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REVIEW ARTICLE

A Comprehensive Review of Nanoemulsions as a Potential Strategy for Treating Neurodegenerative Diseases

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Abstract: Neurodegenerative diseases represent a significant global health burden, characterized by progressive deterioration of the nervous system. Current epidemiological data indicates that neurological conditions affect over 40% of the global population, with projections suggesting this figure will double due to evolving lifestyle factors, socioeconomic conditions, and environmental influences. Among these conditions, Alzheimer's disease stands as the sixth leading cause of death worldwide.
The treatment of neurodegenerative diseases faces substantial challenges, particularly in drug delivery. Key biological barriers, including the blood-brain barrier, blood-CSF barrier, and blood-leptomeningeal barrier, significantly impede drug absorption from circulation into brain tissue. Effective treatment requires deep brain penetration while maintaining maximum therapeutic efficacy. Nanotechnology-based approaches offer promising solutions to overcome these delivery challenges. Nanoemulsions, in particular, represent an emerging pharmaceutical delivery system that demonstrates superior performance compared to conventional methods. Their advantages include enhanced penetration, rapid onset of action, improved drug solubility, and increased stability. This innovative approach addresses the pharmaceutical challenges of drug delivery in neurodegenerative diseases while offering potential solutions for targeted therapeutic outcomes.

Keywords: Neurodegenerative Diseases; Blood-Brain Barrier; Nanoemulsions; Drug Delivery Systems; Brain Targeting.

1. Introduction

According to the World Health Organization (WHO), dementia is described as a syndrome resulting from many diseases that progressively destroy nerve cells and impair brain function. Damage to the brain significantly affects cognitive functions leading to changes in mood, emotional control, behaviour, and motivation subsequently leading to more complicated conditions [1]. Neurodegenerative diseases not only impact physical health but also have a substantial impact on the socioeconomic condition of the country. In India about 8.8 million (7.4%) older people (above 60) have dementia having a high occurrence in women as compared to men and is increasing day by day. Reports showed that one in eight children in India has a neurodevelopment disability, and unhealthy changes in lifestyle worsen the condition in future [2, 3].

Early-stage identification of neurodegenerative symptoms is extremely important in controlling and treating diseases. Preclinical treatment (behavioral symptoms, brain conductivity and electrical conductivity, biomarkers from blood and cerebrospinal fluid, neuroimaging data) considered the factors before the onset of severe clinical symptoms [4]. Clinically while treatment, in disease control management neuroprotective anatomy and physiology of the brain, causes challenges. Naturally, the brain is protected from the entry of high molecular weight substances (toxins) and has very limited permeability for low molecular weight substances (endotoxins) [5]. The blood-brain barrier, blood CSF barrier, and blood leptomeningeal barrier are the main hindrances for the absorption of drugs from blood circulation to the brain.

Nanoemulsions have the advantage of nanosized particles which make them enable to cross these barriers and reach out to the brain cells. With this novel analytical technique, one is able to formulate a targeted drug delivery system which focuses on a specific area. Nanoemulsion provides the maximum permeability, solubility, absorption and bioavailability of the drug. It also reduces the dose and with targeted drug delivery helps to avoid unnecessary exposure of other healthy areas of brain ultimately reducing the side effects [6]. Recent advances in nanotechnology have demonstrated significant potential in treating neurodegenerative diseases, particularly through applications of nanoemulsions, nanoparticles, and nanotubules. Nanoemulsion-based delivery systems have emerged as a promising therapeutic approach, showing remarkable efficacy in controlling neurodegeneration. Multiple experimental

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studies have validated their effectiveness in enhancing drug delivery across the blood-brain barrier and improving therapeutic outcomes in various neurodegenerative conditions. The main objective of this review is to evaluate nanoemulsions as an innovative drug delivery system for overcoming blood-brain barrier limitations in neurodegenerative disease treatment.

