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REVIEW ARTICLE

Inhaled Drug Delivery of Biologics for Therapeutic and Vaccination

Nanotechnology-driven Microemulsion Based Intranasal Delivery to Neurotechnology-driven Neuralink: Strategies to Improve Management of Neurodegenerative Disorders

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Abstract
Neurodegenerative disorder refers to malfunctioning of neurons their degradation leading to death of neurons. Among various neurodegenerative disorders APHD (Alzheimer's, Parkinson's, and Huntington's Disease) are particularly concerning due to their progressive and debilitating nature. The therapeutic agent used for treatment and management of APHD often show unsatisfactory clinical outcome owing to poor solubility and limited permeability across blood brain barrier (BBB). The nose-to brain delivery can overcome this BBB challenge as it can transport drug directly to brain though olfactory pathways bypassing BBB. Additionally, the nanotechnology has emerged as a cutting-edge methodology to address this issue and specifically mucoadhesive micro/nanoemulsion can improve the overall performance of the drug when administered intranasally. Beyond the therapy neurotechnology has emerged as are revolutionary AI-driven BCI (Brain computer interface) aimed to restore independence in patients with function loss due to neuron degeneration/death. A promising BCI Neuralink has been recently explored for clinical trials and results revealed that a quadriplegia bearing person with implanted Neuralink chip was able to perform few normal functions of daily routine such as playing online games, text messaging, reading, and learning foreign languages online through accessing the particular websites. This review will discuss the fundamental concepts of neurodegeneration, application of micro/nanoemulsion through intranasal route and integration of neurotechnology for the management and treatment of APHD.

Keywords alzheimer's · huntington's disease · neuralink · neurotechnology · parkinson's

Introduction

Brain is complex and most important organ of the body protected through skull frame, governed by neurons and separated through BBB (Blood brain barrier). It controls all the functioning of body and thus it considered to be very vital and essential organ. Any imbalance or disruption in neuron functioning leads to complication and if this degeneration continues it causes neuronal mortality give rise to neurodegenerative diseases [1]. Basically neurodegeneration describes the deterioration/ breakdown of the neuron cells in brain causing imbalance in the brain and body functioning leading to various diseases such as Alzheimer Parkinson's etc., characterized by decline/loss in motor function, memory loss, depressed thinking and intellect ability, unclear speech, collectivelyaffecting all the other day to day activities [2]. The neurodegeneration may arise from different regions of the brain viz. cerebellum, brainstem, and hippocampus. The foremost challenge in clearly identifying various neurodegenerative diseases is difficult (Alzheimer disease, Parkinson disease, Huntington disease, amyotrophic lateral sclerosis) owing to overlapping clinical syndromes which are similar in each case, making it difficult to differentiate them from one another [3]. The increasing frequency of neurodegenerative disorders imposes a significant healthcare burden worldwide and is a huge challenge to healthcare professionals. The compromised delivery of drug to the brain and restricted permeation across BBB is the major challenge offered by drug which limits its therapeutic relevance. Thus,

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it is imperative to develop delivery systems that can address these challenges [4, 5]. Last few decades have reported the designing of novel and effective therapeutic strategies which can significantly manage to permeate BBB leading to better management of neurodegenerative [6]. The novel delivery system comprises employment of nano carriers based on physiological processes and understating the mechanism behind BBB. These viable wagons can permeate BBB owing to lipophilic nature, small particle size as well as have modified release pattern, non-toxic nature, biocompatibility and are economic for patient population [7–9]. The nasal cavity is rich in vascularization and olfactory channels which can deliver drug directly to brain in a non-invasive manner. On the contrary these wagons if administered through nasal route often get eliminated via mucociliary secretion and to overcome this, newer viscos or mucoadhesive formulation have been fabricated, which enhances contact time, releasing drug over an extended period of time without getting eliminated [10]. In developing such formulations lipoidal nano-systems specifically micro/nanoemulsion have shown promising results that can efficiently deliver the drug to the brain. These systems can encase proteins, peptides, antibodies, small/large drug molecules leading to improved brain bioavailability and therapeutic efficiency [11, 12].

The review provides an insight of neurodegenerative disease specifically APHD (Alzheimer, Parkinson, Huntington's Disease), importance of intranasal delivery specific to micro/nanoemulsion and a brief vision of neurotechnology's-based BCI (Brain-computer interfaces) devices for management of neurodegenerative disorders. These BCI-implants can bring an improvement in patients suffering from such debilitating conditions and help them to become independent and regain their usual activities.

Complexity in the Human Brain

The brain is a very complex organ that controls and coordinates all the vital and basic functions of body that includes breathing, vision, movements, emotions, thought, memory, hunger, temperature, and every process that is going into body. Also, the brain and spinal cord together forms the central nervous system (CNS) [13]. The basic unit of brain is neuron, and the brain made up of approximately 86 billion neurons, 85 billion other cells, and around 100 trillion connections [14]. Further, the brain functioning is rather much more complex than its structure and the connection between neurons is very intricate to understand. Each neuron connects with thousands or even to ten thousand through synapses every second and the strength and pattern constantly keep changing [15]. The memories are stored in these changing connections, while repeating or reinforcing certain patterns results in habit learning and shaping. However, any disruption, degradation in the neurons lead to neurodegenerative disorder causing brain malfunctioning [16]. The main complexity of brain lies behind three barriers viz. BBB, BCSFB (Blood-Cerebrospinal Fluid Barrier) ACSFB (Arachnoid-CSF Barrier) which disconnects the circulating blood from the brain and extracellular fluid in the central nervous system restricting the entry permeation of almost all the compounds including therapeutic agents. BBB primarily protects brain by restricting entry of harmful substances and pathogens, ACSF barrier located at the arachnoid membrane parts the CSF from blood in subarachnoid space and protect brain through regulation of substance exchange between blood and CSF [17]. The third barrier BCSFB is made up of choroid plexus epithelial cells and regulates the production and composition of CSF fluid facilitating homeostasis and allow permeation of selective molecules, protecting brain [18]. These barriers are also responsible for limiting entry of most of the drugs into brain, specifically meant for neurodegenerative disorders, where a substantial concentration of therapeutic agent in brain tissue is a prerequisite for effective therapy. These limitations often lead to unsatisfactory therapeutic outcome for neurodegenerative diseases therapy.

Neurodegenerative Diseases

Neurons are essential for brain functioning and persistently undergoes neurodegeneration i.e. progressive loss in terms of structure, and/or functions, resulting in brain pathophysiology or sometimes several brain disorders [19]. Neurodegeneration is correlated with synapse dysfunction, neural network disruption, and the accumulation of physiochemically transformed proteins in the various regions of brain. The neurodegenerative diseases comprise Parkinson's disease, Alzheimer's disease, prion disease, motor neuron disease, Amyotrophic lateral sclerosis, Huntington's disease, spinal muscular atrophy, and spinocerebellar ataxia [19]. The neurodegenerative disorders are health concern worldwide and are life threatening as the stages progress. Further, as brain is responsible for proper functioning of body, and its malfunctioning may lead to multiple complications, improper and limited functioning of basic and complicated tasks such as declined memory, difficulty in speaking, weakened motor-activities, body balancing and many more [20, 21].

There are various mechanisms behind neurodegeneration which affects neurons, leading to the progressive loss of neural tissues and neuron death. The pathological mechanisms that contribute to neurodegeneration is represented in Fig. 1.

