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Review Article

Nanotechnology-Based Drug Delivery in Cancer and Neurological Disorders

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ABSTRACT

Nanotechnology has revolutionised drug delivery by enabling the design of nanoscale carriers (1-100 nm) with tunable physicochemical properties that allow precise targeting, improved bioavailability, and controlled release of therapeutic agents. Nanoparticles such as liposomes, polymeric and metallic nanocarriers, dendrimers, and lipid-polymer hybrids have significantly enhanced cancer and Central Nervous System (CNS) therapies by overcoming biological barriers like the tumour microenvironment and the Blood-Brain Barrier (BBB). In oncology, passive and active targeting approaches exploit tumour vasculature permeability and receptor overexpression to achieve localised drug accumulation, while in neuropharmacology, nanocarriers facilitate transcytosis-based transport across the BBB for diseases such as Alzheimer's and glioblastoma. Emerging smart and stimuli-responsive systems further enable site-selective drug release in response to pH, enzyme activity, and redox potential, minimising systemic toxicity. The integration of AI (Artificial Intelligence) into nanocarrier design is accelerating the optimisation of nanoparticle properties and therapeutic precision. Despite these advances, challenges in clinical translation, such as nanoparticle toxicity, manufacturing reproducibility, and regulatory approval, persist. Looking forward, interdisciplinary innovations integrating AI, genomics, and personalised nanomedicine promise a new era of precision drug delivery for oncology and neurological disorders, paving the way toward safer, more effective, and patient-tailored therapeutics.

Keywords: Blood-brain barrier, Cancer therapy, Nanomedicine, Nanotechnology, Targeted delivery.

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INTRODUCTION

Nanotechnology, which involves materials with dimensions ranging from 1 to 100 nm, represents a vital domain that connects biological and physical sciences, significantly altering the landscape of biomedicine. These nanoscale particles exhibit distinct structural, chemical, and biological characteristics, rendering them suitable for a variety of applications, including biosensors, tissue engineering, and, primarily, nanomedicine and drug delivery. In nanomedicine, these diminutive nanospheres (such as liposomes and micelles) function as advanced delivery systems. By either encapsulating or binding therapeutic drugs, nanoparticles are able to transport curative agents to targeted tissues with greater precision and controlled release, thereby enhancing their therapeutic effectiveness. Additionally, they improve oral bioavailability, safeguard drugs from degradation, and enable the delivery of poorly water-soluble medications, underscoring their crucial contribution to the evolution of next-generation medical diagnostics and therapeutics (Patra *et al*., 2018).

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Nanotechnology in drug delivery

Nanotechnology for Cancer Therapy

These technologies have been used to enhance drug delivery and to address various challenges associated with drug delivery in cancer. Effective drug delivery in cancer is crucial for maximising the therapeutic effects of medications while minimising adverse side effects. Numerous nanobiotechnologies, primarily centred on nanoparticles, have been employed to aid drug delivery in cancer treatment. While most early research in nanotechnology was conducted within academic settings, significant advancements for drug delivery applications are now being pursued in industrial contexts (Jain, 2005a).

Cancer is regarded as one of the most formidable diseases in contemporary society, with brain cancer being particularly challenging to identify and treat. This difficulty primarily arises from the obstacles in delivering imaging and therapeutic agents across the blood-brain barrier and into the brain itself. Numerous researchers have discovered that nanoparticles may offer a viable

solution for transporting such agents into the brain. It has been proposed that apolipoprotein E plays a role in facilitating drug transport across the Blood-Brain Barrier. Loperamide, which cannot penetrate the blood-brain barrier but demonstrates antinociceptive effects when directly injected into the brain, was encapsulated in human serum albumin nanoparticles and linked to apolipoprotein E. Mice that received intravenous treatment with this complex exhibited antinociceptive effects in the tail-flick test. The effectiveness of this drug delivery system is contingent upon the recognition of lipoprotein receptors. Kopelman and colleagues developed Probes Encapsulated by Biologically Localised Embedding (PEBBLE) to transport a variety of unique agents on their surface and to perform multiple functions. A target molecule immobilised on the surface can direct the PEBBLE to a tumour.

Additionally, another agent can assist in visualising the target through magnetic resonance imaging, while a third agent attached to the PEBBLE can deliver a lethal dose of drug or toxin to adjacent cancer cells. These three functions can be integrated into a single minuscule polymer sphere, creating a powerful tool against cancer. Furthermore, doxorubicin, when bound to polysorbate-coated nanoparticles, is able to cross the intact blood-brain barrier and is released at therapeutic concentrations within the brain. Advanced superparamagnetic iron oxide particle conjugates can be employed to identify and locate brain tumours more effectively and accurately than previously reported methods. It is recognised that the combination of folic acid with polyethene glycol can further improve the targeting and intracellular uptake of nanoparticles. Consequently, nanomaterials present significant potential as carriers for drugs aimed at targeting cancer cells (Suri *et al*., 2007).

