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ADVANCES IN NOSE TO BRAIN DRUG DELIVERY SYSTEM: OVERCOMING CHALLENGES IN CNS THERAPEUTICS

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ABSTRACT

Administration of nasal medications in the brain has become a promising non-invasive alternative to traditional methods for treating central nervous system (Central nervous system). In this review, taking into account the possibilities of this approach, we will first define a variety of new drug delivery systems, including classification. Then discusses brain complexity, body brain disorders, and nasal physiology, providing the basis for understanding the mechanisms of drug transport. A detailed study of the nasal delivery system is presented by comparing its advantages and disadvantages with other introductory routes. The main focus will explore a variety of nasal dosage forms, moving towards nose-to-brain delivery, particularly designed to treat brain disorders. This review plunges into the mechanisms in which drugs reach the brain via nasal pathways, highlighting intracellular and extracellular pathways. Finally, he demonstrates the application of nasal volume in the treatment of many brain diseases and provides a comprehensive overview of the current state and future directions for the delivery of drugs through the nose.

KEYWORDS: NDDS, Nasal, Brain, Brain Disorder, BBB, Olfaction.

INTRODUCTION

Nasal medication administration has evolved significantly over the years, spending simple noses on advanced nanoparticle- based pharmaceutical aerosols and formulations. The nasal passages offer unique benefits, including rapid absorption of drugs, non-invasive

administration, and the ability to bypass the metabolism of initial passages, making them an attractive alternative to local and systemic treatments. Traditional methods of nasal drug delivery, such as nasal drops and nasal sprays, are widely used due to their convenience and effectiveness. However, technological advances have led to the development of innovative devices such as sonic nebulizers, mucosal atomizers, and sinus implants, which improve drug deposition and absorption. In addition, the use of hydrogels, nanoparticles, and microspheres has improved the stability, retention, and targeted delivery of drugs, particularly in the treatment of neurological disorders.[1]

One of the most promising applications of nasal drug delivery is its potential to bypass the blood-brain barrier (BBB), thereby allowing direct drug transport to the brain. This has significant implications for treating neurodegenerative diseases, pain management, and emergency medical interventions. Various experimental methods, including brain tissue homogenization, radionuclide labeling, and microdialysis, are being used to study the effectiveness of intranasal drug administration. As research advances, new strategies such as thermoreversible mucoadhesive gels and hybrid drug delivery approaches have emerged, paving the way for more effective treatments. The future of nasal drug delivery lies in the integration of nanotechnology, bioadhesive systems and advanced formulation techniques, offering new opportunities for targeted and sustained drug release. This article explores the different nasal drug delivery systems, their mechanisms, advantages, challenges, and their application in brain disorders, highlighting the latest advancements in this field.[2]

1. Novel drug delivery system

In the world of modern medicine, particularly in developing new drug delivery systems (often called NDDs), there's been a big shift toward using more advanced transport methods—and nanoparticles are at the forefront of that movement.

Traditional drug forms, like pills or injections, often come with a number of downsides. They can require large doses, offer low bioavailability (Meaning only a small amount of the drug actually reaches its target), and are often unstable. Many are affected by the body's metabolism during their first pass through the liver, which can reduce their effectiveness. Other issues include fluctuations in drug levels in the blood and drugs being released too quickly. These limitations can affect how well a drug works, how safe it is, how long it lasts on the shelf, and even how likely patients are to stick with taking it. That's where nanoparticles come in. With growing awareness of how substances interact with both human

health and the environment, researchers are turning more attention to nanoparticles—not just because they're efficient, but also because they can be designed with environmental and safety concerns in mind. Nanoparticles are tiny—typically between 10 and 100 nanometers in size—and they're created in various ways for different applications. They're fascinating not only because of how small they are, but also because of the challenge they present in terms of measuring, analyzing, and designing them effectively.[2]

When used in drug delivery, nanoparticles offer some powerful advantages. They can be engineered to carry drugs directly to specific tissues in the body, improving how a drug is absorbed, distributed, and metabolized (this relates to their pharmacokinetics and pharmacodynamics). These nanoparticles can carry small molecules or even larger, complex ones like proteins. Depending on the design, the active ingredient can be dissolved inside the particle, encapsulated within it, or attached to its surface. One of the major benefits of using nanoparticles is that they can improve how drugs interact with their target tissues. For example, they can increase enzyme stability and help drugs remain in the bloodstream longer, improving their overall effectiveness. When designing nanoparticles, scientists must carefully control key features—like how the drug is released, the size of the particles, and the chemical properties of their surface. The earliest nanoparticles used in medicine were made from non-biodegradable polymers like polyacrylamide, polymethylmethacrylate, and polystyrene. These types could hold drugs or proteins either inside the particle or attached to its surface, and the drugs could be added at different stages of the nanoparticle's creation. It's important to note that the term "nanoparticle" doesn't necessarily describe the shape or structure of the system—it's more about the scale and function.[1,3]

1.1 Types of Novel drug delivery systems

1.1.1. Phytosomes

Phytosomes are systems for the delivery of vesicular drugs where herbal extracts or phytoconstones are associated with phospholipids to improve bioavailability. They provide enhanced gastrointestinal absorption, improved therapeutic efficacy, and stability. Due to its lipophilic nature, plant yarns are widely used in cosmetics and pharmaceuticals. The preparation consists of dissolving the phospholipids in an organic solvent containing plant-based plants, followed by drying, film formation and hydration to create a plant-type suspension.[4]

1.1.2.Liposomes

Liposomes are bilayered vesicles composed of phospholipids and are used to encapsulate drugs for improved delivery. They offer passive targeting of tumors, increased stability, reduced toxicity, and enhanced pharmacokinetics. Based on their structure, liposomes are classified as multilamellar vesicles (MLV), large unilamellar vesicles (LUV), small unilamellar vesicles (SUV), giant unilamellar vesicles (GUV), or multivesicular vesicles (MVV). They can be prepared using various methods such as reverse-phase evaporation, extrusion, and freeze-drying (dehydration-rehydration) techniques. Liposomes are widely used in cancer therapy and other medical applications.[5]

1.1.3.Niosome

Niosomes are surface-based nonionic dermatology and encapsulate both hydrophilic and lipophilic drugs. They increase the stability of the drug, reduce toxicity, and provide stable release.

