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Review Article

An overview of intranasal drug delivery systems for Alzheimer's disease

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ABSTRACT

Alzheimer's disease is a neurodegenerative condition with severe consequences interfering with patient quality of life. It is a chronic and irreversible cognitive brain condition in which memory and thinking capacities are severely impaired to the point of preventing the completion of daily activities, because of physical and cognitive limitations. The standard treatment is administered orally; however, it has significant disadvantages, including poor bioavailability, rapid metabolism, restricted uptake into the brain and severe side effects. The intranasal route has been proposed as a promising alternative to deliver drugs and improve the Alzheimer's disease treatment. Still, there is not a clear alternative delivery system available in the market with advantageous bioavailability and safety. The aim of this review is to perform an overview on the strategies for intranasal drug delivery in Alzheimer's disease management. The advantages and disadvantages of this delivery route and the delivery systems developed so far are discussed. A special focus is given on the use of permeation enhancers, the types of intranasal drug delivery devices, as well as possible toxicity concerns.

Keywords: Blood-brain barrier, Central nervous system, Intranasal, Nanoparticle, Neurodegenerative, Permeation enhancer, Protein

INTRODUCTION

Neurodegenerative diseases (ND) are a major challenge in contemporary health in relation to population aging and lifestyles, the number of affected individuals, the impact on the life of patients and their representatives and the economic cost this represents a major challenge.[1,2] People living worldwide currently suffer from neurodegenerative diseases. Alzheimer's disease (AD) is a progressive neurological disease of the brain which leads to memory loss and can seriously affect a person's ability to carry out daily activities.

AD is the most frequent cause of dementia, which is a clinical syndrome with a progressive decline in two or more cognitive domains (memory, language, behavior, personality, executive function and visuospatial function) and represents approximately 80% of all dementia diagnosis.[3] AD etiology both structural and functional damages in the central nervous system (CNS) were observed and two major lesions have been characterized, including extra cellular inclusions of the beta-amyloid peptides (Aβ) in amyloid plaques deposited around the nerve cells.[4] Intracellular aggregations due to the hyper-phosphorylation of the tau proteins aggregating inside neurons using skin, mouth or nose linings could be other ways to give pain medicine.[5] Other work like this has led to lots of new tools and methods that people call controlled-release technology (CRT).

Some CRT examples are skin patches, mouth lining patches, nose and mouth sprays, medicine lozenges, encapsulated cells, gel pills, devices that use electricity to push drugs through the skin and some implantable devices that can be programmed to give medicine. Using skin,

inside of mouth or nose might be other ways to get pain medicine and anesthesia into the system which has led to lot of new tools and methods that are called CRT. Some CRT examples include skin patches, medicine sprays for nose or mouth, medicated lozenges, cells with medicine inside, soft gel pills, devices that push drugs through skin and even implantable devices that gives medicine when programmed.[5,6]

SIGNS AND SYMPTOMS OF ALZHEIMER'S DISEASE

Alzheimer's comes with some signs that include memory loss (especially recent events), difficulty with familiar tasks, confusion and changes in mood and personality. Other symptoms include problems with language, judgment and disorientation. As the disease progresses, individuals may experience increased anxiety, agitation and difficulty with daily living activities struggle with planning and problem-solving, get confused or lose stuff.

Their personality can shift and they might have trouble with speech or writing. Also, their judgment might not be so good and they could struggle with visual information.[4-7]

ETIOLOGY

Genetics and environment both seem to be involved, but age is the biggest factor. Around 3% of people aged 65 years have Alzheimer's, but that number jumps to over 30% by 85 years. Younger people have it, to be around 3% of all cases. Even though more people are getting it as the population ages, the rate seems to be dropping in some countries.[8-10]

Familial Alzheimer's is passed down through families, but sporadic Alzheimer's doesn't have a clear family connection. early-onset cases are familial, caused by mutations in certain genes, late-onset cases are sporadic.