Nanotechnology for Central Nervous System Drug Delivery

Neurological disorders, such as Alzheimer's, Parkinson's, and brain tumours, pose a rapidly escalating global health issue, significantly impacting disability and mortality rates. The main challenge in treating these disorders lies in the difficulty of delivering therapeutic agents across the Blood-Brain Barrier (BBB) and the blood-cerebrospinal-fluid barrier. The BBB consists of tight junctions and is highly selective, limiting the passage of most drugs, particularly lipophilic molecules with molecular weights exceeding 400-500 daltons, while actively effluxing others through transporters like P-glycoprotein (P-gp). To address this challenge, nanotechnology-based drug delivery has emerged as a promising solution. Nanocarriers, generally ranging from 1 to 100 nm in size (for instance, polymeric nanoparticles, liposomes, micelles, and dendrimers), can effectively penetrate the BBB or blood-cerebrospinal-fluid barrier through mechanisms such as endocytosis and transcytosis, facilitating targeted delivery into the Central Nervous System (CNS). This method is essential for enhancing the safety, efficacy, and pharmacokinetic properties of neurotherapeutics by ensuring precise targeting and sustained drug release (Naqvi *et al*., 2020).

Types of nanocarriers

Nanotechnology and drug delivery systems based on nanocarriers are typically employed to enhance the efficacy of therapeutic agents; the most prevalent nanosystems used for the treatment of degenerative diseases include liposomes, polymeric nanoparticles, polymeric micelles, protein nanoparticles, inorganic nanoparticles, carbon nanotubes, polymeric conjugates, hybrid nanoparticles, solid lipid nanoparticles, niosomes, and dendrimers. These systems have been used to transport a broad range of therapeutic agents, including cytotoxic agents, chemosensitizers, small-interfering ribonucleic acid (siRNA), and antiangiogenic agents.

Liposomes

Lipid nanoparticles, liposomes, and specifically nanoliposomes, which are either uni- or multilamellar lipid bilayer vesicles, serve as effective carriers for small molecules, vaccines, peptides, both small and long nucleic acids, and proteins, contributing significantly to the rapid progress in drug delivery systems. All nanovectors possess a fundamental structure that includes a core compartment designated for the delivery of the drug, commonly known as the "payload" or "cargo," which is encased by a solid matrix or, for liposomes, a phospholipid membrane that encapsulates the drug for transport through the bloodstream. This structure enhances the range of solubility profiles of drugs that can be delivered, allowing hydrophobic drugs to be contained within the hydrophobic compartments of the nanovector and hydrophilic drugs to be housed in hydrophilic compartments (Chowdhury *et al*., 2017).

Liposomes are versatile drug carriers: easily tunable in composition, size, and charge; modifiable for targeting; minimally toxic and antigenic; biodegradable; with controllable permeability; and able to encapsulate diverse solutes, including fat-, water-, and amphiphilic molecules-making them highly effective delivery systems. Due to these attributes, research has been undertaken on the intravitreal injection of drug-laden liposomes, demonstrating that drug release can be regulated, the drug's half-life within the vitreous body can be extended, and the drug's toxicity can be mitigated (Honda *et al*., 2013).

Polymeric

These are colloidal carriers, 10 nm-1 μm in size, consisting of synthetic or natural polymers. These nanoparticles provide an alternative to the above-mentioned nanosystems due to inherent properties like biocompatibility, nonimmunogenicity, nontoxicity and biodegradability. Polymeric nanoparticles are classified and comprise nanocapsules and nanospheres. Nanocapsules are systems in which the drug is confined to a cavity surrounded by a unique polymeric membrane, whereas nanospheres are

systems in which the drug is dispersed throughout the polymer matrix. Natural polymers used are gelatin, albumin and alginate in the preparation of nanoparticles synthetic polymers used for nanoparticles preparation of nanoparticles synthetic polymers used for nanoparticles of preparation may be in the form of preformed polymer. For example, polyesters like polycaprolactone.

Metallic Nanoparticles

Metallic Nanoparticles (MNPs) have attracted considerable interest owing to their capacity to enhance the therapeutic index of drugs by mitigating multidrug resistance and facilitating the effective delivery of therapeutic agents through active targeting. Besides drug delivery, MNPs possess various medical applications, including both *in vitro* and *in vivo* diagnostics, and they enhance the biocompatibility of materials and nutraceuticals. MNPs offer numerous benefits in drug delivery systems and genetic manipulation, such as increased stability and extended half-life in circulation, as well as passive or active targeting to specific tissues, and the ability to manipulate genes by delivering genetic materials. The primary objective of this review is to present up-to-date information regarding the current challenges and future prospects of MNPs in drug and gene delivery systems. This study specifically examines the methods for preparing MNPs and their characterisation through various techniques, their applications in targeted delivery, the use of nonviral vectors in genetic manipulation, and the obstacles faced in translating these findings into clinical trials (Shahalaei *et al.*, 2024).