One of the reasons is misfolding of proteins which gradually accumulates. The hallmark of neurodegeneration is marked as aggregation of these protein, and triggers oligomer, where a non-native conformation is adopted, resulting in spreading towards other proteins, translating them into forms. Furthermore, misfolded proteins usually form

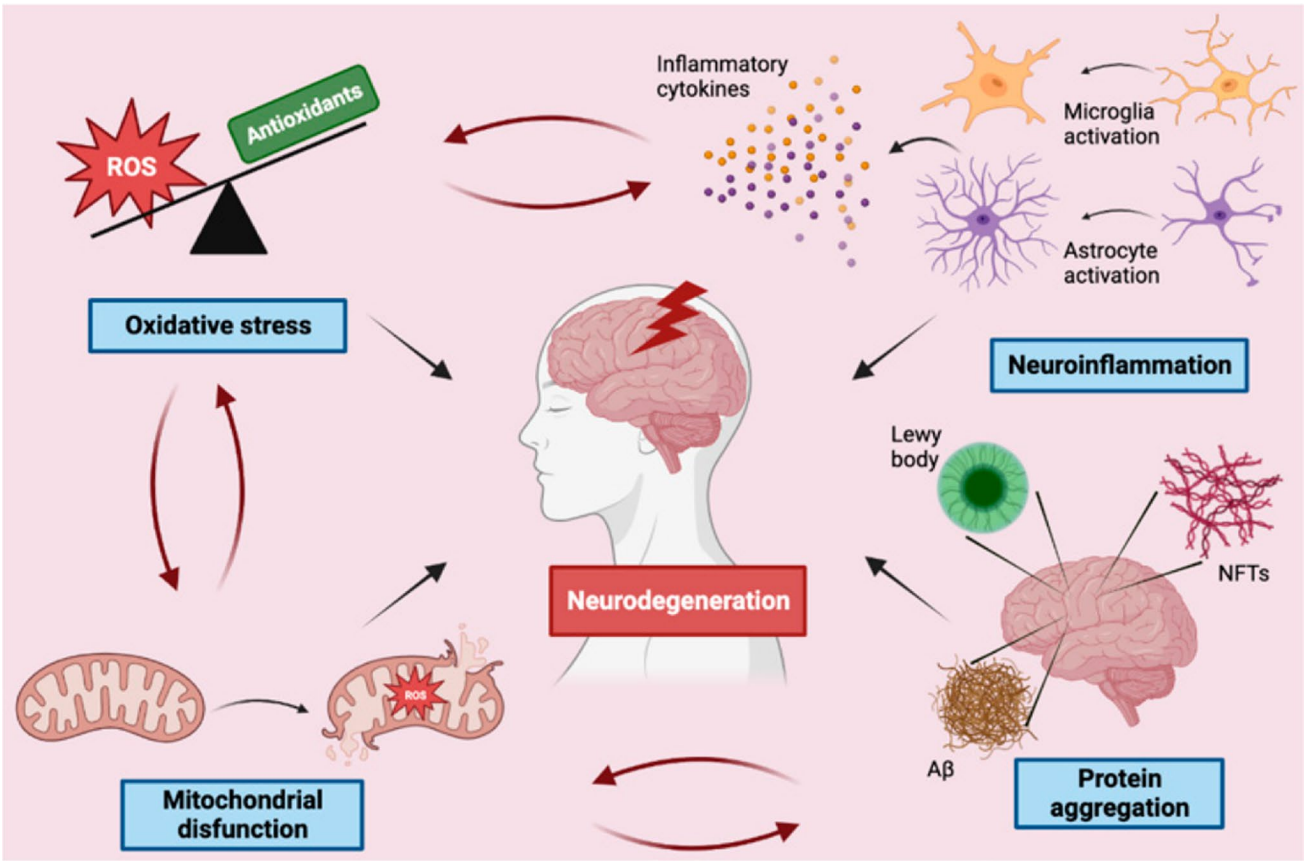

Fig. 1 Schematic representation of various mechanisms responsible for neurodegeneration. ROS-reactive oxygen species, NFTs-neurofibrillary tangles. (Reproduced with permission under CC BY-NC-ND license [22])

β-sheets rich intermolecular structures and assembles into small protofibrils leading to formation of extracellular or intracellular inclusions [23]. Different neurodegenerative diseases showcase specific types of protein aggregation e.g., β-amyloid plaques are confined to Alzheimer's disease; whereas misfolding of Tau protein is observed in all three APHDs; while α-synuclein inclusions is specifically observed in Parkinson's disease [24]. Besides aforementioned mechanism there are several others factors that leads to neurodegeneration comprises inflammation of neurons (neuroinflammation) credited to by microglia, astrocytes, and oligodendrocytes mediated immune response within CNS [25]. Neuroinflammation may lead to partial/complete brain damage, and it is often associated with aging, metabolic diseases, and certain infections. Microglia is involved in maintaining homeostasis, phagocytosis of abnormal proteins as well as responsible for repairing any damage in brain. Microglia has two phenotypes viz. M1 and M2 that have proinflammatory and anti-inflammatory properties respectively. M1 is culprit behind tissue damage as it produces inflammatory cytokines and chemokines, conversely M2 facilitates repair reduced inflammation, and neuronal survival. Likewise, in case of astrocytes, A1 phenotype is reactive astrocytes, causes neuroinflammation, and A2 phenotype assists protection of neurons supporting neuronal survival [26]. Another, contributing factor is dysfunction of mitochondria (caused by aggregation of Aβ and α-synuclein protein) evidenced by altered morphology, mtDNA mutations and impaired electron transport chain which initiates the early stages of neurodegenerative diseases. Contrariwise a normal mitochondrion plays a crucial role in energy metabolism, normal cell cycle, management of neurotransmission and apoptosis. The malfunctioning of mitochondria initiates synaptic and neuronal degeneration ascribing to high energy demand of brain [27]. Oxidative stress stands as a primary contributor to the majority of diseases that brings about ROS/RNS and antioxidant defences potential imbalance [28]. This imbalance results in deterioration or damage of DNA, proteins and lipids. The brain is highly sensitive and vulnerable to oxidative stress owing to high oxygen demand and consumption, polyunsaturated fatty acid rich content and low glutathione levels. The mitochondria is the prime source of ROS, and prolonged ROS exposure causes destruction of mitochondrial components and which

in turn triggers a vicious cycle of increased ROS production and cellular damage. In addition NOX2 (NADPH oxidase enzymes) has significant role in ROS generation responsible for neurodegeneration [29].

Mostly neurodegeneration progress continuously in increasing way, and the therapy is focused on improving the symptoms, pain relief and/or the regaining the body balance and mobility. There are several approaches for disease management that comprises either targeting disease pathogenesis or improving the symptoms as shown in Table I.

Conventional Therapies for Neurodegenerative Disease

Traditional therapies are intended to manage symptoms, delay disease progression, and improve quality of life. These include pharmacological therapies, non-pharmacological techniques, supportive care, lifestyle changes and use of assistive devices. Pharmacological Treatments: Drugs are commonly used to treat symptoms triggered by neurodegenerative disorders. Currently, several drugs exist to manage these symptoms. The drugs help in alleviating some symptoms of this disease; however, the progressive nature of many disorders eventually renders pharmacological therapy insufficient and ineffectual. A significant obstacle of pharmacological therapy is the low drug concentration that reaches the central nervous system (CNS) following administration. This is mostly due to the blood-brain barrier (BBB), which impedes effective transportation of drug to the brain. Levodopa and carbidopa, for instance, is frequently used to treat Parkinson's disease in order to restore dopamine levels and reduce motor symptoms. Cholinesterase inhibitors, such as rivastigmine and donepezil, are used to treat Alzheimer's disease by raising acetylcholine levels in the brain, which improves cognitive performance. Additionally, there are various drugs available which will help in treating symptoms like tremors, muscle stiffness, and sleep difficulties [33, 34].

Non-pharmacological Approaches

This group covers a range of assistive techniques for the management of neurological conditions, including supportive care, lifestyle changes, speech and occupational therapy, and physical and occupational therapy. Improved strength, balance, coordination, and mobility can be achieved with the help of physical and occupational therapy. Speech therapy helps people with speech problems by teaching them vocal muscle strengthening and articulation improvement strategies. Assistance with everyday tasks, emotional support, counselling, and education for patients and their family are all included in supportive care. Furthermore, leading a healthy lifestyle can improve general wellbeing in patients with neurodegenerative illnesses. A healthy diet, stress reduction methods, regular exercise, and enough sleep are a few examples of this. Apart from the above-mentioned approaches, assistive devices can be used. Various assistive devices can enhance independence and quality of life for individuals with neurodegenerative diseases. Examples include mobility aids like canes, walkers, and wheelchairs, as well as devices that assist with communication, such as speech-generating devices or eye-tracking technology [35].

