INNOVATIVE NANOCARRIERS AS NEXT GENERATION DRUG DELIVERY

Komal Dhiman[1], Tanuja Dhiman[1], Nikhil Thakur[1], Vinay Pandit[1], Mahendra Singh Ashawat[1]*

1. Department of Pharmaceutics, Laureate Institute of Pharmacy Kathog, Jawalamukhi, Kangra (H.P.)-176031

Corresponding Author*

Prof (Dr.) Mahendra Singh Ashawat

Email ID: msaresearchg@gmail.com

Abstract

Drug delivery has been transformed by advances in nanotechnology, which have made it possible to create novel nanocarriers that get around the drawbacks of traditional dosage forms. Poor solubility, low bioavailability, quick degradation, non-specific distribution, and unfavorable side effects are common problems with traditional drug delivery methods. By improving drug solubility, stability, controlled release, and site-specific targeting, novel nanocarriers—such as solid lipid nanoparticles, nanostructured lipid carriers, liposomes, polymeric nanoparticles, dendrimers, nanoemulsions, and inorganic nanoparticles—offer intriguing options. These nanocarriers can be designed to increase therapeutic efficacy, lower systemic toxicity, and improve pharmacokinetic and pharmacodynamic characteristics. Moreover, surface modification and functionalization techniques enable nanocarriers to distribute drugs in a targeted and stimulus-responsive manner, which makes them ideal for the treatment of neurological disorders, cancer, infections, and chronic illnesses. There are still issues with large-scale production, long-term safety, regulatory approval, and clinical translation despite their enormous potential. This review positions nanocarriers as next-generation platforms for effective and customized drug delivery by highlighting current developments in novel nanocarriers, their mechanisms of action, therapeutic uses, benefits over conventional systems, and future possibilities.

Keywords: Innovative nanocarriers; Targeted drug delivery; Solid lipid nanoparticles; Active and passive targeting; Blood–brain barrier; Alzheimer’s disease; Skin cancer

1.INTRODUCTION

Nanocarriers come in a variety of forms, all of which are designed to improve therapeutic performance and safety by delivering bioactive chemicals and other pharmacological compounds to specific regions of action. Nanocarriers can be used to more efficiently and biodistribute medicinal molecules with low immunogenic response and minimal adverse effects because they protect the medicine from early degradation and enhance its transport across biological barriers.A number of issues related to traditional drug delivery techniques, including limited target specificity, excessive toxicity, and poor bioavailability, make it difficult to achieve the therapeutic effectiveness of some medications. Therefore, an appropriate nanocarrier system is necessary to guarantee site-specific and regulated therapeutic delivery.

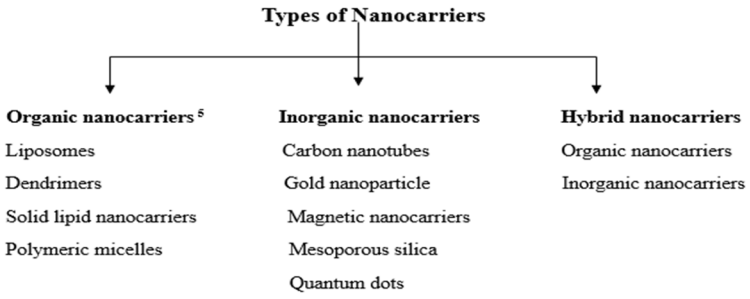
Targeted treatment delivery has shown great promise in nanomedicine, which uses nanoscale nanomaterials for illness diagnosis and treatment. Over the years, a number of materials and nanotechnology-based methods have been developed to identify and treat diseases. The particle sizes of nanocarriers are usually between 1 and 1000 nm. There are many different types of nanocarrier systems accessible, each with unique characteristics and a particular biomedical application. These carriers use passive targeting mechanisms rather than active ones to deliver medications to sick tissues. Peptides and antibodies are examples of active receptor-specific ligands that are chemically bonded to the drug delivery mechanism, allowing for selective interaction with particular receptors, lipids, or antigens at the target region.3

1.2 Physicochemical and Functional Attributes of Nanocarriers

Nanocarriers need to be nontoxic (safe for biological systems) and biocompatible (not causing an immunological reaction). Hydrodynamic size, shape, quantity, surface chemistry, administration technique, immune system response (especially macrophage absorption), and bloodstream residence length all have a substantial impact on the negative consequences of nanocarriers. Toxicological investigations of novel TADS formulations are crucial because of the numerous variables that could affect the toxicity of nanocarriers. Generally speaking, a decrease in particle size increases surface area, which improves chemical reactivity and may result in increased toxicity. Since they exhibit good pharmacokinetic characteristics, nanocarriers with hydrodynamic diameters between 10 and

100 nm are generally thought to be the most appropriate for in vivo drug administration. While larger-sized carriers are rapidly identified by plasma proteins and removed from the systemic circulation by reticuloendothelial system macrophages, nanoparticles with very small dimensions typically experience fast tissue leakage and renal filtration.4

1.3 Types of Nanocarriers[5-14]



1.3.1 Nanocarriers made from organic materials

Liposomes

Liposomes are phospholipid-based compositions that may potentially contain trace amounts of other substances. The Greek words "lipo," which means fat, and "soma," which means body, are the origin of the name. Drugs that either love or repel water can be encapsulated in these phospholipid structures. They are useful in medication delivery systems because of their adaptability. Nevertheless, liposomes have many disadvantages, including a brief half-life in the body following injection and possible problems such chemical degradation, fusion, and clumping during storage. Using an electrostatic deposition technique, liposomes can be coated with polymers like chitosan and alginate to improve their stability both inside and outside the body. (Fig. 1).7

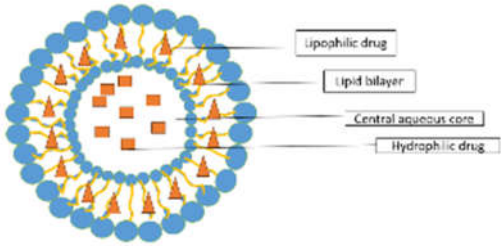


Figure 1: Structure of liposome (Fakhar ud Din et al. 2017)

Dendrimers

Dendrimers, also known as hyperbranched polymers, are useful in many biological domains, especially as adaptable nanocarriers in drug delivery systems.8 The benefits of dendrimers include their ability to either physically encapsulate or covalently bond with drug compounds and ligands, as well as their unique surface end group count, flexible structures, controlled dimensions and forms, multiple attachment sites, and efficient cellular uptake. Among the most popular dendrimers for drug administration are poly amido amine (PAMAM), polypropylene imine (PPI), and poly L-lysine (PLL) (Figure 2).9