Lipid Polymer Hybrid Nanoparticles

The lipid-polymer-lipid hybrid nanoparticle was synthesised using a modified double-emulsion technique and subsequently characterised through a range of analytical methods. In the initial emulsion, small droplets of siRNA solution were dispersed within an organic solvent that contained polymers and cationic Ethyl Phosphocholine (EPC) lipids, using a 25-s probe sonication. Due to their amphiphilic characteristics, Egg Phosphatidylcholine (EPC) lipids were capable of self-assembling tightly at the water-oil interface, with their hydrophilic headgroups orientated toward the aqueous droplets and their lipophilic tails immersed in the polymer phase. This inner lipid layer thus stabilised the aqueous droplets and effectively encapsulated siRNA, similar to how cationic liposomes entrap siRNA. In this context, ester-terminated Poly (lactic-co-glycolic acid) was employed as a model hydrophobic polymer to create the middle polymer layer. The inner lipid layer consisted of 1,2-dimyristoleoyl-sn -glycero-3-ethylphospho-choline, which is noted for its low toxicity and biodegradability. Notably, EPC14:1 demonstrated the highest deoxyribonucleic acid transfection activity among various cationic EPC derivatives and is believed to facilitate cubic phase formation while enhancing cytosolic delivery. In the second emulsion, followed by solvent evaporation, 1,2-distearoyl-sn -glycero-3-phosphoethanolamine -PEGm and lecithin self-assembled around the Poly(lactic-co-glycolic acid) layer, resulting in the formation of the outer lipid-polyethene glycol. surface. It is important to mention that, to prevent liposome/micelle formation, the concentrations of both DSPE-PEGm and lecithin were maintained well below their respective critical micelle concentration. DSPE-PEGm was used to coat the polymer layer, as nanoparticles with methoxyl surface groups are regarded as optimal for drug delivery applications, leading to reduced complement activation compared to nanoparticles with alternative surface groups (Shi *et al.*, 2011).

Nanotechnology in Cancer Treatment

Nanotechnology has brought about a significant transformation in the targeted treatment of cancer. By employing various modifications, nanoparticles can be engineered to alter their size, shape, chemical, and physical characteristics, thereby enabling them to specifically target the intended cells. These nanoparticles can engage neoplastic cells through either active or passive targeting methods (Sutradhar and Amin, 2014).

Targeted delivery

The administration of the medication to the intended tissue can be accomplished mainly through two methods-passive and active.

Passive targeting

Passive targeting takes advantage of the permeability of tumour tissue. Rapid vascularisation to serve fast-growing cancerous tissue lends itself to a leaky and defective architecture, which in turn can be easily accessible to toxic chemotherapeutic drugs. Some drugs can be administered as prodrugs or inactive drugs, which, once exposed to the tumour environment, can be switched on to become highly active. Passive targeting also incorporates the delivery of the drug to the tumour bed through several invasive modalities.

Leaky vasculature

The enhanced permeability and retention effect, as articulated by Maeda, arises from the fact that blood vessels in tumours are more permeable than those in normal tissues, facilitating the easy entry of polymer nanoparticles into tumours. Additionally, tumours are deficient in adequate lymphatic drainage, which leads to the accumulation of drugs. Polymer-drug conjugates take advantage of this phenomenon to administer chemotherapy directly to tumours, resulting in drug concentrations that are 10-100 times greater than those of free drugs.

Tumour Microenvironment Targeting (TAPT)

This passive targeting approach, referred to as tumour-activated prodrug therapy, leverages the distinctive conditions present in the Tumour Microenvironment to activate a therapeutic agent. The drug is introduced as an inactive prodrug linked to a tumour-specific molecule, which is subsequently transformed

into an active compound only upon arrival at the tumour site. The Tumour Microenvironment elevated levels of enzymes such as Matrix Metalloproteinase-2 (MMP-2), which is notably overexpressed in melanoma, are utilised for this activation process. MMP-2 is responsible for degrading the extracellular matrix. Mansour *et al.*, developed a polymer-drug conjugate (a maleimide derivative of doxorubicin combined with an MMP-2-specific peptide) that attaches to albumin. At the tumour location, MMP-2 effectively cleaves this complex, releasing active doxorubicin. Additionally, other characteristics of the tumour site, particularly pH and redox potential, are also employed as triggers for drug release.

Direct tumor targeting

The local application of drugs targets the tumour tissue directly, thereby effectively bypassing systemic circulation and minimising side effects. This technique encompasses methods such as intravesical or intraperitoneal administration; however, intratumoral administration, which involves direct injection into the tumour, is particularly appealing. The direct injection of mitomycin into the tumour tissue has been shown to significantly enhance its concentration at the tumour site while simultaneously reducing overall toxicity (Sinha *et al.*, 2006). Additionally, nanoparticles that are loaded with wild-type p53 DNA and delivered to breast cancer cells exhibited a more pronounced and sustained antiproliferative effect in comparison to alternative delivery methods. Another approach includes Onyx-0115, a modified chimeric adenovirus of Types 2 and 5, which possesses an attenuated E1B-55 kDa gene (Sinha *et al.*, 2006).

Active targeting

Passive targeting strategies exhibit several limitations. Consequently, significant efforts are being made to enhance the accumulation of nanoparticles at the desired site through alternative methods. Targeted delivery and entry into tumour cells can be accomplished using the overexpressed receptors present on the tumour cell membrane, as well as through phagocytosis and endocytosis mechanisms. The transferrin receptor and the folic-acid receptor, which are overexpressed in various cancer types, serve as targets for active drug delivery. Transferrin is a glycoprotein associated with the cell membrane that plays a role in the cellular uptake of iron and the regulation of cell growth. The uptake of iron occurs through the internalisation of iron-loaded transferrin, which is mediated by the transferrin receptor. Likewise, the folic-acid receptor is also a valuable target for tumour-specific drug delivery. It is recognised that the density of folate receptors increases as cancer severity escalates. Active targeting can also be achieved by focusing on biomarkers that are specific to tumours or by leveraging processes that are critical for tumour development, such as neoangiogenesis. CA-125 is an example of such a biomarker for ovarian cancer, being expressed in over 85% of ovarian cancer cases. Despite the well-documented advantages of active targeting, this technology has led to the development of only a limited number of clinically validated nanoproducts thus far (Pillai, 2014).

