Original Article

Applications Of Sustained Release Dosage Form For Neuro Disorder: An Overview

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Abstract

This article offers a comprehensive overview of several facets pertaining to sustained/controlled drug release formulations used in the treatment of neurodegenerative diseases (NDs). Considering the brain's crucial role in the regulation of diverse physiological processes, it can be inferred that neurodegenerative disorders exert a wide-ranging influence on human functionality. These conditions detrimentally affect fundamental capacities such as speech, movement, stability, and balance, as well as more intricate tasks encompassing bladder and bowel functions, along with cognitive abilities. The current neurodegenerative disorders (NDs) consist of a variety of illnesses, including Alzheimer's disease, Parkinson's disease, prion disease, Amyotrophic lateral sclerosis (ALS), motor neuron disease, Huntington's disease, spinal muscular atrophy, and spinocerebellar ataxia, which are often seen. There is a limited number of SRDDS/CRDDS that have been created for various medications aimed at treating neurological disorders (NDs). Consequently, our research efforts are focused on developing a sustained release tablet formulation intended for the treatment of neurodegenerative disorders (NDs).

Keywords: SRDDS; CRDDS; Brain; NDs; PD; AD

Introduction

The Sustained/Controlled Release Medicine Delivery System (SRDDS/CRDDS) aims to release a medicine at a specified pace while minimizing negative effects by keeping the drug level constant for a given amount of time. The development of SRDDS is now receiving more attention since few new medications are emerging from research and development and because inappropriate usage of existing treatments, particularly antibiotics, is contributing to the issue of drug resistance(Sheikh et al., 2016). By extending the duration of the drug's action, reducing dosing frequency, reducing side effects, lowering the required dose used, and providing the shortest time by using the least amount of drug administered by the best route, SR formulations were primarily intended to modify and improve the performance of the drug(Elzoghby et al., 2012). With the use of an initial dose component and a maintenance dose portion, SR dosage forms are intended to rapidly raise a drug's blood level to therapeutic concentrations and then sustain it for a set period of time. After oral administration, the SR of medicines in the GI tract is unaffected by the absorption process. The improvement of medication treatment as determined by the link between SR system benefits and drawbacks is the main objective of SR dosage forms(Tomitaka et al., 2019).

The development of effective therapies for neurological disorders (NDs) is currently impeded by the physiological and anatomical features of the central nervous system (CNS). The central nervous system (CNS) has three physiological barriers that provide significant challenges for medications in terms of permeation and penetration. There are three main barriers that regulate the exchange of substances between the blood and the central nervous system (CNS). The first is the blood-brain barrier (BBB), which consists of capillary endothelial cells that are tightly joined together by tight junctions. The second is the blood-leptomeningeal barrier (BLMB), which interfaces with the cerebrospinal fluid (CSF) and has an endothelium that lacks fenestrations and is also connected by tight junctions. Lastly, the blood-cerebrospinal fluid (blood-CSF) barrier is composed of endothelial cells found in the choroidal blood vessels of the plexuses, which are connected by tight junctions. The BBB has a reduced permeability, and the transportation of molecules across it is contingent upon their physicochemical properties and their interaction with endogenous efflux transporters, including ATP binding cassette transporters. It is well recognized that the blood-brain barrier (BBB) effectively restricts the passage of around 98% of low molecular weight medications and 100% of large molecular weight pharmaceuticals into the brain. Therefore, the blood-brain barrier (BBB) serves as the primary impediment to the transportation of pharmaceutical agents from the systemic circulation to the central nervous system

(CNS), resulting in diminished drug bioavailability inside the brain and therefore hindering the efficacy of therapeutic interventions for neurodegenerative disorders. Numerous tactics aimed at augmenting the translocation of medications across the blood-brain barrier (BBB) and facilitating their transportation into the brain have been investigated, although yielding modest achievements. This article offers a comprehensive overview of several facets pertaining to sustained/controlled drug release formulations used in the treatment of neurodegenerative diseases (NDs).

Rational for SRDDS/CRDDS development

1. To increase a medicine's therapeutic efficacy, SRDDS/CRDDS formulations reduce the frequency of dose while ensuring that the substance is available at the treatment's action site.