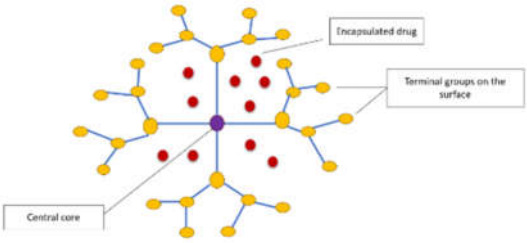


Figure 2: Structure of Dendrimers (Fakhar ud Din et al. 2017)

Solid lipid nanocarriers

Using methods like high-pressure homogenization or micro-emulsification, solid lipid nanocarriers are created by distributing molten solid lipids in an aqueous phase and stabilizing the system with suitable emulsifiers. Lipids that stay solid at room temperature, such as fatty alcohols, fatty acids, steroids, waxes, and mono-, di-, or triglycerides, typically make up these carriers. Drug molecules may be integrated into the core of the solid lipid particles, localized in the shell, or confined within the lipid matrix, depending on the formulation composition and processing conditions. Solid lipid nanocarriers can solve a number of the drawbacks of traditional chemotherapy due to their structural adaptability (Figure 3).11

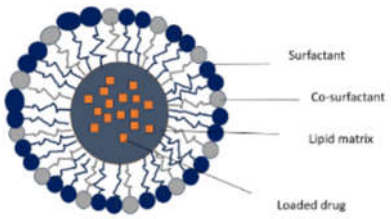


Figure 3: Structure of SLN (Fakhar ud Din et al. 2017)

Polymeric micelles

The formulation and production parameters will determine whether the drug molecules are integrated into the core, shell, or matrix of the solid lipid. This solid lipid nanocarrier can overcome the limitations of traditional chemotherapy due to its adaptability. When the concentration of the block copolymer surpasses a specific threshold known as the critical aggregation concentration (CAC) or critical micelle concentration (CMC), micelles are formed in an aqueous environment. The hydrophobic portions of the block copolymer start to cluster at the CAC or CMC to reduce their interaction with water molecules, resulting in the development of a vesicular or core-shell micellar structure (Figure 4).[12]

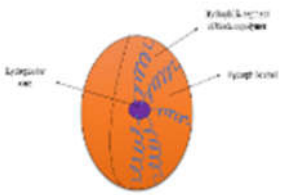


Figure 4: Structure of Polymeric micelles (Fakhar ud Din et al. 2017)

1.3.2 Nanocarriers made from inorganic materials

Inorganic nanocarriers, consisting of gold, magnetic nanocarriers, quantum dots, and mesoporous silica, are efficaciously applied in biosensing, cell labelling, imaging ,targeting, and diagnostics. Additionally, those inorganic nanocarriers show off a synergistic healing impact as well.

Cylindrical Carbon nanotubes

Carbon nanotubes are considered a highly efficient and promising medium for drug transport due to their distinctive biological and physicochemical characteristics. Structurally, they are hollow tubes formed by graphene sheets rolled at specific orientations. Depending on the arrangement of these graphene layers, carbon nanotubes are categorized into single-walled or

multi-walled types. These nanotubes possess exceptionally high aspect ratios, often extending thousands of times their diameter, with cross-sectional sizes ranging from approximately 0.4 to 100 nm. (Figure 5).

Figure 5: Structure of Carbon nanotubes (Kim-Hung Huynh et al. 2020)

Gold nanostructure

Gold nanostructure are diminutive small gold particles, usually measuring between 1 and 100 nm in diameter, and are generally spherical in shape. There exists a variety of anisotropic forms of gold nanoparticles, such as nanostars, nanorods, nanocages, nanoshells, nanoprism, among others.[13]The strong surface affinity of these nanomaterials allows them to conjugate with a wide range of biological entities such as enzymes, sugars, fluorescent tags, peptides, proteins, and genetic material. This interaction enhances the ability of these biomolecules to cross cellular membranes and enables their efficient intracellular transport. (Figure 6).[5]

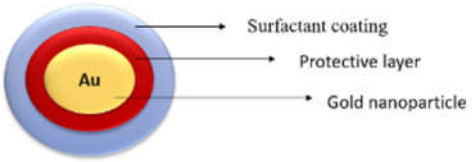


Figure 6: Structure of Gold nanoparticle (Kim-Hung Huynh et al. 2020)

Magnetic Nanoparticles-based carriers

A magnetic middle commonly constitutes the magnetic nanocarrier; in contrast to metallic oxide nanoparticles, metallic nanoparticles generally show off more magnetic properties. These companies may be applied for biosensing programs because of their magnetic traits and modified

properties. Research has proven that superparamagnetic nanoparticles are extra aware of magnetic fields than their paramagnetic counterparts. Owing to its magnetic resonance, the polymer-lined super-paramagnetic iron oxide nanoparticle has determined full-size application in molecular imaging and is therefore hired as a assessment agent throughout the imaging process.[13]

Semiconductor nanocrystals

Semiconductor nanocrystals are colloidal nanocrystals composed of II-VI (e.g., Se, Zn, Te, Cd) or III–V (e.g., In, As, P) elements. Their mild emission, which degrees from UV to close to IR, is size-dependent; large dots (~five nm) emit purple fluorescence, while smaller dots (~2 nm) emit blue fluorescence. In contrast to natural dyes, quantum dots own improved optical properties, extended emission duration, and diminished photobleaching, rendering them perfect for mobile imaging. For example, quantum dot–peptide conjugates can particularly goal tumor vasculature in mice (Figure 7).

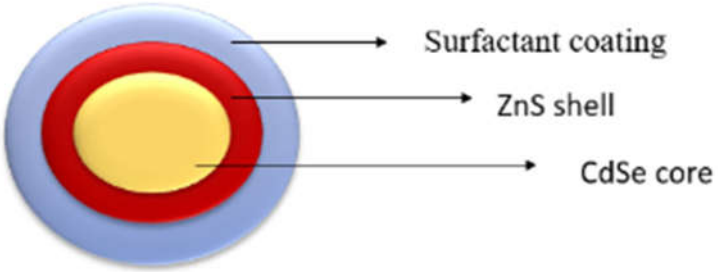


Figure 7: Structure of Quantum Dots (Kim-Hung Huynh et al. 2020)

Mesoporous Silica dioxide

Mesoporous silica possesses a highly ordered, honeycomb-like porous framework that allows the loading of a large number of therapeutic agents. Owing to its ease of synthesis, availability, and biocompatibility, it has gained significant attention in biomedical applications. This carrier system is suitable for entrapping both hydrophilic and hydrophobic drugs and can be further functionalized with ligands to achieve site-specific drug delivery. These features allow mesoporous silica to be efficiently used in both passive and active targeting strategies for cancer treatment, including the delivery of anticancer agents such as camptothecin and methotrexate (Figure 8).[14]

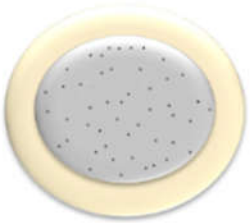


Figure 8: Structure of Mesoporous silica (Kim-Hung Huynh et al. 2020)

Hybrid nanocarriers are delivery systems formed by the combination of two or more organic and/or inorganic nanomaterials, either used independently or integrated into a single platform. These systems may consist of inorganic–inorganic or organic–inorganic material pairings, resulting in enhanced functional properties. Representative examples of hybrid nanocarriers include lipid–polymer composites and ceramic–polymer hybrid systems, which are widely explored for advanced drug delivery applications.