Overcoming Resistance

Alongside the tumour cells, the tumour extracellular matrix contributes to resistance against chemotherapy. The transport of drugs into and throughout the tumour is highly inefficient. This results in areas of varying drug concentrations within the tumour. The areas that receive lower drug concentrations often contain the more aggressive and tumorigenic cells. Therefore, it is crucial to attain therapeutic drug concentrations in these inadequately supplied regions. To tackle the problem of inefficient drug distribution, it is vital to comprehend the mechanisms that regulate drug transport within the tumour. In the subsequent sections, we will present a concise overview of the physiological factors that influence intratumoral drug transport.

Transport Process in Normal Tissues

Tumour physiology presents major obstacles to drug delivery. The driving force for drug transport is inconsistent across the tumour due to differences in lymphatic function. The advancing edge of the tumour has normal lymphatic drainage, maintaining a negative pressure gradient similar to normal tissue. The core of the tumour has collapsed lymphatic vessels and minimal hydraulic conductivity. This lack of drainage often results in the pressure differential being in the opposite direction (from the tumour toward blood vessels). The core also features poor vessel coverage, forcing drug transport to rely on diffusion from the better-perfused peripheral regions.

Transport Process in the Tumour

Tumour physiology poses significant challenges to drug delivery. The driving force behind drug transport varies throughout the tumour because of differences in lymphatic function. The tumour's advancing edge exhibits normal lymphatic drainage, sustaining a negative pressure gradient akin to that of healthy tissue. Conversely, the tumour's core contains collapsed lymphatic vessels and exhibits minimal hydraulic conductivity. This inadequate drainage frequently leads to a pressure differential that is reversed (from the tumour toward the blood vessels). Additionally, the core is characterised by insufficient vessel coverage, compelling drug transport to depend on diffusion from the more well-perfused peripheral regions (Kirtane *et al.*, 2013).

Nanotechnology in neurological disorders

The existing neurotherapeutics face two primary limitations: they encounter restricted entry into brain cells due to the BBB, which results in inadequate brain penetration, as well as limited access for immune cells to the brain (Misra *et al.*, 2003; Nagpal *et al.*, 2013). Most medications used for neural disorders are lipophilic and possess a molecular weight exceeding 400-500 daltons, rendering

them incapable of crossing the BBB in pharmacologically significant amounts (Fischer *et al.*, 1998). Consequently, they fail to pass initial screening, whereas smaller lipophilic compounds, such as alcohol and steroid hormones, can penetrate through a transcellular mechanism. Furthermore, the presence of various transporters on endothelial cells, which exhibit high selectivity, also restricts drug entry. Additionally, tight junctions within endothelial membranes contribute to elevated transendothelial electrical resistance in cerebral microcapillaries (Gloor *et al.*, 2001). The endothelial cells of the BBB impede the passage of both endogenous and foreign substances. ATP-binding cassette transporters located on the endothelial cells further limit the entry of therapeutic drugs, as well as neurotoxic agents, metabolites, hormones, and mediators. These transporters are membrane proteins that require Adenosine Triphosphate (ATP) to facilitate the transport of materials across cell membranes. Notable members of this family include Multiple Drug Resistance Protein 1 (MDR1) or ATP-Binding Cassette subfamily B Member 1 (ABCB1), commonly known as Permeability glycoprotein (P-gp), multiple resistance Protein 4 or ATP-Binding Cassette subfamily C Member 4 (ABCC4), and breast cancer resistance protein or ATP-Binding Cassette subfamily G Member 2 (ABCG2) (Alyautdin *et al.*, 2014). The BBB also plays a crucial role in maintaining ionic homeostasis at synapses, regulating the entry of potassium ions, calcium, and sodium, while ensuring minimal optic concentrations (Naqvi *et al.*, 2020).

Nanomedicine strategies for crossing the BBB

Recent developments in nanomedicine present a significant advantage over small-molecule drugs by improving drug solubility, prolonging retention time, and enabling delivery across the BBB to reach targeted brain areas (Figure 1). In contrast to some small-molecule drugs that depend on passive diffusion across the BBB through a concentration gradient, NPs are generally engineered for active transcytosis utilising one of three main mechanisms, as paracellular transport is typically inaccessible due to the tight junctions of the cerebral endothelium.

The three active mechanisms of BBB transcytosis employed by NPs are:

Carrier-Mediated Transport

This mechanism utilises membrane transport proteins to facilitate the entry of polar molecules (such as sugars or amino acids) into endothelial cells. An example of this is glucose transport mediated by GLUT1.