2. To lower the number of required dosages in order to lower treatment costs.

3. To reduce toxicity brought on by overdose, which is often caused by traditional dosage form.

4. To lengthen the lifetime of an active ingredient in a medication with a short half-life.

A Comparative Analysis of Conventional and Controlled DDS

Traditional drug delivery systems (such as pills, capsules, syrups, etc.) are rapidly removed from the body, resulting in poor maintenance of the desired dosage within the therapeutic range. Following the administration of a single standard dosage, the medication undergoes rapid metabolism, resulting in an initial elevation of drug concentration, which is then followed by an exponential decline(Sun et al., 2003). The duration of the time period may be insufficient to have a substantial therapeutic impact, thus leading to a suboptimal therapeutic response. Various strategies have been pursued in order to ensure that the plasma drug concentration remains above the minimal effective concentration (MEC) while still staying below the hazardous concentration. The administration of numerous doses at regular intervals may seem as a potential alternative to a single dosage(Arafat, 2015). However, this approach might lead to oscillations in the levels of the drug in the plasma, frequently resulting in suboptimal concentrations below the effective threshold and sometimes above dangerous levels. The administration of many doses in a single day leads to suboptimal adherence among patients. An alternative method involves the administration of a dosage above the prescribed amount, resulting in unintended unfavorable consequences beyond the intended therapeutic benefits of the medication. Therefore, the use of controlled release drug delivery systems (CRDDS) is necessary in order to sustain the concentration of drugs in the bloodstream at a consistent rate within the therapeutic range. This allows for an extended period of therapeutic impact to be achieved. Table 1 and Table 2 provide a comprehensive overview of the benefits and drawbacks associated with conventional and controlled DDS(Han et al., 2021; Modi et al., 2013).

Table 1. The conventional DDS has both benefits and limitations

Advantages	**Disadvantages**
Convenience in administration	Poor absorption from site of administration
Non-invasive and better IVIVC	No target specificity
Accurate and measured unit dosage form	Premature excretion from the body
Higher shelf-life	Premature metabolism of the drug
Accommodate patient variation	Poor bioavailability
Flexibility for physician to dose adjustment	Repeated dosing
Low cost	Poor patient compliance

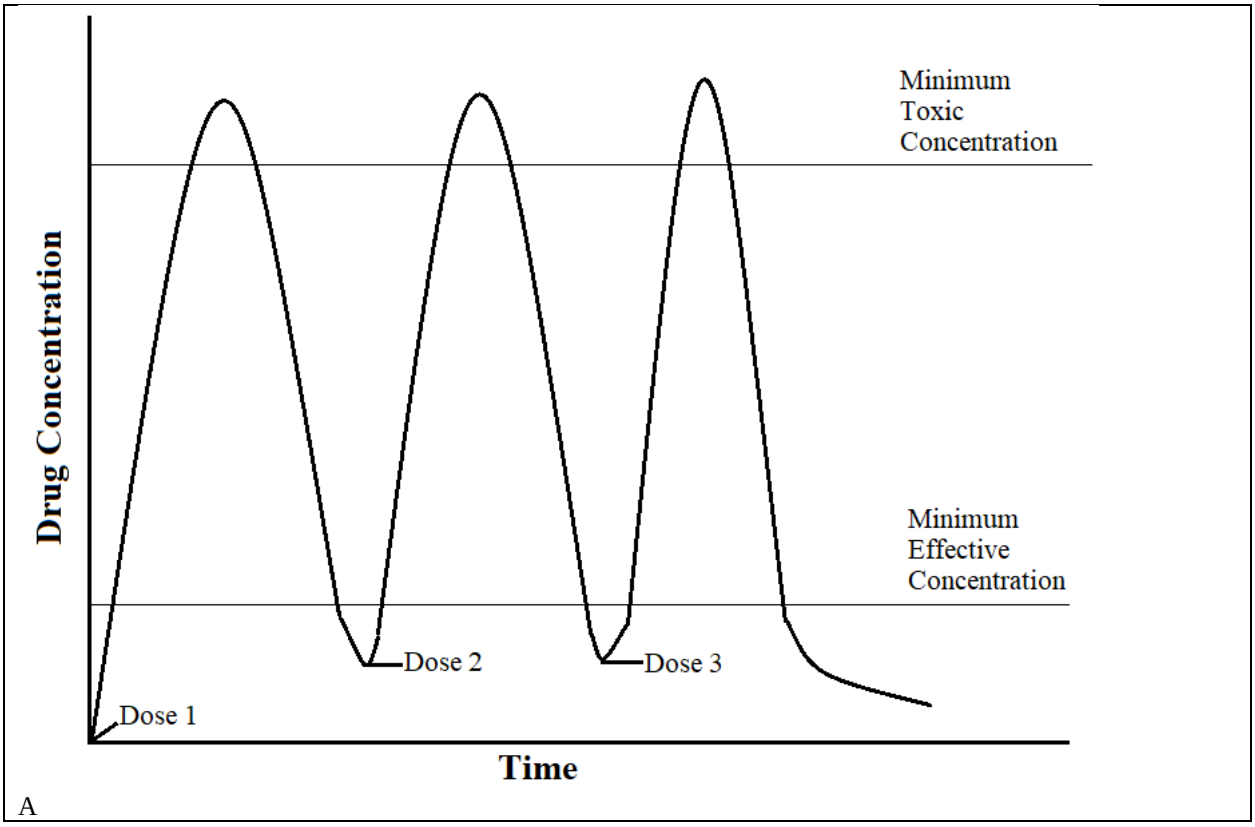
Table 2. Comparing the pros and cons of controlled DDS