2. Targeting Mechanisms

To ensure that medications are delivered accurately to specific sites within the body, nanocarriers employ various targeting techniques. Targeted drug delivery systems consist of two distinct types.

2.1 Active targeting

Active targeting of nanocarrier systems is achieved by functionalizing their surfaces with specific molecules known as ligands, which possess the ability to recognize and bind selectively to receptors expressed on target cells. This targeted interaction enables drug-loaded nanocarriers to accumulate preferentially at diseased sites, thereby improving therapeutic efficiency while reducing unwanted systemic effects.[15] By chemically or physically modifying the ligands, nanoparticles can be engineered to interact with particular receptors or antigens, minimizing nonspecific drug distribution throughout the body and lowering cytotoxicity as well as adverse reactions (Figure 9).[16]

Ligands

Ligand selection is based on their specificity toward receptors that are highly expressed on diseased cells. Frequently employed ligands include antibodies, peptides, and proteins due to their strong receptor-binding affinity. Upon administration, these ligands on the nanocarrier surface bind to corresponding receptors on target cells, promoting site-specific drug delivery.

This receptor-mediated interaction often triggers cellular uptake of the nanocarriers, allowing efficient intracellular transport of the therapeutic agent..[17]

Following cellular internalization, the encapsulated drug is released either by passive diffusion or in response to internal stimuli such as variations in pH, temperature, or enzymatic activity within the target tissue or cells.[15,17]

Examples of active targeting in clinical Practice.[18]

Monoclonal antibody trastuzumab (Herceptin)

This humanized monoclonal antibody binds selectively to the HER2/neu receptor, a protein that is highly expressed in certain breast cancer subtypes.

Albumin-bound paclitaxel (commercially known as Abraxane)

It employs albumin nanoparticles to enhance the delivery of the drug to tumor sites by binding to the gp60 receptor on the surface of endothelial cells.

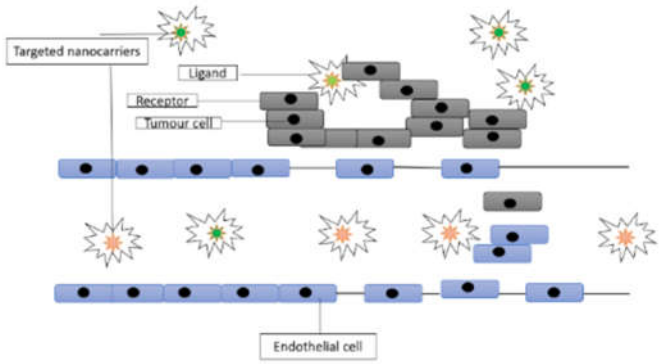


Figure 9: Active Targeting Mechanism[19]

2.2Passive Targeting

Nanocarrier-based drug delivery systems often rely on passive targeting as a key mechanism to direct therapeutic agents to diseased tissues. This strategy primarily depends on the **enhanced permeability and retention (EPR) effect**, a phenomenon observed in certain tissues, particularly tumors, due to their leaky vasculature and poor lymphatic drainage.[20] Nanoparticles exploit these unique biological features to accumulate at pathological sites, where conventional therapies may have limited access (Figure 10).[21]

Passive targeting is most effective for nanocarriers with sizes ranging between 10 and 200 nm. Particles larger than 200 nm may face challenges in crossing tumor blood vessels,

whereas particles smaller than 10 nm are often rapidly cleared by the kidneys.[22] Spherical nanoparticles are commonly used because of their favorable circulation profiles. Additionally, surface modification with polyethylene glycol (PEG) or other "stealth" coatings helps them evade recognition and clearance by the immune system. These design strategies allow encapsulated chemotherapeutic drugs to concentrate more efficiently in tumor tissues, enhancing therapeutic efficacy while reducing systemic side effects.[23] To further improve tissue penetration and drug release, passive targeting is sometimes combined with external triggers such as heat (hyperthermia) or ultrasound, which amplify the EPR effect and promote deeper nanoparticle diffusion.

Clinical Examples of Passive Targeting

Nanoparticle formulations of **sirolimus**, an immunosuppressive agent, have been investigated for the treatment of acute myeloid leukemia (AML). These nanoformulations have demonstrated improved therapeutic outcomes and reduced toxicity compared with conventional drug administration. Sirolimus nanoparticles are currently being evaluated in clinical trials for a variety of applications, including cancer therapy and inflammatory conditions.

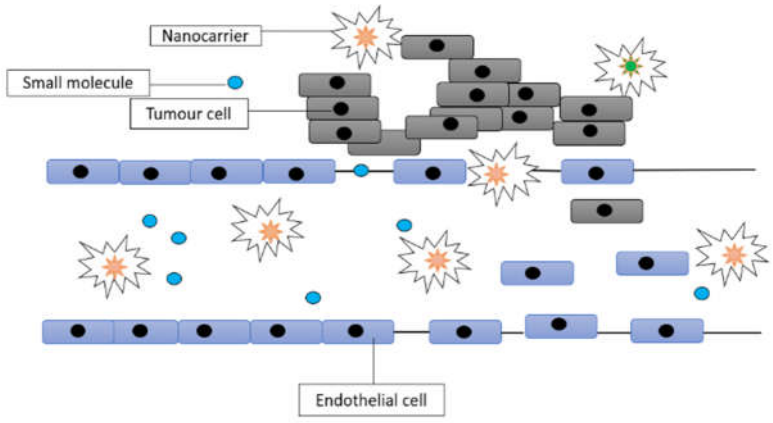


Figure 10: Passive Targeting Mechanism[19]

2.3 Transport of therapeutic agents across the blood–brain barrier[24]

The blood–brain barrier (BBB) is essential for preserving central nervous system (CNS) homeostasis and providing protection against harmful substances. However, its highly selective nature significantly limits the entry of therapeutic agents, making the management of CNS-related disorders challenging. To overcome this limitation, nanocarrier-based drug

delivery systems have gained considerable attention for transporting drugs across the BBB. These nanocarriers are capable of exploiting different physiological transport pathways and can be specifically engineered to achieve optimal drug release profiles and therapeutic effectiveness. Consequently, a wide range of nanocarriers have demonstrated promising potential as functional nanomedicines in preclinical animal models of human diseases. In light of the rapid development of innovative nanocarrier systems, this review presents a comprehensive overview of recent advancements in nanocarrier-mediated drug delivery to the CNS and cancer cells, with particular emphasis on multifunctional nanomedicines and theranostic applications.

