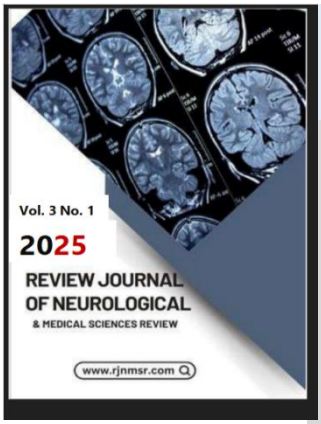

Vol. 3 No. 2 (2025): April - June
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Nanoparticles as Drug Delivery Vehicles a Comprehensive Review on the Influence of Physicochemical Properties on Biological System Interactions

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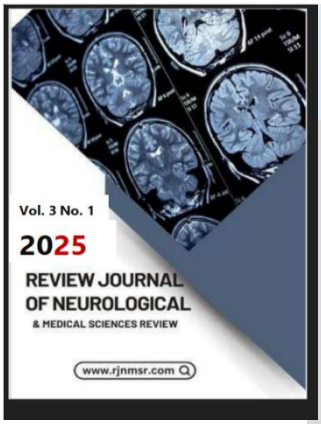
Abstract

Over the past four decades, nanotechnology has experienced exponential growth and continues to advance with sustained momentum. The integration of nanoscale innovations into diverse sectors has fundamentally transformed multiple facets of modern life, ranging from healthcare to the agri-food industry. Engineered nanoparticles have enabled notable advancements, including the substantial extension of food shelf life, enhanced intracellular transport of poorly water-soluble pharmaceutical compounds, and increased therapeutic efficacy of targeted agents such as chemotherapeutics. As a result, nanotechnology has exerted a profound influence on global quality of life and has introduced significant shifts in economic paradigms. This review critically examines the physicochemical properties of nanoparticles that underpin both their functional advantages and potential cytotoxicity. Emphasis is placed on the utilization of nanoparticles across biological disciplines, with particular focus on their roles in drug delivery platforms and the field of nanomedicine. Additionally, the review explores nanoformulations and delivery systems that have attained regulatory approval by the U.S. Food and Drug Administration (FDA). The implications of sustained human and environmental exposure to nanoparticles, due to their increasing prevalence in consumer and clinical products, are also considered. Strategies to mitigate adverse effects while



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maintaining technological progress are highlighted to support safe and sustainable nanotechnology applications.

Keywords: Nanotechnology; nanoparticles, Nanoformulation, drugs administration, nanomedicine,

Introduction

Nanotechnology encompasses the deliberate design, synthesis, and manipulation of materials at the nanoscale, specifically within the dimensional range of 1 to 100 nanometres, to produce nanosystems exhibiting enhanced or novel functionalities. This technological paradigm shift allows for the structural rearrangement of atomic and molecular entities into functional constructs with improved properties and behaviours not observed in their bulk counterparts.[1] For instance, countries such as Ireland have positioned themselves at the forefront of scientific innovation through strategic investment in nanotechnological research and development over the past decade.[2] Nanoparticles, which represent the end products of matter engineered at the molecular level, are typically only marginally larger than individual atoms, a feature that arises from the controlled molecular-level engineering of substances. These particles exhibit distinctive characteristics such as enhanced chemical reactivity, increased stability, and the capacity for spontaneous self-assembly, which collectively render them highly adaptable to targeted modifications for specific applications such as achieving a significantly larger surface-area-to-volume ratio relative to traditional materials. As an emerging interdisciplinary scientific field, nanotechnology has garnered substantial global attention over the past two decades and is rapidly transitioning from academic investigation to industrial application. The considerable economic potential associated with nanoscale innovations is underscored by projections estimating their contribution to the global economy to exceed three trillion U.S. dollars by the year 2020.[3] This substantial economic valuation is primarily attributed to the unique physicochemical behaviours of nanoparticles at the confluence of materials science, chemistry, medicine, physics, and engineering. The nanotechnology domain currently represents one of the most dynamic and fast-evolving frontiers in scientific exploration and technological advancement. Its present state of development spans a diverse array of sectors including, but not limited to, electronics, energy systems, materials engineering, and biomedicine. In the realm of electronics, efforts are centred on the miniaturization of components such as transistors to develop highly compact, efficient, and high-performance devices. Similarly, the energy sector is witnessing the application of nanomaterials in the design of advanced solar energy conversion systems, innovative energy storage

[1] Yusuf, Azeez, Awatif Rashed Z. Almotairy, Hanan Henidi, Ohoud Y. Alshehri, and Mohammed S. Aldughaim. "Nanoparticles as drug delivery systems: a review of the implication of nanoparticles' physicochemical properties on responses in biological systems." Polymers 15, no. 7 (2023): 1596.

[2] Joudeh, Nadeem, and Dirk Linke. "Nanoparticle classification, physicochemical properties, characterization, and applications: a comprehensive review for biologists." Journal of Nanobiotechnology 20, no. 1 (2022): 262.

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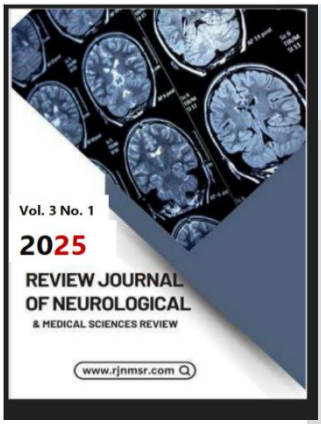

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Review Journal of Neurological & Medical Sciences Review

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P(ISSN) : 3007-3065

devices, and other energy-efficient technologies.[4] In materials science, nanotechnology facilitates the fabrication of substances with superior mechanical, optical, and catalytic properties. Within the biomedical sciences, nanotechnology has catalysed the development of next-generation diagnostic methodologies, therapeutic agents, and tissue-engineering platforms. Collectively, these ongoing advancements illustrate the multidimensional and transformative nature of nanotechnology, highlighting its capacity to deliver unprecedented innovations across multiple scientific disciplines.[5]

