporating drugs that are poorly soluble or unstable within a polymer matrix and for applications requiring an immediate burst release of the drug [34]. Typically, nanoparticles are synthesized using methods such as emulsion, solvent evaporation, or nanoprecipitation, often employing polymers like PLGA (poly(lactic-co-glycolic acid)). [35] Following their formation, the drug is introduced into a solution, where it adheres to the nanoparticle surface. Key factors influencing this process include the drug's charge, hydrophobicity, and interaction with the nanoparticle surface, as well as the solvent environment.To enhance drug loading efficiency, parameters such as pH, ionic strength, temperature, and incubation time are optimized during the adsorption process. This method provides flexibility and efficiency, allowing for the customization of drug release profiles and making it a valuable strategy for diverse therapeutic applications, especially where rapid and localized drug availability is critical.

Chemical Conjugation

Chemical conjugation for drug loading into biodegradable nanoparticles involves the covalent bonding of drugs to the nanoparticle surface or matrix, ensuring a stable and controlled release. This method is particularly advantageous for targeted drug delivery, especially in diseases like cancer where precision is essential. [36] It enhances the pharmacokinetics and pharmacodynamics of drugs, helping to improve therapeutic outcomes and minimize side effects.The process begins with selecting a compatible drug and a biodegradable nanoparticle, commonly made from materials like PLGA. The nanoparticle surface is functionalized with reactive groups, allowing the formation of covalent bonds with the drug. The drug is then conjugated using linkers or coupling agents, and the nanoparticles are purified to remove any unreacted drug or by-products. This approach offers the benefit of precise, controlled drug delivery with the potential for sustained therapeutic effects. [37]

Drug Release Mechanisms

The mechanisms governing drug release in advanced delivery systems are vital to achieving precision in therapeutic outcomes, ensuring the drug is administered at the optimal site, time, and dosage. Diffusion, which involves the transfer of drug molecules from regions of high to low concentration, is influenced by variables such as molecular dimensions and gradient intensity. Polymer matrix degradation, accelerated by enzymatic reactions, facilitates controlled drug release over time. Swelling, triggered by water absorption, expands the nanoparticle structure, enabling enhanced drug mobility. Complementary processes, including osmotic gradients, matrix erosion, and chemical transformations, further regulate release dynamics. Stimuli-responsive nanoparticles, activated by external factors like temperature fluctuations or magnetic fields, allow for precise, on-demand drug liberation. By integrating these sophisticated mechanisms, delivery systems can be tailored for sequential or sustained release, paving the way for personalized therapies that optimize clinical efficacy and minimize adverse effects. [38]

Controlled release drug delivery systems are designed to release medications gradually, improving therapeutic outcomes by reducing dosing frequency and enhancing patient adherence. These systems are tailored to the drug's characteristics, the desired release profile, and the target area in the body. By optimizing the timing and location of drug release,

they not only safeguard the drug from premature breakdown or clearance but also offer commercial benefits, such as extending patent life. A deep understanding of these systems is essential for their development, allowing for the identification of potential challenges and ensuring the reliability of the delivery mechanism.[38]

Therapeutic Nanoparticles in Targeted Drug DeliveryApplications

Targeted drug delivery is a crucial focus in modern medicine, aiming to improve treatment outcomes while reducing unintended side effects. Therapeutic nanoparticles are central to this approach, providing a versatile platform for precise, localized drug delivery. These nanoparticles offer several benefits, including the ability to deliver drugs directly to specific areas of the body, enhancing therapeutic effectiveness and minimizing damage to healthy tissues. Here are some key applications of nanoparticles in targeted drug delivery.

Tumor Targeting

Nanoparticles (NPs) are innovativeapproaches that aims to improve the targeting and delivery of chemotherapeutic agents to tumor sites, reducing side effects on healthy tissues. These NPs exploit the enhanced permeability and retention (EPR) effect, where the leaky vasculature of tumors allows for passive accumulation within the tumor site. By incorporating specific targeting ligands, such as antibodies or peptides, NPs can be actively directed towardstumor cells, improving the specificity of treatment. Additionally, nanoparticles can be designed for controlled release, either in response to the unique tumor microenvironment (e.g., pH or enzymatic conditions) or external triggers like light or ultrasound. The use of biocompatible and biodegradable polymers (e.g., PLGA and chitosan) ensures minimal long-term toxicity, while optimizing nanoparticle size (typically 10-200 nm) enhances tumor penetration. Combining passive and active targeting mechanisms in nanoparticle formulations holds great potential for improving therapeutic outcomes by reducing off-target effects and increasing treatment efficiency.[39] (Shargh et al., 2016).