In addition to the aforementioned approaches, assistive devices can be used to improve independence and quality of life for peoples with neurodegenerative diseases. Examples include assistive equipment for mobility (canes, walkers, wheelchairs), as well as tools for communication (eye tracking, speech generators, etc.) [36].

Challenges with Current Therapy

All the current therapies are targeted on management or controlling the progression of the disease, instead of working on eliminating the root causes. The foremost challenge is lack of ability of most of the drugs to cross BBB (Blood brain barrier), which result in poor accumulation at the desired site and finally lead to subtherapeutic levels making the therapy outcome as unsatisfactory [37]. The BBB is a diffusion barrier that limits entry of various substances present in blood into brain in order to protect and maintain normal brain's functioning and homeostasis. The BBB architecture forms from differential cells viz. neurons, astrocytes, microvascular endothelial cells and basal membranes that fuses together to make physically tight brain capillary system known as BBB. These tight junction lacks any fenestrations resulting in blocking of protein, small molecules diffusion into the brain. Additionally, the endothelial cells are connected to a continuous barrier via inter-endothelial junctions, limiting water-soluble substances transit into brain. The entry of drug molecules is being governed and restricted the diffusion and BBB penetration through the basal lamina, astrocytes, and pericytes which surround endothelial cells. Furthermore, the efflux transporters situated in the brain capillary, strengthen the barrier and facilitate substances return into the plasma that may have entered the brain. Auxiliary, the entry across BBB is also dependent on physiochemical properties of molecules viz. lipophilic nature, molecular weight, size, surface and charge [38, 39]. However, there are certain small molecules that can freely cross BBB facilitated through passive diffusion, while receptor-mediated transportation (insulin transporter, transferrin receptor, and glucose transporter-1) is seen for hydrophilic molecules. The pharmacokinetics of a drug is also crucial in predicting and deciding the concentration of drug in brain [40]. Among the various pharmacokinetic parameter (ADME) binding and distribution of drug plays the most crucial role in influencing drug accumulation in the brain tissue. Donepezil used for the treatment

Table I Pathophysiology of Various Neurodegenerative Disorders and the Mechanism of Drugs Used for their Management [30, 32].

Neurological diseases	Pathophysiology	Symptoms	Mechanism of action
Alzheimer's Disease	Amyloid plaques and tau tangles accumulation in the brain, leading to neuronal death and tissue loss	Memory loss, confusion, difficulty with language and decision-making, mood swings	Antagonize N-methyl-D-aspartate (NMDA) receptor to improve signal-to-noise ratio of glutamatergic transmission e.g. Memantine
			Acts by targeting and removing amyloid-beta plaques e.g. Aducanumab
			Prevent the knockdown of acetylcholine e.g. galantamine, rivastigmine, donepezil
Parkinson's Disease	Degeneration of dopamine-producing neurons in the brain, leading to impaired movement control	Tremors, bradykinesia (slowed movement), rigidity, impaired balance and coordination	Produces dopamine-like effects e.g. pergolide, rotigotine, apomorphine, ropinirole hydrochloride
			Replenish the decreased dopamine levels e.g. Levodopa
			Prevent peripheral breakdown of levodopa e.g. Carbidopa
Amyotrophic Lateral Sclerosis	Gradual and progressive deterioration of motor neurons in the brain and spinal cord	Muscle weakness, difficulty with speaking, swallowing, and breathing, muscle cramps and twitching	Scavenges Free radicals e.g. Edaravone
			Inhibits glutamate receptors e.g. riluzole
Multiple Sclerosis	Autoimmune attack on the myelin sheath of nerve fibers in the central nervous system	Fatigue, weakness, numbness or tingling, muscle spasms, difficulty with coordination and balance	Immunomodulators - Block immune cells from entering the central nervous system, reducing inflammation and preventing relapses e.g. fingolimod, natalizumab,
			Modify the activity of the immune system to reduce inflammation and prevent further damage to the myelin sheath e.g. glatiramer acetate, β-Interferon
Huntington's Disease	Genetic mutation leading to degeneration of nerve cells in the brain, particularly in the basal ganglia	Involuntary movements (chorea), cognitive decline, psychiatric symptoms, difficulty with speech and swallowing	modulation of glutamatergic neurotransmission, potentially reducing excitotoxicity and slowing disease progression e.g. riluzole
			acts primarily as a dopamine receptor antagonist, particularly at the D2 receptors. It can help manage the psychiatric symptoms such as irritability, aggression, and psychosis e.g. heloperidole
			inhibiting vesicular monoamine transporter 2 (VMAT2), thus reducing the levels of dopamine, norepinephrine, and serotonin in nerve terminals e.g. terbenazine

of Alzheimer's disease, has high plasma proteins binding, and thus less amount of free drug is available in circulation, resulting in poor transportation to the brain ascribing to low concentration of free drug [41]. Another such example is influenced through excretion is memantine, which possess fast elimination, leaving a very less amount in plasma, and making drug less available for permeation to brain. However, the BBB crossing and interaction of drug with target cell can be enhanced through nanocarriers via receptor mediated or passive diffusion [42].

Nose to Brain Delivery (Intranasal Delivery)

The above text discusses about the challenges that are encountered in treatment of neurodegenerative disorders, and the prerequisite of developing suitable drug delivery system. The basic disease progression comprises gradual and continuous loss of neuronal subtypes causing neural cell mortality and instigating declined brain function and finally loss of brain function by damaging brain's cortical structure. The therapy for such neurovegetative diseases, needs to be continued throughout life span of patients and mostly oral route is preferred to attain patient compliance and economic viability. However, most of the therapeutic agents such as biologicals, proteins peptides, drug molecules, genes, large molecule drugs and other natural medications employed for the management neurodegenerative disorders possess poor aqueous solubility and permeability, leading to low bioavailability. They often fail to cross BBB leading to subtherapeutic levels and even therapy failure [5, 43]. To overcome this, constrain one approach is to enhance solubility of the neuroactive drugs. However, this approach is plateaued as only improving the solubility doesn't ensure improved permeation across BBB. Thus, an advanced and effective delivery system is required capable of impeding drug delivery across the BBB to improve therapeutic efficacy and clinical outcome [43-47]. The scientists are continuously working on designing the nanocarriers that can facilitate drug transport across the BBB to the desired specific target in the brain that is progressing towards neurodegeneration. The brain targeting can be achieved through various strategies such as intra-parenchymal, intra-ventricular, intrathecal delivery, BBB disruption as well as non-invasive strategies such as prodrug, surface engineering of nanocarriers with some ligands that can specific affinity to some receptors available in brain [48]. Among various approaches intranasal delivery has attained interest of scientist and has been reported to improve permeation across BBB leading to enhanced therapeutic efficacy of drug via direct delivery through olfactory route and/or trigeminal nerve system and are innervating the nasal passage bypassing the BBB [49]. Thus, it is feasible approach to deliver the drug, large proteins and polysaccharides directly to brain through intranasal administration ascribing to unique link present in the brain amongst olfactory and trigeminal nerves and the external environment as well as delivery through intracellular and extracellular pathways [50–52]. The mechanism behind intracellular drug delivery through nasal mucosa comprises a series of transportation process viz. axonal transport to their synaptic clefts, exocytosis into the olfactory bulb, endocytosis by sensory olfactory cells, exocytosis into the olfactory bulb. Simultaneously, the drug is directly transported to CNS through extracellular pathway utilizing paracellular space of nasal epithelium and subsequently through perineural space into the subarachnoid space of the brain [53]. However, both intracellular and extracellular pathways contributes equally in transportation of drug, but intracellular pathway is reasonably slow and incapable of drug delivery beyond the projections of the olfactory bulb limiting payload permeation across various brain regions. The preferred region for nose to brain delivery is olfactory epithelium which is present at the upper nasal cavity as it is highly vascularized and presents effective absorption surface area and direct connection to the CNS, facilitating rapid drug transportation [54, 55]. Further, this transportation can be even enhanced more using suitable cargos bestowed with high entrapment ability, nano size range, flexibility of surface engineering, substantial stability and site-specific targeting attribute [56, 57]. Among the various wagons available lipoidal nanocarriers, soft nanocarriers have attained much attention and scores high success in delivering the encased drug efficiently into the brain vicinity through intranasal route when compared with oral administration [58, 59]. The delivery mechanism of drug through intranasal route is represented in Fig. 2.

