WORLD JOURNAL OF PHARMACEUTICAL RESEARCH
SJIF Impact Factor 8.453
Volume 14, Issue 7, 444-467. Review Article ISSN 2277–7105

ADVANCEMENTS IN INTRANASAL DRUG ADMINISTRATION FOR NEUROLOGICAL DISORDERS – A REVIEW

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Article Received on
06 Feb. 2025,

Revised on 27 Feb. 2025,
Accepted on 19 March 2025

DOI: 10.20959/wjpr20257-36057

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ABSTRACT

Intranasal drug administration is one potential non-invasive treatment technique for central nervous system (CNS) issues. Direct nose-to-brain transfer is made possible by the nasal cavity's distinct structural and physiological characteristics, such as its high vascularization and the existence of olfactory and trigeminal pathways, which bypass the blood-brain barrier (BBB). This approach is especially advantageous for CNS-targeted treatments since it increases bioavailability without causing hepatic first-pass metabolism. The processes of intranasal medication absorption, important formulation techniques, and variables affecting drug efficacy are examined in this article. To maximize drug delivery, a variety of intranasal formulations have been studied, including sprays, gels, nanoparticles, and nanoemulsions. Drug retention has been greatly enhanced by developments in nanotechnology, including polymeric nanoparticles, niosomes, and liposomes. Conditions like Alzheimer's disease, Parkinson's disease, epilepsy, migraines, depression, and even brain tumors may be treated by intranasal administration. The therapeutic feasibility of this method is demonstrated by FDA-approved intranasal formulations for medications such as insulin, sumatriptan, midazolam, and esketamine. To further improve CNS medication targeting, gene therapy and innovative biomaterial-based carriers are being investigated. Notwithstanding its benefits, there are drawbacks, including mucosal irritation, enzymatic breakdown, and patient response variability. To get around these barriers, future research will concentrate on creating novel

approaches such in situ gels and genetic delivery systems, as well as on enhancing device technology and drug formulations.

KEYWORDS: Intranasal delivery, Nasal drug delivery systems, CNS disorders, brain disorders, gene therapy, Nasya karma.

INTRODUCTION

Since the 21st century, intranasal drug delivery system has improved and developed from 1980s. Nasal therapy is also present in traditional medicine in Ayurvedic medicine, which is called Nasya karma.[1] Nasya is the Sanskrit word which is called the nose. It is the procedure where the administration of medicine goes from nose to brain.

From recent time, intranasal drug delivery systems have been implemented mostly with this pathway. There are many advantages, like bypassing the first-pass metabolism, gastric irritations, benefiting the pharmacodynamics and pharmacokinetic actions, having a large surface area, drug availability, and self-medication.[2,3,4,5]

Intranasal routes are used as non-invasive methods. The drug easily enters through local, systemic, and CNS. The CNS contains blood brain barrier (BBB), which protects the brain from potential substances. It is the route that contains highly vascular epithelium by the epithelium's rapid absorption of drug compounds. The intranasal pathway contains olfactory and trigeminal neuroepithelium to nasal mucosa. This can enhance the therapeutic bioavailability.

CNS disorders like migraine, Alzheimer's, epilepsy, Parkinson's disease, brain tumours, and headaches can be treated by administering the intranasal drugs. The various systems use such as nasal pumps, nasal sprays, gels, suspensions, micro emulsions, powders, and mucoadhesive. It is the route chosen alternatively to overcome CNS disorders. By establishing the preclinical and clinical trials. The formulations arenano formulations because of faster diffusion across the nasal mucosa. The nanoparticles are delivered from this route. The molecular weight and size are<1000. The particle sizes are between 10µm and 150µm. Many drugs are approved by the Food and Drug Administration (FDA) to treat CNS disorders like Alzheimer's. The drug used is insulin administered through the nasal route.

Advantages[6,7,8]

1. It can bypass first-phase metabolism.
2. Absorption of drug can be rapid with the vascular mucosa.
3. It has a large surface area.
4. It is non-invasive method.
5. Improve bioavailability by using absorption enhancers.
6. It can bypass Blood brain barrier.
7. It can decrease gastric degradation.
8. Bypass hepatic first-phase metabolism.
9. It is the route most convenient to the patient for long-term therapy.
10. Side effects less.
11. The intranasal route is an alternative to the parenteral route for proteins and peptides.

Limitations

1. It has a small absorption area.
2. It can irritate the nasal.
3. At high concentrations, some surfactants that function as chemical catalysts may damage or even dissolve the membrane.
4. Both ingredients and substances other than the dose form include the potential of causing local side effects as well as irreversible damage to the nasal mucosa's cilia.
5. Systemic toxicity may be caused by absorption enhancers that are not yet clearly established.