Advantages	**Disadvantages**
Controlled or defined drug release	Possible toxicity of materials used
Target specificity	Dose dumping
Long residence of drug	Invasive procedure to implant or remove the system
Protection from metabolism by enzymes/chemicals	Uptake by RES reduces efficacy
Improved bioavailability	Poorer IVIVC
Low dosing frequency	Limited standards
Better patient compliance	Higher manufacturing cost

Controlled DDS

The CDDS is a pharmaceutical approach that ensures a consistent concentration of a medication is maintained in both the bloodstream and tissues over a prolonged duration. Figure 1 depicts the pharmacokinetics (PK) curves illustrating the relationship between the plasma concentration of a medication and time for two distinct delivery systems: standard and regulated. In a traditional administration method, there exists a customary pharmacokinetic profile for repeated administration of oral tablets or injections, whereby the drug concentration varies intermittently over and below the threshold of minimal effectiveness. In contrast, the controlled delivery system exhibits zero-order pharmacokinetics, wherein a singular administration of a regulated drug delivery from a designated formulation or device is seen. The medication concentrations are consistently kept within the therapeutic range. Controlled DDS ensure the maintenance of drug plasma levels by consistently delivering a certain dosage of the medication at predetermined time intervals over a pre-established timeframe. This intervention contributes to the reduction of medication dosage and frequency, hence enhancing patient adherence. Reducing drug exposure to the biological environment may lead to a decrease in drug toxicity and the occurrence of side effects. The total effectiveness of the dose form is enhanced(Siepmann et al., 2012).

The controlled DDS was developed with the objective of decreasing the frequency of dose and enhancing patient adherence. Frequent dosage of drugs may lead to drug toxicity, which can be mitigated by its reduction. This method aids in mitigating the occurrence of repeated drug exposure inside a biological system. It maintains a consistent plasma concentration in the bloodstream(Bundela et al., 2022).