Currently a lot of pre-clinical research is undergoing clinical trials for establishing ability of nose to brain delivery of various drugs/biological molecules for various aliments and are summarized in Table II.

Micro/Nanoemulsion as Efficient Wagons for Neurodegenerative Disorders

As previously discussed, the challenges associated with drugs and therapeutic approaches for the management of neurodegenerative diseases are significant. However, the nanotechnology has emerged as a revolutionary solution to overcome these challenges by offering precise, site-specific targeted drug delivery to the brain. This innovative approach assists to overcome the limitations of conventional therapies, improving therapeutic efficacy and patient outcomes. Drug delivery through nanocarriers has numerous advantages as discussed in above section among which the permeation efficiency to cross BBB is of special interest and nanocarriers can efficiently overcome the BBB [72, 73]. The nanocarriers are also capable of improving the pharmacokinetics of a drug

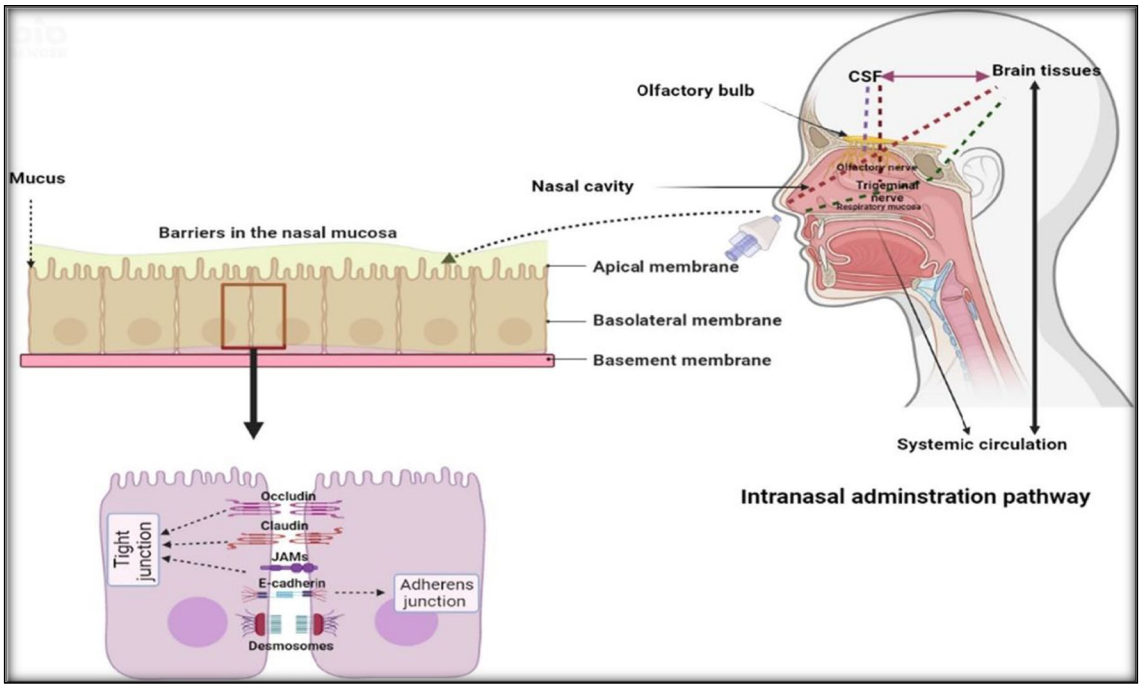

Fig. 2 Nose-to-brain drug delivery. [Reproduced with permission under CC BY-NC-ND license [60]]

when encased into lipoidal wagons (liposomes, NLCs, micelles, nanoemulsion *etc*.), leading to reduced toxicity, improved permeability, brain bioavailability and overall improved therapeutic efficacy [58, 74,75]. These wagons are also capable of protecting the drug from enzymatic degradation during transit before reaching the brain. Furthermore, in addition to lipoidal nano-wagons the other nanocarriers employed for encasing drugs for brain delivery comprises niosomes, liposomes, polymeric and metallic nanoparticles, dendrimers, silica nanodepletor, magnetic nanoparticles etc., which facilitates brain targeting and enhancing retention time through sustained steady-state therapeutic concentrations over extended time span [76]. The literature has reported that lipoidal wagons specially microemulsions and nanoemulsions outperforms conventional therapy as well as other nanoparticulate system in terms of improved drug delivery and therapeutic efficacy of the encased drug [77]. The microemulsion/nanoemulsion offers fabrication flexibility in terms of globule size, surface charge, high kinetic stability, HLB balance, facile surface engineering and scale up which make them ideal cargos for nose to brain delivery targeting the affected nerves [12, 78, 79]. All these attributes make micro/nanoemulsion as a choice for developing brain targeted delivery system meant for intranasal route [80].

Microemulsion/Nanoemulsion as Potential Cargos for Neurodegenerative APHD

The microemulsions and nanoemulsions are biphasic delivery systems ranging in a nanometre range and can effectively entrap lipophilic drugs. The microemulsions are thermodynamically stable and opaque /semi-transparent in nature whereas nanoemulsions are transparent and thermokinetically stable. Both are suitable cargos for drug delivery and offer modified release, improved solubility and enhanced payload in brain vicinity [81].

Alzheimer's Disease

Alzheimer's disease is a progressive neurodegenerative ailment that stands as one of the most prominent disorders across the globe and is recognized by profound dementia. It is a health burden and unfortunately has no satisfactory therapy/ cure currently. The initial stage is characterized by short-term memory loss which progress to more severe disabilities owing to neuronal damage [82, 83]. The aggregation of misfolded tau protein is the basic pathogenesis behind the disease although the pathogenesis is not entirely clear. These malfunctioning of tau protein brings about intraneuronal neurofibrillary tangles and extracellular senile plaques formation leading to neuronal loss

Table II Clinical Trials Studies of the Various Therapeutic Molecules Administered Through Intranasal Route for the Treatment of Neurodegenerative Diseases [61] *Estimated

