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Nose to brain targeting drug delivery system

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ABSTRACT

Numerous neurological conditions, including Parkinson's disease, Alzheimer's disease, schizophrenia, dementia, and brain cancer, are treated with this delivery system. Because it skips first-pass metabolism and delivers a larger dose of medication to the central nervous system at a lower concentration, the nose-to-brain drug delivery system is an intriguing method of delivering an intranasal medicine. Depending on the physiochemical characteristics of the medication, several formulations such as nanoparticals, nanoemulsions, in setu gel, liposome, and hydro gel can be used to treat this kind of illness. This paper highlights some key characteristics of nose-to-brain delivery, including anatomy and the physiology of nose-to-brain transport, as well as potential challenges.

KEY WORD: Nanoparticle, Nose-to-brain, Parkinson's disease.

1. INTRODUCTION

Brain is an important organ in human bodies which control all body function. The mental illness is not easily treatment of neurological diseases such as nervous like Alzheimer's disease, Parkinson's disease, epilepsy, stroke and, migraine (1). The diagnosis and treatment of brain disease CNS for from impressive, owing to the restriction by BBB of drug transport (2). Oral route is popular route but its drug cannot be pass nervous system IN is bypassing BBB is painless treatment of diseases (3). Nose to brain drug delivery system is use for local as well as systemic effect for administration of drug by nasal route the many type of formulation is avaible in market such as Nanoparticle, Nanoemuslion, in setu gel, Lysosome and Hydrogel (4)& (5).Nose to brain targeting drug used in phenytoin sodium (6), olanzapine (7), quetiapine (8), simvastatin (9), rotigotine (10).

1.1 BRAIN ANATOMY

The average brain weighs between 1300 and 1500 grams and is composed of approximately 100 billion neurons, with the ratio of glial cells to neurons in the brain varies by region, is generally closed to 1:1 (11).The brain is an organ made of nerve tissue that control movement, senses, emotion, language, thought, memory, and task-evoked reaction (12).

The brain consists of three main structural divisions:

1. Cerebrum = The largest part of the brain, the cerebrum initiates and coordinates movement and regulates temperature.
2. Cerebellum = A role for the cerebellum in higher cognitive activities has been bolstered by accumulating data from clinical research, functional imaging, and tracing.
3. Brain stream = The brainstem is a part of the brain that connects the brain to the spinal cord and cerebellum, and controls many vital functions.

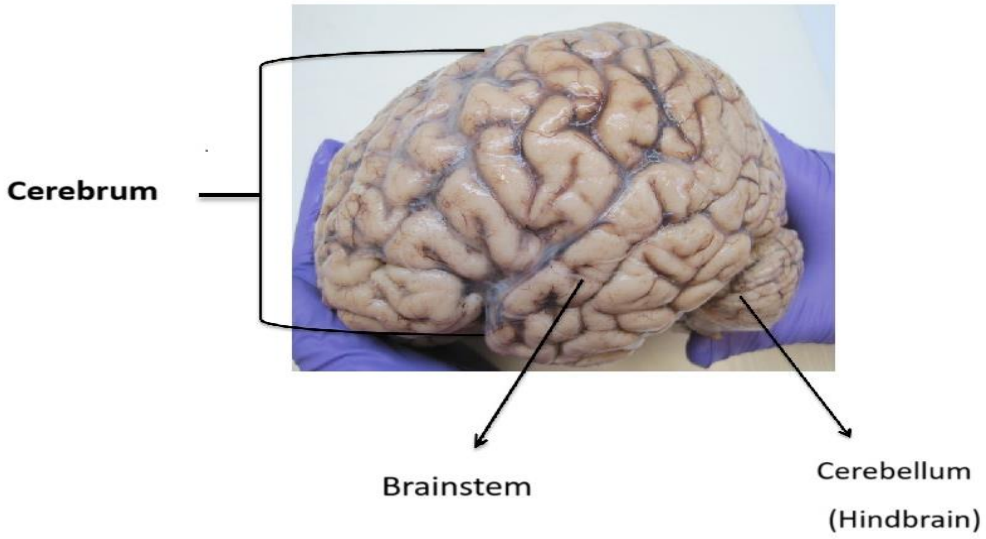


Figure 1 Brain Anatomy

2. NEUROLOGICAL DISEASE

About one billion people worldwide are affected by neurological disease, including people of all ages and races, living in a variety of places, and having a range of socioeconomic backgrounds (13). Deterioration of the central nervous system (CNS) and Peripheral nervous system (PNS) is linked to both common and rare neurological illnesses (14).