Studies have found over 20 genetic risk spots that might play a part in sporadic cases, but often there's no obvious genetic reason. Genetics and environment both appear to be involved, but age is the biggest thing. The chances of having Alzheimer's are about 3% at age 65 and over 30% by age 85. It's less clear how often it happens before 65 years, but it's around 3% of all cases.[10-12] Studies have found over 20 places in DNA that might raise the risk of sporadic cases, but often there's no clear genetic reason.[13]

TYPES OF ALZHEIMER'S DISEASE

There are mainly two types of ADS which include.

Early onset

This type runs in families and is passed down. It's caused by mutations. Only about 10% of people with Alzheimer's show signs before age 65 years.[13]

Late-onset sporadic Alzheimer's disease

This type starts after 65 years. It affects about 20% of people over 85 years and 5% of those over 65 years.[13-15]

PREVALENCE AND INCIDENCE RATE OF ALZHEIMER'S DISEASE

For every 1,000 people, about 11 people will get Alzheimer's each year. For those over 65 years, it's about 15 people per 1,000. In people above 65 years, the world rate is about 21.61 per 100,000. It gets more common as people age progress.[16]

RISK FACTORS FOR ALZHEIMER'S DISEASE

Previous stroke or transient ischemic attack (TIA), high blood pressure, high cholesterol, cardiovascular diseases, diabetes, obesity, sickle cell disease, increasing age, gender (women have a higher lifetime risk). Heredity and race (close blood relations with a history of stroke), Prior stroke (increased risk of having another one). There are lots of possible reasons for this link, such as problems with high insulin levels being toxic, brain blood vessel damage, blood vessel inflammation.[17]

PATHOPHYSIOLOGY

AD is caused by damage to the brain. Two types of damage under the microscopic examination include myeloid plaques and neurofibrillary tangles (NFTs). NFTs usually start in the inner part of the temporal lobe. These brain changes can be there even before someone shows any memory problems. Then, the NFTs spread to the outer part of the temporal lobe before moving to other parts of the cortex (the outer layer of the brain).[18-20] Other things can also worsen AD, like LDL and insulin spikes, brain inflammation, blood vessel problems and issues with how cells clean up waste.

Blood vessels can get damaged and not bring enough blood and food to the brain or remove waste well enough. This leads to long-term inflammation, with certain brain cells (astrocytes and microglia) becoming active. Right now, there are just two kinds of drugs to treat AD. Cholinesterase inhibitors like donepezil, rivastigmine and galantamine can be used for people with mild, moderate or severe AD and Parkinson's dementia. Also, memantine can be used for people with any stage of AD because it affects dopamine and blocks certain receptors in the brain.[21]

Additional factors that may contribute to AD pathology in the brain include abnormal glucose and lipid metabolism, neuroinflammation, abnormalities of the cerebrovascular system and blockade of the endosomal pathway. As a result of the vascular system's impairment, the brain does not receive enough blood and nutrients and metabolic waste products are not removed, which causes astrocytes and microglia to become activated and cause chronic inflammation.[22,23]

CURRENT GUIDELINES FOR MANAGEMENT OF ALZHEIMER'S DISEASE

There are currently only two classes of pharmacological therapy for AD; galantamine, donepezil and rivastigmine are examples of cholinesterase inhibitors that are used to treat patients with mild, moderate or severe AD dementia as well as dementia from Parkinson's disease. Additionally, because memantine is a non-competitive N-methyl-d-aspartate (NMDA) receptor antagonist and a dopamine agonist, it is used in patients with mild, moderate or severe AD.[26] Only two classes of pharmacological therapy are available at this time for AD; cholinesterase inhibitors, such as galantamine, donepezil and rivastigmine, are used to treat patients with mild, moderate or severe AD dementia as well as dementia from Parkinson's disease. Additionally, memantine is used in patients with mild, moderate or severe AD because it is a dopamine agonist and non-competitive N-methyl-d-aspartate (NMDA) receptor antagonist.[27]

