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Nasal Drug Delivery System-A Review

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A B S T R A C T

The nasal route is an alternative to parenteral therapy and is also useful for long-term treatment. It is non-invasive and commonly used for local treatment, but it can also provide systemic therapy since drugs can directly enter the bloodstream. This article provides an overview of intranasal drug delivery, focusing on various aspects, including factors that affect nasal absorption.

There is growing interest in using the nasal route to deliver challenging drugs such as small polar molecules, vaccines, hormones, peptides, and proteins. The nasal cavity's high permeability, rich blood supply, low levels of enzymes, and ability to bypass the liver's first-pass metabolism make it suitable for systemic drug delivery.

Various devices for administering liquid, semisolid, and solid formulations through the nose have been investigated, particularly for treating serious central nervous system (CNS) diseases like Parkinson's and Alzheimer's, which need rapid and targeted delivery of drugs to the brain. However, it's important to remember that the primary role of the nasal airway is to protect the lungs from harmful substances, not to act as a delivery route for medications and vaccines.

The article also discusses new and emerging delivery technologies and devices, highlighting a novel concept called BiDirectional™ delivery. This approach can be adapted to various dispersion technologies for effective nasal drug delivery.

Keywords: Intranasal drug delivery, nose-to-brain delivery, bioavailability enhancement,mucociliary clearance, Absorption enhancers,nanocarriers in nasal delivery, Mucoadhesive formulations, nasal sprays and powders, nasal drug absorption mechanisms, olfactory pathway, nasal mucosa permeability

1. INTRODUCTION :-

Intranasal administration, or delivering medication through the nose, is most commonly used to treat local issues like nasal congestion, allergies, or sinus infections. These problems are often caused by allergies or infections in the upper respiratory system. However, because the nasal cavity has a large surface area and is rich in blood vessels, it also allows drugs to be quickly absorbed into the bloodstream, making it a useful way to deliver medications throughout the body.

Compared to other methods, intranasal delivery has several advantages. It's non-invasive, easy to use, and doesn't require a trained professional or a hospital setting, which can be very helpful in emergencies. For example, it's useful for quickly treating conditions like seizures or opioid overdoses, where rapid action is needed.(1)

The nasal mucosa (lining of the nasal cavity) is a promising way to deliver drugs quickly and effectively. Unlike the digestive system, it doesn't have enzymes that break down drugs, has a neutral pH, and doesn't dilute drugs as much. As a result, many drugs are absorbed better through the nose than when taken orally.This method, used for centuries in Ayurvedic medicine as "Nasaya Karma," has been renewed for delivering medications that need to work fast or in low doses, especially for drugs like proteins and peptides that don't absorb well in the stomach. The nasal route also avoids liver processing, making it efficient for systemic delivery (throughout the body) and ideal for self-use.

Today, it's widely studied for everything from small metal ions to large proteins, showing great potential for a variety of treatments, including hormones and steroids, which absorb especially well through the nose.(2)

1.1] Central Nervous System (CNS) Delivery through Nasal Route:

Delivering drugs through the nose can also target the brain. This works because the drugs can pass through the olfactory pathway, which connects the nose directly to the central nervous system (CNS). This method has been explored for treating conditions like Alzheimer's, brain tumors, epilepsy, pain, and sleep disorders.(3)

The intranasal route is especially useful for delivering drugs to the brain because it allows drugs to bypass the blood-brain barrier, which blocks most medications from entering the brain. Even drugs that do cross this barrier can get more direct access through the nose, which can increase their effectiveness in the brain, allowing for lower doses and fewer side effects.

This direct "nose-to-brain" delivery happens through two main pathways: neuronal transport and passive diffusion. Drugs can travel through the olfactory pathway (from the smell region) directly to the brain or through the trigeminal pathway (from the breathing region). Drugs may also enter the bloodstream from the respiratory region and then reach the brain indirectly by crossing the blood-brain barrier, especially if they have properties that help them dissolve in fats (lipophilic). (4)