Anatomy and physiology

The nose is an intricate organ. It has different processes like deposition, filters, heat, humidity, the inhaled hair, translocation, and absorption. The nasal cavity has five different regions: the nasal vestibule, respiratory area (nasal conchae), olfactory region (olfactory epithelium), and nasopharynx. The nasal cavity starts with the nasal vestibule to the nasopharynx, with a size of 12-14cm and a surface area of the nasal cavity of 150cm with a total volume of 15ml. The nasal cavity lining contains vasculature, mucous glands and hairs. Their function is trapping the dust particles from the inhaled air and also present immunological activities and other functions of the nasal cavity.[9,10]

Nasal cavity

1. Olfactory epithelium
2. Non olfactory epithelium

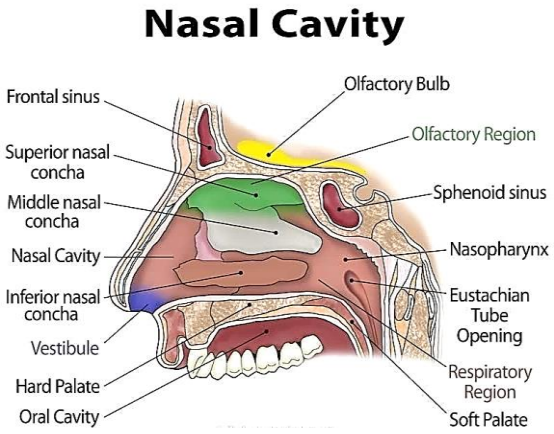

Fig. 1: Anatomy of nasal cavity.[11]

Non olfactory epithelium

- It is the area covered with skin.
- The epithelium cells are like stratified squamous epithelium cells.
- It has many numerous microvilli with which that drug can easily be absorbed.

Olfactory epithelium

- It is a present olfactory region.
- Its neuro epithelium.

The nasal cavity divided into five regions

1. Nasal vestibule

It is the region present in the anterior portion of the nasal cavity just inside the nostril. The area is 0.6 cm2, lined with the stratified squamous and keratinized epithelium cells with sebaceous glands. It also contains hairs that protect from the pathogens. It has the least permeability.

2. Atrium

It is the region present between the nasal vestibule and respiratory region. It contains stratified squamous epithelium in the anterior and pseudo stratified columnar cells with microvilli in the posterior and is less permeable.

3. Respiratory region

It is the region present after the atrium. The respiratory region is also called the conchae. The regions are divided into three: superior, middle, and inferior turbinate. It consists of pseudo stratified columnar epithelium cells, goblet cells, and mucous.

4. Olfactory region

It is region lining superior nasal conchae. It has specialized cells for smell perception. It receives ophthalmic and maxillary divisions of the trigeminal nerve.

5. Nasopharynx

It is present in the upper part. It contains, in the upper ciliated cell's lower part, squamous epithelium.

Mechanism of nasal drug absorption[12,13,14]

The first is an aqueous transport pathway, sometimes referred to as the par cellular pathway. One of this mechanism's key features is

- This is a passive and sluggish path.
- The molecular weight of water-soluble substances and intranasal absorption has an inverse log-log relationship.

A medication with a molecular weight larger than 1000 Daltons showed poor bioavailability.

The transport of lipophilic medications that exhibit a rate dependence on their lipophilicity is accomplished by a second method, which involves transport via a lipoidal pathway and is also referred to as the transcellular process. To help with medication delivery, for instance, chitosan, a naturally occurring biopolymer derived from shellfish, creates tight connections between epithelial cells.

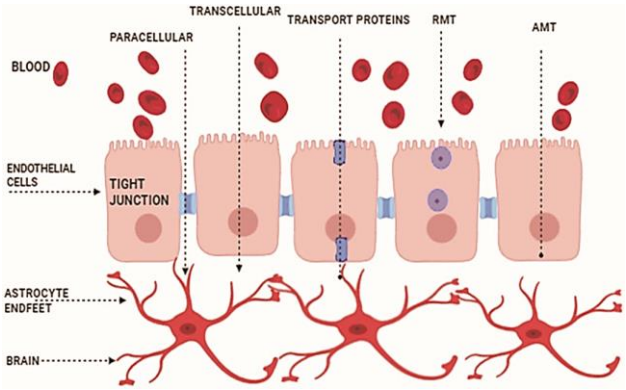

Fig. 2: Mechanism of nasal drug absorption through BBB.[15]

Brain disorders

Table 1: List of Brain disorders along with medications.