2.3. Brain-Targeted Drug Delivery Using Nanocarriers

A wide variety of nanocarrier systems have been designed and evaluated for transporting therapeutic agents across the blood–brain barrier (BBB).[25] These systems differ in their morphology, size, and surface modifications, enabling functionalization and exploitation of their thermal, optical, and biological properties.[26] Commonly utilized nanocarriers include inorganic solid nanoparticles, liposomes, solid lipid nanoparticles, polymeric nanoparticles, and protein-based nanoparticles. In addition, several other platforms such as dendrimers, nanoemulsions, nanosuspensions, and nanogels have been examined for brain-targeted drug delivery. In recent years, there has been a substantial increase in the development of innovative nanocarriers with distinct compositions and functionalities. These include nanomicelles, exosomes,[27,28] metal–organic frameworks,[29] zeolitic imidazolate framework-8 (ZIF-8) nanosheets loaded with curcumin,[30] graphene oxide integrated with naturally derived biomaterials such as laminin, kaolin nanoclay,[31] and laminarin obtained from marine sources.[32] Furthermore, green nanomaterials like zein protein[33] and plant-mediated synthesis of metallic nanoparticles have also gained significant attention.[34]

Extracellular vesicles (EVs) represent a particularly promising class of nanocarriers. These lipid-bilayered nanoparticles are naturally secreted by various cell types and can influence recipient cells by transferring proteins, nucleic acids, and cell-specific surface markers. Based on their size, EVs are classified into apoptotic bodies (1–5 μm), microvesicles (200–1000 nm), and exosomes (30–200 nm).[28]

In summary, both conventional and emerging nanocarriers are being engineered to enable efficient drug transport across the BBB. Each nanocarrier system must be carefully designed to minimize cytotoxicity and can be further optimized through ligand attachment and surface

conjugation. However, the growing introduction of “novel” nanocarriers places the responsibility on researchers to demonstrate clear clinical relevance.[35] Rather than continuously expanding the number of nanocarrier types, future research should prioritize identifying the most suitable and optimized system for specific therapeutic applications.

There is also a pressing need to standardize the physicochemical and biological characterization of nanocarriers intended for BBB penetration to improve their clinical translation. While the tunable nature of nanocarriers makes them highly attractive for biomedical use, it also complicates direct comparison between different systems, particularly during the transition from preclinical to clinical stages.[36,37] Among the various options, EVs may represent a major breakthrough for targeted treatment of neurodegenerative disorders due to their intrinsic cell-targeting ability, immune evasion, biocompatibility, non-toxic nature, and ease of drug loading.[28]

2.4 Delivery Across Skin Cancer Using Multifunctional Bilosomes: A Nanomedicine Approach[38]

The occurrence of malignant melanoma, recognized as one of the most aggressive types of skin cancer, has significantly increased in recent years. This form of cancer metastasizes quickly to essential organs, rendering treatment extremely difficult. Traditional therapies, including surgery, chemotherapy, radiation, and immunotherapy, often encounter limitations due to resistance in advanced melanoma cases. Photodynamic therapy (PDT), which integrates photosensitizers with light to produce reactive oxygen species (ROS), has surfaced as a promising alternative owing to its selectivity and minimal side effects. Nevertheless, its effectiveness in treating melanoma is hindered by the protective effect of melanin and the low bioavailability of various phytocompounds such as curcumin. To address these issues, nanocarriers like bilosomes have attracted interest for their capacity to encapsulate photosensitizers and phytochemicals, thereby enhancing stability, solubility, and targeted delivery to improve anticancer efficacy.

2.4.1 Mechanism of Bilosome-Based Targeted Phyto-Photodynamic Therapy

Bilosomes contain methylene blue (a photosensitizer) within their aqueous core and curcumin (a phytochemical) in their lipid bilayer. Following administration, bilosomes infiltrate the skin and accumulate in melanoma cells. Exposure to laser light activates methylene blue, enabling it to generate ROS that induce oxidative stress and harm malignant cells. Curcumin works synergistically to enhance ROS production, facilitate apoptosis, and inhibit both

metastasis and angiogenesis. This combined effect leads to effective destruction of melanoma cells while preserving normal cells, positioning bilosome-based phyto-PDT as a promising strategy in nanomedicine.

3. Targeted Nanotechnology-Driven Drug Delivery Approaches for Alzheimer's Disease[39]

Alzheimer's disease (AD) is a chronic and progressive neurodegenerative disorder marked by memory loss, cognitive impairment, accumulation of amyloid-beta (Aβ) plaques, tau protein abnormalities, and persistent neuroinflammation. Among these pathological features, neuroinflammation plays a crucial role in accelerating disease progression, making it an important therapeutic target. However, the presence of the blood–brain barrier (BBB) poses a major challenge to the efficient delivery of drugs to the brain, thereby limiting the effectiveness of conventional treatment approaches. Nanocarrier-based drug delivery systems have emerged as a promising strategy to address these limitations by enabling targeted transport, improving BBB permeability, enhancing drug bioavailability, and minimizing systemic side effects. This review highlights recent progress in nanocarrier-assisted drug delivery for AD, with a particular focus on the role of neuroinflammatory processes, the ability of nanocarriers to bypass or cross the BBB, and their potential to regulate inflammatory signaling pathways. Furthermore, the review discusses preclinical evaluation methods and key challenges, such as safety issues, difficulties in large-scale manufacturing, and regulatory barriers that must be overcome for successful clinical translation. Future directions emphasize the convergence of nanotechnology with precision medicine, gene-based therapies, and artificial intelligence to optimize nanocarrier design for individualized AD treatment. With continued advancements, nanocarrier systems hold considerable promise for reshaping therapeutic approaches not only for AD but also for other neurodegenerative conditions.

3.1 Drug Release Mechanisms from Nanocarriers and Their Role in Enhancing Bioavailability During Neuroinflammation

The ability of nanocarrier-based drug delivery systems to provide regulated drug release and improved bioavailability, in addition to their ability to cross the blood–brain barrier (BBB), is crucial to their efficacy in treating neuroinflammation. These characteristics enable effective modulation of neuroinflammatory responses by ensuring that therapeutic drugs reach their

intended areas at optimal concentrations and at appropriate time intervals.40, 41 The capacity of nanocarriers to deliver controlled and extended medication release is a critical component in their design for the treatment of neuroinflammation. Particularly useful in this situation are stimuli-responsive delivery devices that respond to the particular circumstances of the neuroinflammatory milieu. For instance, pH-sensitive nanocarriers take advantage of the slightly acidic conditions that are frequently present in areas of the brain that are inflamed, particularly in Alzheimer's disease (AD).42. These systems are usually made with polymers that, when exposed to lower pH levels, experience physicochemical changes like protonation or hydrolysis, which causes the encapsulated medicine to be released locally.43. This site-specific strategy increases therapeutic efficacy at the damaged area while reducing off-target effects.

