



Oral Delivery Systems for Alzheimer's Disease and Other Neurological Disorders: Recent Advances, Challenges and Future Perspectives

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ABSTRACT

Neurological disorders such as Alzheimer's disease, Parkinson's disease, epilepsy and other neurodegenerative conditions continue to create a major burden on patients, families and healthcare systems. Although several medicines are available, delivering an effective amount of a drug to the brain remains difficult. The blood-brain barrier (BBB) provides essential protection to the brain, but at the same time it restricts the entry of many therapeutic molecules. Oral administration is attractive because it is convenient, non-invasive and generally well accepted by patients. However, conventional tablets and capsules may be affected by poor solubility, gastrointestinal degradation, first-pass metabolism and limited distribution to the brain.

Recent developments in pharmaceutical nanotechnology have opened new possibilities for improving oral drug delivery. Nanoparticles, liposomes, solid lipid nanoparticles, nanostructured lipid carriers, polymeric nanoparticles, nanoemulsions, dendrimers and other lipid-based systems can protect drugs from degradation, improve solubility and modify release. Some formulations are also being designed to interact with biological transport pathways and improve exposure to the central nervous system. This review discusses the importance of oral delivery in neurological disorders, the major barriers to brain delivery, important advanced oral delivery systems, their mechanisms, benefits and limitations, and their possible applications in Alzheimer's disease and other neurological conditions. Although these approaches are promising, their successful translation will depend on safety, reproducibility, scalability and convincing clinical evidence.

Keywords: Oral drug delivery, Alzheimer's disease, neurological disorders, blood-brain barrier, nanoparticles, liposomes, nanocarriers, brain targeting.

1. INTRODUCTION

Neurological disorders cover a broad group of diseases affecting the brain, spinal cord and peripheral nervous system. Alzheimer's disease (AD), Parkinson's disease (PD), epilepsy, multiple sclerosis, Huntington's disease and other neurodegenerative conditions can progressively interfere with normal neurological function.

Alzheimer's disease is one of the most widely recognized neurodegenerative disorders and is characterized primarily by progressive memory loss and cognitive decline. Its pathology is complex and involves amyloid-beta deposition, abnormal tau protein, oxidative stress, mitochondrial dysfunction, neuroinflammation and neuronal injury [1,2].

Developing effective medicines for these disorders is particularly challenging because the brain is protected by the blood-brain barrier. The BBB controls the movement of substances between the circulation and the brain and therefore prevents many potentially useful drugs from reaching their intended site of action. Consequently, a compound can show encouraging activity in laboratory studies but still produce limited therapeutic benefit in vivo [3,4].

The oral route remains one of the most practical approaches for long-term treatment. Tablets, capsules and related dosage forms are easy to administer, non-invasive and suitable for self-administration. At the same time, orally administered drugs may encounter several barriers before they reach systemic circulation, including poor aqueous solubility, chemical or enzymatic degradation in the gastrointestinal tract and hepatic first-pass metabolism.

Advanced oral delivery systems are being developed to address some of these limitations. Nanotechnology-based carriers can improve dissolution, protect sensitive molecules and provide controlled release. In selected cases, surface engineering and targeting strategies may also improve interaction with biological barriers and transport pathways [5-8].

2. ALZHEIMER'S DISEASE AND OTHER NEUROLOGICAL DISORDERS

2.1 *Alzheimer's Disease*

Alzheimer's disease is a progressive neurodegenerative disorder in which memory and other cognitive functions gradually deteriorate. Amyloid-beta plaques and abnormal tau proteins are important pathological features, but they are accompanied by oxidative stress, mitochondrial dysfunction, neuroinflammation and synaptic or neuronal damage [1,2].

Several pharmacological approaches have been explored for symptomatic treatment and disease modification. Nevertheless, achieving adequate and sustained drug concentrations in the brain remains a central challenge. This has encouraged research into delivery systems that can improve exposure at the site of disease.