NCT number and sponsors	Therapeutic molecules and disease	Year of completion	Number of subjects enrolled and phase	Description	References
NCT01398748 Bastyr University	GSH (reduced Glutathione) for Parkinson's	January 2016	34, Phase I single ascending dose escalation study.	CAM therapy (Complementary and alternative medicine), aimed at assessing the absorption profile, safety and tolerability.	(62)
NCT04251585 HealthPartners Institute	Insulin for Parkinson's	July 2024*	30*, Phase II	Aimed at investigating tentative outcomes of intranasal administration of insulin on Parkinson's associated symptoms such as cognition, mood, apathy and motor function for 3week period.	(63)
NCT02064166 Peter Novak	Insulin for Parkinson's	September 2015	15, Phase II	The study involves assessment of improved therapeutic efficacy of intranasally administered insulin for Parkinson disease and multiple system atrophy (MSA) in terms of altered cognitive scale ratings.	(64)
NCT03260920 Lawson Health Research Institute	Syntocinon (Synthetic oxitocin) for frontotemporal dementia/Pick's disease.	December 24*	112*, Phase II	The study is aimed at assessment of the safety, tolerability and improved behaviour effects after intranasally administrated spray in patients having frontotemporal dementia/Pick's disease.	(65)
NCT02324426 University of Washington	GSH	March 2015	15, Phase I	This study's primary goal is to look into the improvement of brain concentration/uptake (accumulation) after 200 mg dose of GSH in Parkinson's patients	(66)
NCT02424708 Bastyr University	GSH	April 2016	45, Phase II	The study explored the improvement in Parkinson's disease patients subsequent to intranasal administration of GSH via a nasal spray.	(67)
NCT05266417 Gateway Institute for Brain Research	Insulin and GSH	August 2024*	56*, Phase II	The study is focused on investigating the safety and therapeutic efficacy of insulin and glutathione in Parkinson's Disease patients.	(68)
NCT01386333 Lawson Health Research Institute	Oxytocin	October 2013	23, Phase I	The study investigates the safety and tolerability of 3 different biweekly doses of oxytocin given through intranasal in patients suffering with Frontotemporal Dementia	(69)
NCT05493462 Zhittya Genesis Medicine, Inc	FGF-1 (human fibroblast growth factor 1)	December 2022*	04*, Phase I	The main aim of this study is to assess safety profile, tolerability and therapeutic efficacy of FGF-1 when delivered through intranasal route in patients with idiopathic, stage III/IV Parkinson's disease.	(70)

Table II (continued)

NCT number and sponsors	Therapeutic molecules and disease	Year of completion	Number of subjects enrolled and phase	Description	References
NCT04110678 International Center for Neurological Restoration, Cuba	NeuroEPO (non-hematopoietic recombinant erythropoietin)	January 2017	26, Phase I&II	The study aimed at A investigating NeuroEPO for its neuroprotective potential in patients with neurological disorders in terms of safety and efficacy when administered intranasally in Patients of Parkinson Disease	(71)

and activation of activation of microglia. Also, the innate immune responses, genetic alterations, systemic neuronal inflammation, ageing are the contributing factors that lead to neuronal degeneration diffuse brain atrophy and synaptic loss [12, 84]. At present, the management of disease symptoms and reduce disease progression are the only therapy available that can improve patient's life quality. Most of the approved drug for treating Alzheimer's often encounters challenges of inadequate solubility and permeability across BBB which leads to unsatisfactory clinical outcomes. Consequently, various formulation scientists have explored an alternative pathway and formulation approach through intranasal route to improve brain bioavailability and therapeutic outcome. However, the nasal clearance poses a barrier for such formulations, which has been addressed through the development of mucoadhesive micro/nanoemulsion as they are bestowed with high permeation potential across BBB, and are discussed in the coming Sections [3, 85].

In recent decades repurposing of drugs has emerged as a new treatment option of an existing drugs as a new indication. The repurposing saves time, risk of unforeseen adverse effects and time for regulatory approval. Working on the same line Wen *et al*., conducted a study and suggested that the NSAIDs (non-steroidal anti-inflammatory) drugs such as ibuprofen, can be prescribed to reduce the Alzheimer's disease development risk. They design microemulsion formulation for intranasal administration that can deliver drug directly to target brain. The colloidal dispersion showed a globule size, zeta potential (electrokinetic potential) and pH of 166.3 ± 2.55 nm, -22.7 mV, and 4.09 ± 0.08 respectively. The drug loaded microemulsion exhibited a drug release of 90%. Further, the result of *in vivo* studies in revealed higher brain uptake of ibuprofen by 4-fold when compared with reference solution, and a 10-fold higher uptake when compared with intravenous and oral administrations. These results that the repurposing strategy of ibuprofen administrated through intranasal route has a promising future for Alzheimer's therapy [86]. Similarly, Wang *et al*. conducted a study on osthole (coumarin compound) loaded microemulsion. Osthole has poor aqueous solubility which limits its clinical application for neurodegenerative diseases. This, challenges were suitably addressed through loading the drug into microemulsion. The microemulsion pharmacokinetics data revealed that subsequent to intranasal administration the drug-loaded microemulsion significantly enhanced brain targeting compared to oral administration. Further, the microemulsion promote cell death inhibition, declined pro-apoptotic protein expression (Bax and caspase-3), conversely displayed enhanced antioxidant enzyme activity (superoxide dismutase and glutathione) in L-glutamate-induced SH-SY5Y cells. Further, in Alzheimer's-induced animal model the Osthole-loaded microemulsion showed improved the spatial memory ability, upgrades

acetylcholine concentration in the cerebral cortex, and decrease acetylcholinesterase activity in the hippocampus of mice. The study conclude that the bioavailability and drug accumulation in brain improved when microemulsion was administered via intranasal route and is a promising alternative [87]. A study conducted by Nasr describes fabrication of a mucoadhesive microemulsion co-loaded with resveratrol and curcumin employing hyaluronic acid- for nose to brain delivery. The spherical globules displayed a droplet size and electrokinetic potential of 115.2 ± 0.15 and of -23.9 ± 1.7 respectively and strong mucoadhesive strength. Concomitantly, the microemulsion prevents degradation, restoring antioxidant attributes of the loaded phytopharmaceuticals during transit and displayed diffusion-controlled release pattern over a period of 6 h with an ex vivo flux of 2.09 and 2.86 μg/cm^2 for curcumin and resveratrol correspondingly across sheep's nasal mucosa. Also, a 9-fold and 7- fold increased AUC_0^7 for curcumin and resveratrol respectively. The results signifies microemulsion as a suitable carrier for co-encasing of two drugs meant for intranasal delivery [88].

Another naturally occurring potent phytochemical curcumin has also reported to have applicability in Alzheimer's therapy, but its clinical application is limited ascribing to poor aqueous solubility and poor permeation to BBB. To address these challenges Phongpradist and coworker developed microemulsion formulation for trans-nasal route. This study depicts the optimisation of KLVFF-conjugated (motif Lys-Leu-Val-Phe-Phe peptide) curcumin-loaded microemulsion-base hydrogel and investigated its physiochemical attributes, aggregation activity, anti- cholinesterase activity. The prepared microemulsion gel exhibited significant hardness and adhesiveness. The optimized KCMEG was subjected to various evaluations viz. pH, Spreadability, and mucoadhesive attributes. The formulation showed substantial mucoadhesive potential, pH of 5.80 ± 0.02 and non-toxic to porcine nasal mucosa (ciliotoxicity). The study suggested that incorporation of carbopol imparts mucoadhesive property to the microemulsion leading to enhanced retention time and finally improved brain delivery of the drug proving intranasal delivery as a promising delivery system for treating Alzheimer's [89]. In a study Zhang *et al*., developed nimodipine-loaded microemulsion for intranasal route and evaluated it for brain uptake against neurodegenerative disorders using various non-ionic surfactants specifically Cremophor RH 40, Labrasol and oils isopropyl myristate, Labrafil M 1944CS. The optimized microemulsion displayed a globules size of 30.3 ± 5.3 nm and displayed no ciliotoxicity. The developed nimodipine-loaded microemulsion revealed peak plasma concentration at 1 h with an absolute bioavailability of 32%. Additionally, the intranasally administered microemulsion displayed a 3-fold elevated olfactory bulbular uptake when compared with i.v. administration, suggesting it as a promising wagon for brain delivery drugs meant for prevention and treatment of neurodegenerative diseases [90]. Suthar *et al*., also formulated dihydroflavone hesperidin-encased microemulsion employing Tween® 80, and Solutol® HS15, aimed at improving solubility and henceforth dissolution of poorly aqueous phytopharmaceutical. The formulated microemulsion displayed fast release pattern which was contrary to naïve drug indicating improved aqueous solubility and dissolution. Further non-toxic attribute was confirmed through nasal ciliotoxicity studies on goat mucosa suggesting microemulsion safety for nose-to-brain delivery. Also, a substantially higher dose-dependent cellular uptake was demonstrated with microemulsion in SH-SY5Y cell lines along with cytocompatibility suggesting that such formulation can be further explored as a promising therapeutic strategy for effective treatment against neurodegenerative diseases [91].