Disorder	Drugs	Route	Patent	FDA approved	Dosage form
Alzheimer's	Insulin	Intranasal, Oral	Jan 1923	2014	Dry powder, conjugated nanogels
	Rivastigmine	Oral, patch	1985	2007	Oral capsule, transdermal al patch
	Donepezil	Oral	-	1996	Tablets, Dry syrup
	Tacrine	Oral	1965	1993	Oral capsule
	Piperine	Oral, Intranasal(exp)	-	-	Capsules, powder, liquid extract, liposomal
	Resveratrol	Intranasal (exp)	-	-	Capsules, powder, liposomal, liquid extract
	Risperidone	Oral, IM	-	2003	Capsules, powder, liposomal, liquid extract
	Ibuprofen	Intranasal, Oral	1961	1984	Oral tablet, ODTs, Oral solution, Liquid suspension, long acting injectable (LAI)
Migraine	Dihydroergotamine	Intranasal	-	2021	Nasal spray, IV, IM
	Sumatriptan	Intranasal	-	Dec 30, 1992	Nasal spray, Nasal powder
	Zolmitriptan	Intranasal	-	Feb 19, 1997	Nasal spray (5mg per spray)
	Butorphanol	Intranasal	-	1979	Nasal spray (1mg per spray)
Parkinson's	Midazolam	Intranasal	-	1985	Nasal spray (5mg /0.1ml)
	Fentanyl	Intranasal	March 19, 2013	1968	Nasal spray (100mcg)
	Pentamidine	Intranasal	-	1986	Nebulized form (300mg in a vial)
	Glutathione	Intranasal, Oral	-	2015	Oral tablets (500mg, 250mg, 100mg)
Antidepression	Esketamine	Intranasal	2014	March 5, 2019	Intranasal spray (25mg)
	Oxytocin	Intranasal	1953	1959	Nasal spray (10units/m l or 20units/ml)
Stroke	Dexamethasone	Intranasal, Oral	-	-	Oral tablets (0.5mg-6mg),

					Inhalation (nebulizer) 0.5mg/ml or 1mg/ml
	Insulin	Intranasal, Oral	Jan 1923	2014	Dry powder, conjugate nanogels
	Midazolam	Intranasal	-	1985	Nasal spray (5mg)
	Oxytocin	Intranasal	1953	1959	Nasal spray (10units/ml or 20unit/ml)
Seizures	Midazolam	Intranasal	1976	2012	Nasal spray (5mg/0.1 ml)
Anticancer	Carboplatin	Intranasal, IV	1979	1989	Injection
	Burse Relin	Intranasal	-	2018	Nasal spray (100mcg)
Autism	Oxytocin	Intranasal	1953	1959	Nasal spray (10units/m l or 20unit/ml)
Allergy	Azelastine	Intranasal	-	2000	Nasal spray (1mg/ml)
	Olopatadine	Intranasal	-	2008	Nasal spray (6mg/ml)
Influenza	Influenza virus	Intranasal	-	2021	Inactivated influenza vaccine (IIV), LAIV
	Zanamivir	Intranasal	-	1999	Inhalation powder (5mg per blister)

Factors affecting

The various factors can influence the absorption from the nasal cavity. Factors like biological factors, physicochemical factors, and physiological factors.

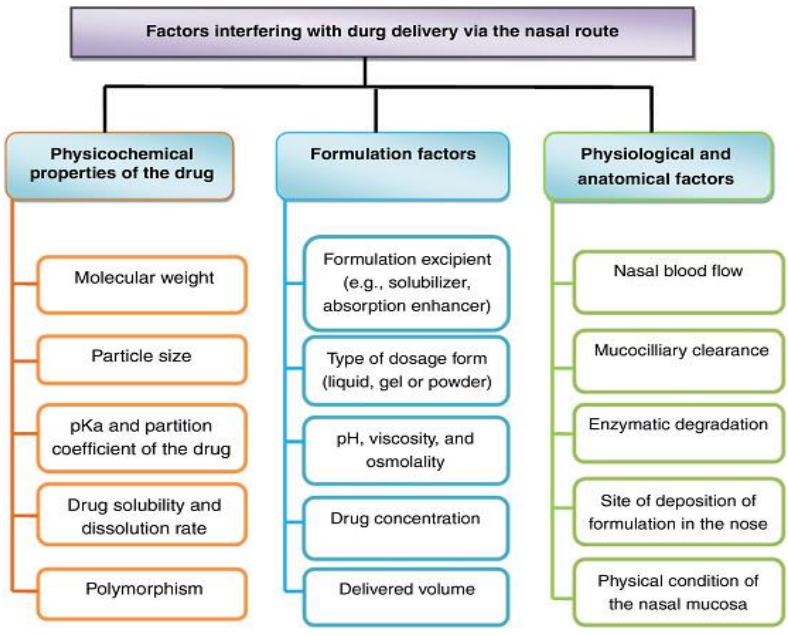

Fig 3: Factors influencing intranasal drug delivery.[16]

A. Physicochemical properties of drug

1. Molecular weight

Up to 300 Daltons, there has been evidence of a linear inverse relationship between medication absorption and molecular structure. It has been shown that when a medication molecule has a molecular weight of more than 1000 Daltons, nasal absorption drastically decreases.

2. Polymorphism

Atoms, ions, or molecules arranged in a regular geometric pattern or lattice that is continuously repeated in three dimensions make up a crystal. The unit cell is the name given to this recurring pattern. The crystalline substance that contains more than one crystalline form is known as polymorphism.

