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ROLE OF SIZE AND CHARGE OF NANOPARTICLES IN PHARMACEUTICAL FORMULATIONS: A COMPREHENSIVE REVIEW

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ABSTRACT

The unique physicochemical characteristics of nanoparticles (NPs), which are mostly controlled by their size and surface charge, have made them a focus of medicinal sciences. These traits play a crucial role in determining how nanoparticles interact with biological systems, proving their importance in therapeutic applications and drug delivery. This review explores the intricate relationship between nanoparticle charge and size, looking at how these characteristics affect important pharmacological aspects like drug transport, bioavailability, toxicity, and therapeutic efficacy. Liposomes, polymeric, metallic, and nanocrystals nanoparticles are among the many types of nanoparticles that are covered, with a focus on their special qualities and uses. In order to shed insight on their functions in cellular absorption, systemic circulation, biodistribution, and elimination, the review critically examines the ways in which size and charge impact pharmacokinetics and pharmacodynamics. Furthermore, it outlines methods for maximizing these variables in order to improve medication administration, reduce side effects, and produce superior therapeutic results. Based on current developments and studies in nanotechnology, this review attempts to provide a thorough grasp of how adjusting the size and surface charge of nanoparticles can help with present pharmaceutical development issues and open the door to more accurate and efficient treatment options.

KEYWORDS: Nanoparticles, size, charge, stability, Toxicity, drug delivery.

1.0 INTRODUCTION

Materials having sizes between one and one hundred nanometers are known as nanoparticles (NPs), and they have unique and frequently improved physicochemical characteristics when compared to their bulk counterparts. They are especially attractive for a wide range of biomedical applications because of these nanoscale properties. A high surface-area-to-volume ratio, adaptable surface characteristics, and the capacity to encapsulate or bind medicinal substances are important characteristics of nanoparticles. Because of these characteristics, nanoparticles are now recognized as potent drug delivery vehicles that enable targeted therapy, controlled release, and increased therapeutic efficacy.[1] The behavior of nanoparticles within biological systems is predominantly influenced by two fundamental factors: size and surface charge. These parameters dictate how nanoparticles interact with cells, tissues, and biological barriers, shaping their pharmacokinetic and pharmacodynamics characteristics. For example, size influences cellular uptake, circulation duration, and biodistribution, while surface charge affects nanoparticle stability, potential aggregation, and interactions with biological membranes and proteins. Understanding these critical factors is vital for developing nanoparticles that optimize therapeutic benefits while minimizing potential adverse effects. This introduction provides a framework for an in-depth examination of the impact of nanoparticle size and surface charge on critical elements of drug delivery, including bioavailability, toxicity, and therapeutic efficacy. By delving into these characteristics, researchers can build pharmacological formulations tailored to specific clinical requirements.[2]

2.0 Significance of Nanoparticles in Pharmaceuticals

The solubility and bioavailability of medications that are poorly soluble can be improved by nanoparticles, which also make it possible to distribute drugs to specific tissues in a targeted manner and alleviate systemic toxicity. Their application encompasses various therapeutic areas, comprising as treatment of cancer, the process of developing vaccines, and the delivery of genes.[3]

3.0 Properties of Nanoparticles

3.1 Size

The surface area, reactivity, and biological interactions of nanoparticles are all correlated with their size. When the nanoparticles are smaller, they can more easily penetrate biological barriers and are frequently absorbed by cells.[4]

3.2 Charge

Stability of nanoparticles & interaction with biological membranes, as well as their general pharmacokinetics, are significantly influenced by the surface charge of the particles. There is a possibility that positively charged nanoparticles will possess enhanced cellular absorption; nevertheless, this may also result in increased toxicity. Negatively charged nanoparticles, on the other hand, may have a lower cellular absorption but are able to be stabilized in biological fluids.[5,6]

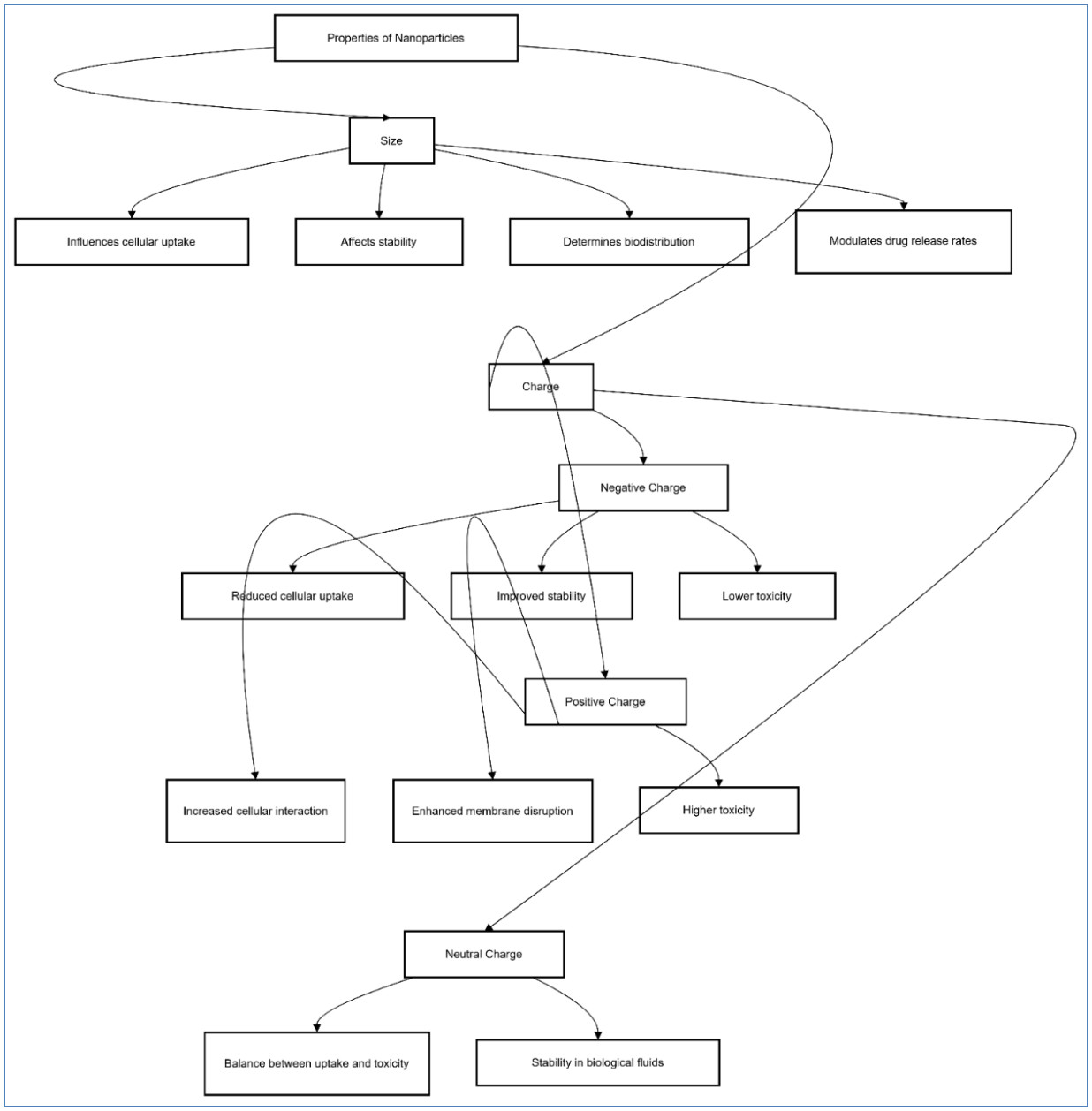

Figure 1: Schemmatic representation of properties of nanoparticles.