Niosomes are biodegradable, non-toxic, and can be administered through multiple routes, including oral, topical, and parenteral. They are classified based on bilayer number, size, and preparation methods, with sizes ranging from nanometers to micrometers. Their advantages include high capacity to load drugs, stability and controlled release.[6]

1.1.4.Transdermal

The permeable form introduced by Gregor CEVC in 1991 is a highly flexible and deformable vesicle designed for the administration of transdermal drugs. They have aqueous nuclei surrounded by viceces, and can easily penetrate the skin, making them superior to liposomes for topical applications. Transmission increases the bioavailability of the drug and can be used to provide pain relievers, hormones and anti -tumor medications. Their ability to adapt and contract through the layers of the skin makes them effective for the administration of non -invasive drugs.[7]

1.1.5.Nanoparticle evaluation

Nanoparticles are evaluated according to their size, morphology, surface loading, density, molecular weight, and effectiveness of drug uptake. Techniques such as photon correlation spectroscopy (PCM), electron microscopy (SEM, TEM, FFEM), and atomic force microscopy (AFM) can help determine particle size and structure.

The specific surface is measured using a sorptometer and electrophoretic mobility is determined by laser Doppler anemometry.

The distribution of molecular weight is analyzed using chromatography on the permeation of frost.[8]

2. Brain and its disorders

2.1. Brain

2.2. The brain is the central organ of the nervous system, processing sensory information, cognition, and motor control. In vertebrates, it develops from the neural tube into the forebrain, midbrain, and hindbrain, with the spinal cord as its extension. Invertebrate brains arise from paired segmental ganglia. The human brain contains billions of neurons, connected via synapses, transmitting signals through axons. The prefrontal cortex is highly developed, managing executive functions. The cerebral cortex processes higher cognition, while the cerebellum refines motor control. Together, the brain and spinal cord form the central nervous system, coordinating body functions and behavior.[9]

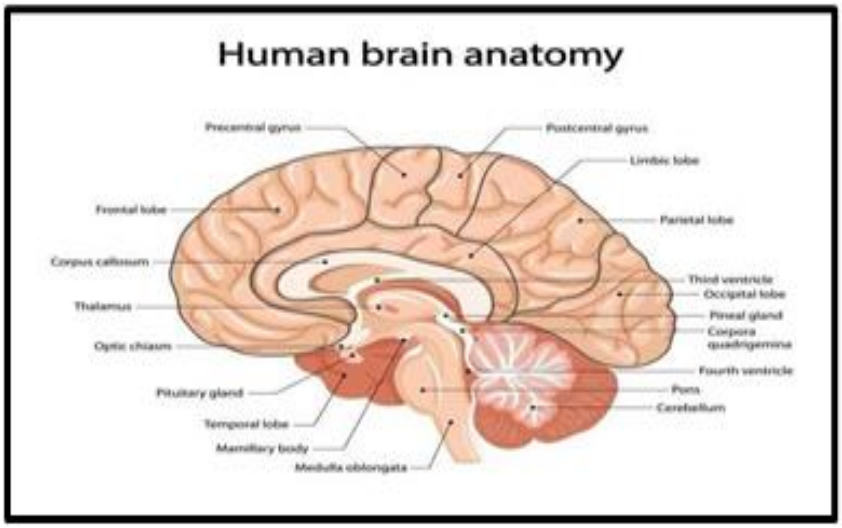

Fig. 1: Brain.

2.3. Disorders of the brain

- **Depression:** The depression is a psychological disease which cause due to the consistent stress about any situation. The depression is result of hormonal changes in hormones like cortisol, dopamine, nor adrenaline, serotonin etc. The long term depression may cause changes in chronophrmacology of human body and give enhancement to other diseases.
- **Anxiety:** The anxiety is a disorder which result in constant fear, excessive stress and

change psychological behavior. The anxiety is cause due to the increase in hormones like cortisol, epinephrine etc.

- **Post-traumatic stress disorder:** There are a lot of types of trauma the mental trauma is caused due to the stress and hormonal imbalance which may results in serious cell injury.
- **Alzheimer's disease**: The Alzheimer's disease is a disease which cause memory loss which can cause due to genetic defect or serious brain injury. It is a type of dementia.
- **Eating problems:** The sudden hormonal imbalance may cause change in appetite which further develop into the loss of weight and energy.
- **Schizophrenia:** These is the disease which resist the person's ability to think and clearly behave. It is due to the imbalance of the hormons like serotonin, dopamine, and glutamate.[10]