3. Partition Coefficient and pKa

Unionized species are better absorbed than ionized species, according to the pH partition hypothesis, and this also holds true for nasal absorption. The nasal absorption of these medications and their pKa are consistently correlated. The concentration of a substance in biological tissues rises as its lipophilicity or partition coefficient does. The rate at which aminopyrine was absorbed rose as pH rose, and it was discovered that this rate closely matched the expected profile. The partition coefficient is a key component influencing nasal absorption.[17]

4. Solubility and Dissolution Rate

Prior to any drug absorption, the drug must dissolve. Since only the molecularly dispersed form of a medication at the absorption site may pass through the bio membranes, drug dissolution is a prerequisite for all drug absorption. The most likely and significant element influencing drug absorption through bio membranes is drug disintegration.

Commonly solubilisers

Glycols, small quantities of alcohol, transcutol (diethylene glycol mono ethyl ether), medium chain glycerides, labrasol (saturated polyglycolysed C8-C10 glycerides), surfactant, cyclodextrin (B- cyclodextrin).[18]

B. Physiological Factors

1. Blood Flow

The blood capillary in the nasal mucosa plays a major role in regulating body temperature and maintaining the humidity of inhaled air. The systemic nasal absorption of medication is greatly influenced by the blood flow rate, which increases the number of drugs that cross the membrane and enter the general circulation.[19]

2. Enzymatic Degradation

Nasal tissues contain a variety of metabolic enzymes; drugs taken via the nasal route may be considerably metabolized across the nasal membrane epithelial barrier, avoiding gastrointestinal and hepatic first-pass effects.

3. Viscosity/gelling

An increase in solution viscosity may offer a way to extend the therapeutic efficacy of nasal preparations, according to research done in 1998 by Pennington etal.[20] Suzuki et al. (1999) Demonstrated that hydroxypropyl cellulose, a drug carrier, was useful for enhancing the absorption of low molecular weight medications, but it had no effect on high molecular weight peptides.[21]

Commonly used gelling agents

Carbopol, cellulose agents, starch, dextran, chitosan etc.

4. Osmolarity

The formulation’s tonicity may have an impact on drug absorption. In the presence of hypotonic solutions, epithelium cell shrinkage has been noted. Additionally, ciliary action is inhibited or stopped by hypertonic saline solutions. The impact of a low pH solution is comparable to that of a hypertonic solution.[22]

5. Drug concentration, dose and volume

Three interconnected factors that affect the effectiveness of nasal delivery are drug concentration, dosage and administration volume. Nasal perfusion tests demonstrated that L-tyrosine’s nasal absorption increased with drug.[23]

6. Absorption enhancers

When a medicine has large molecular size, lacks lipophilicity, poor membrane permeability, or is broken down by amino peptidases, absorption enhancers may be necessary. The boosting

impact may be accelerated by pH and osmolarity, absorption enhancers increase absorption in a variety of ways, including by inhibiting enzymes, increasing nasal blood flow, decreasing mucus viscosity, and enhancing membrane fluidity.[24]

Various enhancers used

Surfactants, phospholipids, chelaters, glycols and cyclodextrins.

7. Preservatives

Since the majority of nasal formulations are aqueous in nature, preservatives are required to stop the growth of microorganisms. Benzalkonium chloride, EDTA, benzoyl alcohol, parabens, and phenyl ethyl alcohol are a few of the preservatives that are frequently employed in nasal formulations.[25]

8. Humectants

Mucous membranes may dry out and develop crusts as a result of allergies and chronic illnesses. Additionally, several antioxidants and preservatives have the potential to irritate the nose, particularly when used in larger amounts. Preventing dehydration requires a sufficient amount of intranasal moisture. Humectants can therefore be added, particularly to gel-based nasal treatments. Humectants prevent nasal irritation and have no effect on how well drugs are absorbed. Typically, examples are mannitol, sorbitol, and glycerin.[25]

9. Antioxidants

Antioxidants may be needed in modest amounts to stop medication oxidation. Tocopherol, sodium bisulfite, butylated hydroxytoluene, and sodium metabisulfite are frequently used antioxidants. Antioxidants often don't irritate the nose or interfere with the absorption of medications. The formulation development program should take into account the chemical and physical interactions of antioxidants and preservatives with medications, excipients, manufacturing tools, and packaging materials.[25]

10. Drugs distribution and deposition

One of the key elements influencing how well drugs are absorbed through the nose is the way they are distributed within the nasal cavity. A drug's absorption efficiency is determined by its distribution in the nasal cavity, which may be impacted by the method of delivery. The site of disposition has a major impact on the nasal dose forms' bioavailability and absorption. A extended nasal residence provided by the nose's anterior region improves medication

absorption. The nasal cavity's posterior chamber will be used to deposit the dose form; it is removed via the mucociliary clearance process, which results in limited bioavailability. The delivery device largely determines the dose forms' distribution and deposition sites.

C. Biochemical factors

1. pH

To avoid irritation, pH should be adjusted. The pH is present in between 4.5 and 6.5. Nasal secretions in adults are 5.5-6.5 and 5.0-6.7 in children and infants.

2. Lipophilicity

The permeation of compounds can increase from the nasal cavity by increasing lipophilicity. Some of the drugs, like propranolol, progesterone, and fentanyl, are absorbed through the nasal cavity. These are the drugs given through intravenous showing nasal bioavailability near to 100%.