BARRIERS THAT PREVENT DRUG ACCESS TO THE BRAIN

The blood–brain barrier (BBB), a significant limiting factor and the blood–cerebrospinal fluid barrier, which isolates the cerebrospinal fluid (CSF) from the systemic circulation and shields it from exposure to any potentially toxic exogenous substance, are the two physiological barriers that the drug must cross to reach the brain.[26-28] The basement membrane, pericytes, astrocytes and endothelial cells that are sealed by tight junctions form the intricate structure known as the blood-brain barrier. By separating brain tissue from the peripheral circulation, the blood-brain barrier permits the CNS to receive essential nutrients and hormones selectively while preventing the entry of neurotoxins or foreign substances, such as medications. It is also in charge of keeping the ion composition ideal for neuronal signalling. Through active transport mechanisms or passive diffusion (both paracellular and transcellular pathways), small lipophilic molecules and some vital nutrients can cross the blood–brain barrier. The basement membrane, pericytes, astrocytes and endothelial cells that are sealed by tight junctions form the intricate structure known as the blood-brain barrier.[29]

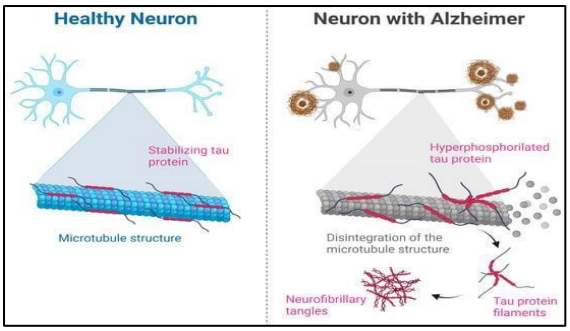

Figure 1: Neurological difference between healthy brain and Alzheimer's brain.[7]

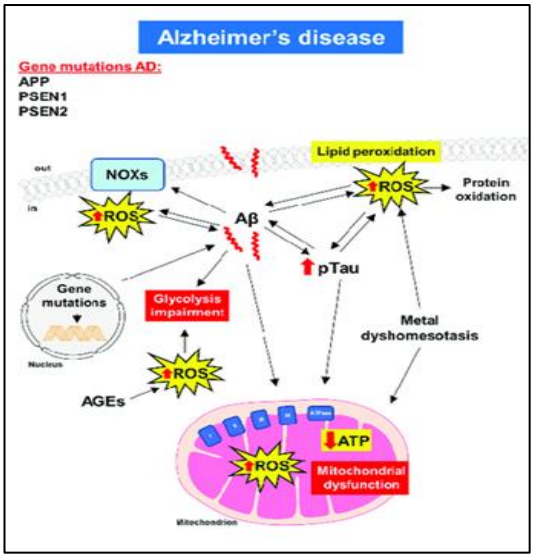

Figure 2: Pathophysiology of AD by neuroinflammation.[24]

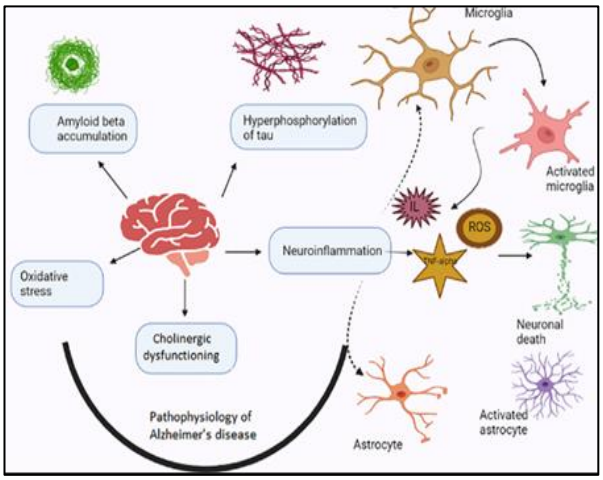

Figure 3: Pathophysiology of AD by oxidative stress.[25]

