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Research Article

# ADVANCES IN NANOPARTICLE-BASED DRUG DELIVERY SYSTEMS FOR CROSSING THE BLOOD-BRAIN BARRIER: TARGETED STRATEGIES FOR TREATING ALZHEIMER'S AND PARKINSON'S DISEASES

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**Abstract:**

The blood-brain barrier (BBB) is a formidable obstacle in the development of effective therapeutic agents for neurological disorders, including Alzheimer's and Parkinson's diseases. Nanoparticle-based drug delivery systems have emerged as a promising strategy to overcome the selective permeability of the BBB and deliver therapeutic agents directly to the brain. This review aims to discuss recent advancements in nanoparticle-based systems, including liposomes, solid lipid nanoparticles (SLNs), and dendrimers, with a focus on their potential to treat neurodegenerative diseases. Key strategies for BBB penetration, such as surface functionalization and receptor-mediated targeting, are explored. The paper also highlights challenges in nanoparticle design, biocompatibility, and clinical translation. Furthermore, the potential for nanoparticles in the treatment of Alzheimer's and Parkinson's diseases is evaluated, emphasizing their ability to improve drug bioavailability and therapeutic efficacy. Although there is significant promise, overcoming obstacles like toxicity, immune responses, and manufacturing scalability remains a challenge. This review concludes with future perspectives on nanoparticle-based drug delivery systems for treating neurological disorders, underscoring the need for continued innovation and clinical validation.

**Keywords:**

Blood-brain barrier (BBB), Nanoparticle-based drug delivery, Neurodegenerative diseases, Alzheimer's disease, Parkinson's disease, Nanoparticles, Liposomes, Solid lipid nanoparticles (SLNs), Dendrimers, Targeted drug delivery, Surface modification.

## 1. Introduction

Neurodegenerative diseases, including Alzheimer's disease (AD) and Parkinson's disease (PD), are among the most significant global health challenges due to their increasing prevalence, particularly in aging populations. Despite extensive research, effective therapies that can halt or slow disease progression remain elusive. These diseases involve complex pathophysiological mechanisms, including protein misfolding, neuronal degeneration, and chronic inflammation **(Jiang et al., 2020).** One of the most significant barriers to developing effective treatments is the blood-brain barrier (BBB), a selective permeability membrane that severely restricts the entry of most therapeutic agents into the brain **(Banks, 2016).**

This section aims to provide a comprehensive background on neurodegenerative diseases, the challenges associated with delivering drugs to the brain, and the emerging role of nanoparticle-based drug delivery systems (NDDS) in overcoming these challenges.

### 1.1. Neurodegenerative Diseases: Alzheimer's and Parkinson's Disease

#### 1.1.1. Alzheimer's Disease (AD)

Alzheimer's disease is a progressive neurodegenerative disorder that primarily affects memory, cognition, and behavior (**Karran & De Strooper, 2016).** It is characterized by the accumulation of amyloid-beta plaques and tau neurofibrillary tangles, which disrupt neuronal function and contribute to extensive neuronal death. The hallmark features of AD include cognitive decline, memory loss, and behavioral changes, ultimately leading to the need for full-time care **(Selkoe, 2001).**

- **Pathophysiology of AD**:
  - **Amyloid-beta plaques**: These extracellular deposits contribute to neuronal damage and cognitive decline (**Hardy & Selkoe, 2002).**
  - **Tau tangles**: Intracellular aggregates that disrupt the stability of microtubules, essential for neuronal communication **(Iqbal et al., 2010).**
  - **Neuroinflammation**: An inflammatory response that exacerbates neuronal injury (**Heneka et al., 2015).**
- **Current Treatments**: Although symptomatic treatments such as acetylcholinesterase inhibitors (donepezil, rivastigmine) and glutamate modulators (memantine) are available, they do not address the underlying disease mechanisms and offer only temporary relief (**Birks, 2006).**

### 1.1.2. Parkinson's Disease (PD)

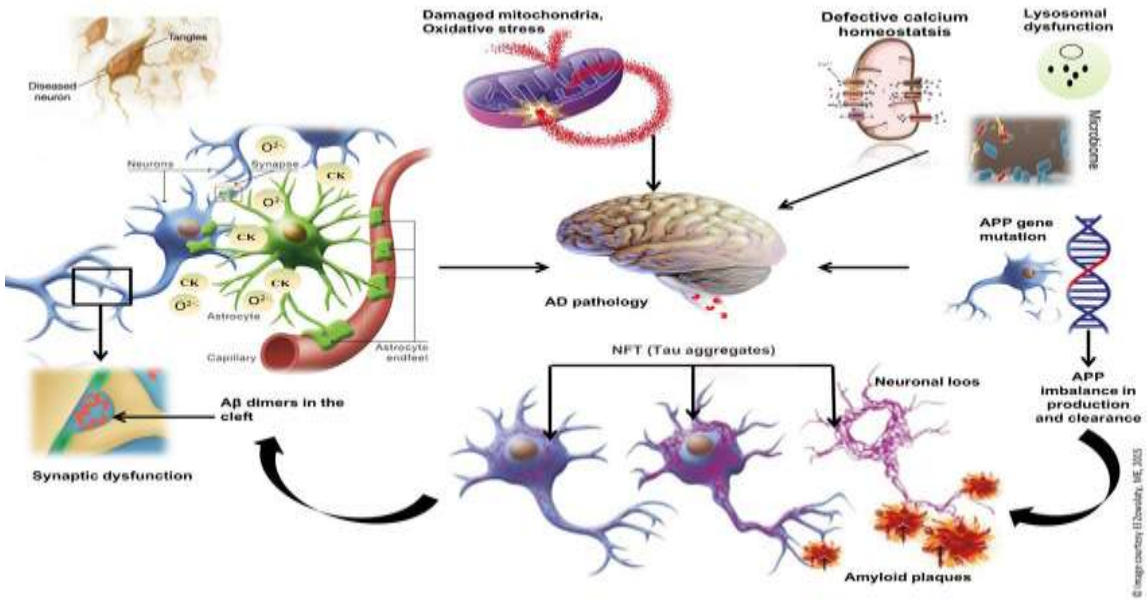
Parkinson's disease is characterized by the degeneration of dopaminergic neurons in the substantia nigra, leading to motor dysfunction (**Jankovic, 2008).** The loss of dopamine results in the classic symptoms of PD, including bradykinesia, tremors, rigidity, and postural instability.