Likewise, the therapeutic efficacy of Donepezil is also compromised and to improve this Espinoza *et al*., developed nanoemulsion formulation for intranasal delivery. The nanoemulsion-based gel was formulated employing Pluronic F-127 and penetration enhance and evaluated for physical attributes, stability release profile, and ex vivo permeation. The prepared formulations displayed monophasic transparent homogeneous and pseudoplastic character and exhibited substantial physical stability. The formulation showed significantly higher permeation through nasal mucosa when compared with free drug credited to bio adhesion and subsequently increased bioavailability [92]. Similarly, Kaur *et al*., attempted development of donepezil-loaded nanoemulsion for intranasal delivery. The donepezil-loaded nanoemulsion was formulated employing labrasol, cetyl pyridinium chloride and glycerol and assessment was performed for numerous *in vitro* and *in vivo* attributes. The donepezil-loaded nanoemulsion exhibited a globule size, electrokinetic potential of 65.36 nm and −10.7 mV respectively. Further a variable percentage release of 99.22%, 98% and 96% was observed over a period of 4 and 2 hours in phosphate-buffered saline, artificial cerebrospinal fluid and simulated nasal fluid respectively. The formulation holds significant antioxidant potential dose-dependent cytotoxicity with no harm to cellular morphology as indicated through giemsa staining images. Further an enhanced uptake was evidenced through scintigrams suggested the nanoemulsion as a promising alternative for brain delivery [93]. Another study conducted Kaur *et al*., describes formulation of memantine-loaded nanoemulsion for Alzheimer therapy. The nanoemulsion displayed an ultra-small globule size of 11 nm, % transmittance of ~99%, and 80% drug release in simulated nasal fluid. The prepared nanoemulsion was found to be non-toxic and holds promising antioxidative potential. Further *in vivo* studies performed with technetium pertechnetate-labelled (radiolabelling) nanoemulsion displayed higher uptake of formulation in animal brains (rats) subsequent to intranasal

administration after 1.5 h suggesting improved and direct delivery to the brain [94]. Similarly, Shah *et al*., conducted a study aimed at developing Rivastigmine-loaded microemulsion/ mucoadhesive microemulsion and it's evaluated its permeation potential through intranasal administration in in-vitro and ex-vivo models. Rivastigmine is a reversible cholinesterase inhibitor and has certain limitations viz. poor bioavailability of 36%, massive first-pass metabolism, which limits its pharmacological usages. On the contrary it holds extensive aqueous solubility due to which it exhibits poor permeability, thus requires repetitive oral dosing frequently. The mucoadhesive microemulsion was formulated employing chitosan. The prepared microemulsion presented droplet size and zeta potential ranging between 53.8 and 55.4 nm, and − 2.73 mV -6.52 mV, respectively. Further, the *in vitro* studies revealed that mucoadhesive microemulsion exhibited Higuchi model ($r^2 = 0.9773$) revealing diffusion mechanism of release, and was found to be non-toxic to nasociliary mucus with a stability hold of 3 months. However, further *in vivo* evaluations are required to establish the improved biodistribution and anti-Alzheimer's potential of the microemulsion formulations [95]. Another study completed by Sharma *et al*., describes formulation morin hydrate-loaded microemulsion for nose to brain delivery. The *in vivo* studies discovered significantly improved drug accumulation in the brain vicinity after intranasal administration of microemulsion relative to naïve morin hydrate. Furthermore, *in vivo* pharmacodynamic parameters in Streptozotocin-induced dementia results suggests a significant improvement in memory in microemulsion fed group when comped with sham control group subsequent to 21 days of treatment [96] .

These studies suggested that the therapeutic performance of the phytopharmaceutical/drugs can be significantly improved via micro/nanoemulsion formulation which can deliver the drug directly to the brain through intranasal administration, leading to enhanced drug accumulation/ concentration in the brain vicinity as these formulations are capable of crossing BBB.

Parkinson's Disease

Parkinson's disease ranks second after Alzheimer's disease in progressive neurodegeneration disorder category. The pathophysiology behind initiation of Parkinson's disease is the damage of dopaminergic neurons in nigro-striatal pathway. These damages lead to conditions like depression, dementia, and finally autonomic dysfunction. As the disease progress the non-motor symptoms often become more prominent. The foremost symptoms of Parkinson's disease includes hypokinesia i.e. suppression of voluntary movements, rigidness of muscles, life-threatening tremors, that usually initiates in the hands leading to muscular rigidness that limits voluntary actions [97]. Numerous studies have reported enhanced therapeutic efficacy of drugs when formulated as micro/nanoemulsions, which are summarized in the following section.

Silymarin is a phytochemical bestowed with numerous therapeutic potentials and has compromised aqueous solubility which limits its applications. To improve its solubility and bioavailability Imran and associates formulated mucoadhesive microemulsion of silymarin and evaluated it for therapy of Parkinson's disease. The optimized Silymarin-loaded microemulsion exhibited a globule size, electrokinetic potential of 61.26±3.65 nm,−24.26±0.2 mV respectively and 97.28±4.87% drug loading. Further chitosan was added to the optimized formulation to attain mucoadhesion. The results of cell lines studies recommended non-toxic behaviour of microemulsion-gel over neuroblastoma cell lines, and good flow through sheep nasal mucosa was observed with mucoadhesive microemulsion when compared with. drug solution, and plain microemulsion as well as exhibited higher diffusion. Also, the mucoadhesive microemulsion showed decline in inflammatory markers, proving a significant progress in neuroprotection in animal model administered with mucoadhesive microemulsion in comparison to plain microemulsion administered animal group [98]. Likewise, Gaba *et al*., developed nanoemulsion formulation of vitamin E loaded naringenin for nose-to-brain delivery aimed at managing Parkinson's disease. The optimized formulation was subjected to various *in vitro* and *in vivo* behavioural studies viz. muscular coordination test, grip strength test, narrow beam test, forced swimming test and akinesia test in 6-OHDA induced- Parkinson animal model. The optimized nanoemulsion displayed a globule size and zeta potential of 38.70 ± 3.11 nm and −27.4±0.14 mV respectively with a suitable viscosity of 19.67 ± 0.25 Pas. The results of behavioural studies revealed the nanoemulsion successfully reversed the Parkinson in animals when administered intranasally as a co-therapy with levodopa. The elevated levels of MDA (Malondialdehyde) and declined levels of GSH and SOD (Glutathione, enzyme superoxide dismutase) were restored towards normal levels subsequent to co-therapy administered via intranasal route. The study suggested the intranasal route can be an alternative for improving therapeutic efficacy of a drug when formulated as nanoemulsion [99]. Likewise, Choudhury and coworker explored the potential of Rotigotine (non-ergot dopamine agonist) as monotherapy as well as a co-therapy with levodopa for the management of Parkinson. Rotigotine has poor aqueous solubility and a very low oral bioavailability of only 1%, with high first-pass metabolism and shorter half-life of 5–7 h. To overcome these challenges the team formulated Rotigotine-loaded mucoadhesive nanoemulsion for intranasal delivery and assessed it for various physiochemical parameters. The Rotigotine-loaded mucoadhesive nanoemulsion displayed a droplet size of 200 nm and withstand thermodynamic