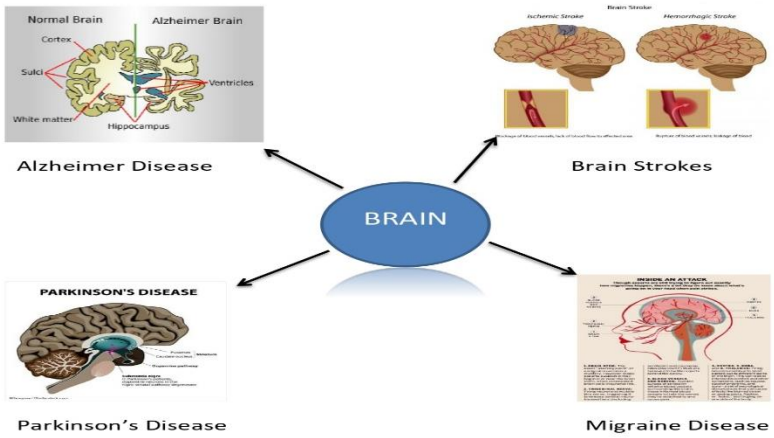


Figure 2 Neurological Disease

a) Parkinson's disease

First described by James Parkinson in 1817 in his essay "an essay on the Shaking Palsy" later termed "Parkinson's disease" by Jean-Martin Charcot in 1867 (15). Parkinson's illness is a neurological condition with ever more complex layers, it has long been distinguished by the loss of dopaminergic neurons in the substantia nigra and the hallmark motor characteristics of parkinsonism linked to lewy bodies (16). Numerous studies show that males are twice as likely as women to get Parkinson's disease, and earlier on disease strikes men 2 years earlier on average than it does women (17). Examining 183 Parkinson's patients in 1967. Bradykinesia, stiffness, postural instability, and resting tremor are a few of them (18). A clinical syndrome has been referred to as "Parkinsonism" (19). Approximately 60,000new cases of Parkinson's

disease (PD) are diagnosed year, affecting up to one million Americans. Seven and ten million people are predicted to be affected globally. The likelihood of PD in men is 1.5 times higher than in women (20).

Symptoms

Since the disease's eponymous physician first characterized it in the early 1800s, Parkinson's disease has been known to exist. PD, also referred to as "paralysis agitans" is uncommon in young people, particularly in those under the age of 40 (21). The neurological condition known as Parkinson's disease (PD) is idiopathic and manifests in both motor and non-motor system.is is a long-term, progressive neurological disease that primarily affects the elderly; however, it can strike those much younger. In terms of neurodenerative diseases, it is the second most prevalent (22). Bradykinesia, stiffness in the muscles rest tremor, and abnormalities in pasture and gait are some of the parkinsonian symptoms (23). age, sex, and the amount of the disease were found to be independently disease, with men between the ages of 60 and 80 having greater incidence of dementia (24).

Degeneration of the Dopamine

↓

Loss of Dopamine and acetylcholine in basal ganglia

↓

Loss of motor control

↓

Abnormal movement, impaired balance and Posture

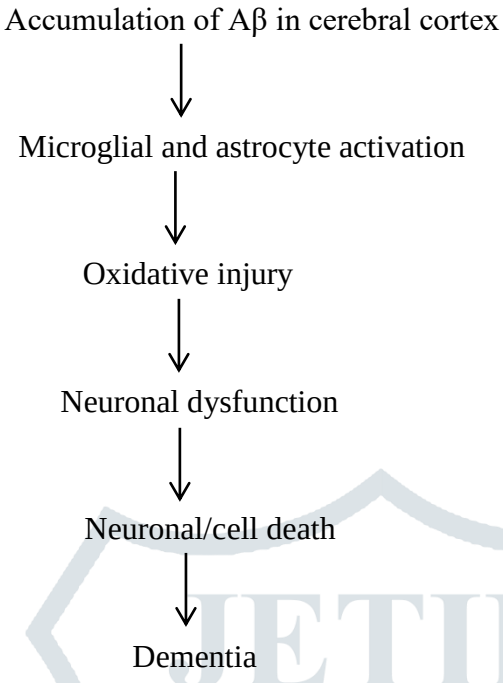
b) Alzheimer disease

According to current estimates, 44 million individuals worldwide are estimated to be living with dementia. When the population ages, it is expected that this will more than treble by 2050, and dementia may cost even more than US$600 billion annually in the USA alone (25) (26). The most prevalent form of dementia is Alzheimer's disease (AD), which is named after the German psychiatrist Alois Alzheimer. It is a slowly developing neurodegenerative condition marked by neuritic plaques and neurofibrillary tangles caused by the buildup of amyloid-beta peptide (Aβ) in the medial temporal lobe, the most affected region of the brain, as well as neocortical structures (27).One of the main causes of dependency, disability, and death is dementia, which is defined as acquired progressive cognitive impairment significant enough to affect activities of daily living (28). Extracellular neuritic plaques and intercellular neurofibrillary tangles made of aggregated β-amyloid (Aβ) and hyperphosphorylated tau protein, respectively, are its most notable neuropathological characteristics. Drug development for AD has focused on disease-modifying therapies that target Aβ in recent decades (29).

Symptoms

Age-related increases in the prevalence of AD are seen in the following demographics: 3% of those 65 to 75, 17% of those 75 to 84 and 32% of those over 84 (30).Men have a 10% lifetime risk of having AD at age 45, whereas women have a 20% lifetime risk (31).As many as 97% of AD patients experience neuropsychiatric symptoms and abnormalities during their illness, which puts a great deal of strain on their careers (32). The incidence of AD seems to decline after age 90 as hippocampal sclerosis becomes increasingly prevalent (33). A cerebral disorder like Alzheimer's disease (AD) or other conditions like intoxication, infection, abnormalities in the pulmonary and circulatory system that reduce the amount of

oxygen reaching the brain, nutritional deficiencies, vitamin B12 deficiency, tumors, and other can cause a progressive loss of cognitive functions (34)