2.2 *Parkinson's Disease*

Parkinson's disease is associated with progressive loss of dopaminergic neurons and impaired dopamine signalling. Dopamine itself has very limited ability to cross the BBB, which is one reason why levodopa, a dopamine precursor, is used clinically.

Advanced oral formulations are being investigated to improve absorption, prolong drug action and potentially provide a more consistent delivery profile [9]. The aim is not simply to increase the amount of drug administered, but to obtain a useful concentration at the appropriate site while reducing unwanted systemic effects.

2.3 *Epilepsy*

Epilepsy is characterized by recurrent seizures caused by abnormal electrical activity in the brain. Although many antiseizure medicines are available, some patients experience inadequate seizure control or adverse effects.

Delivery systems capable of providing controlled release and improving the distribution of selected drugs to the brain may therefore have future value. However, brain targeting must be balanced with the need to maintain predictable systemic exposure and avoid toxicity.

2.4 *Other Neurological Disorders*

Nanocarrier-based approaches are also being investigated for Huntington's disease, multiple sclerosis, stroke, amyotrophic lateral sclerosis and brain tumours. Their versatility is particularly useful because nanocarriers can be adapted to transport small molecules, peptides, proteins and, in some cases, nucleic-acid-based therapeutics [6,10].

3. IMPORTANCE OF ORAL DRUG DELIVERY

The oral route offers several practical advantages compared with invasive administration. It is easy to use, generally well accepted and suitable for chronic treatment. It can also reduce the need for hospital-based administration and may improve adherence when the dosage regimen is simple.

Important advantages include:

- Easy administration
- Non-invasive treatment
- Good patient acceptance
- Convenient self-administration
- Relatively low cost
- Suitability for long-term therapy
- Availability of tablets, capsules, suspensions and other dosage forms
- Potential for improved treatment adherence

The main limitation is that the oral route does not automatically translate into efficient brain delivery. The drug must first survive the gastrointestinal environment, be absorbed, avoid excessive first-pass metabolism and reach the circulation in an active form. Even after reaching the blood, the BBB can substantially restrict its entry into the CNS.

For this reason, advanced oral systems are being studied with the aim of improving the overall pharmacokinetic profile rather than focusing on a single barrier.

4. BLOOD–BRAIN BARRIER AS A MAJOR CHALLENGE

The BBB is a highly selective interface formed by brain endothelial cells with tight junctions and supported by the basement membrane, pericytes and astrocytic components. Together, these structures regulate the movement of molecules between the blood and the CNS.

This barrier is essential for maintaining the brain's chemical environment and protecting neural tissue. However, it also limits the penetration of many therapeutic agents. Small and sufficiently lipophilic molecules may cross more readily, whereas many large hydrophilic molecules, peptides, proteins and other biologics have very limited passive permeability.

Efflux transporters at the BBB can further reduce brain exposure by moving certain compounds back into the circulation. Therefore, an effective delivery strategy needs to improve CNS exposure without causing unacceptable disruption of the barrier [3,4].

5. LIMITATIONS OF CONVENTIONAL ORAL DOSAGE FORMS

Conventional oral dosage forms can present several problems when used for neurological therapy.

5.1 *Poor Solubility*

A number of promising neurological drugs have low aqueous solubility. When dissolution is slow or incomplete, absorption can be reduced and exposure may become variable.

5.2 *Gastrointestinal Degradation*

Acidic conditions, digestive enzymes and intestinal metabolism can degrade some active ingredients before they are absorbed.

5.3 *First-Pass Metabolism*

Drugs absorbed from the gastrointestinal tract can undergo metabolism in the intestinal wall and liver before reaching systemic circulation. Extensive first-pass metabolism may substantially lower bioavailability.

5.4 *Limited BBB Penetration*

Even when sufficient drug reaches the bloodstream, the BBB may prevent an adequate fraction from entering the brain.