Receptor-Mediated Transcytosis

This mechanism is prevalent for larger molecules and NPs, triggered by peptide receptors located on cell membranes. Receptor-Mediated Transcytosis operates as a bidirectional process (from blood to brain and vice versa). The conjugation of BBB receptor ligands to NPs is an effective strategy for enhancing transcytosis.

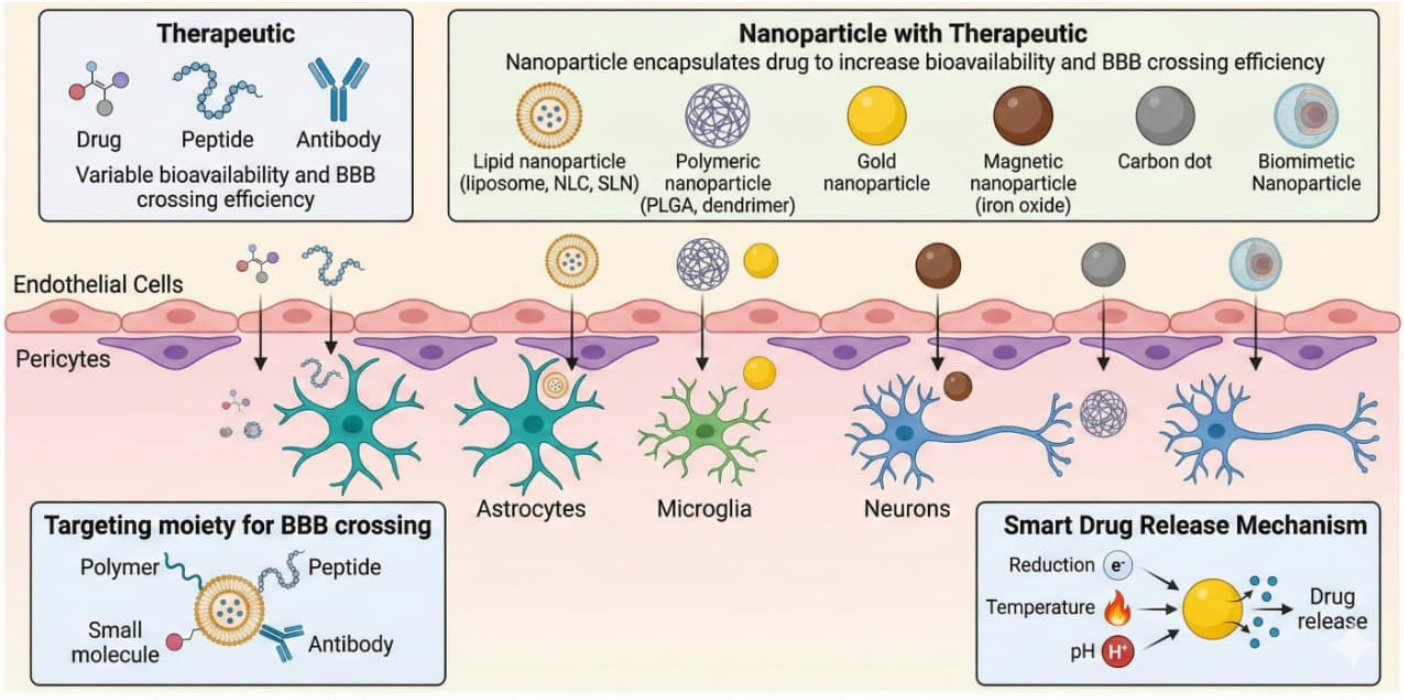

Figure 1: Nanoparticles improve the ability to cross the Blood-Brain Barrier (BBB) for precise delivery. These particles can be designed to utilise the pathways of BBB traversal to specifically target ailments within the brain.

Adsorption-Mediated Transcytosis

This process, which is mediated by clathrin-dependent endocytosis, relies on electrostatic interactions between cationic molecules and the luminal surface of endothelial cells. Adsorption-Mediated Transcytosis is unidirectional (from blood to brain) and permits passage without the need for specific receptor targeting. However, cationic NPs may pose a risk of disrupting cellular membranes and compromising the integrity of the BBB.

Challenges across cancer and brain diseases

Challenges in clinical translation of nanotechnology for cancer diagnosis

Despite the promising advancements in cancer diagnosis figures through nanotechnology, only a limited number of instances have progressed to clinical trials, underscoring the considerable challenges associated with clinical translation. The primary challenge is reliability, as obtaining dependable and quantitative detection results is crucial. This is frequently complicated by issues such as nonspecific binding and aggregation of NP probes, unsuitable detection conditions, and signal fluctuations resulting from the complex compositions of bodily fluids. To achieve clinical validation, it is imperative to thoroughly investigate assay reliability and reproducibility within extensive clinical sample pools. The second significant challenge pertains to the large-scale production of Nanoprobes. Currently, probes are typically manufactured under highly optimised laboratory conditions, which complicates the achievement of consistent, high-sensitivity, and high-reproducibility batches. This is particularly true because even minor variations in the NP's shape, size, composition, charge, and surface coating can significantly impact results. It is essential to simplify synthesis processes to reduce batch-to-batch variability, and addressing the issue of NP aggregation during storage is vital for ensuring long-term stability and cost-effectiveness.