3.3 Mechanism of Action

3.3.1 Cellular Uptake

Size and charge of nanoparticles are effective on mechanisms that are responsible for their absorption. Endocytosis is a process that can be used to take up smaller nanoparticles, whereas phagocytosis is a process that can be used to engulf bigger particles. Additionally, the surface charge has the ability to modify interaction with cell membranes; affects efficiency of uptake.[7,8]

3.3.2 Distribution and Elimination

Depending on their size and charge, nanoparticles have the potential to be dispersed extensively throughout the body. Large, positively charged particles are flushed out of the bloodstream more rapidly than smaller, neutral or negatively charged nanoparticles, which remain in circulation for a longer duration.[9,10]

4.0 Types of Nanoparticles

They are categorized into several categories by their composition and intended applications in pharmaceuticals. This section expands on four major categories: liposomes, polymeric nanoparticles, metallic nanoparticles, and nanocrystals, detailing their characteristics, advantages, and specific applications in drug delivery.[11]

4.1 Liposomes

Liposomes are spherically shaped vesicles composed of phospholipid bilayers. Their capacity to encapsulate both hydrophilic and hydrophobic medications adds to their adaptability as drug delivery systems. Usually between 50 nm to a few micrometers. Charge can be positively, negatively, or neutrally charged, depending on the lipid composition and surface modifications.[12,13]

Advantages

- **Biocompatibility:** Liposomes are generally well-tolerated in biological systems.
- **Targeted Delivery:** The enhanced permeability and retention (EPR) effect enables passive targeting due to their size, while surface changes allow for active targeting to specific cell types.
- **Controlled Release:** It is possible to program the release of a liposome's pharmacological load in response to changes in environmental conditions, such as pH or temperature.[14]

Applications

- **Cancer Therapy:** By increasing drug accumulation in tumour tissues, liposomal chemotherapeutic formulations (such as Doxil®) have demonstrated enhanced efficacy and fewer side effects.
- **Vaccines:** Liposomes can be used as adjuvants or carriers for antigens, improving immunogenicity.
- **Gene Delivery:** They can encapsulate nucleic acids for gene therapy applications.[15]

4.2 Polymeric Nanoparticles

Polymeric nanoparticles are solid colloidal particles with biocompatible polymers as their constituents. Hydrophilic and hydrophobic medications can be incorporated into them, allowing for a variety of drug release properties. The usual size range is 20 nm to 1000 nm. Charge of the surface charge can be modified through the choice of polymers and by adding charged moieties, allowing for manipulation of interactions with cells and tissues.[16]

Advantages

- **Versatility in Drug Loading:** Different polymers optimize drug encapsulation efficiency and release kinetics.
- **Controlled Release Profiles:** Drug release can be tailored through polymer composition and the method of preparation, such as solvent evaporation or nanoprecipitation.
- **Targeting Capabilities:** Surface modifications, such as attaching ligands, can enhance the targeting of specific cells or tissues.[17]

Applications

- **Anticancer Drugs:** Polymeric nanoparticles can improve the solubility and bioavailability of poorly soluble drugs and provide targeted delivery to tumors.
- **Protein and Peptide Delivery:** They can stabilize sensitive biomolecules and control their release, which is critical for therapeutic applications.

- **Vaccine Development:** Polymeric nanoparticles can improve stability & efficacy of vaccines by facilitating targeted immune responses.[18]

4.3 Metallic Nanoparticles

A lot of interest has been sparked by the extraordinary optical, electrical, and catalytic properties of metallic nanoparticles, such as those made of gold, silver, and platinum.

Usually, sizes range from 1 nm to 100 nm. Their interaction with biological systems may be impacted by surface changes and synthesis techniques that alter surface charge.[19]

Advantages

- **Unique Optical Properties:** Surface plasmon resonance is a property of metallic nanoparticles that has imaging and diagnostic potential.
- **Targeted Therapeutics:** Surface modifications allow for attachment of targeting ligands, enhancing delivery of therapeutic agents directly to diseased cells.
- **Antimicrobial Activity:** Silver nanoparticles, in particular, have demonstrated significant antimicrobial properties, making them useful in various biomedical applications.[20]

Applications

- **Cancer Therapy:** Photothermal therapy makes use of gold nanoparticles, which specifically kill cancer cells by absorbing light and transforming it into heat.
- **Biosensing and Imaging:** Their optical properties make them ideal for use in imaging modalities and as contrast agents in diagnostics.
- **Drug Delivery:** To improve the solubility and targeted distribution of therapeutic compounds, metallic nanoparticles can be used as carriers.[21]

4.4 Nanocrystals

Nanocrystals are nanoscale drug particles that can be used to improve the solubility and bioavailability of drugs that have low levels of either. They are made by reducing the size of pharmaceutical molecules to nanometers. Usually, sizes range from 1 nm to 100 nm. Stabilizers and surfactants, which are added during the preparation process to prevent aggregation, can alter the surface charge of nanocrystals.[22]

Advantages

- **Enhanced Solubility:** The large surface area-to-volume ratio of nanocrystals significantly increases dissolution rate of poorly soluble drugs.
- **Improved Bioavailability:** Enhanced solubility translates to better absorption and higher bioavailability in the systemic circulation.
- **Stability:** Surface modifications can enhance the physical stability of nanocrystals, preventing agglomeration.[23]

Applications

- **Oral Drug Delivery:** Nanocrystals can be used to formulate oral dosage forms of poorly soluble drugs, improving their absorption.

- **Injectable Formulations:** They can be employed in parenteral formulations, allowing for rapid drug action.
- **Topical Applications:** Nanocrystals can enhance the penetration of active ingredients in topical formulations, improving therapeutic outcomes.[24,25]

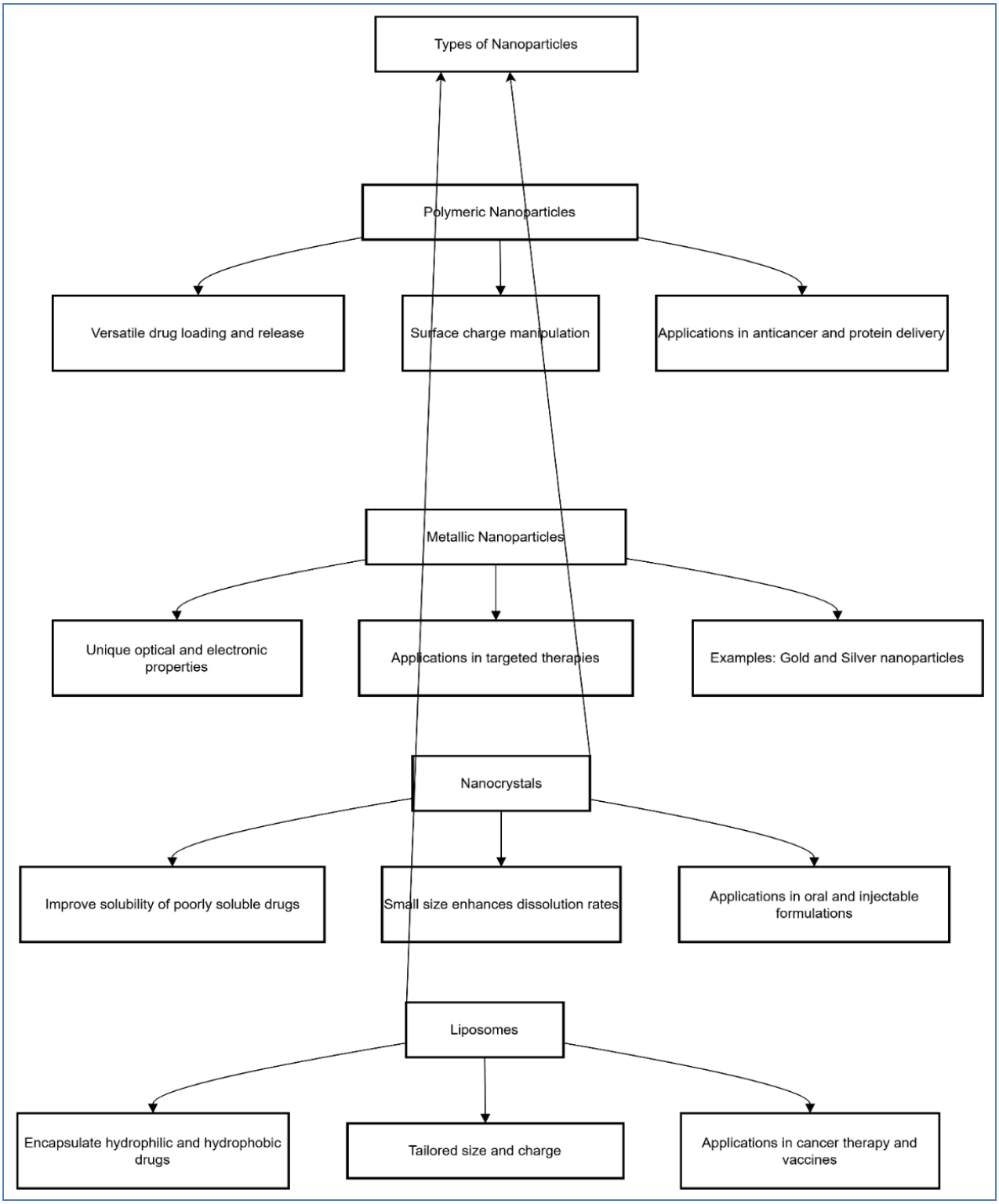

Figure 2: Schematic representation of Types of nanoparticles.