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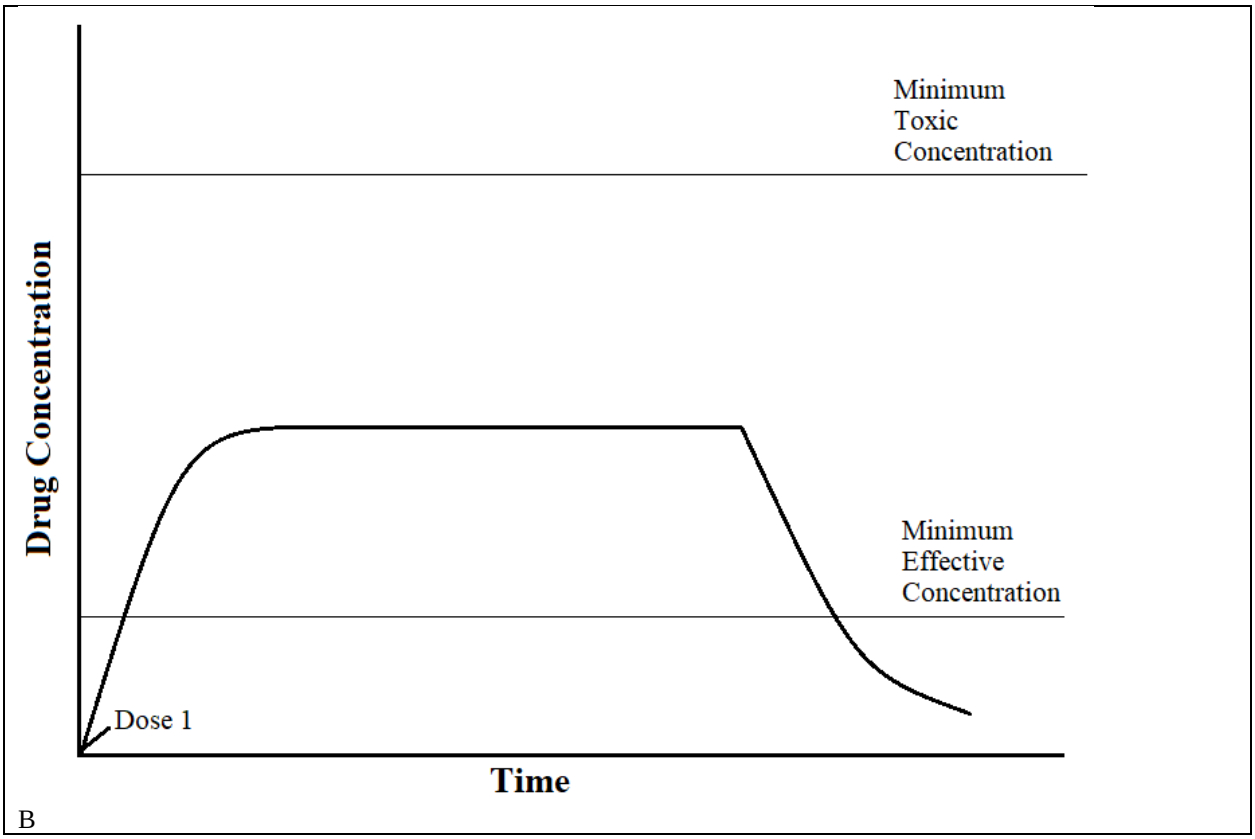

Figure 1. The drug release profile of A) Conventional DDS; B) Controlled DDS

Designing Approaches of Controlled DDS

When developing a controlled release medication delivery system, it is important to take into account a multitude of elements and criteria. The parameters may be roughly categorized into two groups: formulation-related parameters and drug-related parameters. The key elements under consideration in relation to formulation include biomaterial characteristics, mode of administration, pharmacokinetics, and stability augmentation. Furthermore, drug-related factors include the drug's affinity for plasma proteins and its capacity to traverse biological barriers. Additionally, regulatory considerations are of utmost importance when formulating the dosage form(Jain et al., 2022; Lemos et al., 2021).

The investigation of biomaterial features, including biocompatibility, surface chemistry, hydrophilicity, degradation, mechanical characteristics, and rheological properties, is vital. Furthermore, it is important to evaluate the performance of the biomaterials at different pH levels and temperatures. The selection of appropriate biomaterials and the design of dosage forms are crucial considerations in determining the routes of drug delivery. For example, in rectal administration, it is necessary for the biomaterial to have a melting point equal to or higher than 37 °C, or to be soluble at that pH, in order to facilitate the release of the medication. In the context of pharmaceuticals, it is essential to address the stability concerns associated with specific medications, such as peptides, proteins, genes (DNA), growth factors, and colloidal/non-colloidal particles, particularly when exposed to unfavorable environmental conditions. Therefore, it is crucial to include stability improvement strategies during the design phase of controlled release carriers for these drugs. The objective may be accomplished by the integration of specific pharmaceutical agents into customized delivery systems(Park, 2014).