The third challenge involves the necessity to create NP-based devices that are not only highly sensitive but also user-friendly and cost-effective. Numerous academic assays, such as those that depend on intricate confocal Raman microscopes for Surface-Enhanced Raman Scattering studies, are impractical for standard hospital applications; thus, the successful development of Point of Care devices is crucial for clinical implementation.

Lastly, the fourth challenge concerns the potential toxicity of nanoparticles following systemic administration, particularly in

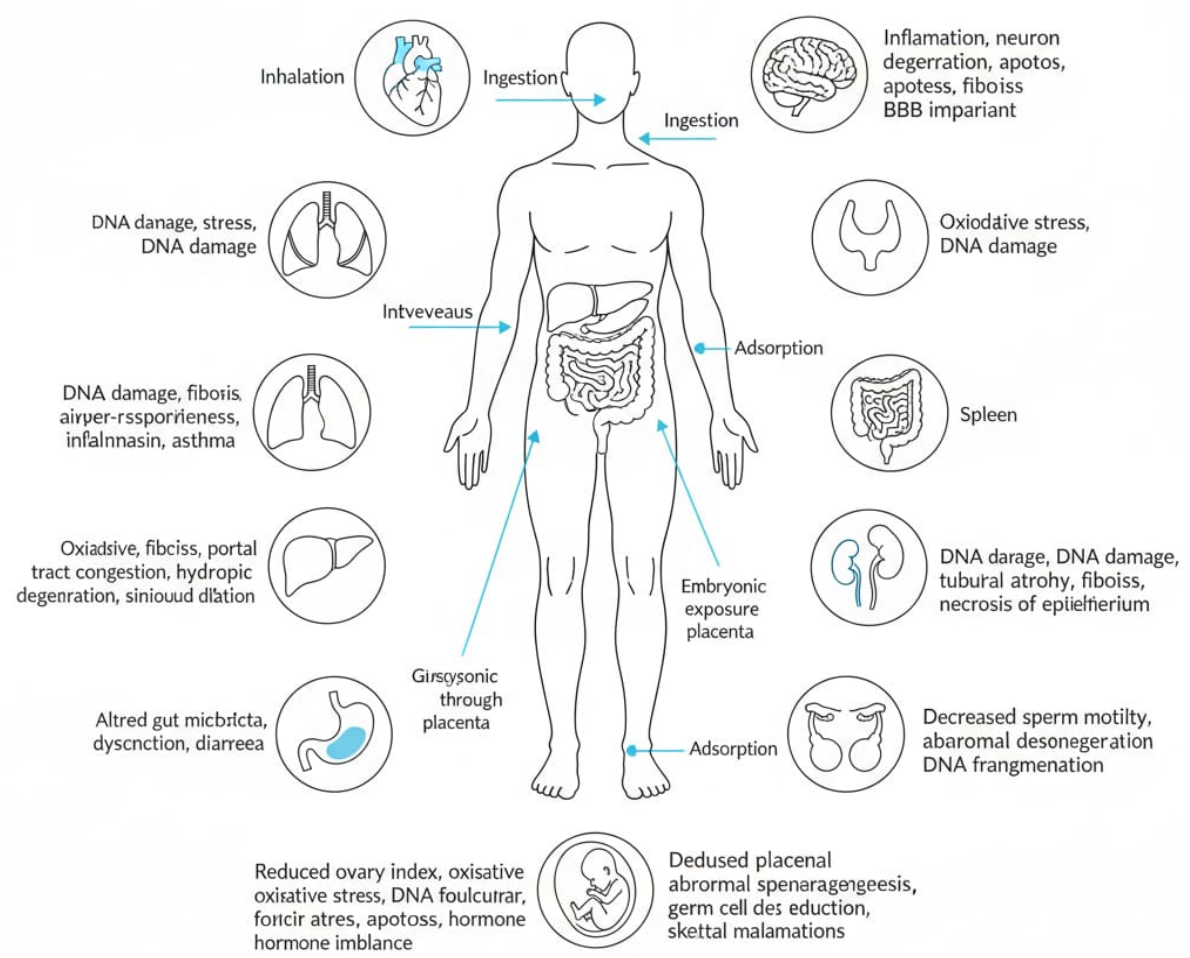

Figure 2: An illustrative image depicting the pathways of exposure and the toxicokinetics of nanoparticles (Malaviya *et al.*, 2019).

the context of *in vivo* imaging. Evaluating toxicity necessitates an examination of how NP characteristics (such as shape, size, charge, and composition), along with their biodistribution, biodegradability, and pharmacokinetic properties, may affect safety (Zhang *et al.*, 2019).

In vitro challenges to model the human brain (CNS)

The primary obstacles in developing *in vitro* models of the human brain arise from its vast multiscale complexity regarding structure, cellular makeup, and functionality. This complexity encompasses the neurovascular unit, which consists of neurones, glial cells (including astrocytes, microglia, and oligodendrocytes), and pericytes, in addition to immune cells and endothelial cells. The brain is interconnected with several essential subunit systems that uphold homeostasis and functionality, such as the endocrine system, choroid plexus, glymphatic system, vascular system, and various barriers (for instance, the blood-brain barrier and the blood-cerebrospinal-fluid barrier). The foremost challenge lies in comprehending how the fundamental neuronal electrical activity translates into higher-order functions such as self-awareness or consciousness, a characteristic of the human brain that remains largely enigmatic. Addressing these structural, functional, and technological hurdles is crucial to creating *in vitro* bioplatforms that faithfully replicate the human brain, thereby enhancing our understanding of neurological disorders and human evolution (Rodrigues *et al.*, 2024).