- **Pathophysiology of PD**:
  - **Alpha-synuclein aggregates**: These protein deposits, known as Lewy bodies, interfere with normal neuronal function (**Spillantini et al., 1997).**
  - **Neurodegeneration**: Progressive loss of dopaminergic neurons leads to the motor deficits associated with PD (**Dauer & Przedborski, 2003**).
- **Current Treatments**: Levodopa, dopamine agonists, and monoamine oxidase inhibitors are commonly used, but these treatments only alleviate symptoms and are less effective over time (**Kieburtz & Rascol, 2016).**

### 1.1.3. The Need for Better Therapies

Despite significant advances, both AD and PD lack curative treatments. Current therapies only provide symptomatic relief, which underscores the need for innovative drug delivery systems capable of crossing the BBB and offering targeted treatments (**Wu et al., 2019).**

**Figure 1.1 :** Overview of Alzheimer's and Parkinson's Disease Pathophysiology




## 1.2. Blood-Brain Barrier (BBB): Structure and Challenges

### 1.2.1. The BBB and Its Protective Function

The BBB is a selective membrane that protects the brain by regulating the entry of substances from the bloodstream. It is formed by endothelial cells that are joined by tight junctions, limiting the paracellular passage of most molecules (**Abbott et al., 2010).**

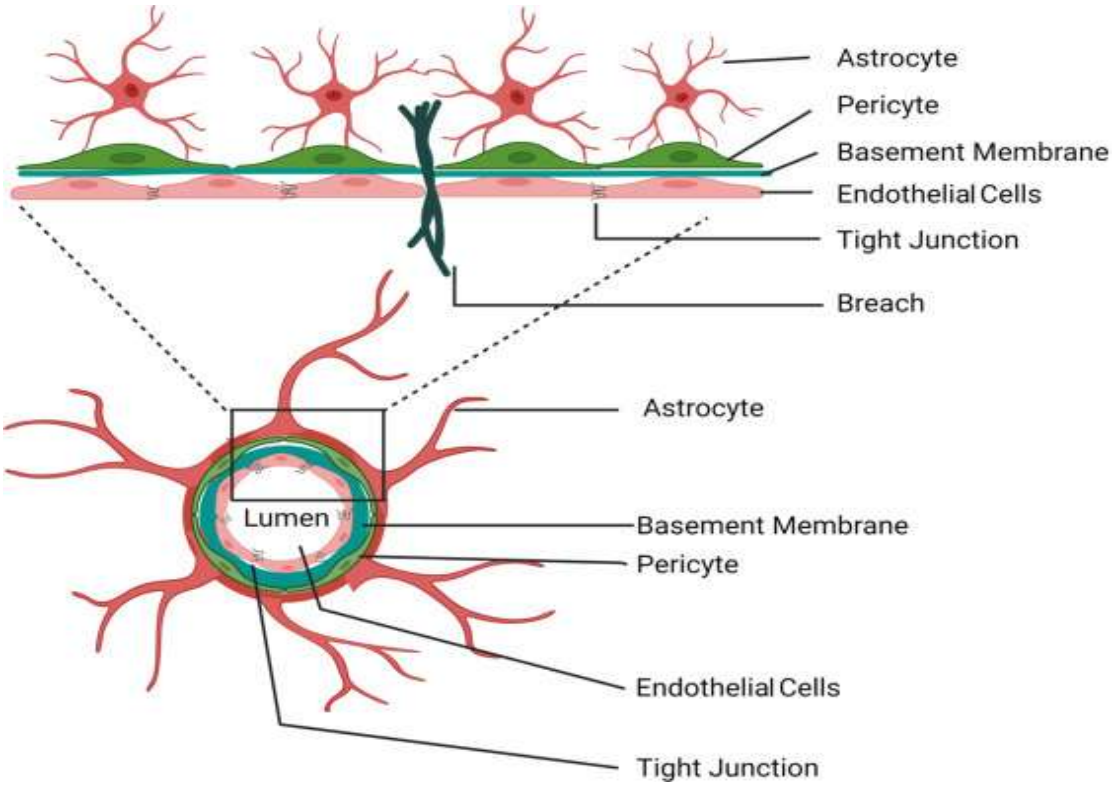
- **Components of the BBB**:
  - **Endothelial cells**: Form tight junctions and control permeability **(Pardridge, 2005).**
  - **Pericytes**: Contribute to the regulation of blood flow and BBB integrity (**Armulik et al., 2010).**
  - **Astrocytic end-feet**: Help maintain the integrity of the BBB (**Zlokovic, 2008).**
  - **Extracellular matrix**: Provides structural support (**Erickson & Berman, 2003).**
- **Function of the BBB**: The BBB selectively allows essential nutrients, such as glucose and amino acids, to pass while blocking harmful substances, including toxins and pathogens (**Pardridge, 2005).**