c) Epilepsy

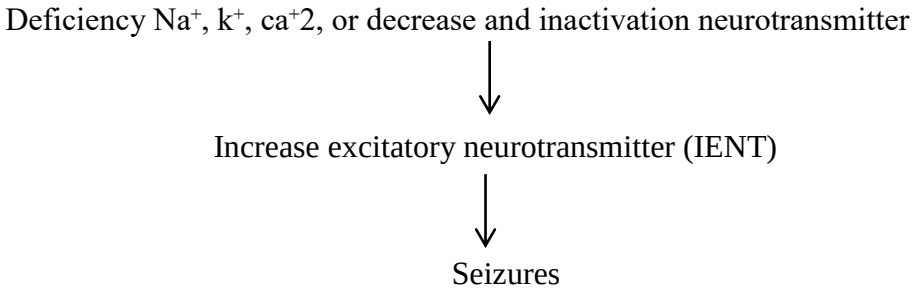
Originating from the Greek term epilambanein which means "to seize" or "attack," epilepsy has been depicted in many ways throughout history by all cultures, implying a mysterious or demonic beginning (35). The earliest documented account of epilepsy can be found in Akkadian cuneiform tablets from the Sakikku period, circa 1000 BC. the Babylonian term for seizures was "miqtu". The assumed cause was a spiritual or possession by the demonic, as was customary (36). Over 70 million individuals worldwide suffer from epilepsy, one of the most prevalent and dangerous brain disorders (37). Epilepsy-related stigma and discrimination are widespread throughout the world (38). A neurological condition called epilepsy causes seizures that can occur randomly and disappear on their own for a brief period of time (39). According to the Global Burden of Disease Study, which was conducted by the World Bank, the World Health Organization, and the Harvard School of Public Health with funding from the Bill and Melinda Gates Foundation, epilepsy accounts for 0.3% of all fatalities globally (40). Epileptic seizures fall into two primary categories:

a) Generalized seizures
   Tonic seizures
   Atomic seizures (drop attacks)
   Clonic seizures
   Myoclonic seizures
   Tonic-clonic seizures (grand mal seizures)
   Absence seizures (petit mal seizures)
b) Partial (focal) seizures

Symptoms

A common responsibility for a doctor is to diagnose and treat epilepsy and seizures. One in ten persons will experience a seizure at some point in their lives (41) .One of the most prevalent diseases affecting both adults and children is epilepsy (42). People of various ages, races, social levels, and geographic locations are impacted by

the widespread medical disorder known as epilepsy. Epilepsy is still diagnosed clinically, although ancillary tests (such as electroencephalograms and imaging) can help identify the type, cause, and prognosis of the condition (43). Low-cost medications such as the classic antiepileptic medications carbamazepine, phenobarbital, phenytoin, valproic acid, and benzodiazepines can be used to treat epilepsy at a reasonable cost (44).

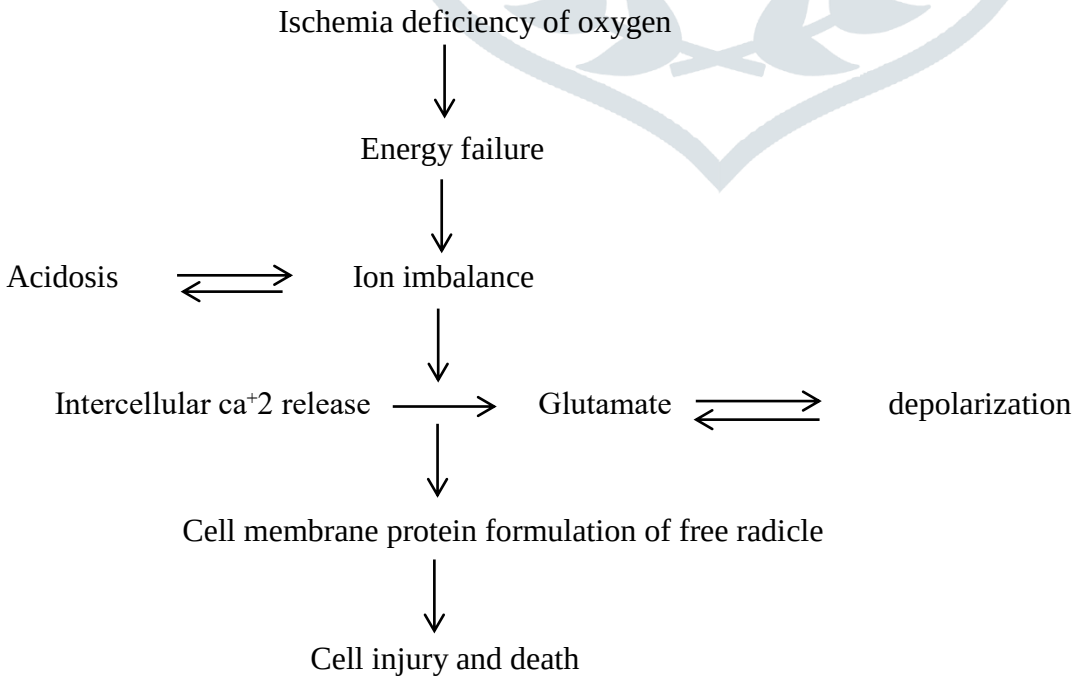


d) Stroke

Worldwide, stroke ranks as the second most common cause of death. It kills over 5.5. Million people a year and affects about 13.7 million people. Ischaemic infarction account for about 87% of strokes; between 1990 and 2016, this frequency has rose, with improved therapeutic intervention and lower mortality rates being the main causes (45).An obstruction in a blood vessel causes an Ischaemic stroke, which is characterized by a limited blood flow to the brain. Hemorrhagic stroke, on the other hand, happen when a blood artery bursts and blood seeps into the cerebral cavity (46). Furthermore, according to demographic data, one in three stroke victims will be 85 years of age or older by 2050 (47).