3. Physiology of nose

The human respiratory system begins with the nose, which not only helps us breathe but also plays a key role in our sense of smell. The shape of your nose is shaped by a combination of nasal bones, cartilage, and the nasal septum—the structure that separates your nostrils and divides the nasal cavity into two parts. When it comes to breathing, the nose does more than just take in air. Inside, the nasal mucosa lines the cavity and helps to warm, moisten, and filter the air before it travels to the lungs. There are also bony structures called nasal conchae (or turbinates), which look a bit like curled shelves and help increase the surface area for this air-conditioning process. Nasal hairs catch larger particles like dust, and if something irritates the nose, sneezing acts as a protective reflex to force it out. Unfortunately, this also means that when we sneeze, we can spread infections. Sneezing releases tiny droplets that can carry pathogens, making it a common way viruses are transmitted. Another major function of the nose is smell. High up in the nasal cavity lies the olfactory epithelium, which contains special sensory cells responsible for detecting odors. The nose also contributes to how we speak. Certain sounds, like nasal vowels and consonants, are produced when air flows through the nose—this is known as nasalization. The paranasal sinuses, which are air-filled spaces in the bones around the nose, help amplify and refine our voice. On a different note, the nose can also be reshaped or repaired through a procedure called rhinoplasty. This kind of surgery can be done to correct structural problems—whether someone is born with them, or they're the result of injury or breathing issues. Rhinoplasty can be reconstructive or, in some cases, purely cosmetic when done for aesthetic reasons.[11,12]

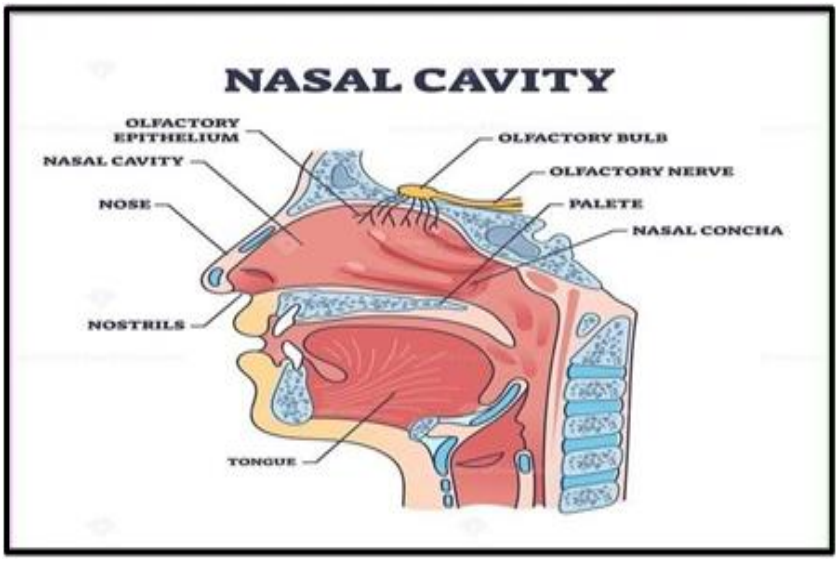

Fig. 2: Physiology of Nose.

4. Nasal drug delivery system

The administration of nasal drugs has become a promising alternative to traditional methods of administration of drugs from the unique characteristics of the nasal mucosa. This provides faster and more efficient absorption of drugs compared to oral administration. The nasal pathway is particularly useful for drugs with insufficient oral bioavailability, such as proteins and peptides, and for their high permeability and lack of significant enzymatic degradation.

Nasal therapy, called Nasaya Karma in the Ayurvedic system of Indian medicine, has been a well -recognized practice for centuries. Traditional medicine systems have used the nasal administration for therapeutic purposes, taking advantage of direct access to systemic circulation and the brain through the very vascularized nasal cavity.[13]

4.1 Nasal medication absorption mechanism

The nasal mucosa acts as a direct entry point for the drug in the systemic circulation using a variety of absorption mechanisms.

- **Transcrash transport:** Murrest molecules pass through epithelial nasal cells by passive diffusion or aggressive transport.
- **Paraclette transport:** Drugs spread through dense compounds between epithelial cells. Average Carrier Transport: Some drugs use certain transport proteins to improve absorption.
- **Endocytosis and transport disease:** Polymers such as peptides and proteins are absorbed through vesicle transport.[14]

4.2 Advantages of nasal medication delivery

Delivery of drugs offers several advantages compared to traditional routes:

It avoids the degradation of the gastrointestinal tract: the absence of pancreas and gastric enzymatic activity protects the drug for decomposition.

The metabolism of the first passage is united: drugs avoid metabolism in the liver, improving bioavailability.

Rapid absorption and onset of action: The rich vascularization of the nasal cavity enables quick systemic absorption, making it ideal for emergency medications.

Enhanced bioavailability of large molecules: Absorption enhancers and specialized formulations improve drug uptake. Suitable for adsorbing agents for diseases: oral administration provides systemic administration of ineffective drugs.

Alternatives to injectable compounds: Particularly useful for peptides and protein drugs that require parenteral administration. Stability of sensitive compounds: Suitable for drugs that break down in the gastrointestinal tract.

Effective for polar compounds: Promotes absorption of aqueous drugs with low lipid solubility. Restrictions on the delivery of nasal drugs.[15]

4.3 Despite its advantages, the nasal drug delivery has certain shortcomings

The incomprehensible toxicity of absorption amplifiers: the long -term effect of absorption amplifiers on the mucous membrane of the nose has not been completely established.

Potential nasal irritation: some compounds can cause discomfort, which makes it less favorable for the patient than oral drugs. Limited Absorbing Surface: The nasal cavity has a much smaller absorbing area compared to the gastrointestinal tract.

Risk of local side effects: Drugs and charges can damage and cause irritation of the nose eyelashes. Possibility of membrane violation: High concentrations of active surface materials used in the composition can impair the integrity of the nasal epithelium.

Mechanical loss of medication: Malast administration can lead to loss of medication in unwanted areas such as light.

5. Comparison of Nasal and Other drug delivery system

The nasal cavity plays an important role in breathing, defense and smell. Epithelial cells form a protective barrier with eyelashes that help clean mucus and trapped particles. Endothelial cells within the blood vessels regulate airflow and inhales hot air. The mucosa secretes mucus containing IgA and lysozyme for trapping pathogens. Neurons in the olfactory area detect

odors and send signals to the brain.