In a similar vein, redox-responsive nanocarriers are made to react to the increased oxidative stress linked to neuroinflammatory conditions. High quantities of reactive oxygen species (ROS) cause disulfide bonds or other redox-sensitive moieties in these systems to break down. For example, a ROS-sensitive ruthenium-based nanoplatform (R@NGF-Se-Se-Ru) has been created to enhance AD therapy by facilitating the removal of amyloid-beta (Aβ) deposits and encouraging neuronal regeneration. When exposed to near-infrared (NIR) light, these nanoclusters inhibit Aβ accumulation and encourage the disintegration of preexisting fibrils. Targeted drug release is made possible by the cleavage of the diselenide bonds inside the nanostructure in ROS-rich conditions.

An enhanced method for creating nanocarriers for neuroinflammatory diseases is the use of externally controlled drug delivery platforms. To accurately control medication release, these systems use external triggers like ultrasound, magnetic fields, electrical impulses, or light irradiation.45. These techniques provide outstanding temporal and spatial control, which makes them particularly useful for treating complicated illnesses like Alzheimer's disease (AD). Because it can temporarily and noninvasively increase the permeability of the blood–brain barrier (BBB), ultrasonography has drawn a lot of attention among these external stimuli. The BBB can be momentarily opened by focused ultrasound in conjunction with microbubbles, allowing for effective and targeted medication delivery into the brain.46. In preclinical AD models, this method has shown encouraging results, especially in improving the removal of amyloid-beta (Aβ) plaques.47 Additionally, early-phase clinical trials have demonstrated that intravenously administered microbubbles combined with magnetic resonance-guided focused ultrasound can safely and reversibly break the blood-brain barrier in AD patients, enabling targeted drug administration without significant adverse effects.

Apart from ultrasound, another useful technique for controlling drug release from nanocarriers is electrical stimulation. It is possible to design drug delivery systems that react to externally induced electric fields by using conductive polymers or electrically sensitive nanoparticles.48. This makes it possible to precisely time the release of drugs to correspond with brain activity or particular phases of neuroinflammation. To enable on-demand, location-specific, and time-controlled medication administration, for instance, an electrically triggered delivery system based on polypyrrole and graphene–mesoporous silica nanocomposites has been created. This platform has demonstrated the therapeutic potential of electrically controlled medication release in AD treatment by preventing Aβ aggregation, lowering intracellular reactive oxygen species (ROS), and shielding cells from Aβ-induced toxicity.

Improving drug bioavailability is a crucial component of nanocarrier-based delivery systems, especially for treatments aimed at neuroinflammation, in addition to controlled release mechanisms.Fifty Many medicinal substances are susceptible to quick breakdown by metabolic enzymes or plasma proteins, which lowers their effective concentration at the target site and shortens their half-life. These medications' stability can be greatly enhanced by encapsulation within nanocarriers, which can also extend their systemic circulation and ultimately boost their therapeutic efficacy.51.

Furthermore, nanocarriers can improve the solubility of medications that are poorly soluble in water, which is a common problem when developing therapies for neuroinflammatory diseases. Because of its many neuroprotective qualities, curcumin, a hydrophobic polyphenolic molecule obtained from turmeric rhizomes, has drawn a lot of attention as a possible treatment for Alzheimer's disease (AD).52. However, its low stability, quick elimination, and poor solubility restrict its therapeutic use.53. In order to get over these restrictions, curcumin has been encapsulated in poly(lactic-co-glycolic acid) (PLGA) nanospheres coated with selenium nanoparticles, which improves its solubility, stability, and bioavailability. This nanocarrier formulation shows promise as a therapeutic approach for AD since it efficiently targets amyloid plaques in AD, lowers the burden of amyloid-beta (Aβ), and enhances cognitive function.

Application of Innovative Nanocarriers

Utilization of NPS in the diagnosis and treatment of brain cancer[55]

Because many therapeutic chemicals cannot reach the afflicted tissue due to the blood–brain barrier, malignant brain tumors are challenging to treat therapeutically. Chemotherapy, physiological techniques, and surgery are examples of traditional therapeutic options that are not very effective. Nanoparticles (NPs) have emerged as viable alternatives for both therapeutic and diagnostic applications in order to overcome these challenges. Iron oxide (Fe_3O_4) and gold nanoparticles (AuNPs) are examples of inorganic nanomaterials that have shown great potential in theranostic applications by serving as both imaging probes and drug delivery vehicles.While AuNPs provide good CT contrast because of their high density, Fe_3O_4 NPs function as MRI contrast agents and can also be used in magnetic hyperthermia. For targeted medication delivery and diagnostic applications, organic nanocarriers such liposomes, dendrimers, hydrogels, and polymers are being thoroughly studied. Furthermore, sophisticated systems such as gadolinium-based NPs and quantum dots have shown increased imaging sensitivity.

Utilization of nanocarrier systems for the delivery of drugs through the skin[56]

In modern pharmaceutics, increasing topical and transdermal medication penetration has become a critical goal. To overcome the limits of the skin barrier and improve medication retention, penetration, and controlled release, a range of nanocarrier systems, such as liposomes, transfersomes, ethosomes, dendrimers, niosomes, nanoparticles, and nanoemulsions, have been developed.

Because of their biocompatibility and ability to reduce toxicity, liposomes are widely used in dermatology and cancer treatment. However, stability issues with standard liposomes led to the development of flexible liposomes (transfersomes, ethosomes) to improve the penetration and distribution of drugs such tacrolimus, ketoprofen, and testosterone. Dendrimers improve drug solubility and penetration by providing specialized surface functionality and multivalency, but their cytotoxicity and poor biodegradation still present problems. Niosomes are useful for treating diseases including hair loss and pigmentation disorders because they increase drug retention in the skin and epidermis while reducing systemic absorption. Because of their stability, controlled drug release behavior, and pH-responsiveness, polymeric and lipid-based nanocarriers, such as solid lipid nanoparticles and nanostructured lipid carriers, have shown great promise for the delivery of anticancer, antidiabetic, and vaccine-related therapeutics. Nanoemulsions are being investigated for their potential to facilitate quick transdermal transfer of analgesic, corticosteroid, and anticancer medications despite their comparatively reduced stability.