Symptoms

We primarily limit this discussion to Ischaemic strokes. Stroke mortality and incidence have been declining during the last few decades (48). Worldwide, stroke ranks as the second most common cause of death.it kills over 5.5 million people a year and affects about 13.7 million people. Ischaemic infractions account for about 87% of stroke; this frequency rose significantly between 1990 and 2016, which was attributed to better therapeutic intervention and primary (first-time) haemorrhages, with secondary (second-time) haemorrhages accounting for an estimated 10-25% of strokes (49). In high-income nations, stroke is the most frequent reason for acute hospitalization in neurology department (50).



e) Migraine

The Greek word hemicranias, meaning "half of the head," is the source of the English name migraine. Given that most people only experience pain in one side of their brain, this is a startling aspect of the illness (51). Hippocrates (c. 460 – 370 B.C.) was the first to describe migraine as intense pain in a part of the brain associated with the dispersion of sight (52). John Fordyce initially noticed polyuria, prodromal melancholy, and the connection between migraine and menstruation in 1758 (53). An estimated 44.5 million persons in the United States, comprising 18% of women and 6% of men, have suffered from migraines, according to a recent report. The prevalence peaks in the 18–44 age range and is higher among Caucasians. According to World Health Organization statistics, migraine is one of the top 40 disorders worldwide that cause disability, even though it is only a minor annoyance for many people. In general practice, headaches account for 4.4% of all medical consultations (54). With an annual cost of over $36 billion, it places a heavy financial load on the US (55). Auras may or may not accompany episodic or chronic migraine attacks. This neurological condition was initially diagnosed as a hypoglycemic headache in the early 1900s (56).

Symptoms

There are several characteristics that migraine and epilepsy have in common, such as genetic component that causes a predisposed episodic pattern, similarities in certain pathophysiological pathways and similarities in clinical presentation and triggers (57).similar to headaches, nausea, and vomiting common supplementary symptoms include photophobia and phonophobia (58).there are two types of migraine: migraine without aura (MO) and migraine with aura (MA). There are two other types of migraine: episodic and chronic. Another severe and uncommon form of MA that Affects and side of the body and briefly produces numbness is called hemiplegic migraine (59).

3. DIAGNOSIS OF BRAIN DISEASE

Intranasal administration was first presented by William H. Frey II in 1989 as a non-invasive method of nose-to-brain transport (60). The diagnosis of neurological illness is becoming one of the most difficult issues in modern medicine. Up to one billion people worldwide suffer from neurological disorders like epilepsy, Alzheimer's disease, stroke, and headaches, according to a recent World Health Organization study. It is estimated that 6.8 million people die each year from neurological disorder. Modern diagnostic tools, such magnetic resonance imaging and eletroence phalograms, generate massive volumes of data in terms of size and dimensions for the goal of identifying, monitoring, and treating neurological problem (61). The BBB makes it very challenging for the scientific community to diagnose and treat neurological diseases. For treatments that reach the brain without breaching the blood-brain barrier or exposing the gastrointestinal tract, the intranasal route has become a popular and unique method (62). Intranasal delivery can deliver drugs directly to the brain via the olfactory and trigeminal nerve pathways, thus attracting much study interest as an alternative to traditional parenteral and oral approaches (63). Neurological illnesses are difficult to diagnose and reply on the physical examination and history (64).

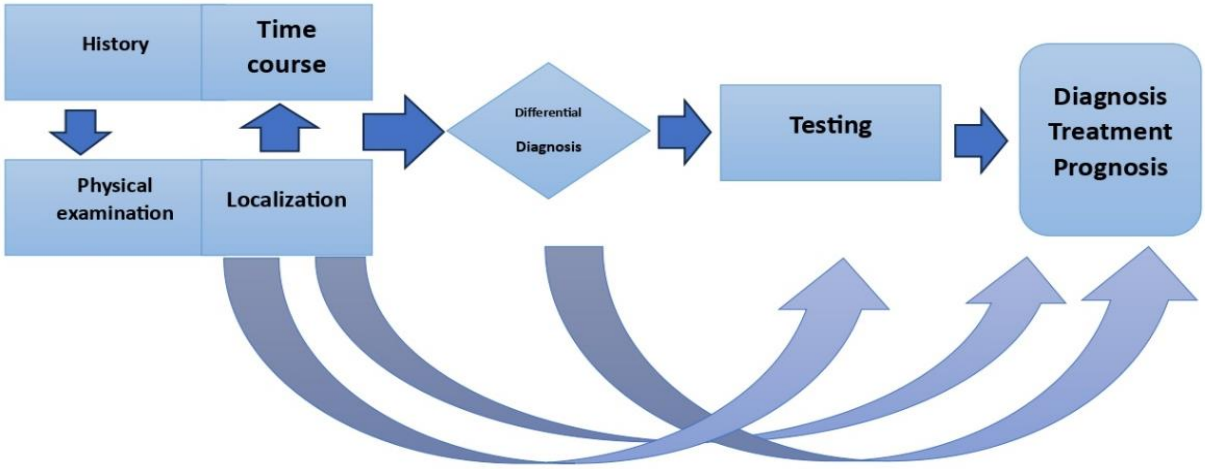


Figure 3 Diagnosis of brain disease

A various types of method used in the diagnosis of brain disease including: -

1. Imaging Test
   i. CT / X-ray (Commuted Tomography)
   ii. MRI (Magnetic Resonance Imaging) (65)
   iii. PET (Positive Emission Tomography) (66)
2. Laboratory Test
   i. Blood test
   ii. Urine test
   iii. Stool test
   iv. Spinal fluid test
3. CSF
4. Biopsy
5. Electroencephalography (EEG) (67)
6. Electromyography (EMG) (68)
7. Deep Learning Techniques (DL modes) (69)
   i. Deep Neural Network (DNN)
   ii. Deep Autoencoder (DA)
   iii. Deep-Belief Network (DBNs)
   iv. Convolution-Neural Network (CNN)
   v. Recurrent Neural Network (RNN)
   vi. Restricted Boltzmann Machine (DBM)
   vii. Support Vector Machine (SVM)
   viii. Diabetic Peripheral Neuropathy (DPN)
   ix. Variation Auto-encoder (VEN)
   x. Deep Long short termmemory (DLSTM)