5.0 Formulation Strategies

The successful application of nanoparticles in pharmaceutical formulations hinges on two key strategies: size reduction techniques and charge modulation techniques. These approaches are critical for optimizing formulations to enhance efficacy, stability & bioavailability.[26]

5.1 Size Reduction Techniques

Size reduction techniques are pivotal in the development of nanoparticles designed to improve the solubility and bioavailability of poorly soluble drugs. Many pharmaceutical compounds, especially those classified as hydrophobic or lipophilic, suffer from limited water solubility, which in turn hampers their absorption in the gastrointestinal tract and diminishes their therapeutic efficacy. By reducing the particle size of these drugs to the nanometer range, their surface area is significantly increased, which can enhance their dissolution rate in aqueous environments and facilitate their absorption into the bloodstream.[27,28] Nanoparticles, with their small size and high surface-to-volume ratio, have the unique ability to dissolve more readily in biological fluids, thereby overcoming one of the primary challenges of drug delivery. This increased solubility enhances the bioavailability of drugs, ensuring that a greater proportion of the active pharmaceutical ingredient (API) reaches the site of action, ultimately improving the therapeutic outcomes. Size reduction also allows for more precise control over drug release profiles, enabling sustained or controlled release of the drug, which can further optimize therapeutic efficacy and minimize side effects.[29]

5.2 Mechanical Milling

Mechanical milling is a widely used technique in pharmaceutical formulations for reducing the size of bulk drug particles to the nanometer scale. This size reduction process typically involves high-energy ball mills, which utilize mechanical forces such as impact, shear, and compression to break down larger particles into smaller, finer ones. The mechanical milling process is particularly effective for reducing the particle size of poorly soluble or hydrophobic drugs, which often face challenges in terms of solubility and bioavailability when used in their bulk form. By reducing the particle size, the surface area of the drug is significantly increased, leading to enhanced dissolution rates and, consequently, improved bioavailability.[30,31]

The process works by placing drug particles and grinding media (such as ceramic, steel, or polymer beads) into a milling chamber. As the chamber rotates or vibrates, the grinding media exerts intense forces on the drug particles, causing them to collide and fracture. Over time, these repeated collisions reduce the particle size, eventually producing nanoparticles or fine powders. The duration of the milling process, the energy input, and the nature of the grinding media all influence the final size and characteristics of the particles. Depending on the milling conditions, the size reduction can range from micrometers to nanometers.[32]

Advantages

- **Cost-Effective:** Mechanical milling is relatively simple and does not require complex equipment.
- **Scalability:** Scaling up this technology for industrial manufacturing is a piece of cake.

  Challenges:
- **Polydispersity:** Mechanical milling can lead to a wide size distribution of particles, which may affect the uniformity of drug release.
- **Heat Generation:** Excessive heat during milling can lead to degradation of thermolabile drugs.

5.3 High-Pressure Homogenization

High-pressure homogenization is an advanced and widely used technique in pharmaceutical formulations to achieve uniform particle size reduction. It involves subjecting a drug suspension to extremely high pressure, typically in the range of 100–1500 bars, and forcing it through a narrow gap, often referred to as a homogenization valve or nozzle. As the suspension passes through this narrow gap, it experiences intense shear forces, cavitation, and impact. These combined mechanical effects effectively break down larger drug particles into smaller, uniform nanoparticles or microparticles.[33] The process not only enhances the surface area of the particles but also improves their dissolution rate, bioavailability, and stability, making it particularly useful for poorly water-soluble drugs. High-pressure homogenization is highly scalable and can be applied for both small-scale laboratory formulations and large-scale industrial production.[34]

Advantages

- **Uniform Particle Size:** This method often produces a more uniform size distribution compared to mechanical milling.
- **Enhanced Stability:** The process can also stabilize the suspension by breaking down agglomerates.[35]

Challenges

- **Equipment Costs:** High-pressure homogenizers can be expensive and require significant maintenance.
- **Limited to Suspensions:** This technique is mainly applicable to liquid formulations, which may limit its versatility.[36]

5.4 Solvent Evaporation

Solvent evaporation techniques are versatile and widely used methods for the preparation of nanoparticles, particularly in the pharmaceutical industry. These techniques involve dissolving the drug or active pharmaceutical ingredient (API) in a volatile organic solvent, which is immiscible with water. The solvent acts as a carrier medium to facilitate the dispersion of the drug at a molecular or nanoscale level. Following this, the organic solvent is gradually evaporated, leading to the formation of nanoparticles as the drug precipitates out of the solution. This process is highly efficient in producing stable nanoparticles with controlled size and morphology.[37]

The solvent evaporation approach can be implemented using various methods, such as nanoprecipitation or emulsion-solvent evaporation. In the nanoprecipitation method, the drug-containing organic solvent is added to an aqueous solution under continuous stirring, resulting in the spontaneous formation of nanoparticles as the solvent diffuses into the aqueous phase and evaporates. Alternatively, the emulsion-solvent evaporation method involves creating an oil-in-water or water-in-oil emulsion by emulsifying the drug solution in an aqueous or organic phase, respectively. As the solvent evaporates from the emulsion droplets, nanoparticles are formed. These techniques are advantageous for their simplicity, scalability, and ability to encapsulate hydrophobic drugs, enhancing their solubility, stability, and bioavailability.[38,39]

Advantages

- **Versatile:** This method can encapsulate many hydrophilic & hydrophobic drugs.
- **Controlled Size:** By adjusting the conditions of solvent evaporation, it is possible to control the final size of the nanoparticles.

Challenges

- **Solvent Residue:** There may be concerns regarding residual solvents in the final product, which can pose safety risks.
- **Process Complexity:** The method may require careful optimization of parameters such as solvent type and evaporation rate.

5.5 Charge Modulation Techniques

Modulating the surface charge of nanoparticles is a critical aspect of nanoparticle design and formulation, particularly in the field of drug delivery and biomedical applications. Surface charge plays a pivotal role in determining the behavior of nanoparticles within biological systems, as it directly affects their interactions with cellular membranes, proteins, and other biological components. By carefully tuning the surface charge, researchers can optimize key parameters such as cellular uptake, systemic circulation time, stability in physiological environments, and the overall therapeutic efficacy of the nanoparticles.[40]

For instance, positively charged nanoparticles often exhibit enhanced cellular uptake due to their electrostatic interactions with the negatively charged cell membranes. However, excessive positive charge may lead to toxicity or rapid clearance by the immune system. Conversely, negatively charged or neutral nanoparticles tend to show prolonged circulation times and reduced immunogenicity, making them suitable for sustained drug delivery. Moreover, charge modulation can also help improve the stability of nanoparticles by preventing aggregation through electrostatic repulsion in colloidal systems. Techniques for modulating nanoparticle surface charge include chemical functionalization with charged polymers, surfactants, or biomolecules, as well as manipulating the formulation parameters during nanoparticle synthesis. The ability to control surface charge enables the development of tailored nanoparticle systems for specific therapeutic or diagnostic applications, ensuring optimal performance and safety in clinical settings.[41]

Advantages

- **Targeting Capabilities:** Charged ligands can enhance specific interactions with cell receptors, facilitating targeted drug delivery.
- **Stability Improvement:** To make nanoparticles more stable in biological fluids, charged groups can be added to them.