Emerging innovations

Smart-Stimuli-responsive

The pathological areas associated with neurodegenerative diseases are frequently marked by unique microenvironmental alterations, including acidic pH levels, increased levels of systemic concentrations, and irregular expression of certain enzymes (for instance, esterases and proteases). These characteristics establish a biological basis and activation mechanism for the development of stimuli-responsive nanocarriers that possess site-specific drug release capabilities. Stimuli-responsive nanocarriers are sophisticated platforms designed to release therapeutic agents in response to particular pathological stimuli, showcasing high spatial accuracy and temporal regulation. In comparison to traditional delivery systems, these platforms facilitate precise on-site drug release within affected tissues, significantly improving targeting efficiency and local therapeutic outcomes while reducing systemic toxicity. In the context of treating neurodegenerative diseases, such systems have shown significant potential, especially in enhancing central drug delivery efficiency, enabling on-demand release, and minimising systemic exposure (Gao *et al.*, 2025).

Artificial Intelligence (AI) driven design and development of nanomedicine nanocarriers

The combination of AI and nanotechnology has transformed the design, enhancement, and use of nanocarriers for breast cancer treatment. This section consolidates progress in machine learning, Deep Learning (DL), and computational modelling to tackle issues in the development of nanocarriers, such as the optimisation of physicochemical properties, tumour heterogeneity, and clinical translation (Shirzad *et al.*, 2025).

Role of AI in enhancing NP drug delivery systems

AI, which includes machine learning and DL, is fundamentally transforming NP drug delivery systems by addressing the significant challenges of high costs and low efficiency in drug development.

AI serves as an advanced computational engine, merging with nanotechnology to enhance every phase of NP development. It is pivotal in data analytics and mining, assisting researchers in compiling and processing the extensive datasets required for NP development, such as preclinical studies involving inorganic NPs, which ultimately suggests improved patient outcomes. The capabilities of AI, including self-correction and pattern recognition, enable the simulation of human intelligence, thereby significantly increasing societal benefits in the medical domain. The primary advantage of AI is its capacity to optimise NP design and enable highly targeted delivery for precision medicine, particularly in intricate fields like cancer therapy. By employing sophisticated algorithms and DL models, AI refines NP characteristics, forecasts complex interactions with biological fluids, cell membranes, and the immune system, and models antibodies for targeted conjugation. This results in the creation of more effective carriers (for instance, optimising ionizable lipids for Lipid NPs utilised in vaccines and gene therapy) that promise enhanced safety, diminished toxicity, and a greater synergistic effect of the drugs. Moreover, AI analyses data produced by diagnostic NPs and multiplex nanosensors to address challenges arising from patient and intratumor heterogeneities. It applies classification algorithms and pattern analysis to this data to accurately recognise biomarker patterns, assess cancer complexity and types, and subsequently customise the therapeutic nanocarriers used, ultimately leading to improved dosing, targetability, and potency (Kapoor *et al.*, 2024).

Cytotoxicity of Nanoparticles

NPs demonstrate considerable cytotoxic effects that lead to decreased cell viability and cell death, with the extent of damage being influenced by their size, concentration, composition, and cellular localisation. A key mechanism of injury is the induction of oxidative stress, which results in membrane damage and inflammation. NPs also initiate regulated cell death (apoptosis) as well as uncontrolled cell death (necrosis).

In particular, Ag NPs promote apoptosis through inflammatory responses that involve the secretion of TNF-α, whereas ZnO NPs not only induce apoptosis but also cause severe genotoxicity, resulting in DNA damage and the formation of micronuclei.

The internal positioning of the NPs is crucial; for example, polymer-coated cerium oxide NPs exhibit the highest toxicity when they are localised within lysosomes.

Moreover, the coating of the NPs plays a significant role in determining this outcome: cationic coatings lead to lysosomal localisation across all cell types, while anionic coatings specifically target lysosomes in cancer cells, illustrating how the design of NPs affects both their toxicity and selectivity.

Toxicity of Nanoparticles in Neuronal Disorders

The CNS is the most sensitive system, consisting of the spinal cord and the brain. It is a fragile organ that requires protection from injury. NPs possess the ability to access the brain through various pathways and mechanisms. They can affect brain physiology and potentially lead to significant side effects (Figure 2). Consequently, it is essential to evaluate the sensitivity of the organ to NPs and take into account various pharmacokinetic parameters, the developmental timeline of the brain, and cell-to-cell interactions that cannot be assessed using *in vitro* models. Due to their distinctive size, substantial surface area, and volume-to-mass ratio (providing a large functional area), NPs exhibit unique physicochemical, mechanical, optical, and magnetic properties (for magnetic NPs), making them more reactive than their bulk counterparts. Based on their physicochemical characteristics, such as size, morphology, and reactivity, these NPs can traverse the BBB and/or travel through the olfactory nerve to reach the brain. The size and shape of the particles, along with the ability of nanoparticles to interact with surrounding tissues, play a crucial role in determining their toxicity. They may lead to an overload of phagocytic cells, resulting in diminished immune function. Additionally, they may not degrade effectively and can accumulate in target organs due to their slow degradation rates. The reduced size of NPs contributes to a larger surface area. When NPs come into contact with the organism, they can impact proteins, enzymes, and the biological functions of the body. Neurones are unable to regenerate following degeneration. Furthermore, most drugs struggle to penetrate the BBB, complicating efforts to repair neuronal damage (Muheem *et al.*, 2021).