The medical and pharmaceutical sciences, in particular, have witnessed an increasing interest in the application of nanoparticles and nanomaterials. Among the most promising avenues is the development of nanoparticle-mediated drug delivery systems. These systems are designed to act as targeted delivery vehicles, capable of transporting therapeutic agents directly to diseased tissues or cellular environments while minimizing off-target effects. Such site-specific delivery is achieved through the engineering of nanoparticles with tailored surface chemistries that facilitate selective interactions with pathological tissues, thereby enhancing drug bioavailability and therapeutic efficacy while simultaneously reducing systemic toxicity. Furthermore, nanoparticles can be optimized for controlled or sustained drug release, offering prolonged therapeutic activity and improved patient compliance.[6] Beyond their therapeutic potential, nanoparticles are also being explored for diagnostic functions. For instance, they serve as high-resolution contrast agents in various imaging modalities and can be functionalized to detect specific biomarkers in complex biological matrices, enhancing sensitivity and specificity in disease diagnosis. In the field of regenerative medicine, nanomaterials are employed as scaffolding platforms that facilitate cellular adhesion, proliferation, and differentiation, and as delivery vectors for biomolecules such as growth factors that are essential for tissue repair and regeneration. While the discipline of nanomedicine is still in its formative stages, the breadth of its potential applications in improving disease diagnosis, treatment, and monitoring continues to expand rapidly.[7]

This review provides a focused examination of the multifaceted role of nanotechnology in selected biological disciplines, with an emphasis on medical applications. Particular attention is devoted to the emerging paradigm of nanoparticle-enabled drug delivery systems as a transformative approach in disease therapeutics. In addition to evaluating the advantages conferred by nanoparticle-

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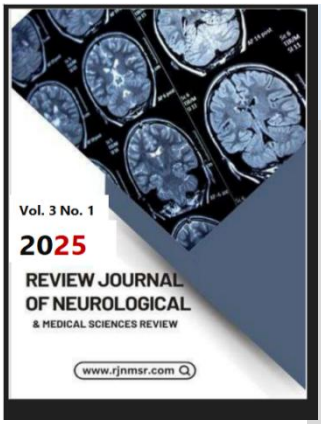

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https://rjnmsr.com/index.php/rjnmsr/about

Review Journal of Neurological & Medical Sciences Review

E(ISSN) : 3007-3073
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based platforms, the review also explores the potential adverse health implications associated with their widespread adoption. The inherent risks linked to persistent nanoparticle exposure, both environmental and biological, necessitate the development of advanced drug delivery strategies and safety protocols aimed at mitigating such unintended consequences. By addressing both the potential and the pitfalls of nanotechnology in biomedicine, this review underscores the imperative for a balanced, responsible, and sustainable integration of nanotechnology into healthcare and biomedical innovation.[8]

Industrial Applications of Nanotechnology

In response to the growing global emphasis on functional and health-promoting food products, nanotechnology has emerged as a transformative tool in enhancing food stability and nutrient assimilation. The integration of nanoscale systems has significantly advanced the preservation of perishables and the targeted delivery of bioactive compounds. One prominent innovation involves embedding nanoparticles into packaging matrices, either as microbial barriers or antimicrobial constituents. Among these, silver nanoparticles (AgNPs) have garnered notable interest due to their inherent bactericidal potential. AgNPs are employed both as components of edible biodegradable coatings especially for perishable commodities like fruits, meats, and poultry and as integrated agents in the structural matrix of packaging materials. Studies exploring their application have demonstrated their capacity to prolong shelf life by suppressing microbial growth, including bacteria such as Escherichia coli and Staphylococcus aureus, and fungal contaminants in a variety of food products, including asparagus, poultry, orange juice, and strawberries. Beyond silver-based agents, zinc oxide (ZnO) and titanium dioxide (TiO_2) nanoparticles exhibit potent antimicrobial properties and have been effectively used against common pathogens in food systems.[9] Their dual utility as both preservatives and functional additives ZnO as a UV-shielding agent and TiO_2 for whitening underlines their significance in modern food technology. Additionally, nano-encapsulation techniques have proven indispensable in enhancing the stability and bioavailability of functional ingredients and flavours. Typically utilising modified polysaccharide matrices such as starch, cellulose, chitosan, and dextrin, these nanocarriers enable controlled nutrient release. Liposomal encapsulations, such as phosphatidylcholine-based systems, have demonstrated superior efficiency in preserving micronutrients like vitamin C, compared to conventional supplementation strategies.[10] Particularly, chitosan-based nanoparticles exhibit enhanced stability for encapsulating bioactives such as

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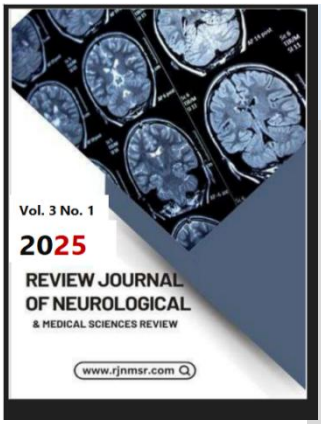

Vol. 3 No. 2 (2025): April - June
https://rjnmsr.com/index.php/rjnmsr/about

Review Journal of Neurological & Medical Sciences Review

E(ISSN) : 3007-3073
P(ISSN) : 3007-3065

curcumin and resveratrol. Furthermore, biodegradable polymers like poly(lactic-co-glycolic acid) (PLGA) have shown promise in incorporating antioxidants and micronutrients within edible matrices. Silica nanoparticles, recognized for their high surface area and low cytotoxicity, have also been utilized as vehicles for nutrient delivery and for enhancing the organoleptic attributes of consumables. While nanotechnology applications in food systems have enabled cost-effective preservation and nutrient enrichment, concerns regarding the unintended ingestion of packaging-derived nanoparticles persist. AgNPs, for instance, may migrate into food products, raising toxicological apprehensions. Although daily intake estimates suggest potential exposures of up to 80 µg, the literature remains divided regarding their safety. Some experimental data suggest negligible adverse effects, while others report systemic accumulation and toxicity in organs such as the liver, kidney, and intestines following ingestion at elevated dosages. The contextual relevance of such findings depends heavily on the actual dietary exposure levels achieved under normal consumption conditions.[11]