Challenges

- **Complexity of Synthesis:** The functionalization process can be complex and may require multiple steps to achieve the desired charge characteristics.
- **Potential Toxicity:** Some ligands may introduce cytotoxicity, necessitating careful selection and optimization.

5.6 Coating with Polymers

Coating nanoparticles with biocompatible polymers is a widely employed strategy to improve their performance and versatility in pharmaceutical and biomedical applications. Polymers such as polyethylene glycol (PEG), chitosan, polyvinyl alcohol (PVA), and other natural or synthetic materials are commonly used to create functional coatings on nanoparticle surfaces. These coatings serve multiple purposes, including modifying the surface charge, enhancing

colloidal stability, and providing a protective barrier against aggregation and opsonization in biological environments.[42] By carefully selecting and tailoring the polymer coating, specific characteristics can be imparted to the nanoparticles to meet the requirements of particular applications. For instance, PEGylation, the coating of nanoparticles with polyethylene glycol, imparts hydrophobicity to the surface, reducing nonspecific protein adsorption and extending circulation time in the bloodstream. Similarly, positively charged polymers such as chitosan can enhance cellular uptake through electrostatic interactions with negatively charged cell membranes, making them suitable for targeted delivery of therapeutics. These coatings also enable further functionalization with ligands, antibodies, or other targeting molecules, allowing for selective delivery to specific cells or tissues. The adaptability and biocompatibility of polymer coatings make them an essential tool for designing nanoparticles with enhanced therapeutic efficacy, reduced immunogenicity, and improved stability in complex physiological environments.[43]

Advantages

- **Stealth Properties:** A coating's "stealth" qualities might help nanoparticles avoid detection by the immune system and remain in the bloodstream for longer.
- **Improved Bioavailability:** Enhanced stability and solubility can lead to better absorption and bioavailability.

Challenges

- **Coating Thickness:** It is important to optimize the polymer coating thickness since it affects the kinetics of medication release and cellular absorption.
- **Cost:** The materials and processes involved in coating can add to the overall cost of formulation.[44,45]

6.0 Toxicity Considerations

The toxicity of nanoparticles in pharmaceutical formulations is a critical concern, particularly as their unique physicochemical properties can lead to unexpected biological interactions. Two primary factors that influence nanoparticle toxicity are their size and charge. This section expands on how these characteristics affect cytotoxicity and biodistribution.[46]

6.1 Cytotoxicity

Cytotoxicity refers to the ability of a substance to cause harm to cells, leading to cellular dysfunction or death. This property is a critical consideration in the development and application of nanoparticles, particularly in the fields of drug delivery, diagnostics, and nanomedicine. Nanoparticles, due to their small size and large surface area, interact with biological systems in unique ways, making their potential cytotoxic effects a major area of study. The size and charge of nanoparticles are two of the most influential factors governing their interactions with cells and tissues, thereby impacting their cytotoxic potential. Smaller nanoparticles have a higher surface-to-volume ratio, which enhances their reactivity and ability to penetrate cellular membranes. However, this increased reactivity can also lead to greater production of reactive oxygen species (ROS) and other harmful byproducts that contribute to cytotoxicity. Larger nanoparticles, while less reactive, may struggle with efficient cellular uptake or cause mechanical damage if improperly designed.[47,48]

Similarly, surface charge plays a crucial role in determining the extent of cellular interaction. Positively charged nanoparticles tend to exhibit stronger interactions with negatively charged cell membranes, potentially leading to enhanced cellular uptake. However, excessive positive charge can disrupt membrane integrity, induce oxidative stress,

and trigger inflammatory responses. On the other hand, negatively charged or neutral nanoparticles often show reduced cytotoxicity but may have limited cellular uptake, affecting their therapeutic efficacy. Understanding the intricate relationship between nanoparticle size, charge, and cytotoxicity is essential for designing safe and effective nanomaterials. By optimizing these parameters, researchers can minimize adverse effects while maximizing therapeutic benefits, paving the way for the successful integration of nanoparticles into biomedical applications.[49,50]

6.2 Size-Dependent Cytotoxicity

The size of nanoparticles is a critical factor influencing their interactions with biological systems, directly impacting their cytotoxic potential. Nanoparticles, by virtue of their nanoscale dimensions, possess unique physicochemical properties such as a high surface-to-volume ratio, quantum effects, and enhanced reactivity. These characteristics enable them to interact more extensively with cellular and subcellular components, which can lead to both beneficial and adverse effects.[51] Understanding the size-dependent cytotoxicity of nanoparticles is essential for their safe and effective use in biomedical applications, including drug delivery, imaging, and diagnostics. Smaller nanoparticles typically exhibit higher reactivity and cellular uptake due to their ability to penetrate biological barriers and access intracellular environments more effectively. However, this increased reactivity can also amplify cytotoxic effects, such as the generation of reactive oxygen species (ROS), disruption of cellular membranes, and interference with normal cellular functions. For instance, nanoparticles smaller than 10 nm can interact with DNA and organelles, potentially causing genotoxicity and mitochondrial damage. Larger nanoparticles, while generally less reactive, may induce cytotoxicity through mechanical damage to cells or accumulation within tissues, leading to inflammation and long-term toxicity.[52] The size of nanoparticles also influences their biodistribution, clearance, and ability to evade the immune system. Extremely small nanoparticles are often cleared rapidly by renal filtration, reducing their efficacy, whereas larger particles may be sequestered by the mononuclear phagocyte system (MPS), triggering immune responses. Thus, the size of nanoparticles must be carefully optimized to balance therapeutic efficacy with minimal cytotoxicity. A comprehensive understanding of size-dependent cytotoxicity is vital for guiding the rational design and development of nanoparticle-based systems for biomedical applications.[53]

6.2.1 Smaller Nanoparticles

- **Increased Cellular Uptake:** Smaller nanoparticles (typically below 100 nm) can more easily penetrate cellular membranes through endocytosis or phagocytosis. This enhanced uptake can lead to higher intracellular concentrations of the nanoparticles, resulting in greater cytotoxic effects.
- **Reactive Oxygen Species (ROS) Generation:** Smaller nanoparticles often exhibit higher reactivity and can induce oxidative stress within cells, causing generation of ROS. Apoptosis and necrosis can be brought about by ROS damage to lipids, proteins, and DNA in cells.

6.2.2 Larger Nanoparticles

- Larger nanoparticles may be less efficiently taken up by cells and may elicit a different immune response, potentially leading to less cytotoxicity. However, they can still cause adverse effects through mechanisms such as physical disruption of cellular structures or triggering inflammatory responses.

6.3 Charge-Dependent Cytotoxicity

The surface charge of nanoparticles is a critical determinant of their behavior in biological systems and plays a significant role in modulating their cytotoxicity. Nanoparticles interact with cells, proteins, and other biomolecules

primarily through electrostatic interactions, and the charge on their surface influences these interactions profoundly. Understanding charge-dependent cytotoxicity is essential for designing nanoparticles with optimized safety and functionality for applications in drug delivery, diagnostics, and nanomedicine. Positively charged nanoparticles tend to exhibit higher cytotoxicity compared to their neutral or negatively charged counterparts. This is largely due to the strong electrostatic attraction between positively charged nanoparticles and the negatively charged phospholipids in cell membranes. Such interactions can enhance cellular uptake, making these nanoparticles effective for drug delivery. However, excessive positive charge can lead to significant membrane disruption, increased production of reactive oxygen species (ROS), and inflammatory responses, all of which contribute to cytotoxicity. Moreover, highly cationic nanoparticles may cause protein denaturation and aggregation, further exacerbating their adverse effects.[54] Negatively charged nanoparticles, on the other hand, often show reduced cytotoxicity due to weaker interactions with cell membranes. While this property makes them more biocompatible, it may also limit their cellular uptake and therapeutic efficiency. Neutral nanoparticles, with minimal charge, are typically the least cytotoxic but may face challenges in achieving targeted delivery or effective interaction with cellular components. The extent of charge-dependent cytotoxicity is also influenced by other factors such as nanoparticle size, shape, and the surrounding biological environment. By precisely modulating the surface charge, either through chemical functionalization or the incorporation of charged polymers or biomolecules, researchers can fine-tune the cytotoxic profile of nanoparticles. This balance between therapeutic efficacy and biocompatibility underscores the importance of charge optimization in nanoparticle design for biomedical applications.[55]

6.3.1 Positively Charged Nanoparticles

- **Enhanced Cellular Interaction:** Increased cellular uptake occurs when positively charged nanoparticles interact favorably with negatively charged cell membranes. This can result in higher cytotoxicity due to the accumulation of nanoparticles within cells.
- **Increased Membrane Disruption:** The positive charge may disrupt cellular membranes, causing leakage of intracellular components and triggering cell death pathways.