3. Pathological conditions

The pathological conditions are common cold, rhinitis, atrophic rhinitis, nasal polyposis, and infections, which can affect the nasal mucociliary transport process for nasal absorption.

4. Mucociliary clearance

Cilia is found on the surface of cells in the respiratory tract. Mucus is propelled backwards in the nose in the direction of the nasopharynx. Nasal cilia can number up to 200 per cell and are comparatively short (5 um). The nasal mucus film is composed of two layers: a lower, more fluid layer that allows cilia to freely move and an upper, more viscous layer. Cilia move metachronosly in two stages: a long recuperation period and a fast propelling stroke.[26,27]

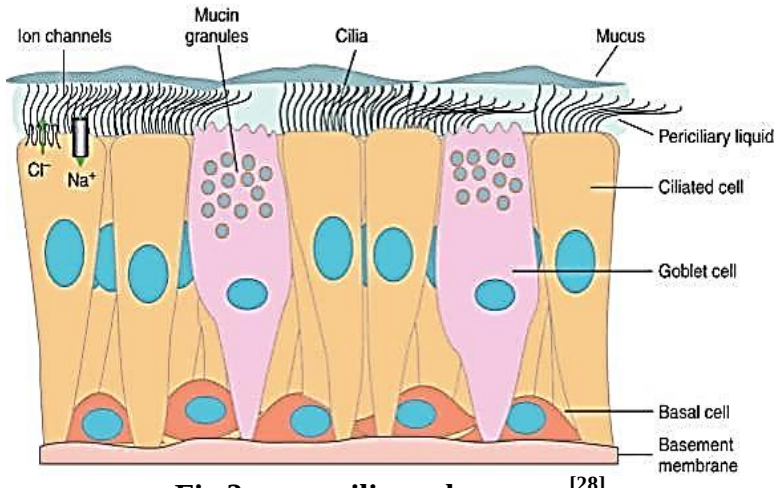

Fig 3: mucociliary clearance.[28]

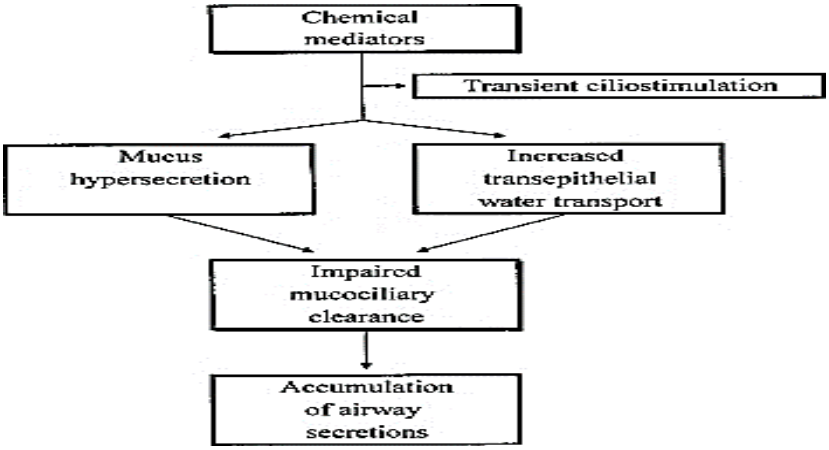

Fig. 4: Mechanism of mucociliary clearance.[29]

Table 2: Mucosal penetration enhancers.[30–38]

Category	Examples
Buffers	Isotonic potassium phosphate buffer, citrate buffer, acetate buffer
Osmotic agents	Sodium chloride, sodium sulphate, sodium acid phosphate
Gelling/viscosity	Carbopol, cellulose agents, starch,dextran, chitosan
Solubilizer	Glycols, small quantities of alcohol, transcutol(diethylene glycol mono ethyl ether)
Preservatives	Parabens, Benzalkonium chloride, phenyl ethyl alcohol, Benzoyl alcohol
Humectants	Glycerine, sorbitol, mannitol
Antioxidants	Sodium metabisulphate, sodium bisulphate, Butylated hydroxytoluene, Tocopherol

Strategies to improve absorption[39]

Here are some of the methods used in nasal drug absorption.

- **Bio adhesive polymer:** Bio adhesive polymers are utilized to enhance the drug's nasal residency and absorption. By creating an adhesive force between the formulation and nasal mucosa.
- **Structural modification:** Without changing pharmacological activity, one can modify the drug structure to improve nasal absorption.
- **Prodrug approach:** Prodrugs are used to improve taste, solubility, odour, and stability.
- **Permeation enhancer:** A variety of permeation enhancers, including cyclodextrins, fatty acids, phospholipids, surfactants, and bile salts, have been used to increase nasal absorption.
- **In situ gel:** There are some of the formulations present that convert into gel after entering into the nasal cavity by the influence of temperature, pH, and ionic concentrations.