During development, the nasal structure comes from cells of ecodalmas and nervous combs. By the fifth week of gestation, nasal pits form, leading to the choanae. By 16 weeks, the turbinates are well-developed. Problems of development can lead to a rejected partition, hypertrophy of turbit or atresia of XEANAL.

The nasal cavity helps breathing by warming, moisturizing and filtering inhaled air. He plays a role in defense, since pathogenic microorganisms from mucus, Iga prevents the attachment of microbial and exile of the cilia. Olifing allows the perception of the smell, helping in detecting danger and affects behavior. The nose cycle, internors stabs and energy help protect your breath. Nasal function provides effective air handling, immune protection and sensory input.[16]

6. Nose to brain

Nasal medication delivery provides a unique opportunity to avoid blood barriers -stratum (BBB) and deliver treatments directly to the central nervous system (CNS). BBB systematically administers drugs that are administered systematically, from achieving therapeutic concentrations in the brain, either orally, intravenously, or via other routes. However, the olfactory and trigeminal nerves that cross the nasal cavity provide direct drug transport routes in the central nervous system, which allows potentially higher bioavailability of the drug in the brain. In addition, alternative routes, such as vascular, verteal and lymphatic trains, can also facilitate the transport of nasal drugs. Despite this possibility, there are currently no drugs available in the trade using nasal delivery to the brain as the main mechanism of action. One of the main challenges in this field is to accurately target spray drug droplets in areas where olfactory neurons are present, as they are important for effective absorption of SNCs. Nevertheless, research efforts have studied this path to treat neurodegenerative disorders, such as Alzheimer's disease and Parkinson, with certain promising preliminary results.

In addition to neurodegenerative diseases, the delivery of nasal drugs has enormous potential for the treatment of a wide range of central nervous system conditions, including brain tumors, epilepsy, stroke and mental disorders. Bypassing the systemic circulation, this route can reduce drug-related side effects and toxicity, making it a safer and more effective alternative to traditional administration of drugs. Advances in nanotechnology, bioadvice

formulations, and devices have been investigated to optimize drug deposits, prolong nasal mucosa stays, and improve transport through the olfactory epithelium. In addition, intranasal administration is a non-invasive and friendly method for patients who provide independent management and can considerably improve patient compliance with more invasive routes, such as intracellic or intra-meal injections. Future developments in medication, carriers based on innovative nanoparticles and administration devices can open the way to clinically viable nose -viable medicinal products, offering a pierced approach for effective and effective treatment of diseases of the nervous system central.[17]

7. Nasal dosage forms

The administration of nasal drugs has traveled a long way, with familiar devices such as nose drops, nasal sprays and even nasal showers widely used around the world. These methods are simple, but researchers continue to refine them to improve the effectiveness of drugs and patient experience.

Nose drops

Nasal drops are one of the oldest forms of administration of nasal medication. Pull the liquid into the glass drop, insert it into the nostrils, and release it by tightening the top on the rubber. These drops are affordable, do not require preservatives and provide effective drugs to the nasal surface. They are commonly found in urinary and saline solutions. But their most important drawback is their troublesome management attitude. The patient must tilt his head back. This can be uncomfortable, especially for people with chronic sinuses.[18]

➢ Nose spray

Nasal sprays are an option for nose delivery. Unlike drops, sprays provide accurate and measured doses and are more effective. They are easy to use, non-invasive, and provide quick relief in the fact that initial metabolism of the priced liver can reduce side effects. Key factors like droplet size and spray direction impact how well the drug reaches its target. Studies have shown that a middle-directed spray with a particle size of around 10 μm delivers the most effective results. Advanced spray technologies continue to enhance drug absorption and effectiveness.[19]

➢ Other innovative devices

Beyond sprays and drops, newer nasal drug delivery devices are making waves:

Sonic nebulizers optimize aerosol deposition in the nasal cavity. Mucosal atomizers turn

liquid medicine into fine mist for deeper penetration.

Sinus implants gradually release anti-inflammatory drugs for long-term effects.

- **Methods for nasal drug delivery**

The nasal cavity's mucus layer can act as both a barrier and a transporter for drugs. Scientists are exploring two main approaches:

Mucosal adhesion systems, which extend the time drugs stay in the nasal cavity.

Mucos is a transmission that helps drugs to move deeper into the tissue for better absorption.[20]

- **Hydrogels and Nanoparticles**

Hydrogels, known for their high water content and tissue properties, are popular in the delivery of drugs. They can be combined with nanoparticles to improve drug absorption, but toxicity concerns remain. Hyaluronic acid, commonly used in skin care, is being investigated for the administration of nasal medications due to its ability to improve permeability. Nanoparticles containing lipid carriers have been found to be game changes. These small media can improve the solubility of the drug and allow better absorption of the brain. Fat microscopic foam liposomes are particularly promising to directly bypass the blood brain barrier and administration of drugs to the brain.[21]

- **Nanopendants and Nanmarjors**

It has been developed to improve the solubility of nasal mucus, nano and nanmallogne residents. These compounds provide increased absorption of drugs and are valuable in the treatment of brain-related diseases. For example, Nanemaru has been studied for the delivery of antiretroviral drugs to the brain by the nose. Despite the promising aspects, further clinical research is needed.

- **Dry powder Composition and Microspheres**

Dried powdered nasal drugs have improved stability and higher drug concentrations compared to liquid solutions. Particles prepared using an expanded drying method quickly dissolve in the nasal mucus designation for rapid relief. Some researchers explore microspheres. It is a number of structured particles that expand the release of drugs and attach to the tissues of the nose.