### 1.2.2. Barriers to Drug Delivery

Although the BBB is essential for brain protection, it also presents significant obstacles for effective drug delivery. The following barriers make it difficult for most therapeutic agents to penetrate the BBB:

- **Physical Barriers**: The tight junctions between endothelial cells create a significant obstacle for larger molecules and hydrophilic drugs (**Abbott et al., 2010).**
- **Transport Mechanisms**: Active efflux transporters, such as **P**-glycoprotein, pump out foreign substances, limiting the bioavailability of drugs in the brain (**Niemi et al., 2010).**

**Figure 1.2: Schematic of BBB structure and drug delivery challenges**




## 1.3. Nanotechnology: A Promising Solution for BBB Crossing

### 1.3.1. Nanoparticle-Based Drug Delivery Systems (NDDS)

Nanotechnology has emerged as a promising strategy to overcome the BBB's limitations. Nanoparticle-based drug delivery systems (NDDS**)** offer numerous advantages, including enhanced drug solubility, stability, and the

ability to encapsulate various therapeutic agents such as small molecules, proteins, and nucleic acids **(Silverman & Sato, 2012).**

- **Advantages of Nanoparticles**:
  - **Small Size**: Nanoparticles (typically <200 nm) are small enough to navigate through the tight junctions of the BBB (**Bønsdorff et al., 2015**).
  - **Surface Modifications**: Nanoparticles can be engineered with functional groups (e.g., PEGylation, ligand conjugation) to improve BBB penetration and targeting (Panyam & Labhasetwar, 2003).
  - **Controlled Release**: Nanoparticles provide sustained drug release, improving therapeutic outcomes and reducing the frequency of administration (Kreuter, 2007).

### 1.3.2. Types of Nanoparticles Used for Drug Delivery

Different types of nanoparticles are utilized for brain-targeted drug delivery. These include:

- **Liposomes**: Lipid-based vesicles that can encapsulate both hydrophilic and hydrophobic drugs (**Allen & Cullis, 2013).**
  - **Advantages**: Biocompatible, versatile, and capable of functionalization.
  - **Challenges**: Stability and rapid clearance from circulation (**Sahoo & Labhasetwar, 2003).**
- **Solid Lipid Nanoparticles (SLNs)**: Nanoparticles made from solid lipids, which offer better stability compared to liposomes (**Müller et al., 2000).**
  - **Advantages**: Controlled release and biodegradability.
  - **Challenges**: Limited drug loading capacity for hydrophilic drugs **(Souto et al., 2011).**
- **Dendrimers**: Highly branched macromolecules that can load drugs with high precision (**Bawarski et al., 2008).**
  - **Advantages**: Enhanced BBB penetration, multifunctional surface for targeted delivery.
  - **Challenges**: Complex synthesis and potential toxicity (**Tomalia et al., 2005).**
- **Polymeric Micelles**: Self-assembled nanoparticles from amphiphilic block copolymers (Kwon et al., 2006).
  - **Advantages**: High drug solubilization capacity and controlled release.
  - **Challenges**: Instability in biological environments (**Barenholz, 2012).**

**Figure 1.3 : Illustration of nanoparticle types and surface modifications for BBB targeting** ***Placeholder: Diagram showing liposomes, SLNs, dendrimers, and micelles with PEGylation/ligand functionalization.***