Application of Nanocarrier-Based Targeted Drug Delivery in Alzheimer's Disease

Targeted medication delivery systems based on nanocarriers are essential for treating Alzheimer's disease (AD). These systems have the ability to deliver neuroprotective substances to impacted brain regions, modulate neuroinflammatory responses, and cross the blood–brain barrier (BBB). Lipid-based nanocarriers, including as liposomes, solid lipid nanoparticles (SLNs), and nanostructured lipid carriers (NLCs), have demonstrated considerable potential in the treatment of AD. These carriers improve the stability and bioavailability of therapeutic compounds, decrease off-target effects, and increase drug accumulation in the brain.

Despite these benefits, a number of obstacles still stand in the way of their clinical application, including toxicity concerns, difficulties in large-scale production, and complicated regulatory requirements. In order to provide individualized and more potent nanocarrier-based treatments for Alzheimer's disease, future advancements in this sector are probably going to depend on the combination of nanotechnology with cutting-edge strategies like gene therapy and artificial intelligence.

Future Perspectives[57,58,59,60,61]

The efficacy of nanocarriers in targeted drug delivery, diagnosis, and therapeutic interventions has been greatly enhanced by recent advancements in nanoparticle surface modification. While other formulations are moving through different phases of clinical evaluation, a number of nanocarrier systems have already received clinical approval for oncological diagnostics and treatments. By using techniques including solubilization, stimulus-responsive release, and passive and active targeting, these delivery systems increase therapeutic efficacy, lower dosage requirements, and lessen systemic side effects.

Despite these developments, biological hurdles, manufacturing scalability, biocompatibility, regulatory compliance, and cost-effectiveness remain major obstacles to the clinical translation of nanocarriers. To increase translational potential, it is advised to use simpler and clinically viable formulations in conjunction with personalized nanomedicine procedures that are customized to each patient's unique genetic and illness profiles.

The mRNA-based COVID-19 vaccines from Moderna and BioNTech/Pfizer, in which nanoparticles effectively carried the mRNA payload, are two examples of how nanocarriers

have been crucial to the creation of vaccinations. The development of sensible chemotherapeutic–nanocarrier combinations, nanotargeted radiopharmaceuticals for cancer treatment, and thorough toxicity evaluations are some of the field's future directions. For nanomedicine to be successfully and safely adopted in clinical settings, strong regulatory guidelines and standardized safety evaluation techniques must be developed.

Conclusions

Because they may specifically target sick regions, increase drug bioavailability, and lessen systemic side effects, nanocarriers have become revolutionary tools in drug delivery, diagnostics, and therapeutic applications.

In preclinical models of diseases including cancer and Alzheimer's disease, a variety of nanocarrier platforms, such as polymeric, lipid-based, dendrimeric, inorganic, and hybrid nanoparticles, have shown encouraging results. By enabling the precise, regulated, and site-specific release of therapeutic substances, these devices enhance the effectiveness and safety of treatment.

Nevertheless, despite these developments, there are still a number of obstacles to the clinical application of nanocarriers, such as biological barriers, problems with large-scale manufacturing, reproducibility, biocompatibility, safety concerns, and regulatory compliance. While AI-driven approaches and computational modeling can help improve nanocarrier design, thorough in vitro and in vivo validation is still necessary. Future research should focus on the creation of intelligent, multipurpose nanocarriers, scalable manufacturing methods, integration with immunotherapy and gene therapy, and customized treatment strategies.

By addressing these issues, nanocarriers have the potential to revolutionize drug delivery methods, offering focused, safer, and more effective treatments while advancing precision medicine.

REFERENCES

1. Nazma SK, Prasant Y. Nanocarriers and their Types for Targeted Drug Delivery. International Journal of Pharmaceutical Sciences Review and Research. 2022;77(1):21-28.
2. Majumdera J, Minko T. Multifunctional and stimuli-responsive nanocarriers for targeted therapeutic delivery. Expert Opinion Drug Delivery. 2021;18(2):205-227, https://doi.org/10.1080/17425247.2 021.1828339.
3. Shah A, Aftab S, Nisar J, Ashiq MN, Iftikhar FJ. Nanocarriers for targeted drug delivery. Journal of Drug Delivery and Science Technology. 2021;62, https://doi.org/10.1016/j.jddst.2021.102426.
4. Shi L, Fleming CJ, Riechers SL, Yin NN, Luo J, Lam KS and Liu GY: High-resolution imaging of dendrimers used in drug delivery via scanning probe microscopy. J Drug Deliv 2011; 2011: 254095. (doi: 10.1155/2011/254095).
5. Chamundeeswari M, Jeslin J, Verma ML. Nanocarriers for drug delivery applications. Environmental Chemistry Letters. 2018; 17:849-865, https://doi.org/10.1007/s10311-018-00841-1.
6. Benita S. Microencapsulation: Methods and Industrial Applications. Boca Raton: CRC Press; 2005, https://doi.org/10.1201/9781420027990.
7. Simstad G, Bo Nystromb, Kaizheng Zhub, Marthe Karoline Gronvolda, Anne Røv-Johnsena, Marianne Hiorth. Liposomes coated with hydrophobically modified hydroxyethyl cellulose: Influence of hydrophobic chain length and degree of modification. Colloids and surface Biointerfaces. 2017; 156: 79-86.
8. Baker JR. Dendrimer-based nanoparticles for cancer therapy. Haematology. 2009;(1):708-719, https://doi.org/10.1182/ asheducation-2009.1.708.
9. Anjali Sharma and Ashok Kakkar. Designing dendrimers and miktoarm polymer based multi-tasking nanocarriers for efficient medical therapy. Molecules. 2015; 20(9):16987-17015, https://doi.org/10.3390/ molecules200916987.
10. Sarad Pawar Naik Bukke, Chandrakala Venkatesh, Shilpa Munishamireddy. Solid lipid nanocarriers for drug delivery: Design innovations and characterization strategies a comprehensive review. Discover Application sciences. 2024; 6, 279, https://doi.org/10.1007/ s42452-024-05897-z.
11. Ahmad J. Lipid nanoparticles-based cosmetics with potential applications in alleviating skin disorders. Cosmetics. 2021; 8(3): 84, https://doi.org/10.3390/cosmetics8030084.
12. Xu Wei, Peixue Ling and Tianmin Zhang. Polymeric micelles, a promising drug delivery system to enhance bioavailability of poorly water-soluble drugs. Journal of Drug Delivery. 2013, 340315, ht t ps:// doi.org/10.1155/2013/340315.
13. Parisa Eslami, Martin Albino, Francesca Scavone, Federica Chiellini, Andrea Morelli, Giovanni Baldi, Laura Cappiello: Smart magnetic nanocarriers for multi-stimuli on demand drug delivery. Nanomaterials 2022; 12(3), 303, https://doi.org/10.3390/nano12030303.
14. Li Y, Li N, Pan W, Yu Z, Yang L, Tang B. Hollow mesoporous silica nanoparticles with tunable structures for controlled drug delivery. ACS Applied Materials and Interfaces. 2017; 9:2123–2129.
15. Shi P, Cheng Z, Zhao K, Chen Y, Zhang A, Gan W, Zhang Y. Active targeting schemes for nano-drug delivery systems in osteosarcoma therapeutics. Journal of Nanobiotechnology. 2023; 21:103-115, https:// doi.org/10.1186/s12951-023-01826-1.
16. Salahpour-Anarjan F. Active targeting drug delivery nanocarriers: Ligands. Nano-Structure Nano-Objects. 2019;19:21-27, https://doi. org/10.1016/j.nanoso.2019.100370.
17. Onzi G, Guterres SS, Pohlmann AR, Frank LA. Active targeting of nanocarriers. The ADME Encyclopaedia. 2021; 1-13.
18. Gradishar WJ. Nab-paclitaxel: A novel Cremophor-free, albumin bound nanoparticle formulation of paclitaxel. Cancer Chemotherapy Pharmacology. 2006; 58(3):417-423, https://doi.org/10.1007/ s00280-015-2833-5.
19. Temidayo O. B. Olusanya, Rita Rushdi Haj Ahmad, Daniel M. Ibegbu, James R. Smith 3 and Amal Ali Elkordy. Liposomal Drug Delivery Systems and Anticancer Drugs. Molecules. 2018; 23: 907-923, htt ps:// doi.org/10.3390/molecules23040907.
20. Miao L, Zhang X. Advances in nanocarriers for drug delivery in cancer. Journal of Controlled Release. 2018; 285:67-83.
21. Maeda H, Matsumura Y. The EPR effect and novel nanocarriers for enhanced drug delivery to tumors. Advances in Drug Delivery Reviews. 2018; 130:84-95.
22. Allen TM, Cullis PR. Liposomal drug delivery systems: From concept to clinical applications. Advanced Drug Delivery Reviews. 2013;65(1):36 48, https://doi.org/10.1016/j.addr.2012.09.037.
23. Liu Y, Zeng X. Nanomedicine for tumor targeting and treatment. International Journal of Nanomedicine. 2019; 14 :8037-8057.