Inflammatory Diseases

Inflammatory diseases are marked by localized tissue inflammation, often rendering challenges for conventional therapies due to their limited targeting capabilities and the potential for adverse effects on healthy organs. Nanoparticles (NPs) offer an innovative solution, harnessing alterations in vascular and immune dynamics at inflamed sites to enhance therapeutic precision. These advanced NPs can be engineered to deliver anti-inflammatory agents directly to affected tissues, significantly reducing systemic drug exposure and associated side effects. Moreover, their capacity for controlled drug release optimizes therapeutic effectiveness while decreasing dosing frequency, thus improving patient compliance. [40] Beyond drug delivery, NPs can be tailored to carry immunomodulatory compounds that regulate the inflammatory response at its origin, offering a dual advantage of precise targeting and immune modulation. This integrative strategy positions NPs as a transformative technology in the treatment of inflammation-driven disorders.(Wang et al., 2021)[41]

Nanoparticles for vaccine/gene delivery

Polynucleotide vaccines, including DNA and plasmid-based formulations, revolutionize immunization by delivering genetic instructions for antigen synthesis directly into host cells. Once inside, these genetic materials prompt the intracellular production of antigenic proteins, strategically positioned to engage professional antigen-presenting cells (APCs). This mechanism uniquely activates both humoral and cell-mediated immune responses, reflecting a natural immune activation process more effectively than extracellular antigen administration.The advantages of DNA vaccines extend beyond their biological function. They are cost-effective, stable, and resilient in storage, making them strong contenders to surpass traditional protein-based vaccines, especially in immunotherapeutic applications. However, the clinical application of these vaccines is constrained by challenges such as achieving precise delivery to target cells, ensuring nuclear localization, and maintaining the stability of the DNA throughout the delivery process. [42]Nanoparticles emerge as a transformative tool in addressing these challenges. By encapsulating plasmid DNA, nanoparticles can protect genetic material from enzymatic degradation, facilitate escape from endo-lysosomal pathways, and enable sustained

gene expression. [43] Research highlights their potential, including the use of PLGA nanoparticles to deliver therapeutic genes like bone morphogenic proteins (BMPs), which are instrumental in enhancing bone regeneration and healing. Advanced nanoparticle systems thus hold significant promise in refining gene delivery techniques and expanding the therapeutic reach of DNA vaccines.

Brain Disorders

Addressing brain disorders is particularly challenging due to the blood-brain barrier (BBB), a physiological safeguard that tightly regulates substance entry into the brain, often obstructing effective drug delivery. Advances in nanoparticles (NPs) have introduced a promising paradigm for precise and effective treatment of neurodegenerative diseases and brain tumors. These NPs leverage cutting-edge strategies, such as ligand-mediated receptor transcytosis and ultra-small particle design (sub-20 nm), to traverse the BBB and achieve localized drug delivery. [44]Functionalized with targeting ligands, these NPs can identify and bind to specific brain cell receptors, enabling precision therapy for diseased neurons or particular cellular populations. [45] Additionally, controlled-release mechanisms inherent in the NP design ensure the sustained and localized release of therapeutic agents, reducing systemic side effects and enhancing treatment adherence. [35] Materials like PLGA polymers, known for their biocompatibility and biodegradability, are commonly employed to encapsulate or conjugate active pharmaceutical ingredients, ensuring compatibility with the brain's unique environment. [46] These advancements collectively mark a significant leap in overcoming the limitations imposed by the BBB, enhancing the efficacy and safety of therapies for complex neurological conditions.

CONCLUSION

In conclusion, nanoparticles (NPs) represent a highly promising platform for the targeted delivery of therapeutic agents, offering significant versatility in transporting a broad range of biomolecules to specific sites within the body.Their unique properties, such as subcellular size, ability to provide sustained release, and biocompatibility with a variety of tissues and cells, make them ideal candidates for enhancing drug delivery systems.However, a deeper understanding of the complex biological interactions and advanced particle engineering strategies is essentialto fully exploit their potential.Specifically, the ability to manipulate particle size, surface characteristics, and release mechanisms is essential for maximizing their therapeutic efficacy.Therapeutic nanoparticles are particularly attractive because they can be designed to degrade into non-toxic by-products, minimizing the risk of long-term accumulation and adverse effects.As research advances, these nanoparticles hold immense promise for improving targeted drugdelivery, with applications ranging from cancer therapy to tissue regeneration, by enabling more controlled, efficient, and localized treatment.

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