The precise localization of a medicine to the specific region where its intended pharmacological action is required is of paramount significance in order to mitigate any potential adverse effects on non-targeted organs. This objective might be accomplished by the use of antibody tagging, the attachment of ligands, and the utilization of targeted delivery methods. The presence of biological barriers poses challenges in effectively delivering drugs to specific anatomical regions such as the brain, bone, and testicles. Pharmaceutical formulations using permeation enhancers and nanocarriers are viable solutions for overcoming physiological barriers and facilitating targeted

medication delivery. It is important to design appropriate animal models for each kind of delivery system in order to achieve optimal in vitro-in vivo co-relationship (IVIVC). This approach serves to establish a connection between animal research conducted in a living organism and the outcomes seen in clinical trials(Fam et al., 2020; Tekade, 2018).

Classification of Controlled DDS

The concept of controlled release refers to the deliberate and regulated release of a substance over a certain period of time. Drug delivery systems may be categorized according to the method by which the drug is released from the dosage form. These categories include dissolution-controlled, diffusion-controlled, water penetration-controlled (specifically osmotic pressure-controlled and swelling-controlled), chemically controlled, and nanoparticle-based systems. The classification of controlled DDS is depicted in Figure 2(Tekade, 2018).

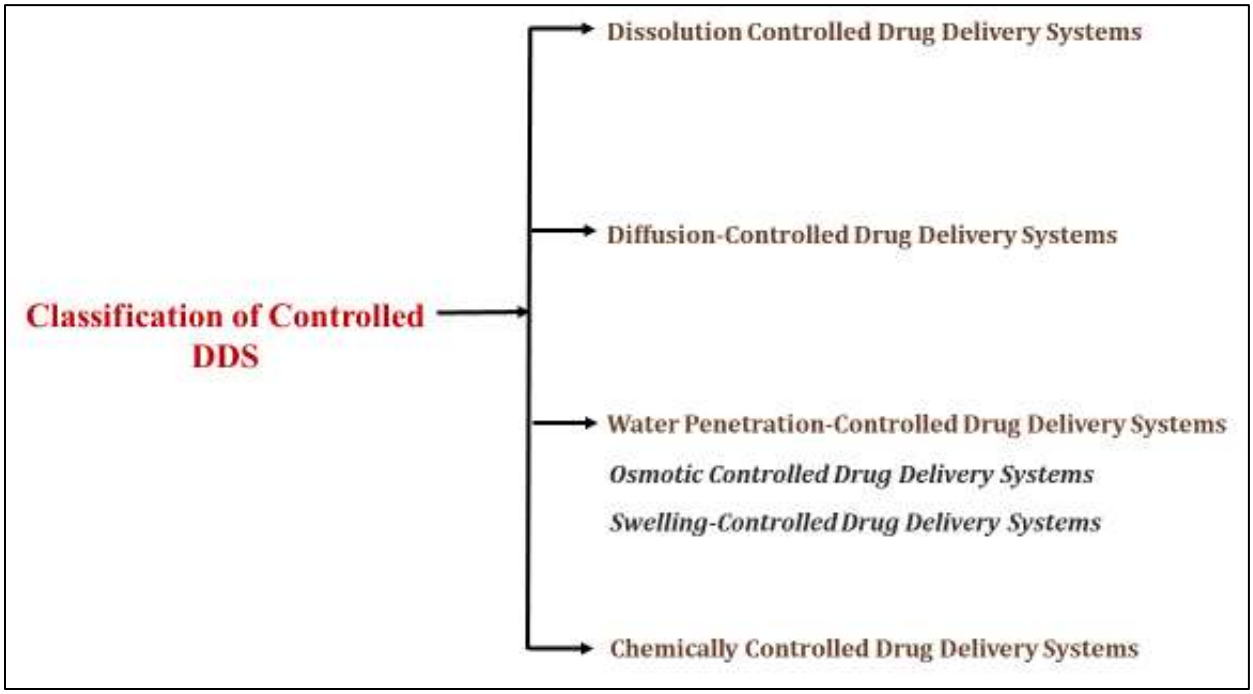

Figure 2. Classification of Controlled DDS

Targeted Controlled DDS for Brain

The brain is the most sensitive part of the central nervous system (CNS), since it connects sensory information from all organs, takes learning and memory into account, and allows for ongoing repairs to sustain active function. Neurological illnesses account for 6.3% of all diseases' worldwide burden due to the ageing of the world's population. Because of the serious health problems and disabilities, they create, many conditions need more extensive medical care. Despite a relatively high blood flow, the transport of medications via the central nervous system is a significant issue. The blood brain barrier (BBB), blood-cerebrospinal fluid (CSF) barrier, blood-retinal barrier, and blood spinal cord barrier are only a few of the barriers the CNS has developed to defend itself. The blood-cerebrospinal fluid barrier (BCSFB) and the blood-brain barrier (BBB) are the two physiological barriers that separate the brain from its blood supply(Hammarlund-Udenaes et al., 2008).