Nanotechnology is increasingly embedded within the cosmetic sector, driven by its capacity to enhance product functionality and user experience. In sun care formulations, nanoscale zinc oxide and titanium dioxide particles are incorporated due to their proficiency in filtering ultraviolet radiation while maintaining aesthetic appeal by eliminating visible white residues typically associated with larger particles. These metal oxide nanoparticles, due to their refined size, retain high UV-blocking efficiency without compromising dermal compatibility. Moreover, lipid-based vesicular systems such as liposomes, ethosomes, and transferosomes are extensively used in topical formulations to improve dermal penetration of active agents. Their phospholipid bilayer structure facilitates fusion with cellular membranes, thereby augmenting transdermal permeability and enhancing the intracellular delivery of encapsulated compounds. In addition to their penetration-enhancing capabilities, liposomes offer structural stability and controlled release characteristics.[12] Silver nanoparticles have also found utility in hygiene and oral care products, owing to their antimicrobial spectrum. They are employed in personal care items such as bathing soaps, mouthwashes, and toothpastes to exert antimicrobial activity against both bacterial and fungal strains. Commercial products, including Silvosept oral rinse and Royal Denta silver-infused oral hygiene tools, exemplify the integration of AgNPs into mass-market applications. Nevertheless, repeated application and chronic exposure to nanoparticulate ingredients in cosmetics raise important toxicological and regulatory considerations, particularly concerning long-term dermal accumulation and systemic absorption.

The concept of applying nanoscale tools in clinical settings was initially envisioned in the mid-20th century, proposing the fabrication of atomically precise mechanical

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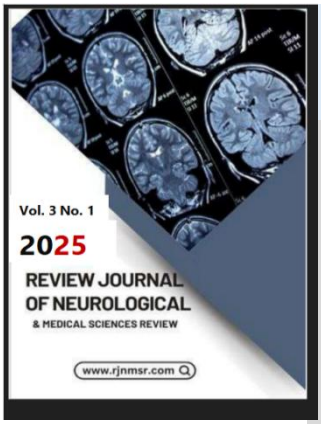

Vol. 3 No. 2 (2025): April - June
https://rjnmsr.com/index.php/rjnmsr/about

Review Journal of Neurological & Medical Sciences Review

E(ISSN) : 3007-3073
P(ISSN) : 3007-3065

systems for diagnostic and therapeutic purposes. Since then, nanotechnology has evolved into a foundational paradigm in contemporary medicine, particularly in the design of advanced drug delivery platforms derived from both natural and synthetic nanomaterials. Recent innovations have included the creation of intelligent nanomachines capable of tumour-specific targeting, exemplified by developments in nanorobotic systems designed to administer chemotherapeutics directly to malignant cells. In the realm of cardiovascular medicine, research has led to the development of nano-devices simulating platelet activity for vascular repair and interventions targeting arterial obstructions.[13] A core application remains the reformulation of pharmacological agents to overcome bioavailability and solubility limitations inherent in traditional drugs. Nanoparticles, owing to their diminutive size and high surface-area-to-volume ratio, facilitate targeted delivery, minimize off-target effects, and permit intracellular access, thereby enhancing therapeutic efficacy in chronic and intractable diseases such as diabetes, malignancies, and nephropathies. Numerous nanoparticle-based therapeutics have secured regulatory approval, with examples spanning nucleic acid-based carriers (e.g., siRNA, mRNA), metallic complexes, and chemotherapeutics. However, cellular internalization challenges persist for certain formulations, necessitating the deployment of auxiliary delivery systems such as liposomes, micelles, dendrimers, and chitosan-based nanoparticles. These carriers support dual encapsulation of hydrophilic and hydrophobic agents, effectively mitigating toxicity profiles and enhancing the therapeutic index. Among the most established nanoparticle-enabled formulations is liposomal doxorubicin (Doxil™), which has received FDA approval for treating cancers such as Kaposi's sarcoma and ovarian carcinoma. Liposomal encapsulation enables tumour-selective drug accumulation, leveraging passive or active targeting mechanisms to concentrate cytotoxic agents within malignant tissues while sparing healthy cells. This strategy significantly boosts drug potency and concurrently attenuates systemic toxicity.[14] For example, encapsulating doxorubicin within dipalmitoylphosphatidylcholine (DPPC)-based liposomes enhances cellular uptake and maximizes anti-tumour activity, setting a precedent for nanocarrier-mediated chemotherapy in clinical oncology.

Nanoparticles have demonstrated considerable utility in biomedical diagnostics, particularly in imaging applications involving internal organs and tissues. This is primarily attributed to their versatile physicochemical attributes such as tunable size, geometry, and magnetic, optical, and electronic properties which facilitate interactions with mammalian cells. Notably, iron oxide and silica-based nanoparticles have been instrumental in developing advanced multimodal imaging platforms, including magnetic resonance imaging (MRI) coupled with optical imaging. These systems offer substantial benefits over conventional modalities like

[13]Yadav, Rutuja Harishchandra, Madhuchandra Kenchegowda, Mohit Angolkar, Meghana TS, Riyaz Ali M. Osmani, Shilpa Palaksha, and Hosahalli Veerabhadrappa Gangadharappa. "A review of silk fibroin-based drug delivery systems and their applications." European Polymer Journal (2024): 113286..