5.5 *Short Biological Half-Life*

Rapid elimination can result in fluctuating drug concentrations and the need for frequent administration. A controlled-release formulation may help maintain exposure for a longer period in appropriate cases.

These limitations explain the continuing interest in advanced oral delivery technologies.

6. NANOPARTICLES FOR ORAL BRAIN DELIVERY

Nanoparticles are small carrier systems that can be engineered to transport drugs with poor solubility, limited stability or unfavourable pharmacokinetic properties. Depending on the formulation, they can be made from polymers, lipids or other biocompatible materials.

Their potential advantages include improved solubility, protection from degradation, controlled release, enhanced absorption and, where appropriate, improved interaction with biological barriers. Surface modification can further introduce targeting ligands or alter the physicochemical properties of the carrier.

In Alzheimer's disease research, lipid-based, polymeric and other nanoparticle systems have been investigated to increase the exposure of therapeutic molecules to the brain [6,7]. Most of this work remains experimental, and the degree of actual BBB crossing depends strongly on the formulation, route and biological model.

7. LIPOSOMES

Liposomes are vesicular carriers composed mainly of phospholipid bilayers. Their structure allows them to incorporate both water-soluble and lipid-soluble compounds, making them versatile drug-delivery systems.

For neurological applications, liposomes can protect sensitive drugs, improve apparent solubility, modify release and potentially reduce exposure to non-target tissues. Their surface can also be engineered with selected ligands or polymers to influence circulation and interaction with biological barriers.

Liposomes have been investigated in Alzheimer's and Parkinson's disease research, but issues such as physical stability, drug leakage, reproducible manufacturing and regulatory characterization still need to be addressed before broad clinical translation [11].

8. SOLID LIPID NANOPARTICLES

Solid lipid nanoparticles (SLNs) are colloidal carriers in which the drug is incorporated into a solid lipid matrix. They can be useful for poorly water-soluble compounds and may provide protection and controlled release.

SLNs have attracted interest for CNS applications because lipid-based systems can improve the handling of lipophilic molecules and may influence interactions with biological membranes. Their advantages include generally good biocompatibility, the possibility of controlled release and protection of the encapsulated drug.

However, limited drug-loading capacity, particle aggregation and changes in the lipid matrix during storage can affect performance.

9. NANOSTRUCTURED LIPID CARRIERS

Nanostructured lipid carriers (NLCs) combine solid and liquid lipids. The less ordered lipid matrix can create additional space for drug incorporation and may overcome some limitations associated with conventional SLNs.

NLCs have been investigated for drugs and natural compounds relevant to neurological disorders. Potential benefits include improved solubility, physical stability, drug loading and bioavailability. Lipid-based nanocarriers are promising for CNS delivery, although the evidence base remains largely preclinical and clinical translation is still limited [12].

10. POLYMERIC NANOPARTICLES

Polymeric nanoparticles can be prepared from biodegradable and biocompatible polymers such as poly(lactic-co-glycolic acid) (PLGA). They are particularly useful when sustained or controlled drug release is desired.

The surface of polymeric nanoparticles can be modified with ligands intended to interact with receptors or transport mechanisms at the BBB. This has led to investigations involving small molecules, proteins and other therapeutic agents for neurological diseases [6,13].

The main challenges include control of particle characteristics, reproducibility, potential polymer-related toxicity and ensuring that laboratory-scale preparation can be translated into robust manufacturing.

11. NANOEMULSIONS

Nanoemulsions are dispersions of oil and water containing very small droplets. They can improve the apparent solubility and dispersion of poorly water-soluble compounds and may enhance gastrointestinal absorption.

Lipid-containing oral formulations can also influence intestinal lymphatic transport for selected drugs, potentially reducing the impact of hepatic first-pass metabolism. However, the extent to which these mechanisms improve brain exposure is formulation-dependent and should not be assumed for every nanoemulsion.