Route for drug delivery nasal

- Comparison of nasal drug delivery system between oral, parenteral and transdermal drug delivery system: -

Sr.no	Parameter	Nasal	Oral	Parenteral	Transdermal
1	Targeted delivery	Yes	No	Yes	Yes
2	Onset of action	Fast	Slow	Fast	Fast
3	Patient compliance	High	High	Low	Low
4	Pain at the site of administration	No	No	Yes	No
5	Intestinal enzymatic degradation	Avoidable	Dominant	Avoidable	Avoidable
6	BBB and CSF bypass	Yes	No	No	No
7	Systemic activity	Yes	No	Yes	Yes
8	Self-administration	Yes	Yes	No	Yes
9	Higher plasma drug level	Yes	No	Yes	Yes
10	Particle size	30-120 micron	5-110 µm	Less than 5µm	10 – 100 nm
11	Mucosal irritation	No	Yes	No	Yes
12	Drug degradation	No	High	No	Low
13	Hepatic first pass metabolism	Avoidable	Dominant	Avoidable	Avoidable
14	BBB penetration	Avoidable	Difficult	Difficult	Difficult
15	Dosage form	Spray	Tablet and capsule	Injection	Patch
16	Example	Zalmitripten Naloxone	Phenytoin	Apomorphine	Ziconotide

4. NASAL CAVITY

The human nasal cavity system is a complicated structure that is between 12 and 15 centimetres long (70)**.** Nasal mucus is typically thought to have an average pH between 5.5 and 6.5 (71). The nasal septum separates its two cavities, each of which has a volume of around 7.5 mL. The mucosa covers the inner surface of the cavities, which has a total surface area of about 150 cm2 and is made up of the lamina propria and epithelium (72). As was previously mentioned, the nasal cavity's unique features-such as high enzymatic activity, quick physical clearance mechanism, poor mucosal permeability, issues with drug deposition brought on by the nasal deposition brought on by the nasal cavity's structural complexity, etc.-all make it more difficult to deliver pharmaceuticals to the brain effectively and in therapeutically relevant amounts (73).

4.1 Mechanism of Nose to brain drug delivery

The nose is a 12–14 cm long chamber with a 150–200 cm2 surface area that is abundant in capillaries and lymphatic tissues. It can be separated into three sections based on its structure and function: the respiratory region, olfactory area, and nasal vestibular area. The nasal vestibular area has virtually no absorption function because of its limited surface area, whereas the olfactory and respiratory sections of the nose absorb drugs the most. The anterior portion contains the nasal vestibular region (74).

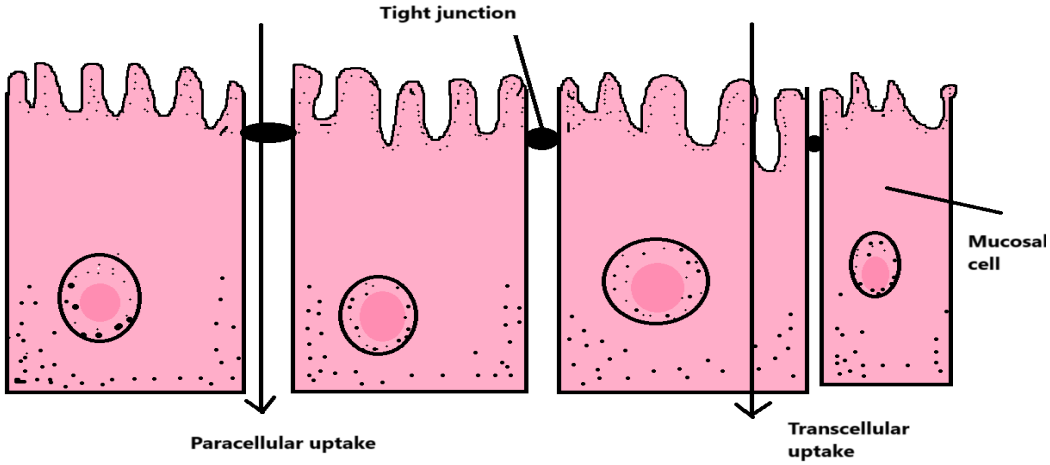


Figure 4 Mechanism of nasal drug delivery system

Paracellular transport= The paracellular/extracellular mechanism is a sluggish, passive water transport pathway that passes via the nasal mucos'a epithelial cell's open clefts or intercellular tight junction. This route is particularly well-suited for tiny hydrophilic compound (75).

Transcellular transport= Transport via a lipoidal pathway by either receptor-mediated endocytosis, passive diffusion, or fluid phase endocytosis is part i=of the transcellular process. Absorption of lipophilic compounds, both big and small.