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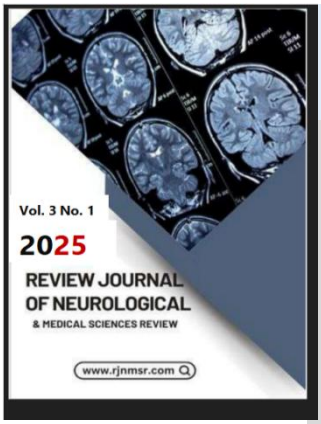

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Review Journal of Neurological & Medical Sciences Review

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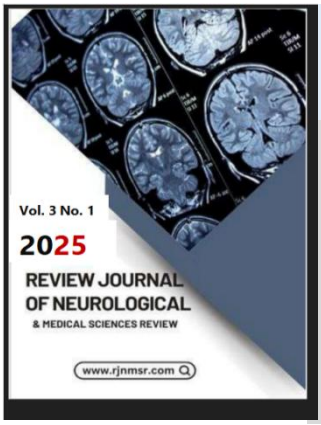
positron emission tomography (PET) and computed tomography (CT), which present inherent radiation risks. Iron oxide, a magneto-responsive and biocompatible element due to its capacity for metabolic degradation, has become a cornerstone in MRI contrast enhancement. These iron oxide nanoparticles (IONPs) possess superparamagnetic behavior, effectively modifying magnetic relaxation parameters of biological tissues and thereby amplifying MRI contrast. This approach has been validated across multiple diagnostic contexts, including oncology, inflammatory disorders, and vascular pathologies. In parallel, silica nanoparticles have emerged as potential X-ray contrast enhancers for CT imaging due to their intrinsic high atomic number, which enhances radiodensity. This facilitates their deployment in disease visualization, particularly for neoplastic and inflammatory conditions. Furthermore, specialized silica-based constructs have been engineered with paramagnetic shells and luminescent cores to enable synergistic magnetic-optical imaging. These nanosystems also allow for functionalization with bioactive ligands or peptides, facilitating specific cellular targeting, notably in oncological diagnostics.[15] By integrating optical and magnetic modalities, these nanostructures permit dynamic tissue monitoring without the reliance on ionizing radiation, thus circumventing limitations associated with PET or CT techniques. In another domain of medical application, silver nanoparticles (AgNPs) are increasingly employed as antimicrobial coatings on clinical textiles, surgical bandages, implantable devices, and diagnostic instruments. Unlike traditional disinfectants that exhibit a transient bactericidal effect, AgNPs retain prolonged antimicrobial activity as long as they remain surface-bound. This sustained efficacy against a broad spectrum of microbial strains underscores their importance in infection control. The integration of nanotechnology into medicine is expanding rapidly, propelled by the distinctive physicochemical characteristics inherent to nanoparticles. However, the formulation of such nanoplatforms mandates careful evaluation of several critical parameters to ensure therapeutic efficacy and safety:

1. **Morphological Precision**: Accurate control of nanoparticle dimensions and morphology is essential to optimize functionality while mitigating cytotoxic potential.
2. **Surface Engineering:** The nanoparticle surface may be chemically modified with targeting agents, including antibodies or polymers. Ensuring the functional groups exhibit specificity, stability, and bioactivity is vital for targeted delivery.
3. **Core Stability:** Given the reactive nature of materials like iron oxide, strategies must be implemented to preserve the core integrity under physiological conditions, preventing aggregation or premature degradation.
4. **Biocompatibility:** It is imperative that the nanoparticle system does not provoke immunogenic, cytotoxic, or pro-inflammatory responses, thus confirming its compatibility with biological systems.

[15] Herdiana, Yedi, Nasrul Wathoni, Shaharum Shamsuddin, and Muchtaridi Muchtaridi. "Scale-up polymeric-based nanoparticles drug delivery systems: Development and challenges." OpenNano 7 (2022): 100048.



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Review Journal of Neurological & Medical Sciences Review

E(ISSN) : 3007-3073
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5. **Payload Kinetics:** For therapeutic delivery, controlled and predictable release kinetics are crucial to achieve optimal pharmacodynamics without compromising safety.
6. **Targeted Accumulation:** Achieving selective biodistribution and accumulation at pathological sites enhances the therapeutic index and minimizes off-target effects.

Physicochemical Characteristics

Nanoparticles possess distinct physicochemical traits that endow them with superior pharmacokinetic and pharmacodynamic profiles compared to bulk-phase substances. As a result, substantial research efforts have focused on manipulating nanoparticle parameters such as geometry, size, surface area, and chemical surface modifications to optimize their performance in clinical applications.[16] Nanostructures such as liposomes, gold nanoshells, and polymeric micelles are synthesized using techniques that afford precise control over their size and shape based on functional requirements. During synthesis, nanoparticles may aggregate into larger assemblies, potentially altering cytotoxic profiles in a composition-dependent manner. Moreover, their surface chemistry can be tailored by grafting biofunctional moieties such as antibodies thus enhancing targeting efficiency in drug delivery systems. Key physicochemical features of nanoparticles include electrostatic charge, aggregation tendencies, surface conjugation potential, and customizable morphologies. These properties confer a heightened reactivity relative to macroparticles within biological environments.[17]

Nanoparticles, generally defined by dimensions ranging from 1 to 100 nanometers, possess exceptionally high surface area-to-volume ratios. This intrinsic characteristic increases their surface reactivity per unit mass compared to bulk materials, rendering even traditionally inert substances like elemental gold chemically active at the nanoscale. Their reduced size also enables deep tissue penetration and interaction with biological fluids, a capability unattainable with larger particles. The size and surface characteristics of nanoparticles influence cellular uptake, distribution, retention, and excretion within biological systems. Due to their size, nanoparticles do not passively permeate cellular membranes; instead, they are internalized via energy-dependent endocytic pathways. Research indicates that particles under 200 nm are predominantly internalized through clathrin-mediated endocytosis, whereas particles around 500 nm enter via caveolae-mediated mechanisms. In immune cell populations such as macrophages, nanoparticles typically undergo phagocytosis. Studies have demonstrated that particles smaller than 500 nm are readily internalized through this mechanism, whereas particles approximating bacterial dimensions (2–3 μm) exhibit maximal phagocytic uptake.