Formulation based on nasal absorption[40, 41]

A. Liquid dosage form

1. **Nasal sprays:** In nasal sprays, both solution and suspension formulations can be formulated. The exact dose of nasal spray is 25-200µL.
2. **Nasal drops:** Among all formulations, nasal drops are among the most straightforward and practical delivery methods. This system's lack of dosage precision is its biggest drawback.
3. **Nasal emulsions, micro emulsions:** The advantage of emulsion is local application by viscosity.

Nanoemulsions (NEs) employ liquid lipids—typically natural lipids like coconut or sesame oil—instead of solid lipids to maximize the solubility of the medicine to be encapsulated. Numerous reviews discuss the use of nanoemulsions to deliver a wide range of medications, including the antipsychotic medications risperidone, ziprasidone hydrochloride, and quetiapine; the antiepileptic medication amiloride; and potential treatments for Alzheimer's disease, such as donepezil, huperzine A, and memantine. Mucoadhesive components can also be added to nanoemulsions to increase their IN delivery capability. For instance, the anti-migraine medication zolmitriptan (ZT) usually has a short half-life (1–2 hours), low oral bioavailability (40%), high fat solubility, and low penetration, indicating the potential benefits of an IN delivery method. Capryol PGMC (propylene glycol monocaprylate), Kolliphore RH40 (polyoxyl 40 hydrogenated castor oil), and Transcutol-P (diethylene glycol monoethyl ether) were combined to form a nanoemulsion. This increased drug permeation from less than 10% in solution (similar to its oral bioavailability) to approximately 70% (NE encapsulated) over the course of two hours. The addition of mucoadhesive chitosan (MNE) further enhanced uptake to >85% during the same time frame.[42,43,44]

4. **Nasal gels:** Nasal gels are highly viscous liquids or suspensions. This approach did not receive much attention until the advent of accurate dosage devices. A nasal gel's benefits include reducing post-nasal drip because of its high viscosity, reducing taste impact because swallowing is less frequent, reducing anterior formulation leakage, reducing irritation by using soothing/emollient excipients, and targeting delivery to the mucosa for improved absorption.

Nano gels have been primarily used for the delivery of peptides, DNA, RNA, growth factors, and other biological hydrophilic therapeutics because of their highly hydrated morphology.

Although their water-swollen structure prevents their use for hydrophobic therapeutic delivery, recent developments in nano gel design are upending this paradigm.

5. **Hydro gels:** The benefits of hydro gels, which are networks of crosslinked polymers inflated by water, include high hydration, physical deformation ability, high loading capacity, and stability potential, especially for pharmaceuticals based on biopolymers (e.g., proteins, peptides, polynucleotides). In order to deliver minimally viscous precursor solutions under the shear stress of nebulisation (facilitating well-distributed spray uniformity and droplet size for optimal deposition) and ensure high retention in the nasal cavity, the polymer matrix can also be produced to respond to physiological stimuli, either by forming the crosslinks (in situ gelling) or by triggering the release of drugs (responsive). The practical benefits of the hydrogel can be combined with the penetrating benefits of nano particles or introducing other kinds of nanoparticles inside a hydrogel.

B. Solid dosage form

1. **Nasal powders:** Powder dosage forms developed mainly lack stability. The greater stability of the medication in the formulation and the lack of a preservative are the benefits of using a nasal dosage form.

2. **Novel drug formulation**

a. **Liposomes**: Phospholipid vesicles called liposomes are made up of lipid bilayers that enclose one or more aqueous compartments that can contain medications and other materials. Among the many benefits of liposomal drug delivery systems is its ability to efficiently encapsulate both big and small compounds with a broad range of pKa and hydrophilicity values. In fact, by improving their membrane penetration, they have been shown to improve the nasal absorption of peptides like calcitonin and insulin. The growing nasal retention of peptides has been blamed for this. defences of the trapped peptides against.

b. **Niosomes:** Niosomes are nanoparticles that mimic bilayer membranes and are composed of non-ionic surfactants like polysorbates and polyglycerols. Because of their synthetic surfactants, they are less toxic and more stable than liposomes, which makes them a less expensive choice. Because niosomes can transport both hydrophilic and lipophilic medications, they can be used in a variety of drug delivery applications.[45,46] An illustration of their efficacy is a zolmitriptan (ZT) niosome formulation, which showed

lower blood retention and increased brain uptake (93%) in comparison to intravenous administration. Niosomes are particularly helpful for intranasal drug administration in the treatment of neurological illnesses because they improve drug bioavailability and allow for specific delivery.

c. **Nanoparticles:** They are made of macromolecular components and can be employed therapeutically as drug carriers or as adjuvants in vaccines, where the active ingredient is chemically attached, dissolved, entrapped, encapsulated, or absorbed.

d. **Microspheres:** A lot of work has gone into creating formulations for nasal medication administration using microsphere technology. The mucoadhesive polymers (chitosan, alginate) that microspheres are often built on offer benefits for intranasal medication delivery. Additionally, microspheres may prolong the medicine's action by preventing enzymatic metabolism and maintaining drug release.[47]

Evaluation of nasal drug formulation

Enhancing the relationship between in vitro test results and in vivo performance is another goal of pharmaceutical research. The aim is to increase the efficacy and efficiency of active principles, formulations, and devices.