6.3.2 Negatively Charged Nanoparticles

- Negatively charged nanoparticles may have lower cellular uptake and, consequently, reduced cytotoxicity. However, they can still induce toxicity via other mechanisms, such as inducing inflammatory responses or through interactions with proteins in the biological milieu.

6.4 Biodistribution and Accumulation

The biodistribution of nanoparticles, or their distribution throughout the body, is a key factor in determining their safety, therapeutic efficacy, and overall suitability for biomedical applications. As nanoparticles are introduced into the body, their size, surface charge, and other physicochemical properties influence how they interact with biological systems, including their ability to target specific tissues, evade clearance mechanisms, and avoid unintended accumulation in non-target sites. A thorough understanding of these interactions is crucial for optimizing nanoparticle-based drug delivery systems, diagnostics, and therapies. Size plays a significant role in nanoparticle biodistribution. Smaller nanoparticles, typically below 10 nm, are often rapidly cleared by the renal system due to their ability to pass through glomerular filtration barriers. While this minimizes long-term retention and potential toxicity, it may reduce therapeutic efficacy by limiting systemic circulation time. Conversely, larger nanoparticles, particularly those

exceeding 200 nm, are more likely to be sequestered by the mononuclear phagocyte system (MPS), leading to accumulation in organs such as the liver and spleen. Intermediate-sized nanoparticles (10–200 nm) often exhibit more favorable biodistribution profiles, striking a balance between prolonged circulation and reduced clearance. Surface charge also significantly impacts biodistribution. Positively charged nanoparticles are more likely to interact with negatively charged cell membranes and serum proteins, enhancing cellular uptake but also increasing the risk of rapid clearance by the immune system or toxicity due to excessive interactions with non-target tissues. Negatively charged and neutral nanoparticles tend to exhibit reduced protein adsorption and immune recognition, leading to prolonged circulation times and more controlled distribution, though they may face challenges in achieving efficient cellular uptake. Additionally, the biological environment, including blood flow dynamics, tissue permeability, and the presence of biological barriers such as the blood-brain barrier, further modulates nanoparticle biodistribution. Strategies such as surface functionalization with targeting ligands or polymers (e.g., polyethylene glycol) can be employed to overcome these challenges, improving site-specific delivery and reducing off-target effects. By understanding and optimizing the interplay between nanoparticle size, charge, and biological factors, researchers can design nanoparticles with improved safety profiles and therapeutic outcomes.[56]

6.4.1 Size and Biodistribution

The size of nanoparticles is one of the most influential factors determining their biodistribution within the body. Nanoparticles interact with various biological systems, and their ability to navigate these systems—reaching target sites while avoiding unwanted accumulation—depends significantly on their dimensions. A precise understanding of size-dependent biodistribution is essential for designing nanoparticles with optimized therapeutic efficacy and minimal side effects. Nanoparticles smaller than 10 nm are often rapidly cleared from the body through renal filtration, due to their ability to pass through the glomerular filtration barrier in the kidneys. This rapid clearance can reduce long-term toxicity, but it also limits the systemic circulation time, which may hinder the effectiveness of therapeutic or diagnostic nanoparticles. Conversely, nanoparticles larger than 200 nm are more likely to be recognized and sequestered by the mononuclear phagocyte system (MPS), leading to their accumulation in organs like the liver and spleen. This size-dependent clearance by the immune system can reduce their availability at target sites while increasing the risk of organ-specific toxicity.[57]

Intermediate-sized nanoparticles, typically in the range of 10–200 nm, often exhibit the most favorable biodistribution profiles for systemic therapies. These nanoparticles are small enough to evade rapid renal clearance but large enough to avoid immediate sequestration by the MPS. Additionally, nanoparticles within this size range are better able to exploit the enhanced permeability and retention (EPR) effect, which allows them to accumulate preferentially in tumor tissues due to the leaky vasculature and poor lymphatic drainage of tumors. Size also affects the ability of nanoparticles to cross biological barriers, such as the blood-brain barrier (BBB). Smaller nanoparticles, often below 50 nm, are more likely to penetrate these barriers, making them suitable for targeting central nervous system (CNS) disorders. However, their small size may also lead to increased distribution in non-target tissues, requiring careful design to minimize off-target effects. To optimize the size-dependent biodistribution of nanoparticles, researchers often employ strategies such as surface functionalization with biocompatible polymers (e.g., polyethylene glycol) or targeting ligands to improve circulation time, enhance tissue-specific targeting, and reduce off-target accumulation. By tailoring nanoparticle size to the specific requirements of a given application, it is possible to achieve an ideal balance between therapeutic efficacy, safety, and controlled distribution within the body.[58]

6.4.1.1 Small Nanoparticles

- **Enhanced Tissue Penetration:** Smaller nanoparticles can more easily extravasate from blood vessels into surrounding tissues, enabling better distribution in target organs. This characteristic can be advantageous for drug delivery but may also raise concerns regarding unintentional gathering in non-target tissues.
- **Accumulation in Organs:** Because of the increased permeability of capillaries in organs like the lungs, liver, and spleen, as well as their capacity to elude the immune system, small nanoparticles tend to collect in these organs.

6.4.1.2 Larger Nanoparticles

- Larger nanoparticles tend to have restricted circulation time and are more rapidly cleared from the bloodstream. The reticuloendothelial system (RES) encompasses organs like the liver and spleen, and their accumulation there might trigger inflammatory reactions or cytotoxic effects.[59]

6.5 Charge and Biodistribution

The surface charge of nanoparticles is a critical factor that significantly influences their biodistribution within the body, affecting their interactions with cells, tissues, and the immune system. As nanoparticles circulate in the bloodstream, their charge determines how they interact with the physiological environment, including cell membranes, proteins, and other biological components, which in turn impacts their ability to reach target tissues or organs, and their rate of clearance from the body. A deep understanding of charge-dependent biodistribution is essential for optimizing the design of nanoparticles for therapeutic and diagnostic purposes. Positively charged nanoparticles tend to exhibit enhanced interactions with negatively charged components of cell membranes due to electrostatic attraction. This can lead to increased cellular uptake, making them effective for drug delivery. However, this enhanced uptake can also increase their recognition by the immune system, particularly by the mononuclear phagocyte system (MPS), which can result in rapid clearance from circulation and accumulation in organs like the liver and spleen. Additionally, the strong electrostatic interactions between positively charged nanoparticles and cell membranes can cause membrane destabilization or oxidative stress, contributing to potential cytotoxicity.[60]

6.5.1 Positively Charged Nanoparticles

- Increased Retention in Tissues: Positively charged nanoparticles may have a higher affinity for negatively charged tissues, leading to increased retention in specific organs, like lungs & kidneys. So can enhance therapeutic effects but may also result in toxicity in these tissues.
- Influence on Immune Response: The charge can influence how nanoparticles interact with immune cells, potentially leading to activation of the immune response, which can have both beneficial and detrimental effects.

6.5.2 Negatively Charged Nanoparticles:

- Negatively charged nanoparticles generally demonstrate longer circulation times due to reduced interaction with plasma proteins and immune cells. This property can enhance their therapeutic potential but may result in accumulation in tissues over extended periods, raising concerns about chronic toxicity.