The BBB is the strongest barrier, preventing toxic chemicals and other dangerous substances from entering the circulation and controlling the flow of nutrients to the brain necessary for optimal operation. The BBB is made up of astrocytes, endothelial cells, tight junctions, pericytes from neurons, and basal membrane. It is a semi-permeable and diffusion barrier. These delivery methods use both blood-to-brain and blood-to-brain directions. However, compared to other transport systems, the blood to brain transport pathway is more crucial for medication administration. Another barrier that follows BBB is BCSFB, which confronts a systemically controlled medication before entering the CNS. This is situated at the choroid plexus, which regulates the flow of blood-to-CSF solutes and secretes new CSF. The complex organ known as the choroidal epithelium performs a wide range of additional tasks,

including neuroendocrine signaling, metabolism, and transport, as well as neuroimmune and neuroinflammatory responses, drug and toxin processing(Pardridge, 2022; Puris et al., 2022).

Neurons are essential to the normal functioning of the human brain because they play a crucial role in communication. The majority of neurons originate in the brain; however, neurons may be found throughout the body. The bulk of neurons are produced by neural stem cells throughout development, but the number decreases considerably in age. Although neurons are not eternal, neurodegeneration, or the gradual loss of neurons, neuron structure, and/or their activities, is important to the pathogenesis of various brain illnesses and a serious health issue. Neurodegeneration is related with synapse malfunction, neuronal network dysfunction, and the deposition of physiochemically changed protein variations in the brain. Neurodegenerative diseases (NDs) are a group of diseases that share the trait of neurodegeneration. Alzheimer's disease, Parkinson's disease, prion disease, Amyotrophic lateral sclerosis, motor neuron disease, Huntington's disease, spinal muscular atrophy, and spinocerebellar ataxia are the most prevalent NDs(Ayub & Wettig, 2022; Islam et al., 2021; Lee et al., 2019).

1) Alzheimer's Disease (AD)

The most prevalent form of dementia, known as Alzheimer's disease (AD) (after the German psychiatric Alois Alzheimer), is characterized by neuritic plaques and neurofibrillary tangles that form in the medial temporal lobe and other neocortical structures of the brain as a result of amyloid-beta peptide buildup. While studying the brain of his first patient, who had memory loss and a change in personality before passing away, Alois Alzheimer discovered the existence of amyloid plaques and a large loss of neurons, and he classified the illness as a terrible disease of the cerebral cortex. In his 8th edition psychiatric handbook, Emil Kraepelin for the first time referred to this medical condition as Alzheimer's disease. Progressive decline in cognitive abilities may be brought on by brain disorders like Alzheimer's disease (AD) or other conditions like intoxications, infections, abnormalities in the pulmonary and circulatory systems that reduce the amount of oxygen delivered to the brain, nutritional deficiencies, vitamin B12 deficiencies, tumours, and other conditions(Deture & Dickson, 2019; Fenclová et al., 2020; Trejo-Lopez et al., 2022).

2) Parkinson’s Disease (PD)

The second most prevalent neurodegenerative ailment after Alzheimer's is Parkinson's disease. Parkinson's disease normally appears between the ages of 55 and 65, affects 1% to 2% of persons over 60, and increases to 3.5% of people between the ages of 85 and 89. The frequency is 1.5 times greater among males than among women, affecting 0.3% of the overall population. Despite contradicting evidence, it's possible that white individuals are more likely than persons of Asian or African origin to get Parkinson's disease. In Canada, 85 200 persons were projected to be living with Parkinson's disease in 2011.The predicted increase in cases of this illness by 2031 is a doubling(Wu & Hallett, 2013).