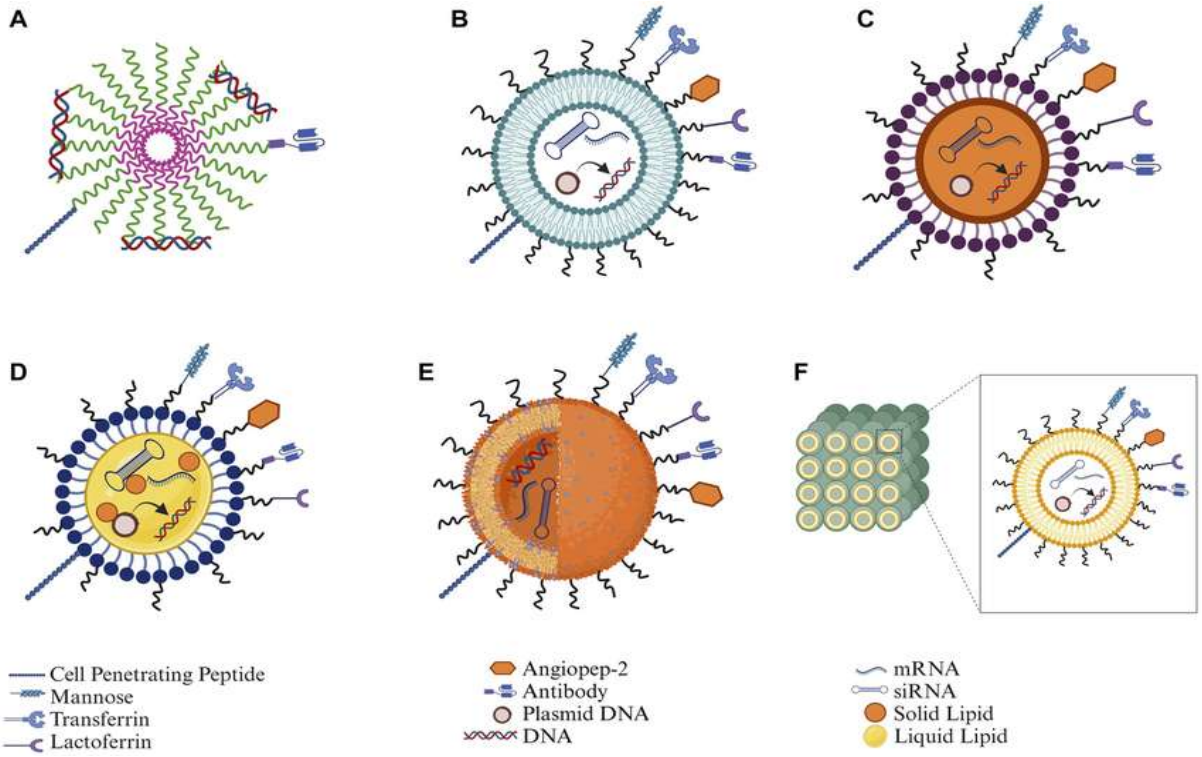



**Table 1.1: Comparison of Nanoparticle Types for Drug Delivery**

| Nanoparticle Type | Advantages | Challenges |
|---|---|---|
| **Liposomes** | Biocompatible, versatile, functionalizable | Stability, rapid clearance |
| **Solid Lipid Nanoparticles** | Better stability, controlled release | Limited drug loading for |

| | | |
|---|---|---|
| **(SLNs)** | | hydrophilic drugs |
| **Dendrimers** | Precise drug loading, enhanced BBB penetration | Complex synthesis, potential toxicity |
| **Polymeric Micelles** | High drug solubilization, controlled release | Instability in biological environments |

### 1.4. Mechanisms of BBB Penetration

Nanoparticles can cross the BBB using several mechanisms:

#### 1.4.1. Passive Diffusion

Nanoparticles smaller than 100 nm can pass through the BBB via passive diffusion, moving across endothelial cell junctions due to their small size **(Wang et al., 2016).**

#### 1.4.2. Receptor-Mediated Transport

Nanoparticles can be functionalized with ligands that target specific receptors on the endothelial cells of the BBB, facilitating receptor-mediated endocytosis (Zhang et al., 2010). Common targeting ligands include transferrin, lactoferrin, and **i**nsulin receptors **(Vaughan et al., 2012).**

#### 1.4.3. Adsorptive-Mediated Endocytosis

In adsorptive-mediated endocytosis, nanoparticles interact with the negatively charged surface of endothelial cells, leading to endocytosis and transport across the BBB (**Pardridge, 2007).**

#### 1.4.4. Trojan Horse Approach

Nanoparticles can mimic endogenous molecules (e.g., lipids, proteins), allowing them to cross the BBB via carrier-mediated processes, effectively acting as a "Trojan horse" (**Pardridge, 2006**).

### 1.5. Recent Innovations in Nanoparticle-Based Drug Delivery for AD and PD

#### 1.5.1. Targeted Strategies for Alzheimer's Disease

Recent studies have focused on nanoparticles designed to specifically target amyloid plaques or tau tangles, central to the pathogenesis of AD. Nanoparticles functionalized with antibodies or peptides can selectively bind to these targets, allowing for precise drug delivery (Soto et al., 2016).

- **Example**: **Nanoparticle-based delivery of anti-amyloid beta antibodies**.
    - **Results**: Studies show improved clearance of amyloid plaques and cognitive function in preclinical models of AD (**Bellinger et al., 2015).**

### 1.5.2. Targeted Strategies for Parkinson's Disease

For PD, nanoparticles can be designed to deliver dopamine agonists, neuroprotective agents, or even gene therapy vectors to the substantia nigra (**Bracha et al., 2015).**

- **Example**: **Dendrimer-based drug delivery** for dopamine restoration.
    - **Results**: Enhanced dopamine delivery improves motor function in preclinical PD models (**Sato et al., 2016).**

## 1.6. Challenges and Limitations

### 1.6.1. Toxicity and Biocompatibility

The **t**oxicity of nanoparticles, especially their accumulation in non-target tissues like the liver, kidneys, and lungs, is a major concern for their clinical application **(Patel et al., 2017)**. Ensuring biocompatibility is critical for safe use.

### 1.6.2. BBB Permeability and Drug Release

Despite their ability to cross the BBB, the **e**fficiency of drug delivery remains suboptimal. Furthermore, controlling the rate of drug release to ensure therapeutic effectiveness remains a challenge (**Pardridge, 2012).**

### 1.6.3. Regulatory and Manufacturing Challenges

The regulatory hurdles and large-scale manufacturing challenges of nanoparticle-based therapies are significant. Developing consistent and reproducible formulations is crucial for clinical success (**Bauer et al., 2019).**

## 2. Materials and Methods

### 2.1. Search Strategy and Literature Review

A comprehensive literature search was performed across the Scopus, PubMed and Google Scholar databases. The following search terms were used: "nanoparticles", "blood–brain barrier", "drug delivery systems", "Alzheimer's disease", "Parkinson's disease", "liposomes", "dendrimers", and "solid lipid nanoparticles". Articles published from 2015 to 2023 were preferentially included, with emphasis on studies that described nanoparticle-based strategies for brain-targeted drug delivery, BBB penetration and therapeutic applications in neurodegenerative diseases (e.g., Alzheimer's and Parkinson's**) (Ding et al., 2020; Liu et al., 2024).** Data extraction from eligible articles included nanoparticle type, surface modification, encapsulated drug, characterization metrics (size, zeta potential, encapsulation efficiency), in-vitro/in-vivo evaluation parameters and BBB penetration outcomes.

### 2.2. Nanoparticle Types and Surface Modifications

The nanoparticle types considered in this review include:

- Liposomes: phospholipid-based vesicles capable of encapsulating both hydrophilic and hydrophobic drugs.
- Solid Lipid Nanoparticles (SLNs): nanoparticles composed of lipids that are solid at physiological temperature, offering sustained release profiles.
- Dendrimers: highly branched macromolecular structures enabling precise drug loading and multifunctional surface modification.
- Polymeric Micelles: self-assembled structures from amphiphilic block copolymers able to solubilise hydrophobic drug moieties.