24. Mulvihill, J. J., Cunnane, E. M., Ross, A. M., Duskey, J. T., Tosi, G., & Grabrucker, A. M. (2020). Drug delivery across the blood–brain barrier: Recent advances in the use of nanocarriers. *Nanomedicine, 15*(2), 137–160. https://doi.org/10.2217/nnm-2019-0367
25. ChhabraR,TosiG,GrabruckerAM.Emerginguseofnanotechnologyinthetreatmentofneurologicaldisorders.Curr.Pharm. Des.21(22),3111–3130(2015).
26. Akhter MH, Rizwanullah M, Ahmad J, Ahsan MJ, Mujtaba MA, Amin S. Nanocarriers in advanced drug targeting: setting novel paradigm in cancer therapeutics. Artif. Cells Nanomed. Biotechnol. 46(5), 873–884 (2018).
27. Yoshioka Y, Ochiya T. Extracellular vesicles as novel nanocarriers for therapeutic delivery. In: Nucleic Acid Nanotheranostics: Biomedical Applications. Filice M, Ruiz-Cabello J (Eds). Elsevier, MA, USA 391–407 (2019).
28. Cunnane EM, Weinbaum JS, O'Brien FJ, Vorp DA. Future perspectives on the role of stem cells and extracellular vesicles in vascular tissue regeneration. Front. Cardiovasc. Med. 5, 86 (2018).
29. SunQ,BiH,WangZet al. O2-generating metal-organic framework-based hydrophobic photosensitizer delivery system for enhanced photodynamic therapy. ACS Appl. Mater. Interfaces 11(40), 36347–36358 (2019).
30. Liu F, Lin L, Zhang Y et al. Two-dimensional nanosheets with high curcumin loading content for multimodal imaging-guided combined chemo-photothermal therapy. Biomaterials 223, 119470 (2019).
31. Rozhina E, Batasheva S, Danilushkina A et al. Kaolin alleviates the toxicity of graphene oxide for mammalian cells. MedChemComm 10(8), 1457–1464 (2019).
32. Yu Y, Wang B, Guo C, Zhao F, Chen D. Protoporphyrin IX-loaded laminarin nanoparticles for anticancer treatment, their cellular behavior, ROS detection, and animal studies. NanoscaleRes.Lett.14(1), 316 (2019).
33. Gagliardi A, Bonacci S, Paolino D et al. Paclitaxel-loaded sodium deoxycholate-stabilized zein nanoparticles: characterization and in vitrocytotoxicity. Heliyon 5(9), e02422 (2019).
34. Karmous I, Pandey A, Haj KB, Chaoui A. Efficiency of the green synthesized nanoparticles as new tools in cancer therapy: insights on plant-based bioengineered nanoparticles, biophysical properties, and anticancer roles. Biol. Trace Elem. Res. (2019) (In Press).
35. Park K. The beginning of the end of the nanomedicine hype. J. Control. Rel. 305, 221–222 (2019).
36. Aur´ıa-Soro C, Nesma T, Juanes-Velasco P et al. Interactions of nanoparticles and biosystems: microenvironment of nanoparticles and biomolecules in nanomedicine. Nanomaterials (Basel) 9(10), 1–20 (2019).
37. Ross AM, McNulty D, O'Dwyer C, Grabrucker AM, Cronin P, Mulvihill JJE. Standardization of research methods employed in assessing the interaction between metallic-based nanoparticles and the blood–brain barrier: present and future perspectives. J. Control. Rel. 296, 202–224 (2019).
38. Waglewska, E., Kulbacka, J., & Bazylinska, U. (2021). Superior drug delivery performance of multifunctional bilosomes: Innovative strategy to kill skin cancer cells for nanomedicine application. *International Journal of Nanomedicine, 16*, 5201–5224.
39. Wang, K., Yang, R., Li, J., Wang, H., Wan, L., & He, J. (2025). Nanocarrier-based targeted drug delivery for Alzheimer's disease: Addressing neuroinflammation and enhancing clinical translation. *Frontiers in Pharmacology, 16,* 1591438. https://doi.org/10.3389/fphar.2025.1591438
40. Qiu, J., Xu, J., and Xia, Y. (2021). Nanobottles for controlled release and drug delivery. Adv. Healthc. Mater. 10 (4), e2000587. doi:10.1002/adhm.202000587
41. Waheed, S., Li, Z., Zhang, F., Chiarini, A., Armato, U., and Wu, J. (2022). Engineering nano-drug biointerface to overcome biological barriers toward precision drug delivery. J. nanobiotechnology 20 (1), 395. doi:10.1186/s12951-022-01605-4
42. Chae, B. J., Lee, K. S., Hwang, I., and Yu, J. W. (2023). Extracellular acidification augments NLRP3-mediated inflammasome signaling in macrophages. Immune Netw. 23 (3), e23. doi:10.4110/in.2023.23.e23
43. Tang, C., Amin, D., Messersmith, P.B., Anthony,J. E., and Prud'homme,R. K.(2015). Polymer directed self-assembly of pH-responsive antioxidant nanoparticles. Langmuir ACS J. surfaces colloids 31 (12), 3612–3620. doi:10.1021/acs.langmuir.5b00213
44. Yuan, X., Jia, Z., Li, J., Liu, Y., Huang, Y., Gong, Y., et al. (2021). A diselenide bond-containing ROS-responsive ruthenium nanoplatform delivers nerve growth factor for Alzheimer's disease management by repairing and promoting neuron regeneration. J. Mater. Chem. B 9 (37), 7835–7847. doi:10. 1039/d1tb01290h
45. Gopalan, D., Pandey, A., Udupa, N., and Mutalik, S. (2020). Receptor specific, stimuli responsive and subcellular targeted approaches for effective therapy of Alzheimer: role of surface engineered nanocarriers. J. Control. release official J. Control. Release Soc. 319, 183–200. doi:10.1016/j.jconrel.2019.12.034