12. DENDRIMERS

Dendrimers are highly branched, three-dimensional macromolecules with multiple functional groups on their surface. Their architecture allows drugs or targeting ligands to be incorporated or attached in a controlled manner.

They have been explored for controlled drug delivery and brain targeting. Nevertheless, their biological behaviour can vary with size, surface charge and chemistry. Potential toxicity and long-term safety therefore require careful evaluation.

13. EXOSOME-BASED DELIVERY

Exosomes are naturally occurring extracellular vesicles released by cells and involved in intercellular communication. They can carry proteins, lipids and nucleic acids, which has made them attractive as potential biological delivery vehicles.

Their natural origin may provide useful interactions with biological systems, but it also introduces substantial manufacturing challenges. Consistent production, purification, characterization, storage and quality control remain important obstacles to clinical translation.

14. ORAL DELIVERY OF PHYTOCHEMICALS

Several plant-derived compounds have attracted interest because of their antioxidant, anti-inflammatory or other neuroprotective properties. Examples include curcumin, resveratrol and quercetin.

A major limitation of many phytochemicals is their poor aqueous solubility, rapid metabolism and relatively low oral bioavailability. Nanocarriers and lipid-based formulations may improve dissolution, protect the compound and increase systemic exposure.

Such approaches have been investigated in experimental models of Alzheimer's disease, Parkinson's disease and other neurological disorders [14]. However, improved formulation performance does not by itself establish clinical efficacy.

15. CURCUMIN AS A POTENTIAL EXAMPLE

Curcumin is a polyphenolic compound derived mainly from *Curcuma longa*. It has been studied for antioxidant and anti-inflammatory effects and has received considerable attention in neurodegenerative disease research.

Conventional oral curcumin has limited bioavailability because of poor aqueous solubility, rapid metabolism and rapid elimination. For this reason, several nanoformulations and lipid-based delivery systems have been developed to improve its dissolution and systemic availability [14,15].

Curcumin illustrates an important principle of advanced oral delivery: improving pharmacokinetics can make a promising compound more suitable for investigation, but increased bioavailability should not be interpreted automatically as proof of improved clinical benefit.

16. TARGETING STRATEGIES FOR BRAIN DELIVERY

Different strategies have been proposed to improve CNS delivery.

16.1 Passive Targeting

Passive targeting depends on properties such as particle size, surface characteristics, composition and interaction with biological barriers. It does not necessarily imply selective delivery to a particular brain cell.

16.2 Receptor-Mediated Transport

Nanocarriers can be decorated with ligands that interact with receptors on brain endothelial cells. Transferrin and insulin receptor pathways have been investigated as examples of receptor-mediated transport mechanisms [4,8].

16.3 Adsorptive-Mediated Transport

Electrostatic interactions between a carrier and the surface of endothelial cells may influence cellular uptake and transport. Surface charge must be carefully controlled because excessive positive charge can increase toxicity or nonspecific interactions.

16.4 Cell-Mediated Transport

Cells or cell-derived vesicles may act as carriers for therapeutic materials. This approach is still being investigated and requires careful evaluation of safety, targeting efficiency and reproducibility.

The overall objective is to improve CNS exposure while preserving the physiological function of the BBB.

17. ROLE OF NANOCARRIERS IN ALZHEIMER'S DISEASE

Nanocarriers are being explored in Alzheimer's disease because the pathology involves several interacting processes rather than a single molecular target. Potential areas of investigation include amyloid-beta accumulation, tau abnormalities, oxidative stress, neuroinflammation, cholinergic dysfunction and neuronal injury.

A carrier can, in principle, improve the stability and pharmacokinetics of an active molecule and may be engineered to influence its distribution. Nanoparticle-based approaches have therefore received substantial attention in experimental Alzheimer's research [7].