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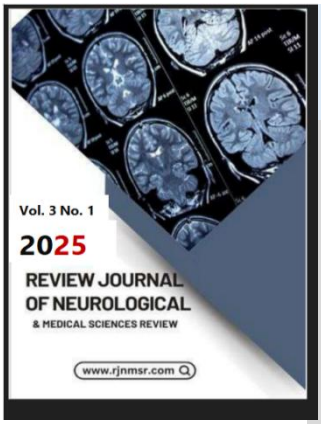

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Review Journal of Neurological & Medical Sciences Review

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Advanced engineering of nanoparticulate systems, such as liposomes, now allows for tailored size profiles to enhance cellular uptake. For example, utilizing extrusion through polycarbonate membranes with defined pore sizes enables the production of uniform liposomal structures. Such methods have demonstrated improved cellular internalization and enhanced therapeutic efficacy in chemotherapeutic delivery, underscoring the impact of nanoparticle dimension control in drug delivery optimization.[18]

The surface chemistry of nanoparticles, including characteristics such as surface charge and the presence of functional groups, plays a pivotal role in determining their physicochemical interactions, biological reactivity, and ultimate functionality. Surface modifications are frequently employed to enhance cellular permeability and internalization. Gold nanoparticles (AuNPs) and DNA molecules have undergone surface engineering through lipid coating, and DNA has also been electrostatically associated with cationic liposomes to promote transmembrane transport, yielding improved intracellular uptake. Liposomes and micelles, which possess lipid bilayers, can integrate with cellular membranes via hydrophobic interactions, thereby facilitating enhanced nanoparticle internalization. Silicon nanoparticles (SiNPs), widely used in optoelectronic applications due to their semiconducting properties, exhibit intrinsic hydrophobicity that limits their applicability in aqueous biological environments, such as tissue imaging. To address this, their surfaces have been modified with silicon dioxide (SiO_2), which increases hydrophilicity and enhances biocompatibility. Zinc oxide (ZnO_2) nanoparticles are prevalent in ultraviolet (UV) protective formulations like sunscreens; however, concerns regarding their cytotoxic potential have emerged. To mitigate these effects, surface functionalization strategies such as coating with poly(methyl acrylic acid) (PMAA) have been employed, which not only reduce cytotoxicity but also preserve their UV-blocking efficacy. Liposomes consist of phospholipid bilayers analogous to the cellular membrane.[19] These phospholipids are amphiphilic molecules containing hydrophilic phosphate-glycerol headgroups and hydrophobic fatty acid tails. The polar headgroups engage in hydrogen bonding within aqueous environments, while the hydrophobic tails align to form a core capable of encapsulating nonpolar compounds, thereby forming stable bilayer structures. The structural mimicry of liposomes enables their adsorption onto cellular membranes, followed by internalization via receptor-mediated endocytosis or direct membrane fusion, resulting in invagination and uptake into the cytoplasm. Furthermore, the physicochemical environment, particularly pH, significantly influences nanoparticle behavior through surface chemistry alterations.[20] This principle is exploited in pH-sensitive drug delivery systems targeting tumor

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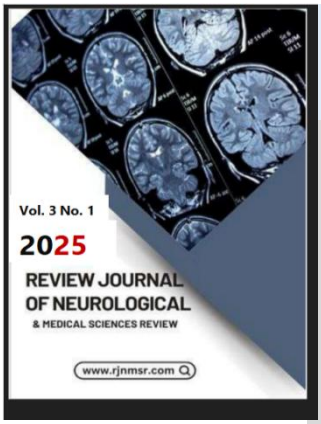

Vol. 3 No. 2 (2025): April - June
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Review Journal of Neurological & Medical Sciences Review

E(ISSN) : 3007-3073
P(ISSN) : 3007-3065

microenvironments, which are characteristically acidic. For instance, gold nanoparticles capped with carrageenan oligosaccharides have been shown to facilitate the release of anticancer agents like epirubicin under acidic conditions, inducing apoptosis in colorectal carcinoma cells. The surface composition of nanoparticles critically impacts their diffusivity within biological matrices and modulates their reactivity, enabling multifunctional applications in biomedical diagnostics, implant coatings, and therapeutic delivery platforms. As an illustration, titanium implants functionalized with silver nanoparticles (AgNPs) have demonstrated efficacy in preventing infections caused by multidrug-resistant bacterial strains owing to AgNPs' inherent antimicrobial properties. Liposomes offer dual compartments an aqueous core and a lipid bilayer facilitating the encapsulation of both hydrophilic and hydrophobic therapeutics. Incorporation of cholesterol into liposomal formulations modulates membrane fluidity, enhancing structural stability akin to native biological membranes. Lipid-coated nanoparticles, such as AuNPs, emulate the physicochemical properties of cell membranes, improving compatibility and promoting intracellular delivery. Additionally, the reactive phosphate headgroups of lipids serve as conjugation sites for ligands, facilitating targeted delivery.[21] Polyethylene glycol (PEG) is often grafted onto liposomal surfaces to evade immune detection by phagocytes, thereby prolonging systemic circulation. PEGylation also provides anchor points for functional moieties like folic acid and monoclonal antibodies, which enhance cellular specificity. Folate is particularly advantageous due to its high-affinity binding to folate receptors, which are overexpressed in malignant cells. In contrast, monoclonal antibodies offer broader targeting capabilities by recognizing diverse surface antigens, enabling precise delivery of nanoparticles or pharmacological agents to neoplastic tissues.[22]