2. Neurodegenerative diseases

Neurodegenerative diseases are syndromes known for their disorders include the loss of neurons and affect the performance of the functional system. The diseases are characterized by continuous and progressive dysfunction of the neuron along with its loss of it [7]. Statistical studies related to degenerative diseases show that in today's era many health issues related to cognitive dysfunction and neurodegenerative disorders include difficulties in learning abilities, schizophrenia, dementia, Alzheimer's and related diseases, Parkinson's disease, neuromuscular diseases, autism, motor disabilities, lateral sclerosis will become life-threatening because it not only affects the mental health but also social and economic life. The major factors associated with such kinds of diseases include chronic hypertension, oxidative stress, abnormalities in the performance of antioxidant enzymes, metabolic-related disorders, older age, genetic factors, environmental factors, mineral deficiency and vascular disorders [8]. Global studies suggest that 131.5 million people will be affected with neurodegenerative diseases by 2025 and this will progressively increase [9].

Clinical manifestation shows there is a deposition of proteins with altered physical physiochemical properties known as misfolded proteins are responsible for neurodegenerative diseases. This altered conformation shows the structural conformation of physiological protein change responsible for the change in the functions and increases in the excessive accumulation at intra and extracellular levels accordingly that it can be responsible for the decline in cognitive functions, propagate and responsible for alteration in brain functions at higher order. Anatomically it involves the neurocortical system, limbic system, entorhinal cortex, and hippocampus. Motor disorders include both hyperkinetic and hypokinetic movement disorders observed with symptoms related to the cerebellar and motor cortical area, thalamus, basal ganglia, and spinal cord [10].

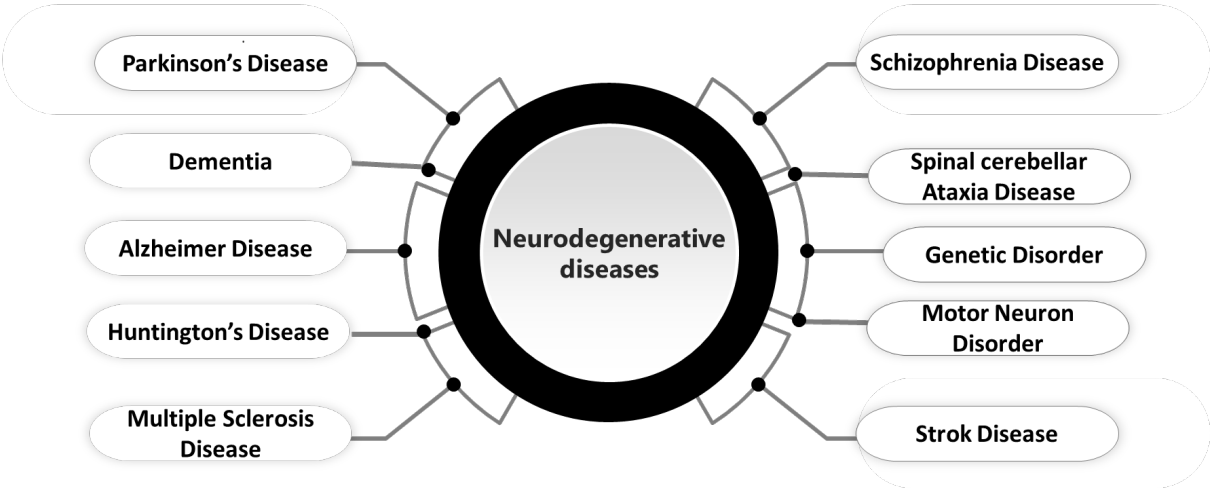

Figure 1. Different Types of Neurodegenerative Diseases

Among all types of neurodegenerative diseases, Alzheimer and Parkinson's and related diseases are in the leading position continuing with Huntington's disease [11].

Alzheimer disease (AD) is responsible for the degeneration of neurons in the brain, especially in the cerebral cortex part of the brain. AD progression can be understood by the formation of plagues and tangles. Formation of amyloid precursor protein plague which is found in the cell membrane of the brain. With normal physiology, this amyloid precursor gets broken by α secretase and γ secretase enzymes and gets solubilized after it's used within the brain. If it is cleaved by enzyme β secretase it forms insoluble fragments responsible for the formation of monomers called amyloid beta will be responsible for the formation of plaques. The unusual formation of plagues in the brain disturbs the neuron signal and causes brain function impairment which is signed with inflammation and damage of neurons. Secondly, tangles form within the cells. Neurons are positioned by microtubules which help in the transportation of nutrients to the brain cell with the help of protein. These microtubules do not break because of plagues present outside the cell, the same initiates the neuronal pathway which ultimately activates the kinase and transfer phosphate. This particular mechanism is responsible for the change in the shape of tau protein which does not support the microtubes and there is the formation of clumps called neurofibrillary tangles that lead to neuronal apoptosis. Both plague and tangle cause the death of neurons and change the functioning of the brain causing brain atrophy. Patients with AD show a damaging effect on language and memory because of brain atrophy. Even though the pathogenesis of AD is not clear, multiple factors include genetic alteration,

congenital immune response, ageing, neuronal inflammation, unbalanced diet responsible for neurodegeneration, synaptic loss and brain atrophy. AD is initially characterized by short-term memory loss with cognitive deficits due to neuronal damage [12-14].