Despite encouraging preclinical findings, many systems remain at the laboratory or early translational stage. Differences between animal models and human disease, uncertainty about long-term accumulation or toxicity, and manufacturing complexity continue to limit clinical translation.

18. ADVANTAGES OF ADVANCED ORAL DELIVERY SYSTEMS

Advanced oral systems may provide several potential benefits:

1. Improved drug solubility
2. Better chemical and physical stability
3. Protection from gastrointestinal degradation
4. Improved oral bioavailability
5. Controlled or sustained release
6. Possible reduction in dosing frequency
7. Potential improvement in CNS exposure
8. Improved convenience and adherence
9. Ability to combine drug delivery with targeting functions
10. Possibility of reducing non-target exposure for selected formulations

19. LIMITATIONS AND CHALLENGES

Despite their potential, advanced delivery systems also have important limitations. Formulation complexity can make manufacturing expensive, while small differences in particle size, surface characteristics or drug loading may influence biological performance.

Other concerns include physical instability, drug leakage, aggregation, possible toxicity, limited long-term safety data and difficulties in achieving reproducible large-scale production. Regulatory assessment can also be challenging because nanomedicines may have several critical quality attributes that need to be controlled simultaneously.

Most importantly, promising results in cell cultures and animal models do not necessarily predict clinical success. Robust pharmacokinetic studies, toxicological evaluation and well-designed human trials are needed before these systems can become routine therapies [6,7,12].

20. FUTURE PERSPECTIVES

The future of oral brain-targeted delivery will depend on a better understanding of BBB biology together with the development of safe and reproducible carrier systems.

Artificial intelligence and computational modelling may assist in selecting carrier size, composition, surface properties and targeting ligands. Stimuli-responsive systems are another area of interest, with formulations designed to release drugs in response to pH, enzymes, reactive oxygen species or other biological signals.

Combination delivery may also be relevant to Alzheimer's disease because several pathological pathways can operate simultaneously. Future work should therefore move beyond simply increasing drug concentration and focus on achieving the right exposure at the right site for an appropriate duration.

Important priorities include:

- Detailed pharmacokinetic and biodistribution studies
- Long-term toxicity evaluation
- Standardized and scalable manufacturing
- Better control of particle characteristics
- More reliable targeting strategies
- Large-scale production methods
- Well-designed human clinical trials
- Clear regulatory pathways

Recent work on engineered nanoparticles highlights the potential of precision delivery, but also reinforces the need to demonstrate meaningful clinical benefit rather than relying solely on improved BBB transport [8].

21. CONCLUSION

Oral drug delivery remains one of the most practical and patient-friendly approaches for long-term management of neurological disorders. Nevertheless, conventional oral formulations can be limited by poor solubility, gastrointestinal degradation, first-pass metabolism, rapid elimination and restricted brain penetration.

Advanced systems such as nanoparticles, liposomes, solid lipid nanoparticles, nanostructured lipid carriers, polymeric nanoparticles, nanoemulsions and dendrimers offer several ways of improving drug stability, bioavailability and controlled release. Some systems may also be engineered to interact with BBB transport pathways.

For Alzheimer's disease and other neurological disorders, these technologies provide a promising research direction, particularly when they are used to solve a clearly defined pharmacokinetic or delivery problem. At present, however, many approaches remain preclinical or early translational. Their eventual success will depend on demonstrating consistent manufacturing quality, acceptable safety, predictable pharmacokinetics and clinically meaningful therapeutic outcomes.

Future research should therefore combine advances in nanotechnology with a deeper understanding of BBB biology and rigorous clinical evaluation. Such an approach will be essential for converting promising experimental delivery systems into practical medicines.

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Kumaravel. D had principal responsibility for the conception, design of the study and drafting of manuscript. P.Ranjitha was responsible for the revision of the manuscript for important intellectual content, Dr. J. Karthi, Dr. S. Swarnalatha contributed towards reviewing of the literature. All authors agreed on the final version of manuscript

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