4.2 Nose to brain drug delivery pathway

Only a small portion of the initial medication dose can actually reach the brain, despite the fact that direct transport of several therapeutic entities to the brain through the nasal cavity has been the subject of numerous research studies. This suggests that the precise pathways and underlying mechanisms are still unclear (76). The vestibular, respiratory, and olfactory zones are the three separate sections of the nose cavity that can be separated according to their respective functions and organizational structures (77). The vestibular, respiratory, and olfactory regions are the three primary regions of the nasal cavity. The first section is the nasal cavity's outermost portion, which is covered in a mucous layer and ciliated hairs, limiting the entry of germs, antigens, and outside particles. Next, blood vessels and trigeminal sensory nerves are supplied to the respiratory area. Lastly, the nasal cavity's top portion contains the olfactory area, which has an epithelium made up of olfactory sensory neurons, basal cells, and supporting cells (78) (79).

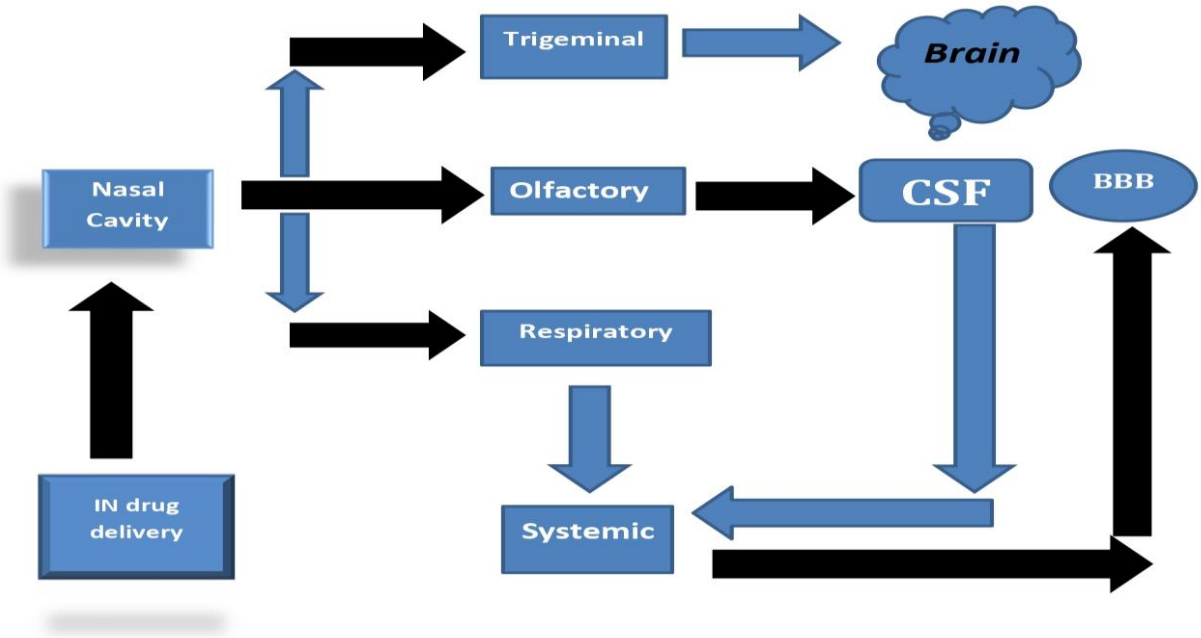


Figure 5 Nose to brain drug delivery pathway

Olfactory nerve pathway= According to some research, the olfactory nerve pathway is how the majority of neurophilic viruses (including rabies, herpetic stomatitis, and horse encephalomyelitis viruses), steroid hormones, metal ions (including nickel and cadmium), and proteins reach the brain (80). The olfactory and trigeminal routes are the two main pathways that the N2B drug delivery pathway suggests for drug transport through the nasal epithelium and into the brain (81). The olfactory route, which is situated in the olfactory area on the roof of the nasal cavity, is the predominant N2B drug delivery mechanism (82). The olfactory region in humans is about 60 μm thick and occupies 2-12.5 cm2, which is a small portion of the nasal cavity's overall surface area (about 1.25–10%), despite the fact that there are large differences in the reported numbers (83). These compounds are taken up at the axon terminals of olfactory neurons by pinocytosis, endocytosis, or simple diffusion after passing through the olfactory mucosa (84).

Trigeminal pathway= Following intranasal administration of iodine-125-conjugated insulin-like growth factor 1, strong radioactivity was seen in the trigeminal nerve, trigeminal branch ganglia, and olfactory bulb. The concentration of this radioactivity was ten times higher in the trigeminal nerve than in the olfactory bulb, indicating that the trigeminal nerve may occasionally act as a conduit for drugs to enter the brain after intranasal administration. However, compared to the olfactory nerve, the transit time along the trigeminal nerve has been observed to be 17–56 hours greater (85).

5. Why in is better reason?

A simpler and more direct method of brain targeting is nose-to-brain administration, which eschews invasive procedures and bloodstream clearance (86). The painless, non-invasive method known as nose-to-brain medication delivery allow medications to enter the brain without crossing the blood-brain barrier (87). The intranasal route of transportation avoids adverse effects and increases the effectiveness of neurotherapeutics by delivering the medications directly to the brain without systemic absorption. Many drug delivery systems (DDSs) have been researched over the past few decades in an effort to target the brain through the nasal route. In the nasal mucosa and central nervous system (CNS), novel DDSs such as nanoparticles (NPs), liposomes, and polymeric micelles have shown promise as practical instruments for brain targeting without causing harm (88).

Advantages

- Self-administration.
- Improve convenience and compliance.
- First pass metabolism is absence.
- Speedy drug absorbance.
- Fast onset of action.
- High nasal bioavailability for smaller drug molecules.
- Massive nasal tissue layer extent for dose absorbance.
- Less risks of infection.