Advanced nanotechnology

Inorganic nanoparticles such as gold and graphene quantum points have been studied for their ability to improve drug administration. They are very promising, but their long-term impact on human health remains a subject of study. In the same way, carbon nanotubes offer exciting potential, but cause safety problems, as they can damage cells with prolonged exposure.[22]

- **Future delivery of nasal drugs**

As studies develop, the line between the adhesion of mucous and penetration systems is blurred. The future is probably a hybrid approach that combines the two benefits, which will allow for more efficient, targeted and durable release of the drug. Thanks to the achievements in the field of nanotechnology and innovative design of devices, nasal drug delivery is becoming a powerful tool for the treatment of a wide range of diseases, from respiratory diseases to neurological disorders.

7.1 Aerosoles

Pharmaceutical aerosols consist of fine drug particles (solid or liquid) suspended in a propellant and released as a fine spray when activated. They are primarily used in Metered-Dose Inhalers (MDIs) and Dry Powder Inhalers (DPIs) for treating respiratory diseases like asthma, COPD, cystic fibrosis, and respiratory infections.

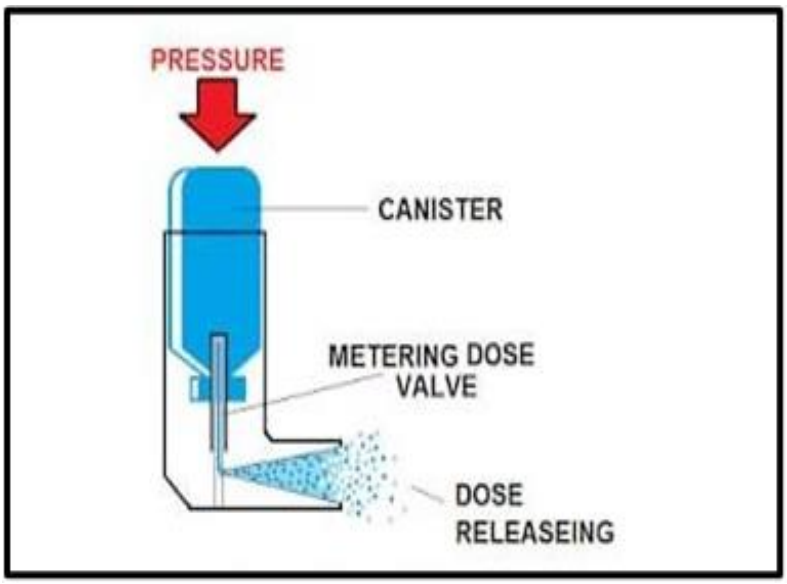

Fig. 3: Aerosoles.

Types of pharmaceutical aerosols

Dose the inhaler (MDI) and enter the exact dose of the drug using the fuel. Traditional drugs

include salbutamol, salmeterol, fluticasone, cerotide and the fetus. These help to relieve the muscles of the breathing tube and reduce inflammation. Dry Powder (DPI) Powder Inhaler - Provides powder medication directly to the lungs, often filling to aid in dispersion. The ideal particle range is 1-5 microns for effective inhalation.

Application

A) Inhaled medication, skin use, or simple administration of the body cavity.

A) Some aerosols (e.g. ethyl chloride) provide a cooling effect when used. It is used for asthma, mpoc, diabetes, angina and much more.

B) The DPIs built are effective in providing medication with high doses when ventilating the mechanical and low nasal cannulas (LFNC) with low speed. Pharmaceutical aerosols provide effective administration of drugs, rapid effects and improvements in patient convenience, making them valuable options for respiratory and systemic treatments.[23]

7.2 Nasal sprays

Nasal sprays are liquid compositions that deliver drugs directly to the nasal cavity. They are widely used for local and systemic delivery of drugs to prevent rapid absorption, non-invasive properties, and metabolism of initial passages.

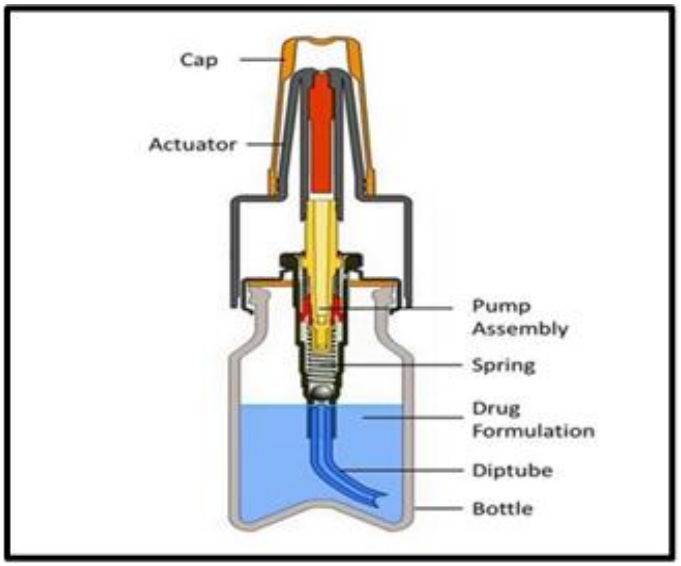

Fig. 4: Nasal sprays.

Nasal sprays types

Decongestant nasal sprays - Contain vasoconstrictors (for example, oxymmetazoline, phenylephrine) to reduce nasal congestion.

Antihistamine nasal sprays - Used for allergies, containing drugs such as azélastine or lolopatadine. Steroidal nasal sprays - Contain corticosteroids (For example, fluticasone, budesonide) to reduce the inflammation of allergic rhinitis and sinusitis. Saline Saline Sprays - Help moistened nasal passages and clear mucus. Antiviral/antibacterial nasal propellants are known to be infected with drugs such as povidone iodine and mupirocin.