FUTURE PERSPECTIVES

Personalised and Next-Generation Nanomedicine

Personalised medicine for cancer

Despite significant advancements in the development of new cancer therapies, the management of cancer remains unsatisfactory. There is a growing acknowledgement that no single therapeutic agent produces uniform effects across a broad patient population with the same diagnosis. This realisation has prompted initiatives aimed at personalising cancer treatment, as elaborated upon in other sources. The personalised approach to cancer management is supported by enhanced understanding of the molecular mechanisms underlying cancer, as well as progress in molecular diagnostics and proteomic technologies, which are being further improved through the advent of nanobiotechnologies. The most profound influence of nanobiotechnology is observed in molecular diagnostics for cancer, commonly known as nanodiagnostics (Jain, 2005b).

Future prospects of nanotechnology in drug delivery

The future of drug delivery is poised to be significantly influenced by the advent of emerging nanotechnologies and enhanced interdisciplinary collaborations. Innovations such as nanorobots, conceptualised as molecular machines, offer unmatched precision for intricate tasks including targeted drug delivery, tissue repair, and real-time disease monitoring at the cellular level. Furthermore, exosomes, which are naturally occurring and exhibit high biocompatibility, are being recognised as sophisticated delivery systems for therapeutics such as ribonucleic acid and proteins, showcasing inherent targeting abilities and considerable potential in gene therapy and cancer treatment as a natural alternative to synthetic carriers.

This progress presents considerable promise for global health, especially in areas with limited resources. Nanomedicine enhances the bioavailability and therapeutic effectiveness of medications, allowing for reduced dosages and lowering treatment expenses, which is vital for improving accessibility in developing nations. The adaptability of nanocarriers also facilitates the precise delivery of crucial agents, such as vaccines, addressing pressing unmet medical requirements in regions battling infectious diseases. The full potential of these advancements will be achieved through interdisciplinary partnerships, combining the knowledge of nanotechnologists, biologists, and healthcare professionals. Moreover, the fusion of nanotechnology with disciplines like genomics, personalised medicine, and AI is anticipated to transform healthcare. This collaboration will allow the creation of highly targeted treatments tailored to an individual's genetic makeup, with AI supporting real-time monitoring and predictive modelling to enhance drug delivery based on patient-specific reactions, thus maximising effectiveness and minimising adverse effects (Bhatta *et al.*, 2023).

CONCLUSION

Nanotechnology-based drug delivery systems have emerged as a promising approach to overcome many limitations of conventional drug therapy, particularly in the treatment of cancer and neurological disorders. By utilising nanoscale carriers such as liposomes, polymeric nanoparticles, metallic nanoparticles, and lipid-polymer hybrid systems, drugs can be delivered more

precisely to target tissues with improved bioavailability, controlled release, and reduced systemic toxicity. These systems are especially valuable in overcoming major biological barriers such as the tumour microenvironment and the blood-brain barrier, thereby enhancing therapeutic efficacy in difficult-to-treat diseases. However, despite significant advancements, challenges such as nanoparticle toxicity, large-scale manufacturing, reproducibility, and regulatory approval still limit their widespread clinical application. Continued interdisciplinary research integrating nanotechnology with artificial intelligence, genomics, and personalised medicine is expected to further optimise nanocarrier design and improve patient-specific therapies. Overall, nanomedicine holds great potential to revolutionise future drug delivery strategies and contribute to safer, more effective, and targeted treatment options for complex diseases.

ABBREVIATIONS

CNS: Central Nervous System; **BBB:** Blood-Brain Barrier; **AI:** Artificial Intelligence; **P-gp:** P-Glycoprotein; **siRNA:** Small-Interfering Ribonucleic Acid; **MNPs:** Metallic Nanoparticles; **EPC:** Ethyl Phosphocholine / Egg Phosphatidylcholine; **DSPE-PEGm:** 1,2-Distearoyl-sn -Glycero-3-Phosphoethanolamine-Polyethylene Glycol; **TAPT:** Tumour-Activated Prodrug Therapy; **MMP-2:** Matrix Metalloproteinase-2; **ATP:** Adenosine Triphosphate; **MDR1:** Multiple Drug Resistance Protein 1; **ABCB1:** ATP-Binding Cassette Subfamily B Member 1; **ABCC4:** ATP-Binding Cassette Subfamily C Member 4; **ABCG2:** ATP-Binding Cassette Subfamily G Member 2; **NPs:** nanoparticles; **GLUT1:** Glucose Transporter 1; **TNF-α:** Tumor Necrosis Factor-alpha; **ZnO:** Zinc Oxide; **Ag:** Silver.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

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