1. In vitro nasal permeation studies[48,49,50]

Various methods are used to determine the drug diffusion.

To study the diffusion of the drug, two ways are present.

a. In vitro diffusion studies

In the glass, the nasal diffusion cell is constructed. The recipient chamber with the water jacket has a 60ml total capacity and a flanged top of around 3mm. The lid has three openings: one for a donor tube chamber, one for a thermometer, and one for sampling. The donor chamber is 10cm long, and the donor tube chamber is 60ml, and the flanged top is present 3mm. The 10cm donor chamber has a 1.13cm internal diameter. Take the nasal mucosa of sheep and keep it in distilled water; place a few drops of gentamicin injection. It is connected to the donor chamber tube once all of the blood has been extracted from the mucosal surface. The donor chamber tube is positioned so that it barely makes contact with the recipient chamber's diffusion medium. Samples (0.5ml) from the recipient chamber are drawn and moved to amber-coloured ampoules at prearranged intervals. The removed samples are

appropriately substituted. A suitable analytical approach is used to evaluate the number of drugs in the samples. In vitro, one investigation revealed that over 95.2% of the medication was released from the formulations in just two minutes when the temperature was kept at room temperature throughout the experiment.[49,50,51,52]

b. In vivo nasal absorption studies[50,55,56,57]

- Animal models for nasal absorption studies
- In animal models, there are two types, namely whole animal or in vivo models or ex vivo models.
- In vivo models are rabbit model, dog model, monkey model and rat model.

i) Rat model: Sodium pentobarbital is injected intraperitoneally to put the rat to sleep. A polyethylene tube is used to cannulate the trachea after a neck incision is done. A second tube is sent through the oesophagus and into the nasal cavity's back. To prevent the medication solution from being emptied from the nasal cavity through the mouth, the nasopalatine tract channel is blocked. Either the cannulation tubing or the nostrils is used to deliver the medication solution to the nasal cavity. Blood samples are taken from the femoral vein. The drug can only be absorbed and transferred into the systemic circulation by penetration and/or diffusion through the nasal mucosa because all likely discharge valves are blocked.

ii) Rabbit model: 1. It enables pharmacokinetic investigations similar to those conducted on large animals (e.g., monkeys). 2. It is widely accessible, reasonably priced, and simple to maintain in lab environments. 3. The blood volume (about 300 ml) is sufficient. 4. To enable regular blood draws (1–2 ml). As such, it makes it possible to fully characterize absorption and determine a drug's pharmacokinetic profile. Depending on the goal of the study, rabbits (about 3 kg) are either kept conscious or put under anesthesia. The anesthetized rabbit in the anesthetized model receives an intramuscular injection of a ketamine and xylazine mixture. A nasal spray of the medication solution is sprayed into each nostril while the rabbit's head is kept upright. Using a heating pad, the rabbit's body temperature is maintained at 37°C during the experiment. An indwelling catheter is used to get blood samples from the artery or vein in the border of the ear.

2. Ex vivo nasal perfusion models[55,61,50,58-60]

The surgical setup is identical to that of the in vivo rat model. To reduce the amount of the drug solution lost during perfusion experiments, a funnel is positioned between the nose and reservoir. A peristaltic pump is used to move the medication solution through the rat's nasal cavity from a reservoir that is kept at room temperature. Through the funnel, the perfusion solution exits the nostrils and returns to the reservoir. The reservoir's medication solution is constantly agitated. The residual drug concentration in the per fusing fluid is measured to assess the amount of drug absorbed. Stability issues could cause the drug's activity to be lost during the experiment. This is particularly true for medications made of proteins and peptides that are susceptible to aggregation and proteolysis. Ex vivo nasal perfusion research may employ rabbits as their animal model. Parenterally administered urethane-acepromazine is used to put the rabbit to sleep. A polyethylene newborn endotracheal tube is used to cannulate the trachea after a midline incision is made in the neck. They isolate and ligate the oesophagus. Flexible Tygon tubing is placed into the proximal end of the posterior region of the nasal cavity after the distal end is sutured shut. To prevent the medicine solution from draining, the nasopalatine tract, which joins the nasal cavity to the mouth, is sealed with an adhesive. The drug in the isotonic buffer solution is using the peristaltic pump.

Future prospects[62]

The IN pathway is still generally understudied for many treatments, despite the fact that numerous IN small-molecule and peptide formulations have been studied to address various CNS delivery issues. Initially thought to be ineffective or impracticable to use because of low bioavailability, low plasma stability, and/or safety concerns, drugs or other therapeutics like peptides, plasmids, or vaccines may become feasible through IN delivery and/or (even if they were previously ineffective via the IN route) new IN excipients. The two main technological areas listed below—new excipient design and the delivery of various bioactives—will present unique chances to take advantage of the advantages of IN delivery for significant therapeutic impact.