Medication-administered system sprays are used for rapid absorption of drugs such as Noxson (treatment of opioid overdose) and desmopressin (diabetic treatment). The benefits of nose spray.

Rapid absorption and quick action initiation.
It circrats the digestive system and avoids enzyme degradation and metabolism of initial passages. Compared to injection, it is invasive and less user-friendly.

It is effective for both localized (Nasal congestion, allergies) and systemic treatments (hormones, pain relief, emergency medicines).[24]

Restrictions on the nasal sprays

Potential nasal irritation and dryness with prolonged use.
The risk of systemic side effects with excessive use (for example, overloading sets with decongestant contacts). Limited surface investigation compared to other drug agency routes.
Clear mucosa permits can reduce drug maintenance times and affect efficiency.

Applications

Nasal sprays are used to facilitate allergies, cold treatment and flu, moving the nose, hormone therapy, pain treatment and emergency treatment methods, such as an opioid overdose . Studies continue to improve compounds for better absorption, longer retention and wider medical applications.

7.3 Thermoreversible mucoadhesive gels

Nasal drug delivery systems have a high absorptive potential owing to the high permeability and perfusion rate of the nasal mucosa.

Factors like the lack of pancreatic and gastric enzymatic activity, neutral pH, and less dilution by gastrointestinal contents make the nasal route more permeable for drug absorption.

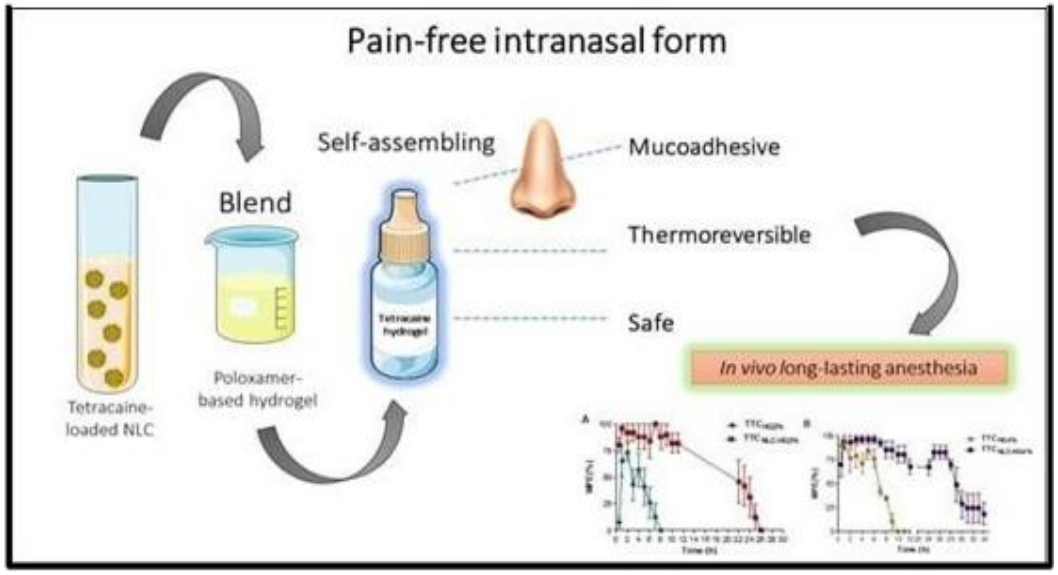

Fig. 5:Thermoreversible mucoadhesive gels.

Gels are polymer networks that improve drug absorption by increasing contact time instead of introducing them from mucosal properties. Thermore cutting gels are particularly useful for nasal delivery as they travel from liquid to frost when exposed to body temperature, resulting in longer retention and absorption of drugs.[25]

Polymers used in body temperature-compatible gels

Poloxamers (eg, F127 Pluronique) - Copolymer temperature temperature block of poly(ethylene oxide) and poly(propylene oxide).

MucoAD-Stained Polymer - Improves bioavailability by improving the stay of medication in the nasal cavity. Other environmentally friendly polymers - used to modulate the gelification temperature and viscosity.

Advantages of thermoreversible nasal gels

Improved bioavailability compared to the administration of oral drugs. Nose for a long time for a permanent release of the drug.

The viscosity is less than dosing and promotes their demands. Provides gel formation at body temperature and effective nose maintenance.[25]

8. Nasal dosage forms used in the brain disorders

Nasal delivery to the brain occurs in four main routes: The pathway of the olfactory nerve, the pathway of the epithelial odor, the pathway of the tridumo nerve, and the pathway of blood circulation. The controversial nerve pathway allows the substance to bypass the

hematon sale barrier (BBB). This is absorbed by olfactory neurons through pinocytosis, endocytosis, or diffusion. Nevertheless, this process is relatively slow, occupying from several hours to 24 hours, which limits its immediate clinical application. The epithelial path of the olfactory mucous membrane is considered more effective, since drugs can reach the brain and cerebrospinal fluid (CSF) within a few minutes. It contributes to the transport of small molecules such as lidocaine, dopamine, and insulin, and functions through transformation and paraaxial mechanisms. The neural pathway of the trijumo transports material through the ophthalmology and maxillary branches of the trijumo nerve in the cerebral stem, and also plays a role in nasal delivery. Nevertheless, this road is much slower than the path of the olfactory nerve. In some cases, it may take 17-56 hours. Finally, the pathway of blood circulation allows lipophilic drugs to enter the brain after systematic absorption by the capillary network of the nasal mucosa, but must always pass through the BBB.[26]

8.1 Common experimental methods used in intranasal drug delivery research

Currently, there is no universally accepted in vitro method for evaluating brain-targeted drug delivery via nasal administration. Most research relies on pharmacokinetic and pharmacodynamic techniques. Typically, the following elements are used in experimental methods:[27]

8.1.1 Puncture method

Procedure

A small incision is made after the established dorsal side of the mouse head and neck. Fomovo Magnum is exposed, and the syringe is inserted into the brain tank for extracting the spinal fluid (CSF).