Multiple motor and nonmotor brain pathways are involved in the neurodegenerative illness known as Parkinson's disease. A premature selective loss of dopamine neurons and a buildup of Lewy bodies, which are made of misfolded α-synuclein and accumulate in several systems of Parkinson disease patients, are its two main pathologic features. It's not apparent which procedure starts off. According to pathologic studies, neurons degenerate in stages over a long period of time, with each damaged place correlating to a particular symptomatology of Parkinson disease. On a pathologic examination, the substantia nigra shows a 30–70% cell loss when motor symptoms first appear. The basic goal of treatment is to regulate the malfunctioning circuit and replace dopamine using dopaminergic drugs. Dopamine deficiencies outside of the basal ganglia or in the serotonergic and noradrenergic systems are associated with cognitive impairment, mood disorders, and problems of impulse control. Pathologies outside of the brain, such as those of the spinal cord and peripheral autonomic nervous system, have been linked to autonomic dysfunction(Elbaz et al., 2016; Sveinbjornsdottir, 2016).

3) Huntington's Disease (HD)

Huntington's disease (HD), a totally penetrant neurological disorder, is caused by a dominantly inherited CAG trinucleotide repeat increase in the Huntington's gene on chromosome. In comparison to East Asia, the frequency is 10-100 times greater in the population derived from Europe. Mutated huntingtin causes neuronal dysfunction and loss at the cellular level through a number of mechanisms, including the disruption of proteostasis, transcription, and cell function, as well as direct toxicity of the mutant protein. The brain is impacted with the striatum's early macroscopic changes as the illness progresses. Palliative care and symptom management are the mainstays of treatment since there are currently few drugs that can alter the course of the illness. Recent years have seen tremendous advancement in our

understanding of the cellular pathology and severe structural alterations to the brain that take place as the condition worsens. Over the last 10 years, there has been a significant surge in medical research and potential therapy alternatives. The most hopeful new therapies target lowering levels of mutant huntingtin. Antisense oligonucleotide therapy is one tactic, however, and clinical studies are now being carried out for it(Jurcau, 2022; McColgan & Tabrizi, 2018; Saldert et al., 2021; Snowden, 2017).

Current Therapeutic Approaches to Treat ND

The management of NDs typically follows a disease-specific approach. Presently, a number of acknowledged treatment strategies are available, either of which aim to address the disease's pathophysiology or lessen its symptoms. The various therapeutic approaches that are presently being employed to address major neurological disorders are outlined in Table 3(Lamptey et al., 2022).

Table 3. The therapeutic strategies employed in the management of NDs

Neurological Disorder	**Drugs Class**	**Mechanism**	**Drugs**
Alzheimer disease	Amyloid-directed antibody	Acts by targeting and removing amyloid-beta plaques	Aducanumab
	Cholinesterase Inhibitors	Prevent the knockdown of acetylcholine	Donepezil, rivastigmine, galantamine
	Glutamate regulators	Antagonize N-methyl-D-aspartate (NMDA) receptor to improve signal-to-noise ratio of glutamatergic transmission	Memantine
Parkinson disease	Dopamine supplements	Replenish the decreased dopamine levels	Levodopa
	Decarboxylase inhibitors	Prevent peripheral breakdown of levodopa	Carbidopa
	Dopamine agonist	Produces dopamine-like effects	Apomorphine hydrochloride, pergolide, pramipexole dihydrochloride, ropinirole hydrochloride, rotigotine
Amyotrophic Lateral Sclerosis	Glutamate-receptor antagonist	Inhibits glutamate receptors	Riluzole
	Free-radical scavanger	Scavanges free radicals	Edaravone