stability testing. The chitosan was added to impart mucoadhesion that improves contact time leading to enhanced permeation. The permeation studies showed 85.23 ± 0.39% permeation of rotigotine through nasal mucosa over an extended period of time credited to chitosan coating which was 1.40 times better than naïve drug. The study suggested promising approach for improving delivery of rotigotine to the brain, leading to improved bioavailability and e better management of Parkinson's disease [100]. Following the similar approach Nehal *et al*., developed Ropinirole hydrochloride-loaded nanoemulsion using nigella oil for nose-to-brain delivery, targeting improved therapeutic outcomes for Parkinson's disease. They initiated the study exploring interaction of ropinirole and thymoquinone with TNF-α and NFK-β receptors through in silico assessment. The results of in silico studies suggested considerable interaction of both with NFK-β (hydrogen bond with residue Arginine 201 and residue Arginine 253). The prepared nanoemulsion displayed a globule size, zeta potential and pH of 183.7±5.2 nm, 24.9 mV and 5.8±0.18 respectively. Further the *in vitro* release and permeation studies demonstrated an increase of 2 folds and 3.4 folds correspondingly in comparison to drug suspension indicating possibility of enhanced bioavailability and therapeutic efficacy. The results of neurobehavioral activity and biochemical parameters were in good agreement with the findings of pharmacokinetic experiments. Also, the results of histopathological and immunohistochemical analysis revealed that 6-OHDA induced toxicity was significantly reversed and improvement in Parkinson's disease was witnessed [101]. Another study conducted by Kumar *et al*., demonstrated fabrication of lisuride-laden nanoemulsion for brain delivery via intranasal route. The prepared nanoemulsion was evaluated for Dopamine levels, pharmacokinetic, and antioxidant activity. The results of *in vivo* studies indicated higher levels of various antioxidant enzymes (GSH, SOD) in animals administered with nanoemulsion through intranasal route when compared with groups having intravenously administered drug suspension in haloperidol-induced Parkinson animal model. The lisuride-laden nanoemulsion group also showed decreased the dopamine loss and the pharmacokinetic studies revealed significantly enhanced dopamine levels upto 17.48 ± 0.05 ng/mL when compared with toxic group (7.28 ± 0.02 ng/mL) suggesting improved therapeutic efficacy and better management of Parkinson's disease [102]. One more study executed through Adangale and coworkers formulated Chrysin-loaded microemulsion to overcome physiochemical challenges meant for intranasal delivery and assessed for its anti-Parkinson potential in a rotenone-induced animal model. Chrysin is a potent flavone, but its clinical application is compromised due to poor aqueous solubility, vast pre-systemic metabolism and constrained oral bioavailability. The prepared microemulsion exhibited a globule size of 365.03 ± 6.8 nm, and a electrokinetic potential of -24.86 ± 2.286 mV and ex vivo permeation of 68.67% over a period of 24 h and holds a non-irritant attribute to the nasal mucosa. Concomitantly, the findings of *in vivo* studies revealed a significant augmentation in locomotor activity and catalepsy score in Chrysin-loaded microemulsion intranasally administered group when compared with orally administered suspension group. Further, raised dopamine levels along with SOD, GSH, and catalase levels were noticed in Chrysin-loaded microemulsion intranasally administered group when compared with the other groups suggesting improved antioxidant potential of Chrysin averting neuronal injury in Parkinson's. Additionally, the brain distribution studies displayed enhanced chrysin concentration in brain tissue i.e. 8.3212 ± 1.8125 µg/mL subsequent to intranasal administration when compared with both intranasally/orally administered suspension (5.0879 ± 0.0058 µg/mL; 4.1364 ± 1.1095 µg/mL) groups. The *in vivo* studies gives an auxiliary proof of considerable targeting and anti-Parkinson's potential of Chrysin when formulated as intranasal microemulsion with boosted antioxidative properties suggesting it as a suitable drug cargos for overcoming challenges associated with such drugs [103].

The afore-mentioned studies supported that nanoemulsion formulations can significantly enhance drug bioavailability and therapeutic efficacy by facilitating direct drug transport to the brain. Therefore, it can be concluded that unmodified nanoemulsions as well as surface-engineered nanoemulsions are promising strategic approaches, offering convincing results for the improved management of Parkinson's disease and associated symptoms. This suggests that nanoemulsions could play a crucial role in developing more effective treatments for neurological disorders.

Huntington's Disease

Huntington's disease is a fatal neurodegenerative disease. It is progressive having autosomal dominant and fully penetrant neurodegenerative disease illustrated by gradual chorea deterioration and cognitive and psychiatric disruptions. The pathophysiology involves an increase in CAG (glutamine) trinucleotide repeats in exon 1 of the huntingtin (htt) gene located at 4p16.9. The htt is widely expressed in CNS and involved in signalling of internal cell, prevention of neuronal toxicity and maintaining cyclic adenosine monophosphate response element binding protein [104]. Moreover, the accumulation and aggregation of proteolytic htt fragments initiates a cascade and signals that results in neuronal dysfunction, mitochondrial dysfunction and energy depletion. These changes go together with neurochemical alterations that involves glutamate receptors as well as other receptors such as dopamine and adenosine receptors that are responsible for proper motor functions [105]. Various pieces of literature have reported improved therapeutic efficacy of drugs when

formulated as micro/nanoemulsion and are summarized in following section.

A study conducted by Arora *et al*. presented the formulation of Tetrabenazine-loaded nanoemulsion and its subsequent *in vitro* and *in vivo* evaluation. Tetrabenazine recognized for its ability to alleviate chorea symptoms related with Huntington's disease through depletion of monoamines within pre-synaptic vesicles. However, it holds poor aqueous solubility, high first pass metabolism resulting in compromised oral bioavailability. Thus, an attempt was made to address these problems through formulating nanoemulsion for treating and managing hyperkinesia associated with this disease. The optimized nanoemulsion displayed a droplet size, zeta potential of of 0.198 ± 0.005 and -9.63 ± 0.63 mV respectively. The nanoemulsion exhibited 1.68 times enhanced permeation in comparison to tetrabenazine suspension. The MTT assay revealed non-toxic attribute of nanoemulsion in neuro-2a cell lines and higher cell viability when compared with placebo and aqueous drug suspension. Subsequent to intranasal administration tetrabenazine nanoemulsion displayed a improved Cmax value of 3.497 ± 0.275 µg/mL, and AUC value of 29.196 ± 0.870 µg h/mL when compared with plasma profile having Cmax and AUC value of 1.400 ± 0.084 µg/mL, and 12.925 ± 0.340 µg h/mL respectively at the end of 12 h suggesting higher concentration and retention in the brain tissue. Concomitantly, the histopathological images of porcine nasal mucosa no disruption of cell architecture subsequent to intranasal administration of tetrabenazine nanoemulsion proving its delivery potential and alternative route for management of hyperkinesia associated Huntington's disease [106]. Another study executed by Shah *et al*., reported a comparative evaluation and fabrication of quetiapine loaded microemulsion and nanoparticles to improve brain transportation of quetiapine through intranasal route. Quetiapine is an antipsychotic drug and is hindered by poor oral bioavailability, high first-pass metabolism, which results in unsatisfactory clinical outcomes. The microemulsion and nanoparticles exhibited a particle size of 50 nm and 131 nm respectively. The chitosan coated mucoadhesive microemulsion displayed superior diffusion when compared with nanoparticles, credited to chitosan permeation-enhancing effect. The quetiapine-loaded nanoparticles permeation was 1.3 times lesser than that of mucoadhesive microemulsion owing to hydrophilic nature. Furthermore, a 1.9-folds higher concentration of drug in brain tissue was observed with intranasally administered mucoadhesive microemulsion when compared with nanoparticles indicating superior delivery and permeation potential of mucoadhesive microemulsion credited to a combination of factors viz. enhanced contact time and lipophilic nature that enables opting of olfactory route bypassing BBB for drug transportation and alteration in tight junction through chitosan as well as ultra-small globule size. Concomitantly, the gamma scintigraphy images gives an auxiliary proof of enhance delivery of drug to brain suggesting delivery potential of mucoadhesive microemulsion and its dominance over nanoparticles [107].

The studies mentioned above provided support for the proposal that microemulsion/nanoemulsion formulations can considerably enhance drug bioavailability and therapeutic efficiency of a drug through intranasal administration enabling direct delivery to the brain. Subsequently, it can be inferred that mucoadhesive micro/nanoemulsions and surface-engineered nanoemulsions exemplify hopeful strategic methodologies, bringing convincing outcomes for the enhanced management of Huntington's disease and associated symptoms. This highlights the potential of micro/nanoemulsions to play a pivotal role in the development of new and more effective therapies for neurological disorders.