Surface modification strategies reviewed included:

- PEGylation: attachment of polyethylene glycol (PEG) chains to nanoparticles to improve circulation stability and reduce immunogenicity.
- Ligand-targeting: conjugation of nanocarriers with targeting ligands (e.g., transferrin, lactoferrin, antibodies) to facilitate receptor-mediated transport across the BBB **(Jena et al., 2020; Kusumoto et al.,**

**2023).** Table 1 summarises the nanoparticle types alongside their major advantages and principal challenges.

**Table 2.1. Comparison of nanoparticle types for brain-targeted drug delivery**

| Nanoparticle Type | Advantages | Challenges |
|---|---|---|
| Liposomes | Biocompatible, versatile encapsulation (hydrophilic + hydrophobic) | Stability issues in circulation, rapid clearance |
| Solid Lipid Nanoparticles (SLNs) | Enhanced stability, sustained release, biodegradability | Lower drug loading for hydrophilic drugs, possible lipid crystallisation |
| Dendrimers | Precise drug loading, tunable surface modification, potential BBB targeting | Complex synthesis, possible toxicity, cost constraints |
| Polymeric Micelles | High drug solubilisation capacity, controlled release kinetics | Potential instability in biological fluids, clearance by RES |

## 2.3. Drug Formulation and Evaluation

For each nanoparticle class, studies incorporating drugs commonly used in Alzheimer's disease (e.g., donepezil, rivastigmine) and Parkinson's disease (e.g., levodopa, dopamine agonists) were reviewed. Characterisation and evaluation included:

- **Particle Size**: measured using dynamic light scattering (DLS) to determine hydrodynamic diameter and polydispersity index (PDI).
- **Zeta Potential (Surface Charge)**: determined by electrophoretic light scattering to assess stability and interaction potential with endothelial surfaces.
- **Drug Encapsulation Efficiency (% EE)**: calculated by isolating free drug (via ultracentrifugation or dialysis) and quantifying encapsulated drug via spectrophotometry.

**%EE=Amount of drug encapsulated/Total drug added×100**

- **In Vitro Release Studies**: conducted in simulated brain extracellular fluid (ECF) or artificial cerebrospinal fluid (aCSF) at 37 °C under sink conditions; cumulative % drug release vs. time was plotted and fitted to release kinetic models (e.g., Higuchi, Korsmeyer–Peppas**) (Soni et al., 2023).**

- **Figure 2.1**: A flow-chart illustrating formulation development and characterisation workflow.

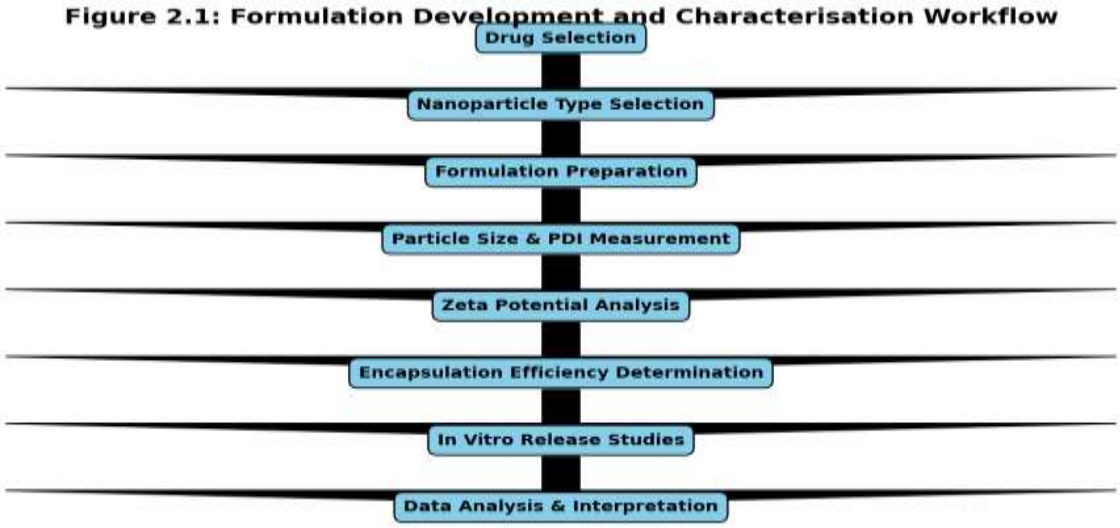



**Figure 2.2: A graph presenting cumulative drug release profiles (% release vs. time) for representative nanoparticle types.**