Literature Review of some Formulations of NDs Drugs

In light of the increasing incidence of AD and the potential hazards associated with current treatment methods, a novel approach including the use of oil in water (o/w) nanoemulsion (NE) containing donepezil was developed to investigate the intranasal route of drug delivery. The NE was formulated using labrasol at a concentration of 10%, cetyl pyridinium chloride at a concentration of 1% in 80% water, and glycerol at a concentration of 10%. The medication was incorporated into the NE at a concentration of 1 mg/ml. The NE that was created underwent characterization in terms of particle size, polydispersity index (PDI), and zeta potential. In order to examine the release of the medication, in vitro release tests were done. Additional in vivo investigations were conducted on Sprague Dawley rats to examine the drug transport route from the nose to the brain using technetium pertechnetate (^{99m}Tc) tagged formulations. The NE exhibited a particle size of 65.36 nm, a polydispersity index (PDI) of 0.084, and a zeta potential of -10.7 mV. The results of the in vitro release investigations showed that the maximal release percentages were 99.22% during a 4-hour timeframe in phosphate-buffered saline, 98% within a 2-hour timeframe in artificial cerebrospinal fluid, and 96% within a 2-hour timeframe in simulated nasal fluid. The cytotoxicity and antioxidant activity of the NE exhibited a correlation with the dosage, as seen by the dose-dependent cytotoxicity and percentage of radical scavenging activity (%RSA). The giemsa staining pictures further corroborated that the created formulation does not have any discernible influence on cellular shape. The scintigrams showed a peak level of norepinephrine uptake in the brain. The results

indicated that the formulated nasal emulsion containing donepezil hydrochloride has the potential to be used as a novel therapeutic strategy for AD via the transfer of drugs from the nasal cavity to the brain. The provided content is a graphical representation that summarizes the main points or findings of a research study in a visual format(Kaur, Nigam, Bhatnagar, et al., 2020).

A formulation and evaluation of an intranasally administered in situ gel, based on a nanostructured lipid carrier loaded with resveratrol, was conducted. A lipid carrier containing resveratrol was created using a process including melt emulsification and probe sonication. The carrier was then characterized and optimized. The incorporation of nanostructured lipid carrier into an in situ gel was subsequently performed, followed by a comprehensive characterization of the resulting system. The resveratrol nanostructured lipid carrier was created and assessed for several parameters including particle size (132±12 nm), polydispersity index (0.165±0.002), zeta potential (−23±4 mV), drug loading (10±3%), and entrapment efficiency (74±6%). A pharmacokinetic investigation demonstrated that the in situ gel formulation exhibited increased drug distribution in the brain, suggesting that the new formulation is both safe and effective when administered through the nasal route. Therefore, it was determined that the medication may have been absorbed partly by the olfactory channel from the formulated product, suggesting that the intranasal route has potential as a viable technique for treating AD(Rajput & Butani, 2019).

The use of a nanoemulsion containing memantine for intranasal administration, with the aim of circumventing the blood-brain barrier, in order to address the therapeutic needs of individuals suffering from Alzheimer's disease. The nanoemulsion was created using the techniques of homogenization and ultrasonication. The nanoemulsion that was created underwent characterization, and further analysis was conducted to assess its in vitro release and antioxidant capability. The in vivo experiments were conducted by labeling the memantine compound with technetium pertechnetate. The determined nanoparticle size of about 11 nm and the observed transmittance percentage of approximately 99% were reported in the finalized NE. The results of the in vitro release assays demonstrated that there was an 80% release of the medication when exposed to simulated nasal fluid. The results of the study indicate that the nanoemulsion exhibited a cell survival rate of 98%. Additionally, the antioxidative tests provided evidence that the incorporation of memantine inside the nanoemulsion effectively maintained its antioxidative properties. The gamma imaging and biodistribution findings further substantiated the increased absorption of the formulation, as shown by a radioactivity level of 3.6±0.18% per gram in the brains of rats that received intranasal administration after 1.5 hours. The nanoemulsion that has been produced has promise as a carrier for memantine, enabling direct administration from the nasal cavity to the brain(Kaur, Nigam, Srivastava, et al., 2020).

Conclusion

Given the brain's role in regulating various bodily functions, it follows that neurodegenerative diseases have a broad impact on human functioning, impairing both fundamental abilities such as speech, movement, stability, and balance, as well as more complex tasks including bladder and bowel functions, and cognitive abilities. The prevailing NDs encompass a range of conditions, with Alzheimer's disease, Parkinson's disease, prion disease, Amyotrophic lateral sclerosis (ALS), motor neuron disease, Huntington's disease, spinal muscular atrophy, and spinocerebellar ataxia being among the most frequently encountered. There are very leass amount of SRDDS/CRDDS are developed on different drugs for the treatment of NDs. Therefore we are planning to work on sustained release tablet formulation for the treatment of NDs.

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