However, the microemulsion based delivery systems have shown promising *in vitro* results, no human studies or clinical studies have either not conducted or were found to be unsuccessful. Though, a few clinically relevant studies conducted to assess nose-to-brain delivery, which showed improved uptake of loaded molecules into brain vicinity, while some showed contradictory results, suggesting a struggle for assurance of efficacy and safety of this delivery system and need further detailed investigations. Another issue with micro/nanoemulsion is low viscosity which result in easy drainage and mucociliary clearance through nasal cavity, and to address this a mucoadhesive polymers such as chitosan can be added. However, addition of such polymers prolongs residence time in nasal cavity but may be a cause of irritation. Additionally, the high percentage of surfactant in micro/nanoemulsion can also cause irritation and altered permeability of nasal mucosa and may cause ciliotoxicity and need detailed and long-term evaluations [95, 108].

Nanotechnology to Neurotechnology: Recent Advances

It has been discussed in detail that progression of neurodegenerative disease is swift, enormously incurable and burdensome medical conditions, and there is no particular therapy available till date, management of disease and associated symptoms are the only solution available today. The management includes an attempt to slow down the progression, reducing the risk factors, maintaining good lifestyle, and coping with ageing related problems. The problem becomes unmanageable when the patient has reached the last stage and there is complete function loss, specifically motor dysfunction which makes the patient bed ridden and he/she is deprived of doing day today activities. Recently numerous AI-based tools are under research to manage the important basic task of such patients.

The clinicians, molecular biology scientist, formulation specialist are continuously putting in efforts to find a suitable and effective therapy to cure neurodegenerative diseases. Recently AI (Artificial intelligence) has also joined the battle and is being leveraged to improve the diagnosis, treatment, and management of neurodegenerative disorders. The latest advancement employment application of BCI (brain-computer interface), that can direct form communication channels connecting the CNS and the external environment, eliminating the need to utilize the peripheral nervous system [109]. Various neurotechnological research is advancing rapidly, leading to the emergence of number of startups and large groups in this area such as Neuralink, Newronika, Paradromics, Bioinduction and many others [110]. Recently "Neuralink®" (Elon Musk enterprises), has invented Neuralink a BCI brain implant bestowed with smart technology capable of personal monitoring through direct communication between the brain and computers as shown in Fig. 3 [111].

It is a coin-sized small implant implantable device, that is surgically implanted in brain through sophisticated surgical robot and contains a numerous flexible ultra-thin tiny electrode that penetrate the brain's surface. The Neuralink acts as a Trojan horse from which the embedded electrodes that detects electrical signals produced through neurons causing brain simulation by delivering electrical pulses. Further this implanted device transmits neural data (wirelessly) to the external devices for processing. This data is employed to control computers, devices, prosthetic limbs, facilitating patient to regain lost motor function with neurological conditions [113]. The prime goal of Neuralink is to develop input-output platform competent of interfacing with every attribute and thought process of the human brain to address weakening brain and CNS illnesses. The foremost research was focused on restoration of digital independence to the patients suffering from quadriplegia due to neurological disorders (spinal cord injury or amyotrophic lateral sclerosis). This implant is designed with 1,024 electrodes distributed across 64 flexible leads/threads that records the neural activity. Recently in January 2024 clinical trial on human was conducted for the first time implanting Neuralink into brain named as PRIME Study (Precise Robotically Implanted Brain-Computer Interface). The results revealed that the implanted BCI device successfully detect and transmits patient's neural signals. Furthermore, it was effectively integrated with their end-to-end BCI system for various applications specifically playing chess and Sid Meier's Civilization VI online games on computer without moving [114]. The study suggested that the Neuralink's BCI chip is a revolutionary advancement in neurotechnology and promising tool for effective management of patients with lost motor functions. The BCI is conferred with precise stimulation linked with real-time neural monitoring, and amalgamation with advanced drug delivery systems. However still more robust and extensive clinical trials involving a large number of subjects are required to translational transformation of Neuralink and similar implants from bench to bedside. Additionally, efforts are needed to scale up production and ensure economic viability for commercial use.

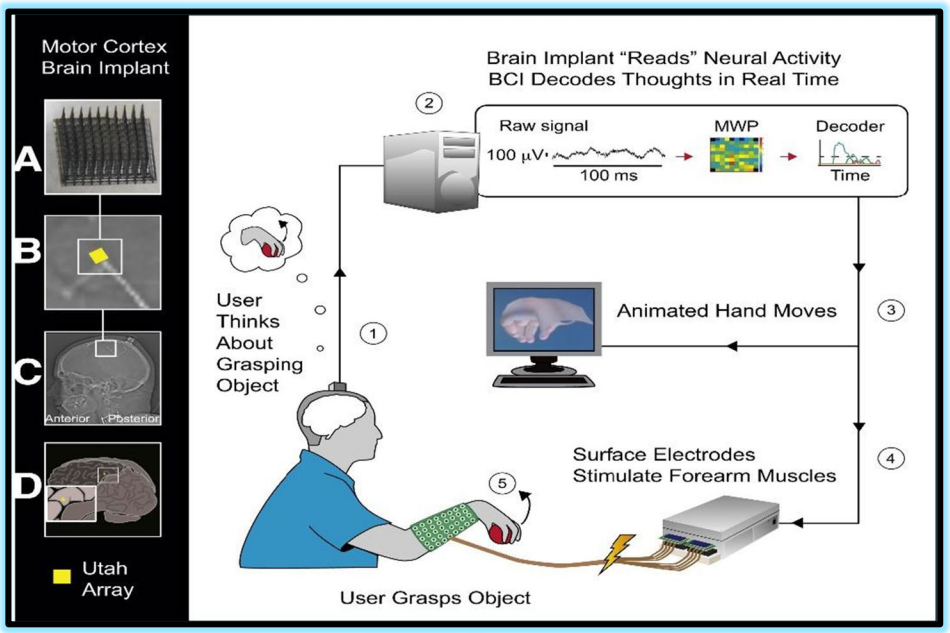

Fig. 3 Cortical implant and NeuroLife BCI-FES system, showing **A** 96-channel Utah MEA. **B** array orientation in yellow **C** CT image displaying implant location. **D** Interpretation of the location of the array on the precentral gyrus. Reproduced with permission under CC BY-NC-ND license [112]

Conclusion

The treatment of neurodegenerative diseases is most challenging credited to barriers viz. blood- CNS barriers (BBB) which restrict the entry of most of the therapeutic agents to brain. The use of soft nanocarriers for nose-to-brain delivery has successfully demonstrated the improved therapeutic efficacy of drugs for the management of neurodegenerative disorders. Various pre-clinical studies witnessed that the nasal drug delivery directly transport the drug to the brain vicinity bypassing BBB resulting in enhanced brain accumulation administered as micro/nanoemulsion and mucoadhesive micro/nanoemulsion. Such formulation meant for intranasal administration present an alternative to conventional therapies to improve clinical outcome of the patients. More stringent evaluation of micro/nanoemulsion based delivery systems is required to prove its potential in clinical trials and clinical usage. Furthermore, multifunctional nanotechnology strategy could be devised to develop an amalgamation of therapeutic and diagnostic tools that can precisely and concurrently identify and target prime pathways/ molecules involved in neurodegenerative disease. Apart from nanotechnology recent advancement in neurotechnology's such as Neuralink displayed their potential and future scenarios in managing the patients with lost motor function, and focusing on making such patients independent. Neuralink offers new hope for patients suffering from such debilitating conditions. However still continuous and more stringent research is required in collaboration with clinicians, neurotechnologists, AI specialists, engineers is essential to address the associated challenges and ensure success throughout clinical trials, clinical application, and ethical approval for both the developed delivery systems as well as BCI-implants. This could herald a new era for BCI-based neurorehabilitation, a predicted surge among researchers, clinical practitioners, engineers, and entrepreneurs.

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Declarations

Conflict of interest The authors declare no competing interests.

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