The extracted CSF is analyzed for a quantitative assessment of the content of drugs. Benefits: Provides a direct measurement of the concentration of drugs in the CSF.

Useful to determine the presence of the drug in the brain.

Limitations

Only allows for a single-point measurement at a fixed time, making it difficult to analyze drug concentration changes over time.

Post-extraction, the CSF does not replenish sufficiently, affecting intracranial pressure. A large number of animals are required to obtain important data.

It does not distinguish between the distribution of drugs in different regions of the brain.

Current experimental methods used in searching for intranasal drug administration

Currently, there is no universally accepted in vitro method to assess the administration of targeted brain drugs via nasal administration. Most studies are based on pharmacokinetic and pharmacodynamic techniques. As a rule, the following elements are used in experimental methods:

8.1.2 Brain tissue homogenization method

Procedure

The entire brain is collected from the animal at a specific time after administration of the drug. Meninges and blood spots are carefully removed. Different areas of the brain (for example, olfactory bulb, cerebellum) are separated.

The samples are suspended, homogenized and pre-treated to analyze the concentration of the drug. Advantage: It allows for detailed spatial analysis of drug distribution in the brain.

Drug concentrations can be measured through accurate time intervals after administration. One of the most commonly used methods in research.

Boundary: Large sample sizes are required to take into account individual variability between animals. Destructive Methods - Each brain can only be used once.

It does not provide continuous concentration or actual data.

8.1.3 Radionuclide labeling method

Procedure

Drugs are labeled with radioactive isotopes before administration.

After administration, the distribution of the drug in brain tissue is measured using radiometric techniques.

advantage: It is extremely sensitive and ensures rapid detection of drug distribution.

Eliminates the need for a boring stage of drug extraction and reduces the treatment time of the sample. Suitable for research into peptide and protein-based drug delivery.

Limit: Active drugs, metabolites, and conjugates cannot be distinguished. Special radiographs and expertise are required.

8.1.4 Radiation exposure risk should be considered. Brain microdialysis

Procedure

Microdialysis probes are surgically embedded in specific brain regions.

The probe continuously samples extracellular fluids, allowing real-time drug concentration measurements.

Advantage: Provides continuous, actual time mode monitoring of drug levels.

It maintains normal physiological conditions without significantly changing the amount of CSF. Measure the free (unlinked) concentration of biologically active agents.

It is useful for studying pharmacodynamics and the deep distribution of brain drugs. Boundaries: Requires high precision instrumentation and specialized expertise.

Expensive and not suitable for large -scale studies. Technically it's difficult to play.

8.1.5 Pharmaceutical mechanical evaluation methods

Procedure

If direct drug measurements are not practical, pharmacological effects (e.g., behavioral, physiological, or biochemical responses) are monitored. These effects are used to eliminate the absorption and activity of drugs in the brain.

Advantage: It is non-invasive and does not require complex tools. It helps to assess the functional effects of drugs on the central nervous system.

Limit:

8.1.6 Indirect methods - drug concentration cannot be determined accurately. Individual variability and external factors can affect outcomes.

It is difficult to correlate pharmacological effects with precise levels of drugs in the brain.[27]

9. Mechanism of nose to brain delivery

Currently, the exact route to be transported to the brain after absorption across the nasal mucosa remains unknown. However, four major approaches have been identified so far.[28]

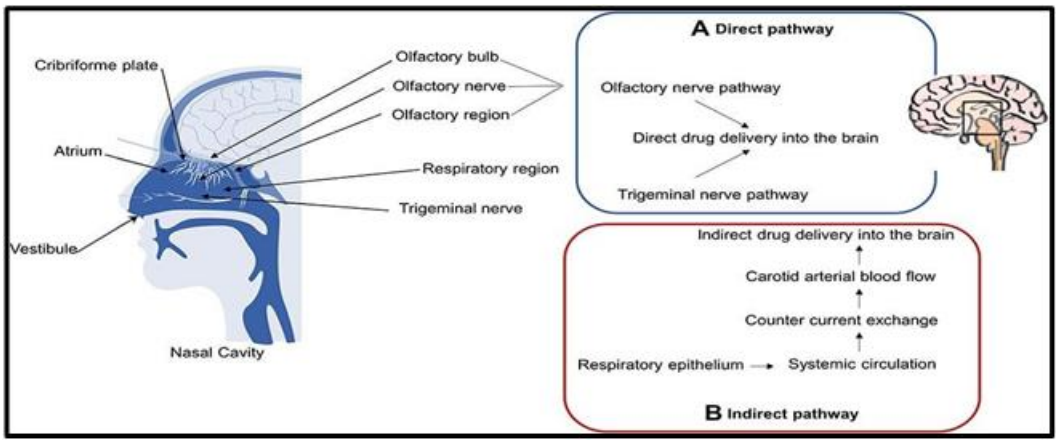

Fig. 6: Mechanism of nose to brain delivery.

9.1 Olfactory nerve pathway

Some research suggests that certain neurological viruses—like rabies or the herpes-related encephalomyelitis virus—as well as substances like steroid hormones, metal ions (such as cadmium and nickel), and even some proteins, can enter the brain through the olfactory nerve pathway. This route starts in the nose, where these substances pass through the olfactory mucosa and are absorbed by the endings of olfactory neurons. They do this through processes like pinocytosis (a form of cellular "drinking"), endocytosis, or even simple diffusion.