The sample solution was prepared by transferring 0.16 mL of Lenacapavir sample to a 100 mL volumetric flask. The solution was sonicated for 30 minutes and centrifuged to ensure complete dissolution. A 5 mL aliquot was further diluted to 50 mL with diluent and filtered through a 0.45 µm filter before analysis [17].

2.1. Challenges for treatment of neurodegenerative diseases

The drug and the formulations specifically targeted for the central nervous system have to overcome the barriers including blood brain barrier (BBB) formed by particular cerebral endothelial cells. This BBB has low permeability for the low molecular weight molecules that depends on the physicochemical properties of the drugs and their interaction with ATP binding cassette transporters. BBB absolutely restricts high molecular weight molecules. The BBB acts as a vital barrier in the transportation of drugs from the systemic circulation to the central nervous system targeted region. Less bioavailability in targeted areas is the leading cause of failure of the treatment in neurodegenerative diseases. The second barrier is blood-cerebrospinal fluid barrier a natural barrier composed of tight junctions, having no fenestrae and low pinocytotic activity. The specific structure of the blood CSF barrier restricts the entry of high molecular structure and hence the efficiency of the drug in treating the diseases. Along with the blood CSF barrier blood leptomeningeal barrier also plays an important role in barrier in transportation of drugs across the CNS [15,16]

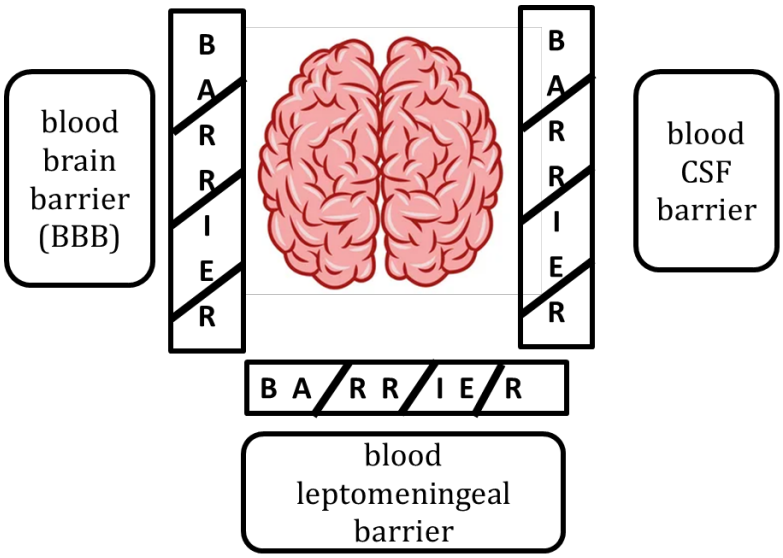

Figure 2. Different barriers to the efficient formulation of neurodegenerative diseases

As neurodegenerative diseases have a very complex nature their interactions between the accumulated proteins and brain pathology are still not fully understood. Such a complicated involvement of pathophysiology and etiology makes the treatment difficult. Most of the treatment gives symptomatic relief but is not able to stop or slow down the progression of diseases.

There are different drug delivery approaches including blood blood-brain barrier disruption approach, chemistry-based delivery system, biotechnology-based, intra-cerebral, intrathecal, intra-nasal drug delivery system and non-invasive drug delivery system for efficient delivery. Novel approaches like nanoparticles, tissue engineering, implants, and induced pluripotent stem cell approaches with advanced technology give auxiliary effects [17].

2.2. Treatment modalities for neurodegenerative diseases

As per a report, 7.7 million cases of dementia are diagnosed each year still very few drugs and treatments are available to cure or control the disease. Very few drugs have been approved by the US Food and Drug, Administration (US-FDA) (for example; aducanumab, galantamine, memantine, donepezil, and rivastigmine) [18].