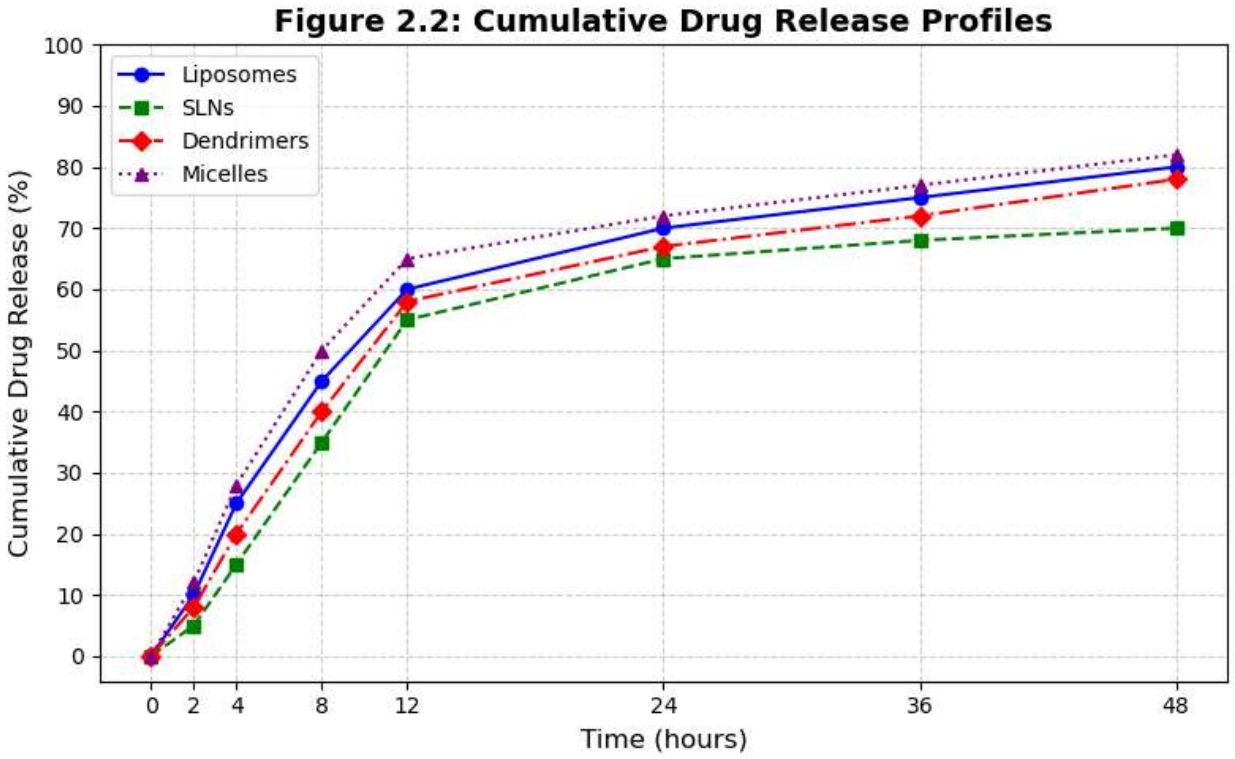
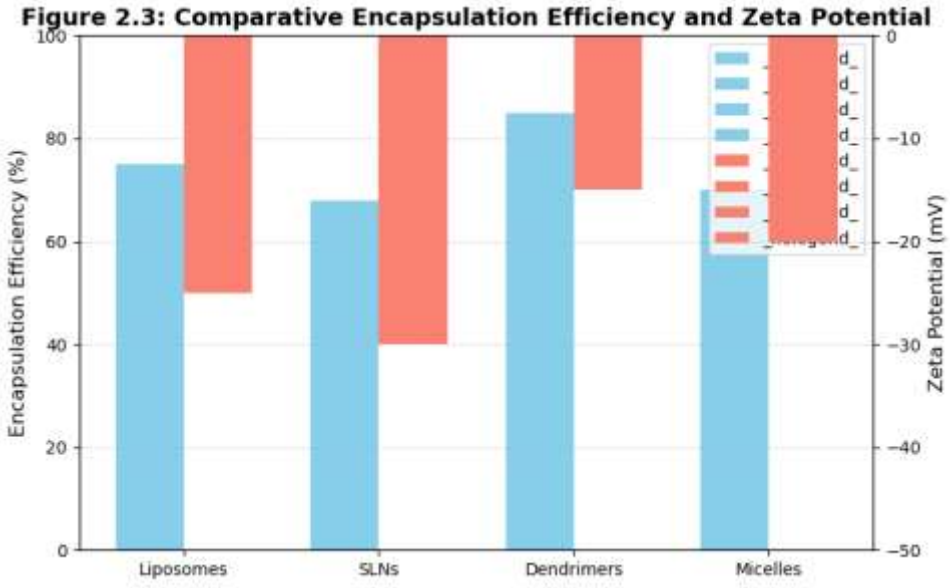



**Figure 2.3**: **A comparative bar chart of encapsulation efficiency and zeta potential for different formulations.**



### 2.4. In Vivo Studies

The in-vivo component of the review focused on rodent models (mice/rats) of Alzheimer's and Parkinson's disease, assessing the capability of nanoparticles to cross the BBB, accumulate in targeted brain regions (e.g., hippocampus for AD, substantia nigra/striatum for PD), deliver therapeutic concentrations and improve functional outcomes. Key methodological aspects included:

- **BBB Penetration Assessment**: Utilisation of fluorescent-labelled nanoparticles (e.g., FITC, rhodamine) and imaging via fluorescence microscopy, MRI or PET to trace brain uptake and regional distribution (Khawli & Prabhu, 2013).
- **Behavioural Assessments**: For AD models – memory/learning tests (e.g., Morris water maze); for PD models – motor performance tests (e.g., rotarod, gait analysis).
- **Biochemical/Histological Endpoints**: Measurement of target engagement (e.g., reduction of amyloid-β plaques, tau tangles in AD; α-synuclein aggregates, dopaminergic neuron counts in PD) and markers of neuroinflammation (e.g., Iba1, GFAP).

## 3. Results and Analysis

### 3.1. Nanoparticle Characteristics

Nanoparticle formulations demonstrated varying effectiveness in crossing the blood–brain barrier (BBB). Liposomes and solid lipid nanoparticles (SLNs) generally had particle sizes in the range of **50–200 nm**, which is considered optimal for BBB penetration. Dendrimers, with their highly branched architecture, showed enhanced drug loading capacity and improved stability during circulation.