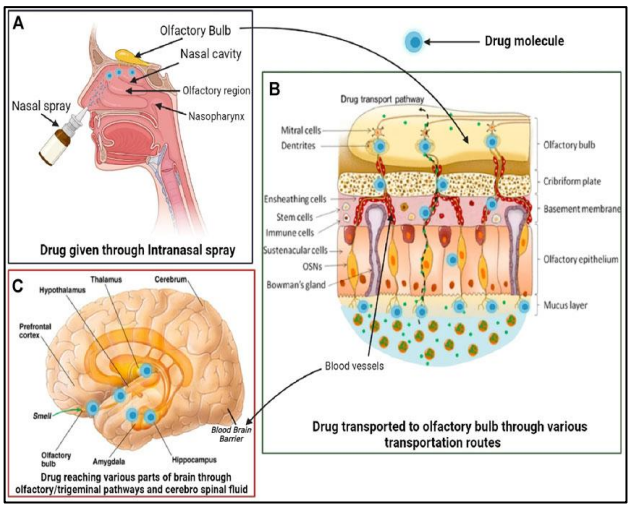

Figure 4: Intranasal drug administration of drug.[35]

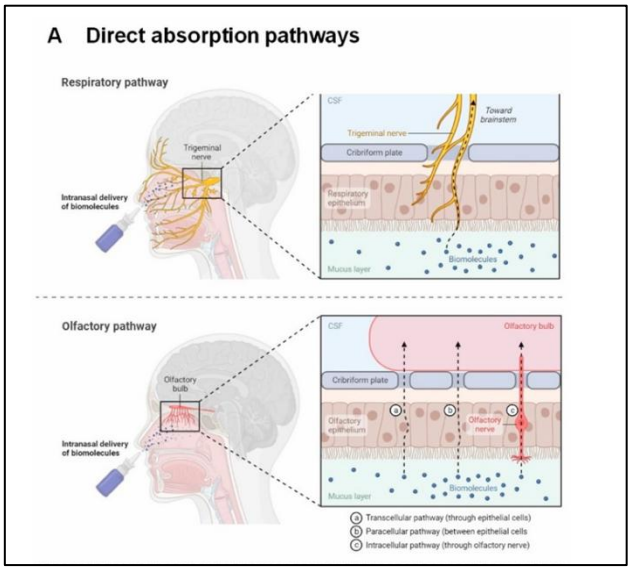

Figure 5: Direct absorption mechanism through olfactory nerve and trigeminal route.[36]

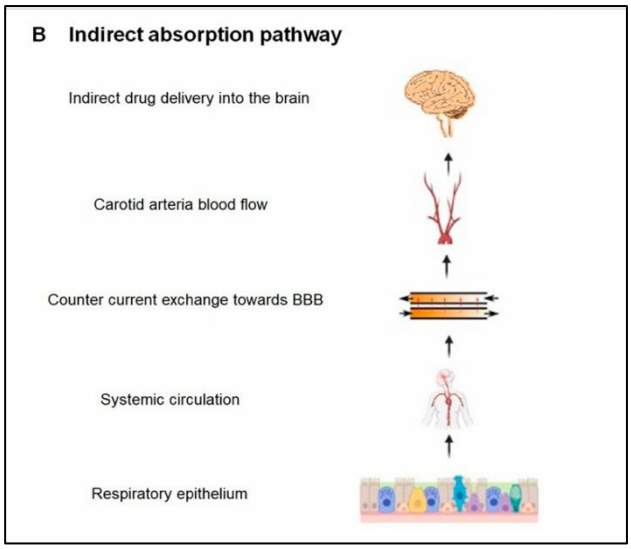

Figure 6: Indirect absorption mechanism by systemic route.[36]

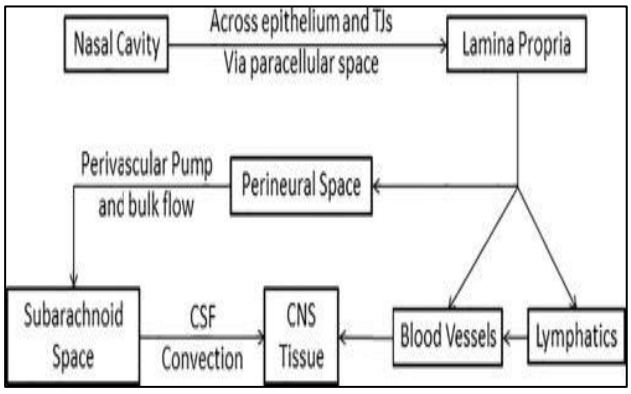

Figure 7: Extracellular mechanism for intranasal drug delivery.[46]