Table 1. Current pharmaceutical approaches for treatment of neurodegenerative diseases

Treatment	Mechanism of action	Drug Example
Monoclonal antibodies	Helps in clearance of amyloid beta plagues (Protein misfolds and self assembles).	Aducanumab
Acetyl choline (Ach) Inhibitors	It acts as inhibitor for central Ach-esterase (pseudo-acetyl cholinesterase) through competitive inhibition or noncompetitive inhibition and increase the level of Ach in brain region	Tacrine, Donepezil, Galantamine, Rivastigmine
N- Methyl D-Aspartate (NMDA) Antagonist	Acting by voltage dependent N- Methyl D-Aspartate antagonist prevent malfunctioning of glutamate mediated neurotransmission at NMDA receptor.	Memantine

Table 2. Experimental pharmaceutical approaches for treatment of neurodegenerative diseases

Amyloid beta pathology	γ secretase inhibitors	Avagacestat (BMS-708163), Semagacestat (LY-450139).
	β secretase inhibitors	Elenbecestat (E2609), Lanabecestat, Verubecestat, Atabecestat, Umibecestat (CNP520)
	α secretase inhibitors	APH-1105, Etazolato (EHT0202).
	Aggregation inhibitors	Scyllo inositol, Peptidomimetics.
	Metal Interfering drugs	Deferiprona, Dyshomeotaisis
	Immunotheraly which improves amyloid beta plagues	Active immunotherapy (CAD 106, CNP520,GV1001) and passive immunotherapy (Crrenezumab, Gantenerumab)
Tau Pathology	Tau protein hyperphosphorylation inhibitors	Lithium chloride
	Tau protein aggregation inhibitors	Methylene Blue
	Immunotherapy	Anti tau vaccines
Other Treatment under Investigation	Nano medicine	Use of nano-transporters, nanotubes as a vehicles to cross blood brain barrier
	Intravenous immunoglobulin	-
	Plasma exchange	-
	Stem cell	-
	Intranasal insulin	-
	Hepatocyte growth factors	-
Alternative Therapies	Physical Activities	Aerobic exercise
	Diet	Nutritious diet with antioxidant
	Sleep Pattern	Bright light therapy, melatonin therapy
	Complementary therapy	Aromatherapy and music therapy

3. Nanoemulsions for neurodegenerative diseases

Nanotechnology has recently shown its tremendous applicability because of nanoscale features. The targeted drug delivery has the advantage of acting at specific, desired and required target areas without interfering with other areas. It helps to not only to reduce the side effects on untargeted cells but also reduce the dose. In the present case drug has to cross the blood brain barrier with improved lipophilicity, solubility and size reduction [19,20].

Reduced size of large drug molecules along with increased solubility can be achieved through the formation of nanoemulsion. Along with improved bioavailability nanoemulsion helps in the application by various ways including the parenteral, nasal, ocular and oral routes. Due to their lipid composition having great potential to cross the blood-brain barrier [21]. Nanoemulsion is a biphasic dispersion system consisting of a dispersed phase and a continuous phase that can be stabilized by selected emulsifying agents including cosurfactant and cosurfactant. Nanoemulsion having globule size in the range of 10nm to 1000 nm serve as a carrier for drugs. They are further classified as water in oil and oil in water emulsion. Nanoemulsion and microemulsion are differentiated depending upon their size and preparation methods. Administration of nanoemulsion by the intravenous way and the intranasal route is more effective because of its size (10 ppm to 100 ppm) [22-24].