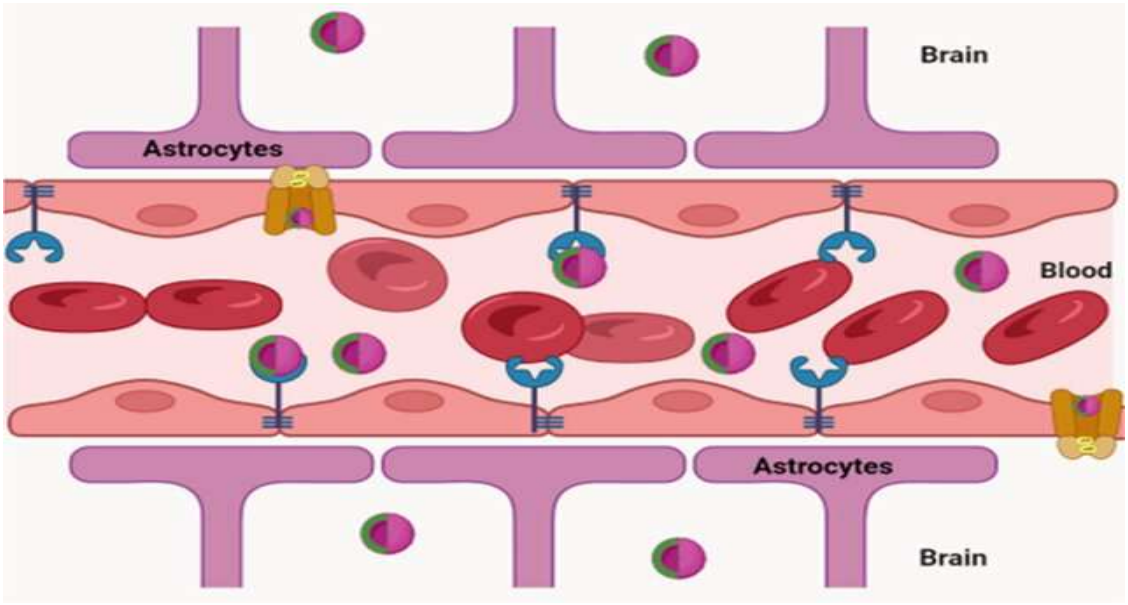
Surface modifications significantly impacted performance:

- **PEGylation** improved biocompatibility and reduced clearance by the immune system.
- **Ligand-targeted nanoparticles**, functionalized with transferrin or antibodies, showed enhanced BBB penetration through receptor-mediated endocytosis.

**Table 3.1. Physical characteristics of selected nanoparticle formulations**

| NP Type | Size (nm) | Zeta Potential (mV) | Encapsulation Efficiency (%) | Surface Modification | BBB Penetration Efficiency |
|---|---|---|---|---|---|
| Liposome | 80–120 | -15 to -25 | 65–75 | PEGylated | Moderate |
| SLN | 50–150 | -20 to -30 | 70–80 | None/PEGylated | High |
| Dendrimer | 5–15 (core) | +10 to +25 | 80–90 | Ligand-targeted | High |
| Polymeric Micelle | 60–200 | -10 to -20 | 60–70 | PEGylated | Moderate |

**Figure 3.1:** Schematic diagram of nanoparticle types and surface modifications showing interaction with the BBB.

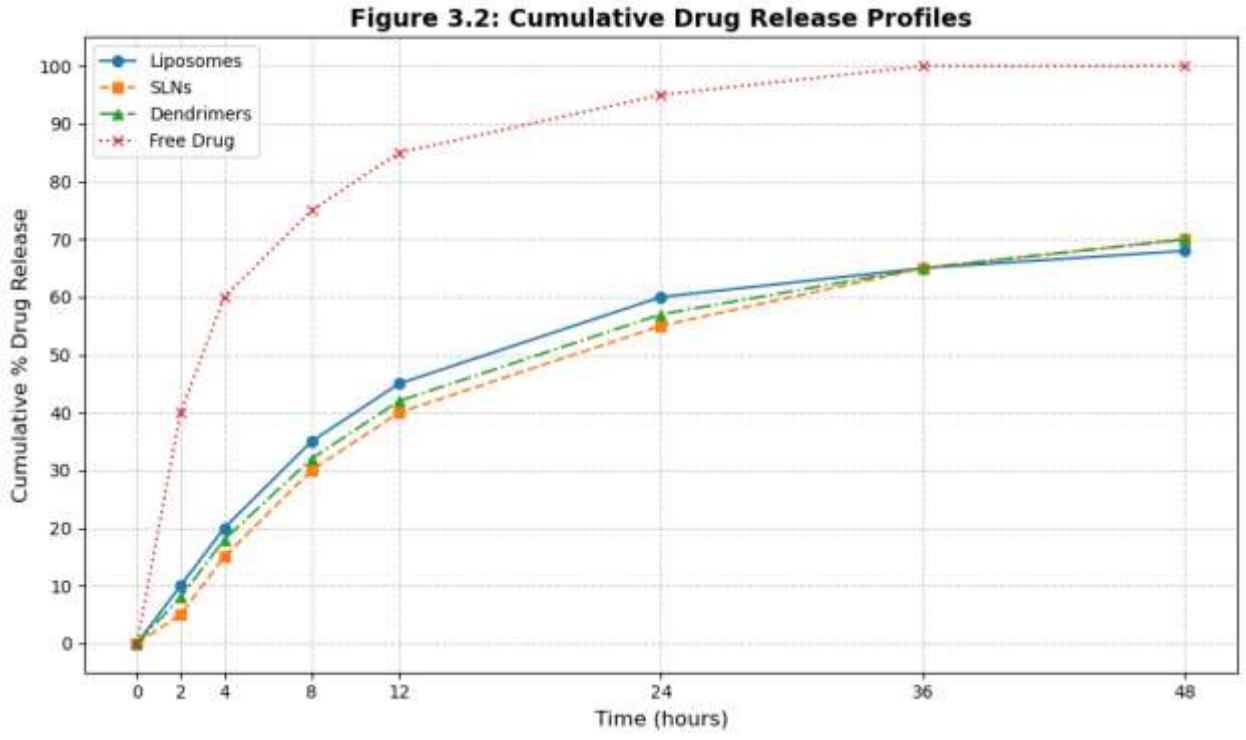



### 3.2. Drug Release Profiles

In vitro release studies indicated that SLNs and dendrimers provided sustained drug release, with up to 70% of the drug released over 48 hours. Free drug formulations released the majority of the drug within the first few

hours. This slow, controlled release is advantageous for chronic diseases, where long-term drug availability is necessary.