7.0 Clinical Applications

7.1 Cancer Therapy

Nanoparticles have emerged as a powerful tool in cancer therapy due to their unique physicochemical properties, such as small size, high surface area, and the ability to be functionalized for targeted delivery. These properties enable

nanoparticles to overcome many of the challenges associated with conventional cancer treatments, such as poor drug solubility, nonspecific distribution, and resistance to therapeutic agents. By tailoring nanoparticles for specific applications, they can improve the effectiveness of existing cancer therapies while minimizing side effects, ultimately offering more precise and personalized treatment options for patients. In cancer therapy, nanoparticles can be used to deliver anticancer drugs directly to tumor sites, thereby increasing the local concentration of the drug and reducing systemic exposure, which minimizes adverse side effects. The small size of nanoparticles allows them to penetrate the leaky blood vessels that characterize tumor vasculature, a phenomenon known as the enhanced permeability and retention (EPR) effect. This targeted delivery improves the accumulation of therapeutic agents in the tumor, enhancing their efficacy. Additionally, nanoparticles can be engineered to carry multiple therapeutic agents simultaneously, allowing for combination therapies that target different pathways involved in tumor growth and resistance mechanisms.[61]

7.2 Vaccine Development

Nanoparticles have shown great promise in advancing vaccine development due to their ability to enhance immune responses, improve stability, and enable controlled release of antigens. Their small size, large surface area, and versatile surface chemistry allow them to effectively mimic pathogens, facilitating the activation of both the innate and adaptive immune systems. These properties make nanoparticles ideal carriers for vaccines, especially for those targeting infectious diseases, cancer, and other immunological disorders.[62]

7.3 Gene Delivery

Gene delivery is a critical area of biotechnology and medicine, aiming to introduce genetic material (such as DNA, RNA, or gene-editing tools like CRISPR) into a patient's cells to treat various diseases, including genetic disorders, cancer, and viral infections. Nanoparticles have emerged as one of the most promising vehicles for gene delivery, offering numerous advantages in terms of targeting, controlled release, biocompatibility, and the ability to overcome biological barriers. By incorporating genetic material into nanoparticles, the potential for safer, more efficient, and localized gene therapies has significantly improved.[63]

7.4 Regulatory Considerations

The unique properties of nanoparticles such as their small size, large surface area, and the ability to modify their surface chemistry offer significant advantages for therapeutic and diagnostic applications. However, these same properties also introduce complexities that must be carefully considered in regulatory frameworks for clinical translation. As nanoparticles interact with biological systems in ways that differ from traditional small molecules or macromolecules, understanding the implications of their size, charge, and other physicochemical characteristics is crucial for ensuring their safety, efficacy, and appropriate use in clinical settings. Nanoparticles behave differently than conventional drugs or biologics, potentially exhibiting unique toxicological profiles that arise from their nanoscale dimensions. For example, smaller nanoparticles may have enhanced cellular uptake and tissue penetration, but they may also accumulate in organs such as the liver, spleen, and kidneys, raising concerns regarding toxicity and long-term effects. The surface charge of nanoparticles can further influence their interactions with cells, proteins, and immune components, potentially leading to cytotoxicity, inflammatory responses, or immune system activation. Therefore, regulatory agencies must assess how these properties impact the biodistribution, toxicity, and therapeutic outcomes of nanoparticle-based therapies. In addition to the safety concerns, the efficacy of nanoparticle-based therapies must also

be thoroughly evaluated. Nanoparticles often serve as carriers for drugs, genes, or imaging agents, and their performance in delivering these agents to the target site is heavily dependent on their physicochemical properties. Regulatory agencies need to develop appropriate guidelines for evaluating how these nanoparticles interact with biological barriers, achieve targeted delivery, and release their payload in a controlled and predictable manner. Furthermore, the use of nanoparticles in combination with other therapies, such as gene editing or immunotherapy, adds an additional layer of complexity that requires careful consideration in clinical trials.[64,65]

8.0 Future Directions

Advancements in nanotechnology are rapidly transforming the landscape of medicine, offering exciting possibilities for the development of novel nanoparticles with highly optimized size, charge, and surface properties. These innovations have the potential to revolutionize various therapeutic fields, from cancer treatment and gene therapy to vaccine development and regenerative medicine. The ability to precisely tailor nanoparticles to achieve specific biological interactions and deliver therapeutic payloads with unparalleled precision opens up new avenues for overcoming the limitations of conventional drug delivery systems. One of the key future directions in nanoparticle-based therapies is the development of "smart" or "stimuli-responsive" nanoparticles that can respond to specific environmental cues, such as changes in pH, temperature, or the presence of certain enzymes. These nanoparticles are designed to release their therapeutic cargo only under specific conditions, such as within a tumor microenvironment or in response to a particular biomarker, thus minimizing off-target effects and improving the precision of treatment. For instance, nanoparticles that are sensitive to the acidic environment of tumors could release anticancer drugs only at the tumor site, thereby enhancing therapeutic efficacy while reducing systemic toxicity. Another important area of development is the engineering of nanoparticles with tailored surface properties to enable more efficient targeting and reduced immune recognition. By modifying the surface charge, hydrophobicity, or functionalizing nanoparticles with targeting ligands (such as antibodies, peptides, or aptamer), it is possible to direct nanoparticles to specific cells or tissues, improving the selectivity and efficacy of treatments. This is especially important for diseases such as cancer, where targeted drug delivery can enhance therapeutic outcomes while minimizing damage to healthy tissues. Additionally, the ability to deliver multiple agents simultaneously, such as chemotherapy drugs and gene-editing tools, offers the potential for synergistic therapies that target multiple pathways of disease progression.

9.0 CONCLUSION

Nanoparticles possess a unique set of properties that significantly influence their behavior and performance in pharmaceutical formulations. Among these properties, size and charge are two of the most critical factors that govern their interactions with biological systems. The size of nanoparticles determines their ability to penetrate biological barriers, their rate of clearance from the body, and their distribution within tissues. Meanwhile, the charge on the surface of nanoparticles affects their interactions with cells, proteins, and immune components, influencing cellular uptake, biodistribution, and potential toxicity. Together, these properties have a profound impact on the efficacy and safety of nanoparticles in drug delivery applications. In the development of efficient medication delivery systems, understanding how the size and charge of nanoparticles interact with the human body is paramount. Nanoparticles in the optimal size range can exploit mechanisms such as the enhanced permeability and retention (EPR) effect, which enables them to accumulate preferentially in tumor tissues or sites of inflammation, allowing for targeted therapy with minimal off-target effects. The surface charge of nanoparticles is equally important, as it affects their stability in biological fluids, their ability to cross cell membranes, and their interaction with the immune system. Both size and

charge can also influence the release profile of the drug encapsulated within the nanoparticle, determining how quickly or slowly the drug is delivered to the site of action. The design of nanoparticle-based drug delivery systems must account for these critical properties to ensure optimal performance. For instance, nanoparticles that are too large may not effectively cross biological barriers, while those that are too small may be cleared too quickly by the immune system. Similarly, nanoparticles with a highly positive or negative charge may exhibit undesirable interactions with serum proteins or immune cells, potentially leading to toxicity or immunogenicity. Thus, fine-tuning the size and charge of nanoparticles is essential for developing formulations that are both effective and safe.

Continued research in nanoparticle design and optimization holds tremendous potential for advancing the efficiency and safety of these systems in clinical applications. As researchers gain a deeper understanding of the relationship between nanoparticle properties and their biological effects, new strategies will emerge to overcome existing challenges, such as the rapid clearance of nanoparticles or their tendency to induce immune responses. This ongoing research is crucial for realizing the full potential of nanoparticles in a wide range of therapeutic areas, from cancer and gene therapy to vaccine delivery and regenerative medicine. Moreover, as nanoparticles move toward clinical applications, regulatory agencies must establish clear guidelines to ensure their safety and efficacy. This includes standardized testing protocols for assessing the impact of size and charge on the behavior of nanoparticles in biological systems, as well as evaluating long-term safety. By aligning advances in nanoparticle science with regulatory frameworks, the path will be paved for the successful integration of nanoparticles into clinical practice, providing patients with more effective and safer treatment options. In summary, the continued exploration of the fundamental properties of nanoparticles, particularly size and charge, is essential for the development of more efficient and safe drug delivery systems. With ongoing research and optimization, nanoparticles hold great promise for revolutionizing the way we treat diseases, offering personalized, targeted, and effective therapies with minimal side effects.