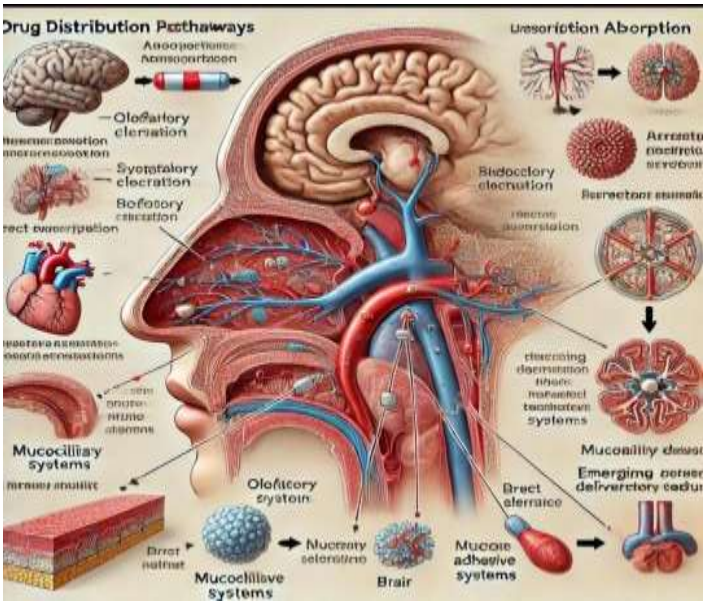

Figure 1. Drug distribution pathways associated with intranasal administration. (1)

1.2] Potential Uses of the Nasal Cavity for Drug Delivery

The nose is a convenient option for drug delivery because it's easily accessible and has a large surface area. Developing nasal drug products is a key task, tailored to the treatment goals. Key factors to consider in product development include whether it's designed for:

a) Local delivery

b) Systemic (whole-body) delivery

c) Single or repeated doses. (5)

A. Local Delivery:

Nasal delivery is helpful for treating specific nasal issues (like congestion or allergies) because it minimizes side effects throughout the body compared to oral medications. Small doses work well and have low risk of toxicity. Common drugs for this purpose include decongestants, antihistamines, and corticosteroids.

B. Systemic Delivery:

Delivering drugs through the nose can also provide fast, effective absorption throughout the body, often quicker than oral or intravenous routes. This includes pain relievers, heart medications (like propranolol and carvedilol), hormones (such as levonorgestrel and insulin), anti-inflammatory drugs, and antivirals. Examples in the market are migraine treatments like zolmitriptan and sumatriptan.

C. Nasal Vaccines:

Since the nasal lining is the first contact point for inhaled germs, it's a strong candidate for vaccines, especially for respiratory infections. Nasal vaccines can boost important antibodies in the blood and nasal passages. Examples of intranasal vaccines include those for influenza, respiratory syncytial virus, and parainfluenza.(3)

1.3] Advantages of Nasal Drug Delivery:

1. Fast absorption through the nose's rich blood supply
2. Large nasal surface area helps with dose absorption

3. Quick onset of action
4. Non-invasive and easy to use
5. Bypasses the blood-brain barrier for certain drugs
6. Avoids breakdown of the drug in the stomach
7. No liver metabolism, so the full dose reaches the body
8. Good absorption for small drugs
9. Absorption enhancers can help larger drugs be absorbed better
10. Useful for drugs not suitable for oral use
11. Alternative to injections, especially for proteins and peptides
12. Convenient for patients needing long-term treatment
13. Better absorption, meaning smaller doses can be effective
14. Fewer side effects due to low dose
15. Easy for self-administration
16. Direct access to both the bloodstream and brain
17. Lower risk of overdose.
18. Simple to formulate. (6)

1.4] Limitations of Nasal Drug Delivery:

1. Limited dose volume (25–200 µL) for nasal delivery
2. Large molecules (over ~1 kDa) can't be absorbed well
3. Effectiveness can be impacted by nasal conditions (like congestion)
4. Large differences in absorption between species
5. Natural defenses like mucociliary clearance affect drug absorption
6. Some drugs can irritate the nasal lining (e.g., budesonide)
7. Limited understanding of all mechanisms involved
8. Potential toxicity from absorption enhancers isn't fully known
9. Smaller absorption area than the digestive system
10. Possible nasal irritation, making it less comfortable than oral delivery
11. Enzymes in the nose can limit drug absorption. (7)