Once inside the neurons, these substances travel along the axons, crossing the cribriform plate (a sieve-like bone structure) and reaching the olfactory bulb, eventually making their way into the brain (specifically the limbic system). This olfactory nerve pathway is currently considered one of the most direct routes for delivering drugs to the brain through the nose, effectively bypassing the blood-brain barrier (BBB), which normally acts as a protective filter for the brain.

That said, axonal transport is quite slow. Depending on the drug, it can take anywhere from a couple of hours to as long as 24 hours for it to reach the brain. The speed depends on the drug's properties and ranges widely—from as slow as 0.1–1.4 mm per day to as fast as 20,000 mm per day. Because of this, while the nerve route is important, it's not always the most efficient for fast drug delivery.[28]

9.2 Epithelial route (Olfactory mucosa pathway)

Another, often faster, pathway is through the olfactory mucosa itself. This is called the epithelial or "nasal-to-brain" route. Here, drugs pass directly through the nasal lining into the brain tissue. Small molecule drugs like lidocaine, dopamine, and even insulin can enter the brain this way.

This pathway has two main components

1. **Transcellular transport** – Where drugs move through the cells themselves, either by passive diffusion, using transport proteins, or entering the cytoplasm of supporting cells.
2. **Paracellular transport** – Where drugs slip between cells, through tiny gaps in the tissue.

Once past the nasal lining, the drugs can travel to nearby neurons, the surrounding cerebrospinal fluid (CSF), or even into the bloodstream. Compared to the slower nerve route, this mucosal path offers much quicker access to the brain— sometimes within minutes of

nasal administration.

9.3 Trigeminal nerve pathway

There's also a third route: the trigeminal nerve pathway. This nerve has branches in both the olfactory and respiratory regions of the nasal cavity. It connects directly to the brain, entering through the cribriform plate and ending near the olfactory bulb.

In one study, researchers used a special radioactive marker attached to insulin-like growth factor 1. After nasal delivery, they found very high levels of this marker in the trigeminal nerve—ten times more than in the olfactory bulb—suggesting this nerve could be a significant pathway for drug delivery to the brain. However, the downside is that it's even slower than the olfactory nerve route, with transport times ranging from 17 to 56 hours.

9.4 Bose circulation skills

Lipophilic drugs with low molecular weight is mainly in the brain after absorption in general circulation through the rich hair network in the lamina propria of the respiratory region. However, after entering the general circulation, drugs must cross the BBB to reach the SNC; Thus, this route is a limiting factor in the therapeutic application of many drugs.

Following nasal administration, a drug will eventually reach the CNS through one or more of the aforementioned pathways, with differences in drug properties, formulations, and routes of administration dictating the dominant pathway of a drug delivery system.[29]

10. Application of nasal dosage forms in brain disorders

The route of administration of nasal brain drugs is designed to bypass the effective transport of drugs into the hemateencal barrier (BBB) and the central nervous system. Key formulation strategies include:

10.1 Intranasal solutions

The solution of the drug administered by nasal spray provides rapid and effective administration of brain drugs compared to oral or intravenous routes. Examples include diazepam, ketamine, zolmitane, naloxone, and fentanyl.

Improvements in formulations, such as the use of surfactants (such as dozil-β-D-maltopyranosides) may improve the permeability of the drug via the nasal mucosa.

10.2 Mucoadhesive dosage forms

It is designed to improve nose retention and improve drug absorption by overcoming mucosal clearance.

Examples include thermosensitive gels, chitosan-based compounds, and hyaluronic acid drugs, which improve the bioavailability and transport of drugs in the brain. Certain molecules, such as lectins (e.g., aggregates of embryonic wheat) increase adhesion to the olfactory mucosa and contribute to brain-directed delivery.

10.3 Nanoformulations

Nano Formulations (e.g., nanoparticles, nanomursi, liposomes, nanozossans) enhance brain drug stability, bioavailability, and targeted delivery. Nanoformulations protect drugs for enzymatic degradation and can be modified by ligands (for example, Odoranaleleject) to improve the aim of the olfactory mucosa and improve brain absorption.

CONCLUSION

Intranasal drug administration is a promising approach targeting the brain and bypasses the hemato brain disease barrier (BBB) through several transport methods. These include the olfactory nerves, epithelial odor pathways, trigal nerves, and systemic circulation. Among these, the epithelial pathway offers the fastest drug absorption, facilitating rapid entry into cerebrospinal fluid (CSF) and brain tissue within minutes. In contrast, the olfactory and trigeminal nerve pathways allow direct transport but at a slower rate, limiting immediate clinical applications. The experimental methods used in intranasal drugs include pharmacokinetic and pharmacodynamic studies. Methods such as a puncture method, homogenization of brain tissues, marking of radionuclides, cerebral microdialysis and a pharmacological response, help analyze the distribution and efficiency of drugs. While each method has its advantages, limitations such as invasiveness, cost, and technical complexity remain challenges.

Key formulation strategies to enhance intranasal drug delivery include intranasal solutions, mucoadhesive dosage forms, and nanoformulations. Intranasal solutions provide rapid and efficient transport of drugs, while mucoadhesion formulation improves nasal retention and absorption. Nanoforming such as nanoparticles, liposomes, and nanoemulsions improves drug stability, bioavailability, and targeted administration by protecting the drug from enzymatic degradation and improving mucosal membership. In general, the delivery of nasal drugs has great potential for the treatment of neurological disorders, offering an effective and non -

invasive alternative to traditional drug roads. Future research should focus on optimizing compositions and administration mechanisms to improve the absorption, distribution and therapeutic efficiency of drugs.

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