10.0 REFERENCES

1. Kengar MD, Jadhav AA, Kumbhar SB, Jadhav RP. A Review on Nanoparticles and its Application. Asian journal of pharmacy and technology, 2019; 9(2): 115-24. DOI: 10.5958/2231-5713.2019.00022.1.
2. Khan I, Saeed K, Khan I. Nanoparticles: Properties, applications and toxicities. Arabian journal of chemistry, 2019 Nov 1; 12(7): 908-31. DOI: 10.1016/j.arabjc.2019.01.001.
3. Medina C, Santos-Martinez MJ, Radomski A, Corrigan OI, Radomski MW. Nanoparticles: pharmacological and toxicological significance. British journal of pharmacology, 2007 Mar; 150(5): 552-8. DOI: 10.1038/sj.bjp.0707137.
4. Díaz-Torres R, Lopez-Arellano R, Escobar-Chávez JJ, García-García E, Domínguez-Delgado CL, Ramírez-Noguera P. Effect of size and functionalization of pharmaceutical nanoparticles and their interaction with biological systems. Handbook of Nanoparticles. Switzerland: Springer, 2016; 1041-60. DOI: 10.1007/978-3-319-48366-1_43.
5. Guo D, Xie G, Luo J. Mechanical properties of nanoparticles: basics and applications. Journal of physics D: applied physics, 2013 Dec 3; 47(1): 013001. DOI: 10.1088/0022-3727/47/1/013001.
6. Zein R, Sharrouf W, Selting K. Physical properties of nanoparticles that result in improved cancer targeting. Journal of Oncology, 2020; 2020(1): 5194780. DOI: 10.1155/2020/5194780.

7. He C, Hu Y, Yin L, Tang C, Yin C. Effects of particle size and surface charge on cellular uptake and biodistribution of polymeric nanoparticles. Biomaterials, 2010 May 1; 31(13): 3657-66. DOI: 10.1016/j.biomaterials.2010.01.030.
8. Bannunah AM, Vllasaliu D, Lord J, Stolnik S. Mechanisms of nanoparticle internalization and transport across an intestinal epithelial cell model: effect of size and surface charge. Molecular pharmaceutics, 2014 Dec 1; 11(12): 4363-73. DOI: 10.1021/mp500418y.
9. Yildirimer L, Thanh NT, Loizidou M, Seifalian AM. Toxicology and clinical potential of nanoparticles. Nano today, 2011 Dec 1; 6(6): 585-607. DOI: 10.1016/j.nantod.2011.10.001.
10. Jo DH, Kim JH, Lee TG, Kim JH. Size, surface charge, and shape determine therapeutic effects of nanoparticles on brain and retinal diseases. Nanomedicine: Nanotechnology, Biology and Medicine, 2015 Oct 1; 11(7): 1603-11. DOI: 10.1016/j.nano.2015.05.001.
11. Hasan S. A review on nanoparticles: their synthesis and types. Res. J. Recent Sci., 2015; 2277: 2502. DOI: 10.1016/j.rjrs.2015.04.001.
12. Bhatia S, Bhatia S. Nanoparticle's types, classification, characterization, fabrication methods and drug delivery applications. Natural polymer drug delivery systems: Nanoparticles, plants, and algae, 2016; 33-93. DOI: 10.1007/978-3-319-29681-0_3.
13. Mohanraj VJ, Chen YJ. Nanoparticles-a review. Tropical journal of pharmaceutical research, 2006; 5(1): 561-73. DOI: 10.4314/tjpr.v5i1.14664.
14. Youns M, D Hoheisel J, Efferth T. Therapeutic and diagnostic applications of nanoparticles. Current drug targets, 2011 Mar 1; 12(3): 357-65. DOI: 10.2174/138920111795495012
15. Anton N, Benoit JP, Saulnier P. Design and production of nanoparticles formulated from nano-emulsion templates—a review. Journal of controlled release, 2008 Jun 24; 128(3): 185-99. DOI: 10.1016/j.jconrel.2008.02.008.
16. Merisko-Liversidge EM, Liversidge GG. Drug nanoparticles: formulating poorly water-soluble compounds. Toxicologic pathology, 2008 Jan; 36(1): 43-8. DOI: 10.1177/0192623307312575.
17. Kumar R, Dalvi SV, Siril PF. Nanoparticle-based drugs and formulations: current status and emerging applications. ACS Applied Nano Materials, 2020 May 29; 3(6): 4944-61. DOI: 10.1021/acsanm.0c00280.
18. Dave V, Tak K, Sohgaura A, Gupta A, Sadhu V, Reddy KR. Lipid-polymer hybrid nanoparticles: Synthesis strategies and biomedical applications. Journal of microbiological methods, 2019 May 1; 160: 130-42. DOI: 10.1016/j.mimet.2019.01.012.
19. Mohanraj VJ, Chen YJ. Nanoparticles-a review. Tropical journal of pharmaceutical research, 2006; 5(1): 561-73. DOI: 10.4314/tjpr.v5i1.14664.
20. Leo E, Scatturin A, Vighi E, Dalpiaz A. Polymeric nanoparticles as drug controlled release systems: a new formulation strategy for drugs with small or large molecular weight. Journal of nanoscience and nanotechnology, 2006 Sep 1; 6(9-10): 3070-9. DOI: 10.1166/jnn.2006.481
21. Choi SJ, Lee JK, Jeong J, Choy JH. Toxicity evaluation of inorganic nanoparticles: considerations and challenges. Molecular & Cellular Toxicology, 2013 Sep; 9: 205-10. DOI: 10.1007/s12930-013-0034-1.
22. Bakand S, Hayes A. Toxicological considerations, toxicity assessment, and risk management of inhaled nanoparticles. International journal of molecular sciences, 2016 Jun 14; 17(6): 929. DOI: 10.3390/ijms17060929.

23. Maurer-Jones MA, Bantz KC, Love SA, Marquis BJ, Haynes CL. Toxicity of therapeutic nanoparticles. Nanomedicine, 2009 Feb 1; 4(2): 219-41. DOI: [10.2217/17435868.4.2.219].
24. Kong B, Seog JH, Graham LM, Lee SB. Experimental considerations on the cytotoxicity of nanoparticles. Nanomedicine, 2011 Jul 1; 6(5): 929-41. DOI: 10.2217/nnm.11.26.
25. Baetke SC, Lammers TG, Kiessling F. Applications of nanoparticles for diagnosis and therapy of cancer. The British journal of radiology, 2015 Oct 1; 88(1054): 20150207. DOI: 10.1259/bjr.20150207.
26. Zhang L, Gu FX, Chan JM, Wang AZ, Langer RS, Farokhzad OC. Nanoparticles in medicine: therapeutic applications and developments. Clinical pharmacology & therapeutics, 2008 May; 83(5): 761-9. DOI: 10.1038/sj.clpt.6100400.
27. Zazo H, Colino CI, Lanao JM. Current applications of nanoparticles in infectious diseases. Journal of Controlled Release, 2016 Feb 28; 224: 86-102. DOI: 10.1016/j.jconrel.2016.01.020.
28. Han X, Xu K, Taratula O, Farsad K. Applications of nanoparticles in biomedical imaging. Nanoscale, 2019; 11(3): 799-819. DOI: 10.1039/C8NR08622K
29. Wei A, Mehtala JG, Patri AK. Challenges and opportunities in the advancement of nanomedicines. Journal of controlled release, 2012 Dec 10; 164(2): 236-46. DOI: 10.1016/j.jconrel.2012.09.020.
30. Rai R, Alwani S, Badea I. Polymeric nanoparticles in gene therapy: New avenues of design and optimization for delivery applications. Polymers, 2019 Apr 25; 11(4): 745. DOI: 10.3390/polym11040745.
31. Khan Y, Sadia H, Ali Shah SZ, Khan MN, Shah AA, Ullah N, Ullah MF, Bibi H, Bafakeeh OT, Khedher NB, Eldin SM. Classification, synthetic, and characterization approaches to nanoparticles, and their applications in various fields of nanotechnology: A review. Catalysts, 2022 Nov 8; 12(11): 1386. DOI: 10.3390/catal12111386.
32. Kamaly N, Xiao Z, Valencia PM, Radovic-Moreno AF, Farokhzad OC. Targeted polymeric therapeutic nanoparticles: design, development and clinical translation. Chemical Society Reviews, 2012; 41(7): 2971-3010. DOI: 10.1039/C2CS15360D
33. Poonia M, Ramalingam K, Goyal S, Sidhu SK. Nanotechnology in oral cancer: A comprehensive review. Journal of Oral and Maxillofacial Pathology, 2017 Sep 1; 21(3): 407-14.
34. Siavashy S, Soltani M, Ahmadi M, Landi B, Mehmanparast H, Ghorbani-Bidkorbeh F. A comprehensive review of one decade of microfluidic platforms applications in synthesis of enhanced carriers utilized in controlled drug delivery. Advanced Materials Technologies, 2022 Oct; 7(10): 2101615.
35. Thakur R, Arora V. Comprehensive review on polymeric and metal nanoparticles: Possible therapeutic avenues. International Journal of Polymeric Materials and Polymeric Biomaterials, 2023 Dec 12; 72(18): 1489-509.
36. Budiman A, Rusdin A, Wardhana YW, Puluhulawa LE, Cindana Mo'o FR, Thomas N, Gazzali AM, Aulifa DL. Exploring the Transformative Potential of Functionalized Mesoporous Silica in Enhancing Antioxidant Activity: A Comprehensive Review. Antioxidants, 2024 Aug 1; 13(8): 936.
37. Fukuda R, Shima R, Shibukawa S, Murakami T. Comprehensive Analysis of Drug Loading into Engineered Lipoprotein Nanoparticles toward Their Eye Drop Application. ACS Applied Bio Materials, 2023 Dec 29; 7(1): 99-103.
38. Moradi F, Dashti N. Targeting neuroinflammation by intranasal delivery of nanoparticles in neurological diseases: A comprehensive review. Naunyn-Schmiedeberg's Archives of Pharmacology, 2022 Feb; 395(2): 133-48.
39. Meka VS, Sing MK, Pichika MR, Nali SR, Kolapalli VR, Kesharwani P. A comprehensive review on polyelectrolyte complexes. Drug discovery today, 2017 Nov 1; 22(11): 1697-706.