INTRANASAL ROUTE FOR DRUG ADMINISTRATION NASAL CAVITY ANATOMY

The nasal cavity primary role is to facilitate breathing and smell. It also serves as a protective barrier by warming, humidifying and filtering air before it enters the lower respiratory tract. In the same way, it is made up of two symmetrical cavities lined with mucosa and separated by the nasal septum. Three regions are then separated into these cavities.

Vestibular region

This is the most anterior region, with squamous epithelial cells as the predominant cell type and nasal hairs to filter inhaled particles. Drug absorption is extremely restricted in this area.[32] Respiratory regions: The respiratory region has the greatest vascularity and the largest surface area (approximately 130 cm^2), making it the perfect location for drug systematic absorption. It includes the nasal turbinate that protrude from the nostrils' lateral walls. The four primary cell types are basal, ciliated, goblet and non-ciliated columnar.

Additionally, the trigeminal nerve's maxillary and ophthalmic branches innervate the respiratory region.[33-35] The nasal cavity's roof is home to the olfactory region, which makes up only 10% of the entire nasal cavity. Trigeminal neurons, cilia, support cells, olfactory nerve cells and basal cells are among the various cell types. Furthermore, drugs can be directly transported to the brain through the olfactory region.

INTRANASAL ABSORPTION

Crossing the mucous layer is the first stage of drug absorption from the nasal cavity. The main mucus protein that can bind solutes, mucin, prevents drugs from diffusing. It is easy for small, lipophilic, non-ionized particles to get through this mucus layer. Therefore, a drug's molecular weight and lipophilicity can significantly affect how quickly and to what extent it is absorbed through the nose.[36] Other physicochemical characteristics of the medication and its formulation, along with certain physiological aspects of the nose, must be taken into account as they may also affect the drug's bioavailability and ability to travel from the nose to the brain.[37]

Direct absorption mechanism

Olfactory sensory neurons

The olfactory nerve pathway is the main and direct pathway for transportation of drugs from the nasal cavity to the brain, obstructing the BBB. Two transport mechanisms are available to the brain once the drug has passed through the nasal mucosa and reached the olfactory receptors: the intracellular route, where the drug is taken up by the olfactory neurons via endocytosis and the extracellular route, where the drug passes through the

nasal epithelium through the tight junctions between the supporting cells and the olfactory nerves.[38]

The chemicals enter the olfactory bulb and the CSF in both situations by passing through the cribriform plate, which divides the brain from the nasal cavity. If the medication mixes with the brain's interstitial fluid, it can then be transferred from the CSF to the brain.[39] The intracellular pathway is adequate and takes a few hours to several days for the active fraction to reach the various parts of the brain.[40]

Indirect absorption mechanism: the systemic route

Respiratory epithelium has a rich vasculature, a portion of a drug deposited in the nasal cavity may be absorbed, enter the systemic circulation and enter the brain through the blood-brain barrier, depending on how long the drug is there. After being administered via the nose, this is a secondary route for the drug to reach the brain. Compared to hydrophilic and high molecular weight molecules, small lipophilic molecules are much easier to enter the bloodstream and cross the blood-brain barrier.[41,42]

Additionally, the active ingredients that take this route are metabolized by the kidneys and liver, resulting in a very small amount of drug that ultimately reaches the brain. This amount is determined by the drug's molecular weight (less than 500 Da) and partition coefficient (0.5–6.0). Unwanted side effects in other peripheral organs are also more likely to occur.[43-45]

Mechanism

The flow chart shows the main features of the extracellular mechanism for delivery to the central nervous system after intranasal administration.