In addition to tunable size, the morphological configuration of nanoparticles can be precisely manipulated during synthesis. The final shape is typically determined during the nucleation phase, where primary nanoparticle seeds aggregate and serve as a structural template for subsequent crystal growth. Morphology significantly influences the physicochemical behavior and biological interactions of nanomaterials. Spherical nanoparticles are generally internalized more efficiently by cells compared to rod-shaped or tubular configurations. This disparity arises due to morphological effects on endocytotic pathways, particularly the kinetics of membrane deformation and wrapping. Rod-shaped nanostructures may hinder actin-mediated cytoskeletal dynamics, thus reducing cellular uptake.[23] This observation may account for the predominance of spherical nanocarriers in therapeutic applications. Nonetheless,

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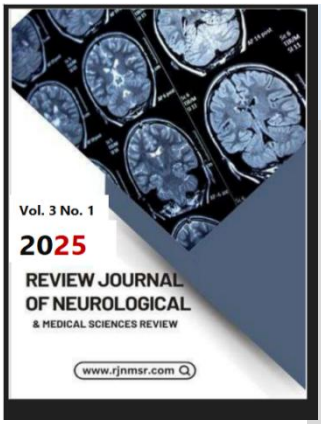

Vol. 3 No. 2 (2025): April - June
https://rjnmsr.com/index.php/rjnmsr/about

Review Journal of Neurological & Medical Sciences Review

E(ISSN) : 3007-3073
P(ISSN) : 3007-3065

emerging research highlights the functional versatility of non-spherical nanoparticles. For instance, elongated rod-like nanoparticles exhibit superior loading capacity and extended systemic residence compared to their spherical or shorter counterparts. Other morphologies, including nanoflowers and nanoprisms, are under investigation; however, their irregular geometries may impair functional performance relative to more conventional shapes. Nanoparticle shape is a key determinant in endocytic routing, which proceeds via clathrin-dependent or clathrin-independent mechanisms. Spherical or near-spherical particles are preferentially internalized through clathrin-mediated endocytosis, a highly selective process requiring specific size and symmetry. These particles fit within clathrin-coated pits that facilitate vesicular internalization. Conversely, irregular or complex-shaped nanoparticles often bypass this route and instead utilize less selective clathrin-independent pathways. Morphologies such as rods or bristles may disrupt membrane integrity or become transiently lodged in the lipid bilayer, thereby evading internalization altogether.[24] These morphological influences have profound implications for the design of nanocarriers, as the shape directly affects bioavailability, biodistribution, and cellular targeting efficiency.

Nanoparticle-Induced Cytotoxicity

The rapid advancement and widespread integration of nanotechnology into multiple domains of human activity have raised significant apprehensions regarding the biological risks associated with heightened human exposure. This concern has driven the emergence of nanotoxicology a dedicated subfield focused on elucidating the toxicological profiles of nanoparticles. Recent investigations have underscored a paradox wherein the physicochemical attributes of nanoparticles that enhance their pharmacological efficacy concurrently contribute to their cytotoxic potential. Empirical research utilizing diverse cellular models and experimental conditions has demonstrated the toxicological effects of various nanoparticles. For example, carbon nanotubes have been found to negatively impact microbial biodiversity in soil ecosystems, hinder the proliferation of aquatic organisms such as Daphnia magna, Chlorella vulgaris, and Oryzias latipes, and provoke oxidative damage, membrane disruption, and inflammatory responses in human pulmonary epithelial A549 cells.[25] The size-dependent cytotoxicity of nanoparticles appears to be mediated by their ability to penetrate tissue matrices and infiltrate cells, where they interfere with intracellular structures and promote excessive generation of reactive oxygen species (ROS). Elevated ROS levels are known to precipitate oxidative stress, leading to alterations in signal transduction pathways, genomic instability, and ultimately apoptotic or necrotic cell death. Nanoparticles are frequently subjected to surface modifications to optimize their functionality, although such alterations can inadvertently exacerbate their toxicological impact. The surface reactivity of nanoparticles dictates their interactions with biological macromolecules, potentially

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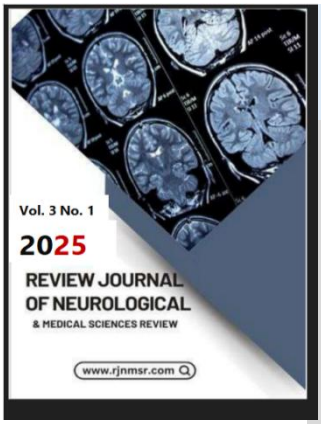

Vol. 3 No. 2 (2025): April - June
https://rjnmsr.com/index.php/rjnmsr/about

Review Journal of Neurological & Medical Sciences Review

E(ISSN) : 3007-3073
P(ISSN) : 3007-3065

disrupting homeostatic cellular functions. For instance, gold nanoparticles with surface charges have exhibited differential cytotoxicity; charged variants elicit greater oxidative stress and mitochondrial dysfunction than their neutral counterparts.[26] Similarly, anionic cyanoacrylic nanoparticles have demonstrated heightened cytotoxicity in macrophages compared to cationic analogs, potentially due to preferential uptake driven by electrostatic interactions with negatively charged lipid A moieties in bacterial membranes. Conversely, aminated iron oxide nanoparticles, characterized by a net positive charge, have been shown to exhibit increased cellular uptake and toxicity in Chinese Hamster Ovary (CHO-K1) cells when compared with their PEGylated equivalents, which display reduced cellular internalization due to steric hindrance. The incorporation of polyethylene glycol (PEG) typically enhances bioavailability and minimizes immunogenic responses, although it may concurrently attenuate cytotoxicity through decreased intracellular accumulation. In addition to size and surface chemistry, nanoparticle geometry specifically aspect ratio has been implicated in modulating cytotoxic outcomes. Nanoparticles with elevated aspect ratios are less readily cleared from biological systems, leading to prolonged bioavailability and increased toxicity. These elongated particles have shown toxicity profiles comparable to fibrous materials such as asbestos, inducing macrophage apoptosis during phagocytic activity and presenting potential oncogenic risk. Supporting this, comparative analyses of gold nanospheres and nanorods (under 50 nm) with larger morphologies such as nanostars, nanoflowers, and nanoprisms (over 200 nm) have revealed enhanced cytotoxicity in the former, likely due to superior cellular internalization and maximized intracellular interactions.[27]