6. Nano-formulation

6.1 Nanoparticle

Drug delivery studies have been carried out using nanoparticulate formulations (nanoemulsions, lipids, or polymer particles) in order to address the extremely poor drug transfer levels observed with traditional solution nasal formulations. In essence, these formulations have the potential for improved penetration or an extended residence period in the nasal cavity (89). Nanoparticles can improve nose-to-brain drug delivery by protecting the encapsulated drug from extracellular transfer by P-gp efflux proteins and from chemical or biological degradation (90).

Types of nanoparticles - poly (L-Lactide-co-glycolide) Nanoparticle and Lipid Nanoparicles (91)

Sr. no	Drug	Nano - System type	Use	Excipient	Carrier	Method formulation	Reference
1	Doxycycline	Nanoparticle	Anti-inflammatory	Poly (methacrylic acid, methyl methacrylate) 1:2, 2-hydroxypropyle methyl ether and phthalic acid ester, HPMCP HP55, Doxycycline helicate.		Nano precipitation	(92)
2	Simvastatin	Nanoparticle	Heart related problem, Schizophrenia, Epilepsy, Parkinson's disease.	Chitosan, Lecithin (Lipoid s45), Labrafac^{TM}35-1, Capryol^{TM}PGMC, Cell lineRPMI2650(CCL-30).	BBB and CNS	Nanoprecipitation, emulsification and homogenization-extrusion	(93), (94)
3	PLGA-Diazepam	Nanoparticle	Anxiety, Seizures, Sweating, Sleeping	Poly (D, L-lactide-co-glycolide) (PLGA)50:50 and poloxamer 407, Acetone, Diazepam	BBB	Nano precipitation, emulsion solvent evaporation method	(95)
4	Rotigotine	Nanoparticle	Parkinson's disease & Alzheimer disease	Glipizide, Chitosan (75-85% deacetylated), Acetic acid glacial,	BBB	Solvent injection Method	(96)

				Lecithin and Poloxamer407			
5	Phenytoin	Nanopart icle	Epilepsy, Seizures	Phenytoin sodium, bovine serum albumin (BSA) and trypsin, PBS And BSA-ester Cyanine5.5	CNS	Using melt emulsification with ultra-sonication method	(97)

6.2 Nanoemulsion

One effective way to deliver medications directly into the brain by intranasal delivery is with nanoemulsions (98). Oil-in-water (O/W) or water-in-oil (W/O) dispersion of two immiscible liquids stabilized with the help of one or more suitable surfactants (99). Are known as nanoemulsions (NEs). They have a mean droplet diameter of roughly 100nm (100), While upper size limits of up to 300nm (101)have been described in the literature.

Sr no	Drug	Nano-system type	Use	Excipient	Carrier	Method of preparation	Referenc e
1	Risperidone	Nanoemu lsion	Mental health, Schizophrenia ,bipolar disorder	Medium chain triglycerides (MCT), soybean oil (Lipoid purified Soybean oil700), Sodium oleate (Lipoid Sodium oleate B) and Polysorbate 80 (polyoxyethylensor bitan monooleate)	BBB	Simple emulsification	(102)
2	Amisulpride	Nanoemu lsion	Schizophrenia , Depression& Anxiety	Gellan gum, Labrasol, MaisineCC, and Transcutol HP, Poloxamer 407, Tweens	BBB, CNS	Low energy emulsification method, Aqueous Titration	(103)
3	Aripiprazole	Nanoemu lsion	Mental health condition includes: schizophrenia , bipolar disorder	Captex300, Capmul PG 8 and Capmul MCM, Maisine, Peceol, labrafac PG8, Tween 80	BBB	Spontaneous emulsification method	(104)
4	Quetiapine	Nanoemu lsion	Schizophrenia , bipolar mania	Capmul MCM (CPM), Transcutol P and Emalex LWIS 10, Tween 80, PEG 400 (PEG), propylene glycol (PG), acetonitrile (HPLC grade)	BBB	Ternary-phase study using ultra probe sonicator	(105)

5	Asenapine maleate	Nanoemulsion	Schizophrenia, Mental condition	Labrafac PG 8, labrafacWL1349, Peceol, Maisine capmul MCM	CNS	BOX- Behnken design	(106)

6.3 In setu gel

Of these, in situ gelations seem to be a promising method that prolongs the drug release, decreases the outflow of the supplied dose via mucociliary clearance, increases the drug retention duration in the nasal cavity, (107).

Sr. No	Drug	Nano-System type	Uses	Excipient	Carrier	Method	Reference
1	Resveratrol	In setu gel	Neuroprotection Brain injury Brain Tumor treatment	Gellan gum and Xanthan gum, Capmul MCM and Acrsol K150, Poloxamer188 and Tween80	CNS	Melt emulsification-probe sonication	(108)
2	Simvastatin	In setu gel	Brain tumor, Neurological disorder, Brain edema	QRC & Poloxamer 188, Poloxamer 407, Carbopol 934 P and Chitosan	BBB	Modified Nanoprecipitation method	(109)
3	Flibanserin	In setu gel	To treat generalizes hypoactive sexual desire disorder (HSDD), premenopausal women with acquired.	Compritol®888 ATO (Glyceryl behenate) and Gelucire®44/14, (St Louis, MO, USA), and L-phosphatidylcholine (soya95%)	BBB	Hot emulsification-ultra sonication method	(110)
4	Tetrandrine	In setu gel	Used to treat microwave induced brain damage	Poloxamer407, Poloxamer188; β-cyclodextrin(β-CD), Sulfobutyl ether-β-cyclodextrin (SE-β-CD) and HP-β-CD	BBB, CNS	Cold Method	(111)
5	Moxifloxacin hydrochloride	In setu gel	To treat a variety of bacterial infection	Sodium alginate and HPMC-K4M, Benzalconium chloride, Moxifloxacin hydrochloride	CNS	Mixing the drug with a polymeric solution, and then adding preservative and other ingredient	(112)