Benefits of intranasal route of admiration

It includes nose-to-brain delivery

This method of drug administration gives preference to medications with the lowest oral bioavailability.[46] Compared to conventional drug delivery methods, the intranasal route offers a direct transport pathway into the central nervous system, among other advantages. Moreover, it eliminates the drawbacks of the blood-brain barrier, making it a useful delivery method.[47] Nasal route benefits the intranasal route has several advantages over other routes, including the following.[48]

It avoids the blood-brain barrier. The method of drug delivery is non-invasive, safe and convenient. In the gastrointestinal tract (GIT), it stops the breakdown of drugs. Additionally, it avoids the liver's first-pass metabolism. It makes medications with low molecular weight more bioavailable.

The nanotechnology includes

Nanoparticles

The solid, colloidal nanoparticles range in size from 1 to 1000 nanometres. Only the tiniest nanoparticles, ranging in size from 1 to 100 nm, can achieve paracellular transport via tight junction penetration through the mucosal membrane. This is the best kind of delivery system for nasal vaccines. For example, miR-132 balances neuron morphology and maintains neuron survival. Additionally, following cerebral hemorrhage, it improves the microenvironment of hematoma lesions, reduces cell death and exhibits protective effects following cerebral ischemia. When administered intranasally to a mouse model, wheat germ agglutinin (WGA), nanoparticles (NPs) and miR132 significantly raise the levels of synaptic protein expression in the mouse model of AD.[49]

Polymer-based nanoparticles

Chitosan is the result of deacetylating chitin from the crustacean cell. Intranasal delivery uses chitosan because of its bio-adhesive qualities, which prolong the drug's nasal residence time by preventing nasal clearance. For instance, Memantine-HCl cross-linked chitosan nanoparticles were prepared and the poly-dispersibility index and particle size were optimized. The nanoparticle size was determined to be 129 nm at 4 hours of stirring, 1000 rpm of stirring speed and a 2:1 concentration ratio of chitosan and tripolyphosphates (TPP). Memantine-loaded chitosan nanoparticles, when taken intranasally, may represent a novel delivery method for the treatment of Alzheimer's disease.[50] Poly (lactic-co-glycolic acid) (PLGA) is another polymer with which nanoparticles can be administered intranasally. The main test involves intranasal delivery of olanzapine-loaded PLGA nanoparticles for improved drug absorption.[51]

Microemulsions

Targeting the brain is accomplished with the help of intranasally administered micro-emulsions. The combination of a mucoadhesive agent and clonazepam in a microemulsion formulation provides a rapid onset of action and a longer duration of action.[52]

Hydrogels

Targeting the brain is accomplished with the help of intranasally administered micro-emulsions. The combination of a mucoadhesive agent and clonazepam in a microemulsion formulation provides a rapid onset of action and a longer duration of action.[52]

Challenges and Future Directions

Even with the recent increase in the number of approved nanomedicines, many nations still lack well-defined regulatory frameworks that control the use and marketing

of drug formulations based on nanocarriers. A comprehensive framework for nanocarrier evaluation and approval must be developed by international regulatory agencies in concert, as this regulatory gap has impeded the full clinical translation of nanomedicine.[53] Many safeties, toxicity and compatibility evaluations for nano-formulations in the absence of clear guidelines still employ techniques that were first created for traditional pharmaceuticals.

Aspects including physical characterization, spray plume geometry, rest-time stability, particle size distribution, photostability and microbiological safety are all covered in the requirements set forth by the FDA and EMA for assessing intranasal formulations. The type of formulation determines these requirements (e.g., A. (powder, spray or suspension), the method of administration and the intended application. Nevertheless, there are still no standardized procedures for carrying out these assessments.[54] The lack of widely recognized regulatory standards continues to impede the scalability and wider clinical application of nanomedicine-based drug delivery platforms, despite significant advancements in this area. The intricacy of nanostructured formulations makes process validation and regulatory evaluation even more difficult. It is imperative that international regulatory agencies work together to create a uniform framework for intranasal nanocarrier systems that incorporate these issues.[55]

Systems that promote nasal permeability

An extremely thin layer of lipophilic mucus envelops the nasal cavity. The protective mucosal lining and the tight junctions in the olfactory and respiratory epithelium function as a selective filter to slow the diffusion and penetration of medications through the nasal mucosa.[56] Furthermore, the primary transport mechanism from the nose to the brain is transcellular diffusion, which primarily permits the passage of low molecular weight and lipophilic substances.