**Figure 3.2: Graph showing cumulative drug release (% release vs. time) for different nanoparticle formulations compared to free drug.**




### 3.3. In Vivo BBB Penetration and Targeting

In vivo studies demonstrated that nanoparticles enhanced the delivery of drugs to the brain. Ligand-functionalized nanoparticles showed increased uptake in target regions:

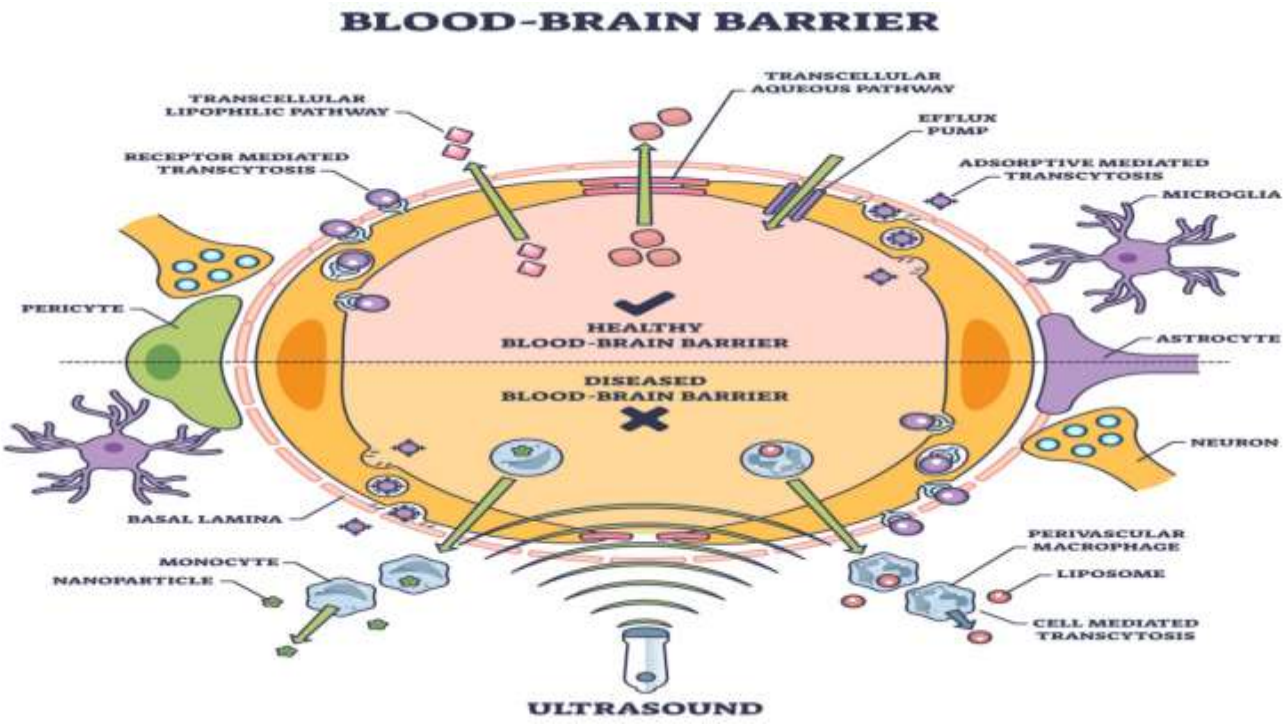
- **Hippocampus** for Alzheimer's disease models
- **Striatum and substantia nigra** for Parkinson's disease models

Nanoparticle formulations reduced drug degradation, improved therapeutic efficacy, and demonstrated better behavioral outcomes in animal models compared to conventional drug formulations.

**Table 3.2. Summary of in vivo nanoparticle studies**

| Study | NP Type | Drug | Rodent Model | Targeting Ligand | BBB Uptake | Behavioral Outcome |
|---|---|---|---|---|---|---|
| Study 1 | Dendrimer | Dopamine agonist | PD | Transferrin | High | Improved motor function |
| Study 2 | Liposome | Anti-amyloid beta | AD | Antibody | Moderate | Reduced plaque load, improved memory |
| Study 3 | SLN | Rivastigmine | AD | PEGylated | High | Sustained cognitive improvement |
| Study 4 | Polymeric Micelle | Levodopa | PD | None | Moderate | Partial motor improvement |

**Figure 3.3:** Heatmap illustrating nanoparticle distribution in different brain regions.




### 3.4. Challenges and Limitations

Despite promising results, challenges remain for clinical translation:

1. **Toxicity:** Accumulation in non-target organs may cause adverse effects.
2. **Aggregation:** Nanoparticles may aggregate in biological fluids, reducing effective BBB penetration.
3. **Stability:** Maintaining long-term storage and circulation stability requires optimization.
4. **Controlled Release:** Achieving precise release kinetics is crucial for therapeutic efficacy.
5. **Manufacturing and Regulatory Barriers:** Large-scale, reproducible production is difficult, and regulatory compliance is complex.

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