1. **Gene therapy:** Gene therapy offers a potentially alternative source of any protein treatment, since IN delivery of proteins only causes a portion of the necessary dose to reach the brain target regions. Since monogenic disorders are caused by a single gene mutation that makes it easier to identify the defective sequences, they are usually considered to be excellent candidates for gene therapy. For example, compared to the control group, a single intravenous (IV) administration of an adeno-associated viral

(AAV) vector coding for the mutant surviving motor neuron 1 gene (which causes spinal muscular atrophy type 1) led to longer survival and improved motor function. Gene therapy is more difficult to cure conditions like Alzheimer's disease, which can be brought on by environmental factors and mutations in several genes; For instance, although attempts to transfer the AAV2 nerve growth factor (NGF) gene intracerebrally were made, the limited distribution and inaccurate stereotactic targeting prevented NGF expression from reaching the cholinergic neurons. Therefore, better gene delivery to the Central nervous system.

Since vector viruses like AAV9 are safer than lentiviral therapy, several groups have shown that IN gene therapy delivers to the central nervous system. However, because of the generally significant immune response obtained on a second dosage based on the immunogenicity of the viral protein, currently approved AAV gene treatments are restricted to a single administration even though AAV is non-pathogenic. In order to avoid these inherent hazards, non-viral gene therapy is being researched more and more. It has been demonstrated that cationic polymers, cationic lipids, nanoparticles, and bare DNA all offer better safety profiles and are less expensive to produce than viruses. For example, polyelectrolyte complexation with 10-kDa polyethylene glycol has been used in the past to deliver non-viral IN pGDNF.

There are numerous innovative transfection designs that could be applied to CNS-targeted IN delivery, especially those that make use of cationic liposomes. In this perspective, it is very interesting that liposomes have the ability to transport the hydrophilic transfection agent in their aqueous core while simultaneously encouraging mucoadhesion (by the cationic charge, which is also anticipated to improve DNA loading) and transcellular absorption (via the lipophilic shell). For instance, transfection-induced luciferase activity increased approximately 1:2:5 times when mRNA + lipid nanoparticles made of cholesterol, the cationic lipid dioleoylphosphatidylethanolamine (DOPE), one of the myristatic acids, retinoic acid (nuclear homing via vitamin A scaffold), or tocopherol succinate (most hydrophobic) were added. The IN vaccine has also been administered using DOTAP, which is similarly shaped and functionalized. Liposomes that combine DOTAP with cholesterol and 1,2-distearoyl-sn-glycero-3-phosphoethanolamine-N-[methoxy(polyethyleneglycol)-2000 and mRNA show fluorescent protein gene expression in the brains of mice. The widespread use

of this strategy remains limited by the generally lower transfection efficiency of non-viral vehicles, requiring better ways to transfer DNA and RNA in this situation.

2. Enhancement Drug Delivery Efficacy

Nasal sprays indicate that in order to take advantage of the IN delivery channel and guarantee that the right dosages of medications are continuously administered, more manageable and less user-dependent procedures must be developed. Fast-dissolving films inserted into the nose have been used to administer insulin directly to the olfactory region as an alternative to sprays. Mohamad et al., for instance, significantly enhanced olfactory performance in 49 post-COVID-19 patients with anosmia by encapsulating insulin in a thin film of hydroxypropyl methyl cellulose and polyvinyl alcohol that dissolves in less than a minute after that is delivered in the nasal cavity. The absence of motile cilia in the olfactory region reduces drug clearance, although mucocilliary clearance normally restricts drug absorption. This suggests that fast-dissolving films may be used to deliver treatments in this location. Although this method presents translational challenges because the thickness and size of the film must be specific to the nasal cavity and patients may experience some short-term discomfort as the film dissolves, the location and amount of drug administered would be more consistent based on the defined size and shape of the film. On the other hand, there are a lot of potential benefits to creating portable IN spray devices that the entire range of patient populations targeted for IN CNS therapy can utilize directly and effectively. The recently released Precision Olfactory Delivery (POD) system, for instance, is a delivery device that targets the upper nasal area and uses biphasic emission to release the medicine first and then push the formulation deeper into the upper turbinates. The effectiveness of the device in delivering several CNS medications, including carbidopa/levodopa (Parkinson's disease), olanzapine (acute agitation), and dihydroergotaminemesylate (approved for migraines), is presently being tested in a number of clinical trials. The viability of IN delivery for the large potential target patient population would also be significantly impacted by other creative ways to guarantee uniform, even, and ideally automated sprays.

CONCLUSION

A possible non-invasive method for treating CNS diseases, intranasal medication administration improves drug absorption and avoids first-pass metabolism. Different formulations, including sprays and nanoparticles, enhance therapeutic results and bioavailability. This strategy is being optimized by continued research in enhanced drug

carriers and gene therapy, despite certain drawbacks such as nose discomfort and absorption issues. There is a lot of promise for intra nasal delivery in future medicinal applications.

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