Nanoparticles utilized in drug delivery typically measure between 10 and 1000 nanometres, with at least one dimension under 100 nanometres. Their diminutive scale and tunable surface characteristics confer numerous pharmacological advantages, yet these same properties may also potentiate adverse biological effects. Smaller nanoparticles penetrate cellular membranes more efficiently; however, if their systemic clearance is inadequate, residual particles may accumulate and exert toxic effects, particularly if their pharmacodynamic activity is sustained. This retention is particularly problematic when the therapeutic agent itself is cytotoxic, as unintended exposure may compromise non-target tissues. The suboptimal solubility of approximately 70% of pharmaceutical compounds contributes to their limited bioavailability and necessitates innovative delivery strategies.[28] Nanoparticle-mediated drug delivery systems (DSSs) offer a sophisticated means of improving therapeutic index by enhancing tissue targeting and minimizing collateral toxicity.

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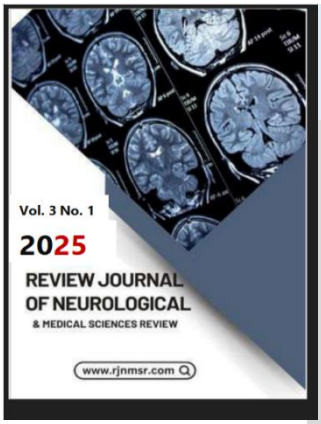

Vol. 3 No. 2 (2025): April - June
https://rjnmsr.com/index.php/rjnmsr/about

Review Journal of Neurological & Medical Sciences Review

E(ISSN) : 3007-3073
P(ISSN) : 3007-3065

These platforms have revolutionized therapeutic paradigms, particularly in the context of oncology and neurodegenerative disorders, by facilitating localized delivery of active agents and circumventing systemic side effects associated with conventional formulations.[29]

Lipid-based delivery platforms encompass a spectrum of formulations, primarily categorized into micelles and liposomes. Micelles arise through the spontaneous aggregation of amphiphilic molecules in aqueous environments, forming nanoscopic vesicles ranging from 5 to 50 nanometres. These structures encapsulate hydrophobic drugs within their lipid core, thereby augmenting aqueous solubility and bioavailability by shielding the hydrophobic payload from the aqueous milieu. Liposomes are spherical vesicles composed of lipid bilayers, typically spanning 10 nanometres to several microns. These bilayers mimic biological membranes, featuring hydrophilic exteriors and interiors that sandwich a hydrophobic core. Liposomes accommodate hydrophobic agents within their bilayers and hydrophilic compounds within their aqueous cores.[30] This dual encapsulation capacity renders liposomes particularly effective in cancer therapeutics, where precise delivery and minimized systemic exposure are paramount. Conventional chemotherapeutics often lack tumour specificity and readily diffuse out of tumour microenvironments, contributing to cytotoxicity in normal tissues. Liposomes, through the enhanced permeability and retention (EPR) effect, preferentially accumulate within tumour interstitium due to the relatively leaky vasculature and impaired lymphatic drainage characteristic of neoplastic tissues. Despite their inherent instability and brief systemic half-life, liposomes have benefitted from advancements such as PEGylation, which involves the covalent attachment of PEG chains to phosphatidylethanolamine moieties (e.g., DSPE-PEG). This modification imparts hydrophilicity, reduces renal clearance, and prolongs circulation time. PEGylated liposomes serve as platforms for further functionalization using chemical conjugation techniques such as click chemistry, whereby ligands like azide-tagged antibodies are linked to dibenzocyclooctyne-functionalized liposomes via azide-alkyne cycloaddition. This functionalization enhances pharmacokinetic and pharmacodynamic profiles by promoting targeted cellular uptake and controlled drug release, thereby mitigating adverse effects. A prominent clinical application is Doxil®, a PEGylated liposomal formulation of doxorubicin, which demonstrates reduced cardiotoxicity and enhanced tumour specificity. While PEGylation enhances pharmacokinetics, it may simultaneously impede endosomal escape and intracellular delivery due to reduced uptake.[31] Liposomes can also be modified to facilitate selective targeting by

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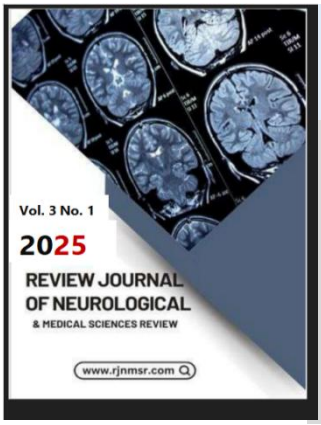


Vol. 3 No. 2 (2025): April - June
https://rjnmsr.com/index.php/rjnmsr/about

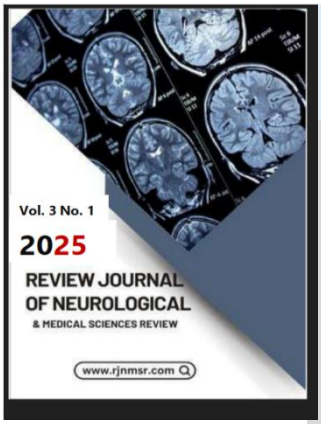
Review Journal of Neurological & Medical Sciences Review

E(ISSN) : 3007-3073
P(ISSN) : 3007-3065

conjugating them with biomolecules (e.g., peptides or antibodies) that bind specific surface receptors overexpressed in tumour cells. Upon receptor-mediated endocytosis, the encapsulated drug is released following endosomal degradation via the lysosomal pathway. Lipid nanoparticles (LNPs) represent another class of lipid-based carriers, particularly effective for nucleic acid delivery. These constructs typically incorporate cationic or ionizable lipids, neutral lipids, and stabilizers like cholesterol to optimize encapsulation efficiency, structural integrity, and cellular uptake. LNPs can be tailored with ligands to enhance specificity for target cells or tissues. Recent applications have demonstrated their efficacy in gene therapy, such as CRISPR-Cas9 delivery for the treatment of Duchenne muscular dystrophy. In such formulations, dystrophin mRNA and genome-editing components are encapsulated within LNPs and systemically administered, leading to efficient gene delivery to muscle cells and subsequent phenotypic improvement. Engineered LNPs incorporating PEGylated lipids and cationic moieties demonstrate improved stability and biodistribution, underpinning their growing relevance in precision medicine.