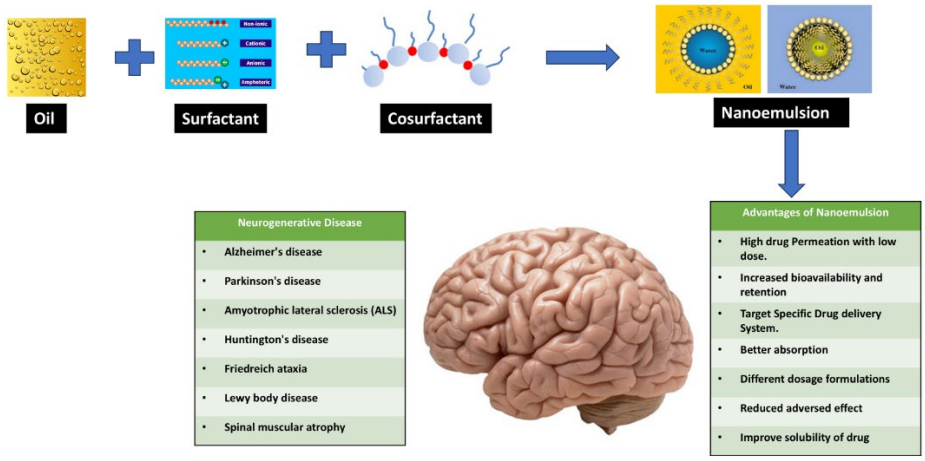

Figure 3: Nanoemulsion overview (images taken from open-access sources)

It can be employed by topical, ocular, nasal, oral, intraperitoneal and intramuscular route. Nanoemulsion is significantly employed because of its unique advantages includes increases solubility of less soluble drugs, hydrophobic drugs, improve the pharmacokinetic profile and reduces the side effect by target drug delivery system [25,26].

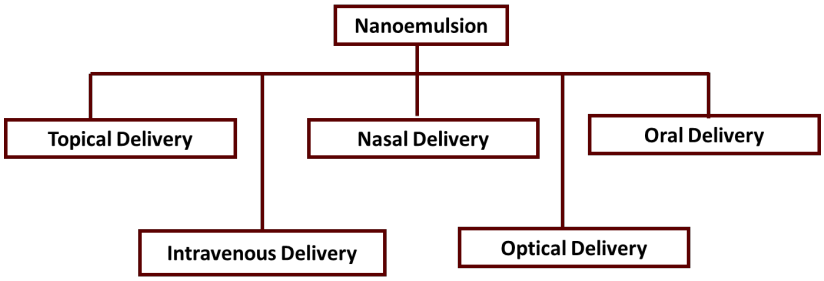

Figure 4: Different routes of administration of nanoemulsion

Table 3. Literature on nanoemulsions used in the treatment of neurodegenerative diseases

Name of the drug	Name of the neurodegenerative disease	Method Employed	Route of administration	Reference
Resveratrol	Parkinson's Diseases	Spontaneous emulsion method in adjuvant with high-pressure homogenization	Intranasal	[27]
Memantine	Alzheimer disease	Homogenization and ultrasonication methods	Intranasal	[28]
Rivastigmine	Alzheimer disease	Low energy method	Intranasal	[29]
Resveratrol	Alzheimer disease	Low energy method - ultrasonication	Intranasal	[30]
Donepezil	Alzheimer disease	Pre-homogenization with ultrasonication	Intranasal	[31]
Tacrine HCl	Alzheimer disease	Spontaneous emulsification followed by sonication	Nanoemulgel	[32]
Citicoline	Alzheimer and dementia diseases	Emulsification	-	[33]
Quetiapine	Psychotic disorder	High sheer method	Intranasal	[34]
Ziprasidone HCl	Psychotic disorder	Aqueous titration method	Intranasal	[35]
Letrozole	Epilepsy	Aqueous microtitration method	Intranasal	[36]
Rizatriptan	Migraine	Aqueous titration method	Intranasal	[37]
Levodopa	Parkinson's Disease	Response surface methodology	-	[38]
Galantamine	Neurodegenerative Diseases	Low energy emulsification method	Intravenous	[39]
Riluzole	Amyotrophic lateral sclerosis	Phase titration method	Intranasal	[40]

4. Conclusion

Nanoemulsions represent a promising advancement in the therapeutic approach to neurodegenerative diseases. Their unique physicochemical properties enable enhanced drug penetration across the blood-brain barrier, improved bioavailability, and targeted delivery to affected brain regions. Evidence from various studies demonstrates their potential in improving therapeutic outcomes while minimizing side effects. While challenges remain in optimizing formulation parameters and scaling up production, nanoemulsion-based delivery systems offer a viable strategy for addressing the current limitations in neurodegenerative disease treatment.

Compliance with ethical standards

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Conflict of interest statement

The authors declare no conflicts of interest.

Statement of ethical approval

The present research work does not contain any studies performed on animals/humans subjects by any of the authors.

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