Smaller lipophilic molecules are therefore better suited for the nasal route, while large, polar and hydrophilic medications like proteins and peptides have poor nasal permeability. Both new drug carriers which will be discussed later and the use of appropriate absorption promoters can enhance the nasal absorption of polar medications.[57]

New drug carriers as a potential strategy

New drug carriers based on nanotechnology have demonstrated the capacity to get past the resistance caused by secretion systems, mucociliary clearance and epithelial tight junctions. Along with improving solubility or transport through biological membranes, they also enable drugs to be shielded from chemical or metabolic degradation, which improves orientation and reduces systemic side effects.[58] Because of this, they have attracted the most attention in research in recent years. The right choice of excipients, the physicochemical characteristics (drug charge, zeta potential, particle size and size distribution), biodegradability, biocompatibility, release profile and safety profile must also be considered. Various nanotherapeutic strategies have been explored for intranasal treatment of ATD, including polymeric and inorganic nanoparticles and lipid-based nanocarriers.[59] Lipid-based nanocarriers show promise as treatments for ATD because they can transport drugs from the nose to the brain.[60]

They overcome issues like cytotoxicity that are related to polymeric nanoparticles and provide increased brain-targeting potential, quick brain uptake, biodegradability and bio-accessibility. Because lipid-based nanocarriers immobilize drugs in a solid lipid matrix that readily biodegrades, they can incorporate both hydrophilic and lipophilic drugs, offer protection and provide controlled drug release.[61-63] Lipid-based nanocarriers can be liposomes, noisome, solid-matrix lipid nanoparticles, microemulsions and nano-emulsions. Due to their benefits, the latter have attracted more attention recently. Lipid-based nanocarriers that have been investigated for drug delivery to the brain through the nasal route will be covered in detail in the section that follows.[64,65]

Nanostructured lipid carriers for intranasal delivery

Solid matrix lipid nanoparticles are aqueous dispersions of solid particles, typically ranging in size from 100 to 300 nm. They can be made of physiological lipids and stabilized by one or more emulsifiers. Nanostructured lipid carriers (NLCs) and solid lipid nanoparticles (SLNs) are the two varieties. While NLCs exhibit a disorganized internal lipid matrix made up of a mixture of solid and liquid lipids, they are referred to as second-generation lipid nanoparticles.[66]

In contrast, SLNs present a lipid matrix made up of a single solid lipid with a highly organized structure. Since most hydrophobic molecules exhibit better solubility in liquid than in solid lipids and because the encapsulated drug is less likely to be expelled during storage, the disruption of the lipid matrix caused by the liquid lipid in the case of NLCs enables higher encapsulation efficiency (EE). E. enhanced stability. The current research focus is as a result.[66]

CONCLUSION

Nasal drug delivery has gained attention in being an attractive alternative to treating Alzheimer's disease, bypassing some of the constraints existing with traditional oral drugs. Through avoiding the blood–brain barrier by passing through the olfactory and trigeminal pathways, this route allows direct drug transport to the CNS with higher bioavailability, faster administration and lower systemic toxicity.

A number of formulations, such as nanoparticles, liposomes and gels, have demonstrated potential to improve the permeation and retention of drug in nasal mucosa. Moreover, it has been observed that the application of permeation enhancers and new delivery devices has greatly increased drug absorption and targeting efficiency. But, despite decades of progress, problems persist. Nasal anatomy variabilities between patients, mucociliary clearance and possible local toxicity, however, are still hurdles for clinical translation.

Furthermore, durability data and standardized transduction platforms do not exist, thus hampering wide acceptance. In summary, although intranasal drug delivery is an exciting frontier in the therapy of AD, more preclinical and clinical studies are necessary to refine formulations, to ascertain the safe use of IN drug delivery in patients and to develop robust delivery systems for IN drug. Through further development and testing, intranasal delivery may become an important partner in advancing the care and quality of life for patients with Alzheimer's disease.

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