46. Ogawa, K., Kato, N., Yoshida, M., Hiu, T., Matsuo, T., Mizukami, S., et al. (2022). Focused ultrasound/microbubbles-assisted BBB opening enhances LNP-mediated mRNA delivery to brain. J. Control. release official J. Control. Release Soc. 348, 34–41. doi:10.1016/j.jconrel.2022.05.042
47. Lipsman, N., Meng, Y., Bethune, A. J., Huang, Y., Lam, B., Masellis, M., et al. (2018). Blood-brain barrier opening in Alzheimer's disease using MR-guided focused ultrasound. Nat. Commun. 9 (1), 2336. doi:10.1038/s41467-018-04529-6
48. Gadhave, D. G., Sugandhi, V. V., and Kokare, C. R. (2024). Potential biomaterials and experimental animal models for inventing new drug delivery approaches in the neurodegenerative disorder: multiple sclerosis. Brain Res. 1822, 148674. doi:10.1016/j.brainres.2023.148674
49. Wu, L., Wang, J., Gao, N., Ren, J., Zhao, A., and Qu, X. (2015). Electrically pulsatile responsive drug delivery platform for treatment of Alzheimer's disease. Nano Res. 8 (7), 2400–2414. doi:10.1007/s12274-015-0750-x
50. Deng, B., Liu, S., Wang, Y., Ali, B., Kong, N., Xie, T., et al. (2024). Oral nanomedicine: challenges and opportunities. Adv. Mater. (Deerf. Beach, Fla) 36 (6), e2306081. doi:10. 1002/adma.202306081
51. Huang, L., Huang, X. H., Yang, X., Hu, J. Q., Zhu, Y. Z., Yan, P. Y., et al. (2024). Novel nano-drug delivery system for natural products and their application. Pharmacol. Res. 201, 107100. doi:10.1016/j.phrs.2024.107100
52. Hamaguchi, T., Ono, K., and Yamada, M. (2010). REVIEW: curcumin and Alzheimer's disease. CNS Neurosci. and Ther. 16 (5), 285–297. doi:10.1111/j.1755 5949.2010.00147.x
53. Maiti, P., and Dunbar, G. L. (2018). Use of curcumin, a natural polyphenol for targeting molecular pathways in treating age-related neurodegenerative diseases. Int. J. Mol. Sci. 19 (6), 1637. doi:10.3390/ijms19061637
54. Huo, X., Zhang, Y., Jin, X., Li, Y., and Zhang, L. (2019). A novel synthesis of selenium nanoparticles encapsulated PLGA nanospheres with curcumin molecules for the inhibition of amyloid β aggregation in Alzheimer's disease. J. Photochem. Photobiol. B, Biol. 190, 98–102. doi:10.1016/j.jphotobiol.2018.11.008
55. Aghebati-Maleki, A., Dolati, S., Ahmadi, M., Baghbanzhadeh, A., Asadi, M., Fotouhi, A., Yousefi, M., & Aghebati-Maleki, L. (2019). Nanoparticles and cancer therapy: Perspectives for application of nanoparticles in the treatment of cancers. *Journal of Cellular Physiology, 234*(10), 16971–16988. https://doi.org/10.1002/jcp.29126
56. Escobar-Chávez, J. J., Díaz-Torres, R., Rodríguez-Cruz, I. M., Domínguez-Delgado, C. L., Morales, R. S., Ángeles-Anguiano, E., & Melgoza-Contreras, L. M. (2012). Nanocarriers for transdermal drug delivery. *Research and Reports in Transdermal Drug Delivery, 3*, 3–17. https://doi.org/10.2147/RRTD.S32621
57. **Wang, K., Yang, R., Li, J., Wang, H., Wan, L., & He, J.** (2025). *Nanocarrier-based targeted drug delivery for Alzheimer's disease: Addressing neuroinflammation and enhancing clinical translation.Frontiers in Pharmacology, 16,* 1591438. https://doi.org/10.3389/fphar.2025.1591438
58. Wang, L., Shi, Y., Jiang, J., Li, C., Zhang, H., Zhang, X., Jiang, T., Wang, L., Wang, Y., & Feng, L. (2022). *Micro-nanocarriers based drug delivery technology for blood-brain barrier crossing and brain tumor targeting therapy* [Review]. *Small, 18*(45), e2203678. https://doi.org/10.1002/smll.202203678 (pubmed.ncbi.nlm.nih.gov)
59. Pucci, C., Martinelli, C., & Ciofani, G. (2019). *Innovative approaches for cancer treatment: current perspectives and new challenges*. *Ecancermedicalscience, 13*, 961. https://doi.org/10.3332/ecancer.2019.961 (pubmed.ncbi.nlm.nih.gov)
60. Khizar, S., Alrushaid, N., Khan, F. A., Zine, N., Jaffrezic-Renault, N., Errachid, A., & Elaissari, A. (2023). *Nanocarriers based novel and effective drug delivery system*. *International Journal of Pharmaceutics, 632*, 122570. https://doi.org/10.1016/j.ijpharm.2022.122570 (pubmed.ncbi.nlm.nih.gov)
61. Alshawwa, S. Z., Kassem, A. A., Farid, R. M., Mostafa, S. K., & Labib, G. S. (2022). *Nanocarrier drug delivery systems: Characterization, limitations, future perspectives and implementation of artificial intelligence*. *Pharmaceutics, 14*(4), 883. https://doi.org/10.3390/pharmaceutics14040883 (mdpi.com)