40. Palakurthi SS, Shah B, Kapre S, Charbe N, Immanuel S, Pasham S, Thalla M, Jain A, Palakurthi S. A comprehensive review of challenges and advances in exosome-based drug delivery systems. Nanoscale Advances, 2024.
41. Bhat AA, Gupta G, Afzal M, Thapa R, Ali H, Alqahtani SM, almalki WH, Kazmi I, Alzarea SI, Saleem S, Subramaniyan V. Polyphenol-loaded nano-carriers for breast cancer therapy: a comprehensive review. BioNanoScience, 2024 Jan 10: 1-9.
42. Kumar B, Pandey M, Aggarwal R, Sahoo PK. A comprehensive review on invasomal carriers incorporating natural terpenes for augmented transdermal delivery. Future Journal of Pharmaceutical Sciences, 2022 Dec 2; 8(1): 50.
43. Patel PR, Haemmerich D. Review on electrospray nanoparticles for drug delivery: Exploring applications. Polymers for Advanced Technologies, 2024 Jul; 35(7): e6507.
44. Lan H, Jamil M, Ke G, Dong N. The role of nanoparticles and nanomaterials in cancer diagnosis and treatment: a comprehensive review. American Journal of Cancer Research, 2023; 13(12): 5751.
45. Bahri F, Mansoori M, Vafaei S, Fooladi S, Mir Y, Mehrabani M, Hojabri Y, Nematollahi MH, Iravani S. A Comprehensive Review on Ginger-Derived Extracellular Nanoparticles: Feasible Therapeutic Nano-Agents against Diseases. Materials Advances, 2024.
46. Noor L, Hafeez A, Rahman MA, Vishwakarma KK, Kapoor A, Ara N, Aqeel R. Demystifying the Potential of Embelin-Loaded Nanoformulations: a Comprehensive Review. AAPS PharmSciTech, 2024 Oct 21; 25(8): 249.
47. Rehan F, Ahemad N, Gupta M. Casein nanomicelle as an emerging biomaterial—A comprehensive review. Colloids and Surfaces B: Biointerfaces, 2019 Jul 1; 179: 280-92.
48. Koo OM, Rubinstein I, Onyuksel H. Role of nanotechnology in targeted drug delivery and imaging: a concise review. Nanomedicine: nanotechnology, biology and medicine, 2005 Sep 1; 1(3): 193-212.
49. Shabir I, Dar AH, Dash KK, Srivastava S, Pandey VK, Manzoor S, Manzoor S, Bashir I. Formulation, characterization, and applications of organic Pickering emulsions: A comprehensive review. Journal of Agriculture and Food Research, 2023 Nov 22; 100853.
50. Bahadur S, Sharma M. Liposome based drug delivery for the management of psoriasis-A comprehensive review. Current Pharmaceutical Biotechnology, 2023 Sep 1; 24(11): 1383-96.
51. Kulkarni M, Patel K, Patel A, Patel S, Desai J, Patel M, Shah U, Patel A, Solanki N. Nanomaterials as drug delivery agents for overcoming the blood-brain barrier: A comprehensive review. ADMET and DMPK, 2024 Feb 13; 12(1): 63-105.
52. Kulkarni M, Patel K, Patel A, Patel S, Desai J, Patel M, Shah U, Patel A, Solanki N. Nanomaterials as drug delivery agents for overcoming the blood-brain barrier: A comprehensive review. ADMET and DMPK, 2024 Feb 13; 12(1): 63-105.
53. Kalhapure RS, Suleman N, Mocktar C, Seedat N, Govender T. Nanoengineered drug delivery systems for enhancing antibiotic therapy. Journal of pharmaceutical sciences, 2015 Mar 1; 104(3): 872-905.
54. Khan ZA, Tripathi R, Mishra B. Methotrexate: a detailed review on drug delivery and clinical aspects. Expert opinion on drug delivery, 2012 Feb 1; 9(2): 151-69.
55. Patel K, Shah S, Patel J. Solid dispersion technology as a formulation strategy for the fabrication of modified release dosage forms: A comprehensive review. DARU Journal of Pharmaceutical Sciences, 2022 Jun; 30(1): 165-89.

56. Mobeen H, Safdar M, Fatima A, Afzal S, Zaman H, Mehdi Z. Emerging applications of nanotechnology in context to immunology: A comprehensive review. Frontiers in Bioengineering and Biotechnology, 2022 Nov 14; 10: 1024871.
57. Alfatama M, Choukaife H, Alkhatib H, Al Rahal O, Zin NZ. A comprehensive review of oral chitosan drug delivery systems: Applications for oral insulin delivery. Nanotechnology Reviews, 2024 Feb 21; 13(1): 20230205.
58. Lalotra AS, Singh V, Khurana B, Agrawal S, Shrestha S, Arora D. A comprehensive review on nanotechnology-based innovations in topical drug delivery for the treatment of skin cancer. Current Pharmaceutical Design, 2020 Dec 1; 26(44): 5720-31.
59. Singh L, Kruger HG, Maguire GE, Govender T, Parboosing R. The role of nanotechnology in the treatment of viral infections. Therapeutic advances in infectious disease, 2017 Jul; 4(4): 105-31.
60. Ma P, Mumper RJ. Anthracycline nano-delivery systems to overcome multiple drug resistance: A comprehensive review. Nano today, 2013 Jun 1; 8(3): 313-31.
61. Kumar R, Dalvi SV, Siril PF. Nanoparticle-based drugs and formulations: current status and emerging applications. ACS Applied Nano Materials, 2020 May 29; 3(6): 4944-61.
62. Devalapally H, Chakilam A, Amiji MM. Role of nanotechnology in pharmaceutical product development. Journal of pharmaceutical sciences, 2007 Oct 1; 96(10): 2547-65.
63. Baetke SC, Lammers TG, Kiessling F. Applications of nanoparticles for diagnosis and therapy of cancer. The British journal of radiology, 2015 Oct 1; 88(1054): 20150207.
64. Mishra BB, Patel BB, Tiwari S. Colloidal nanocarriers: a review on formulation technology, types and applications toward targeted drug delivery. Nanomedicine: Nanotechnology, biology and medicine, 2010 Feb 1; 6(1): 9-24.
65. Khezri K, Saeedi M, Dizaj SM. Application of nanoparticles in percutaneous delivery of active ingredients in cosmetic preparations. Biomedicine & Pharmacotherapy, 2018 Oct 1; 106: 1499-505.