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6.4 Lyposomes

Bangham and Horne initially described liposomes in 1961 at the Babraham Institute in Cambridge (113). Liposomes are the first nanodrug delivery system that has been successfully modified for application in real-time clinical settings (114). Liposomes are artificially made phospholipid vesicles that are either nano- or micro-sized (115). Liposomes are a highly effective novel drug delivery system that uses cutting-edge technology to transfer active molecules to the site of action. Currently, a number of formulations of liposomes are being used in clinical settings (116). Liposomes are a very useful resource, reagent, and tool in many scientific domains, such as mathematics and theoretical physics, biophysics, chemistry, colloid science, biochemistry, and biology. Liposomes have been on the market ever since (117).

Sr. No	Drug	Nano system Type	Uses	Excipient	Carrier	Method Of Preparation	Reference
1	Sertraline	Liposome	Depression, Stress Disorder,	Hydrogenated phosphatidylcholine, Sertraline hydrochloride, Polyethylene glycol 4000, Rhodamine and NIR dye, 1,1-dioctadecyl-3,3,3,3-tetramethylin-dotricarbocyanine	BBB	Lipid film hydration method	(118)
2	Risperidone	Liposome	Schizophrenia, Bipolar disorder, Treat mental health condition	Soya phosphatidylcholine, Cholesterol, Octadecylamine/ Stearylamine, Sephadex-G25 and Triton®-X100, Distearylphosphati-dylethanolamine-mPEG-2000	CNS	Lipid film hydration method	(119)
3	Docetaxel	Liposome	Cancer therapy brain targeting	DTX (bulk drug) and Duopafei® (batch 1070172TA), DTX and Paclitaxel, PE, Cholesterol	BBB	Both thin – film dispersion method	(120)
4	Dopamine	Liposome	Parkinson disease& Brain disease	1,2-dioleyl-sn-glycero-3-phosphochloline (DOPC), and L-α-phosphatidic acid (PA), Alabaster, Texas red, Ammonium sulfate,	CNS	Solvent injection method	(121)

				Levodopa(L-DOPA)			
5	Baicalin	Liposome	Cerebral ischemia reperfusion injury	RAW264.7 mouse macrophage, BA raw material, BA standard (NO. MUST-18010410, purity98%) Quercetin (purity98%) Cholesterol and soybean	CNS	Reverse evaporation method	(122)

6.5 Hydrogel

Hydrogels are thought to be the ideal platform for customized healthcare because of their remarkable mechanical properties, appealing biocompatibility, and remarkable softness (123). Hydrogels are networks of highly hydrated mesh made of natural, synthetic, or semi-synthetic polymers that are crosslinked either physically or covalently (124). Hydrogels and hydrogel drug delivery systems are often categorized as either natural or synthetic. Chitosan (125), alginate (126), fibrin (127), gelatin (128), and hyaluronic acid-based hydrogels (129) are examples of natural hydrogels, whereas poly(ethylene glycol) (PEG) (130) and poly(vinyl alcohol) (131) are examples of common synthetic hydrogels.

Sr. No	Drug	Nano system Type	Uses	Excipient	Carrier	Method Of Preparation	Reference
1	Methotrexate	Hydrogel	Lymphoma malignancies	Chitosan, pentasodium triphosphate	BBB	Ionic gelation method	(132)
2	Cinnarizine	Hydrogel	Treat microwave-induced brain injury, Motion sickness	Pluronic f-127, Sodium dihydrogen, Phosphate, Sodium choate and sodium deoxychlolate, Citric acid and Chloroform	BBB	Thin film hydration tech. Inclusion complexes: grinding and freeze-drying	(133), (134)
3	Cannabidiol	Hydrogel	Parkinson's disease, Schizophrenia	Hydroxypropy-β-cyclodextrin, Tetra-butyl alcohol, potassium chloride and heparin sodium, poloxamer188, and poloxamer 407, sodium chloride, sodium deoxychlolate	CNS	Solvent evaporation Method	(135)

4	Chitosan	Hydrogel	To treat brain cancer	TMZ and Vitamin E (DL-alpha tocopherol), Gelucire 44/14, Transcutol®, Labrafil, Labrasol, CapmulPG8, Plurol, Tween80	BBB	High-pressure homogenization (HPH) tech.	(136)
5	Rotigotine	Hydrogel	Parkinson's disease	Sodium carboxymethyl cellulose (Na,CMC),Rotigotine (RTG), methyl cellulose	BBB	Dual-centrifugation technique	(137)

Conclusion

A good strategy for brain-targeted medication therapy in the therapy of neurological disorders is nose-to-brain administration. Understanding the blood-brain barrier's function as well as the distinct structure of the respiratory and olfactory regions of the nose is necessary for the development of nasal formulation. Compared to other methods, a N2B delivery mechanism is advantageous for overcoming the blood-brain barrier. Techniques for nasal drug delivery, such as the use if nanoemulsion in nasal formulation, allow for precise brain targeting and blood-brain barrier crossing. Additionally, the precise targeting lowers the potential of circulatory toxicity. Patient compliance and reduced administering a medication frequency are two key benefits of the N2B delivery method over traditional therapy. For the advancement of

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