Conclusion and Future Directions

The rapid progression of nanotechnology has significantly reshaped numerous industrial and scientific domains, notably medicine, food technology, cosmetics, and personal care. These developments have not only enhanced functional outcomes across sectors but have also substantially contributed to the growth of global nanotechnology markets, reinforcing its economic significance on a worldwide scale. In clinical practice, the incorporation of nanocarrier systems has revolutionized the administration of several therapeutic agents known for their adverse side effect profiles. For instance, cytotoxic drugs that were previously constrained by systemic toxicity have been effectively reformulated within nanoscale delivery platforms, enabling improved tolerability and expanded clinical utility. In the agri-food sector, metallic and polymer-based nanostructures have been deployed to extend product shelf life, reduce microbial contamination, and enhance overall food quality, thereby contributing to increased profitability and supply chain resilience. Despite these advancements, notable concerns persist. Due to their high surface area-to-volume ratio and inherent surface reactivity, engineered nanoparticles frequently demonstrate unpredictable interactions with biological and ecological systems. Their ubiquity in commercial goods, coupled with frequent human and environmental exposure through industrial effluents and domestic waste streams, presents a potential toxicological burden. Although currently marketed nanomaterials may not exhibit acute toxicity, cumulative and chronic exposure, whether direct through consumption or indirect via environmental dissemination, poses a latent risk. Alarmingly, there remains a dearth of comprehensive in vivo and ecotoxicological evaluations addressing the long-term biological impact of these materials. This scientific gap underscores the urgency for methodologically robust investigations into nanoparticle exposure, incorporating multifactorial parameters such as ambient environmental variations, exposure concentrations relevant to real-world scenarios, and the diversity of biological species potentially affected. Such data are indispensable for informed regulatory and policy decision-making. Another critical



Vol. 3 No. 2 (2025): April - June
https://rjnmsr.com/index.php/rjnmsr/about

Review Journal of Neurological & Medical Sciences Review

E(ISSN) : 3007-3073
P(ISSN) : 3007-3065

limitation in biomedical nanotechnology involves the immunological fate of nanoparticles following systemic administration. The innate immune system, particularly through macrophage-mediated phagocytosis, actively identifies and eliminates exogenous particulates, including nanoscale constructs. Consequently, strategies aimed at reducing immunogenicity and prolonging systemic circulation such as surface engineering, PEGylation, or active targeting are imperative to ensure therapeutic efficacy. Additionally, a pivotal barrier to clinical adoption lies in the physicochemical consistency and stability of nanoparticle formulations. Variability in key properties such as particle size, shape, surface charge, and hydrophobicity can drastically alter biodistribution, pharmacokinetics, and therapeutic outcomes. Therefore, achieving reproducible synthesis and standardized characterization protocols is essential for regulatory compliance and translational viability. Regulatory frameworks governing the development and commercialization of nanoparticle-enabled medical technologies remain in a nascent stage. The approval processes require rigorous safety and efficacy evaluations to meet emerging standards, posing substantial challenges for both academic researchers and industry stakeholders. Navigating these evolving regulatory landscapes necessitates interdisciplinary coordination and alignment with evolving international guidelines. While nanotechnology offers transformative potential in biomedicine, several pivotal challenges must be addressed. These include mitigating nanoparticle-induced toxicity, circumventing immune system clearance mechanisms, ensuring formulation reproducibility and physicochemical stability, and aligning with stringent regulatory requirements. Proactively overcoming these obstacles is critical to fully harnessing the clinical and societal benefits of nanoparticle-based innovations.

Conflict of Interest

The authors declare no conflict of interest.

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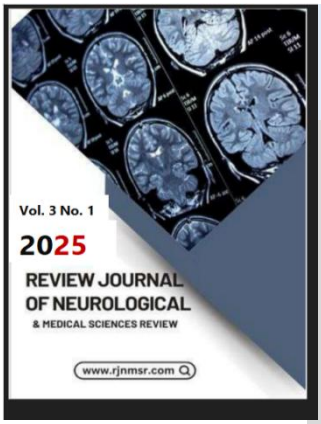

Vol. 3 No. 2 (2025): April - June
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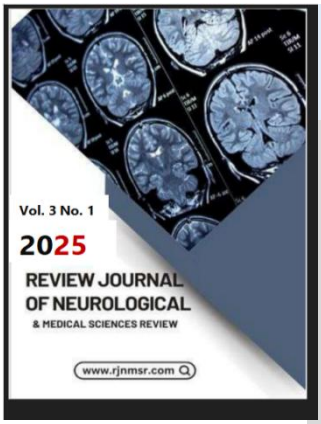

Vol. 3 No. 2 (2025): April - June
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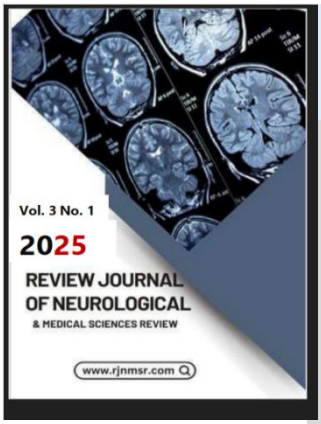

Vol. 3 No. 2 (2025): April - June
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