2.ANATOMY AND PHYSIOLOGY OF NASAL CAVITY :-

Researchers became interested in using the nasal route to deliver medication throughout the body due to the high amount of blood vessels and the permeability of the nasal lining, which allow drugs to be absorbed quickly. In humans and many animals, the nasal cavity has two main functions: breathing and smelling. It also plays a protective role by filtering, warming, and humidifying the air before it reaches the lower airways. The nasal cavity, which extends about 12–14 cm from the nostrils to the back of the throat, has a surface area of about 150 cm^2 and a volume of around 15 ml in an adult.(8)

The nasal cavity is divided into different parts: the nasal vestibule, inferior, middle, and superior turbinates, the olfactory region, the frontal and sphenoidal sinuses, and the cribriform plate of the ethmoid bone. It also contains the nasal-associated lymphoid tissue (NALT) located mainly in the nasopharynx, which helps with immune defense. The nasal cavity is lined with mucus and hairs that trap particles and pathogens, and it supports functions like mucociliary clearance, immune activities, and metabolism.(9)

The nasal cavity is covered by a mucous membrane that has two main types of epithelium (cell layers): the non-olfactory and olfactory areas. The non-olfactory area includes the nasal vestibule, which has a skin-like lining, while the respiratory region has an epithelium with tiny hair-like structures called

microvilli that increase the surface area for drug absorption. A central wall called the septum divides the nasal cavity into two symmetrical halves, each containing four main regions: the nasal vestibule, atrium, respiratory region, and olfactory region, each with unique structure and function.(10)

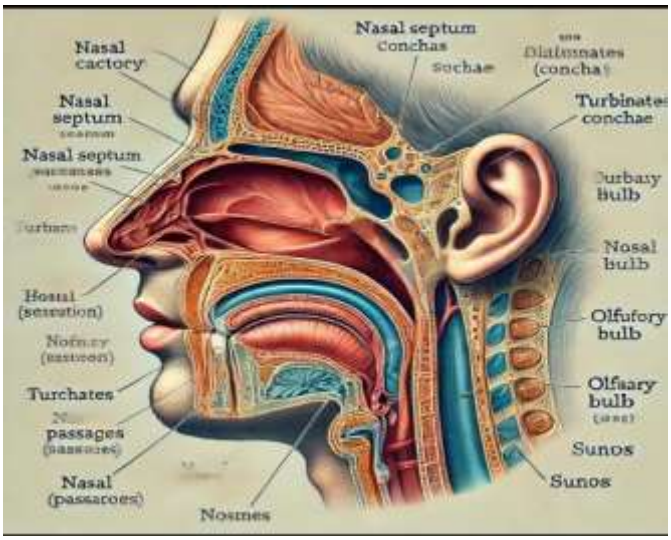

Figure 2 : Schematic of a saggital section of nasal cavity .

The nasal vestibule is the front part of the nasal cavity, just inside the nostrils, covering about 0.6 cm². It has nasal hairs (vibrissae) that filter particles from inhaled air. This area is lined with a tough, layered skin-like lining and contains sebaceous glands.The atrium lies between the nasal vestibule and the respiratory region. Its front part has a layered, skin-like lining, while the back has cells with tiny hair-like structures (microvilli).The respiratory region is the largest part of the nasal cavity, also known as the conchae. It includes the superior, middle, and inferior turbinates and is the main area for drug absorption. This area has a mucous membrane with cells, glands, and cilia—tiny hairs that help clear mucus.

The olfactory region is located at the top of the nasal cavity, extending slightly along the septum and side wall. It contains neuro-epithelium, the only part of the central nervous system exposed directly to the environment, with specialized cells for detecting smells.(11)

The nasal mucus membrane is a thin, 5 µm layer with two parts: a sticky outer layer and a fluid inner layer. It consists mainly of water (95%), with small amounts of mucin, electrolytes, proteins, lipids, enzymes, antibodies, and cell debris.(12)

2.1] Epithelial cells in the nose serve two main functions:

1. Form a barrier against infections and allergens.

2. Work with mucus and cilia to clear mucus and particles from the nasal cavity.

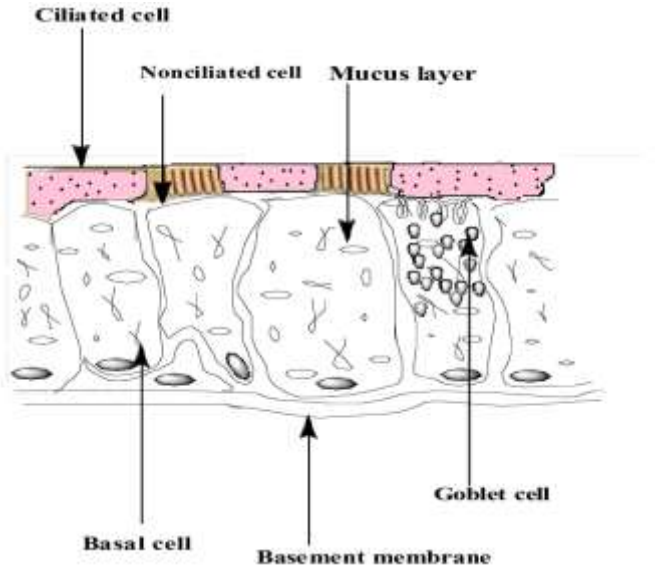

Figure 3 : Cell type of the nasal epithelium

The nasal cavity has a rich blood supply to support heating, humidification, smell, clearance, and immune functions. This allows for quick fluid exchange between blood vessels and nasal tissue, with capillary flow at 0.5 ml/g/min.(13)

2.2] Main arteries:

Sphenopalatine artery (from maxillary artery)

Anterior ethmoidal artery (from ophthalmic artery)

Facial artery branches (supplying the vestibule)(14)

3.DRUG ABSORPTION MECHANISM :

1. Paracellular Absorption (Intercellular):

This type of absorption happens between cells, in the spaces that connect them.

It's typically slow and passive, meaning it doesn't require energy from the body.

Paracellular absorption is common for larger molecules, like peptides and proteins, that pass through tight junctions between cells.(20) (21)

2. Transcellular Absorption:

In this pathway, drugs pass directly through the cells.It's common for lipophilic (fat-loving) drugs because they can dissolve in cell membranes.

There are two types:

Passive Diffusion: The drug moves on its own from areas of high concentration to low concentration without needing energy.

Active Transport: The body uses energy to move the drug, often against a concentration gradient, to help it reach its target.(21)(20)

3.Transcytosis:

In transcytosis, a cell takes in the drug particle by surrounding it in a small bubble-like structure called a vesicle.

The vesicle then moves the drug through the cell and releases it on the other side.

This process usually requires energy and is less common but useful for moving larger particles.(22)

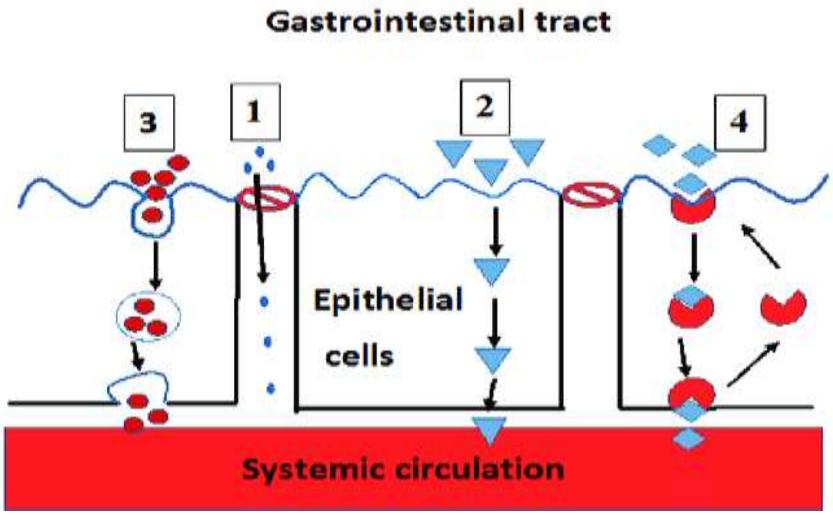

Figure 4: Drug transport pathways across the epithelium. , paracellular transport , transcytosis, Carrier mediated transport, andintercellular tight junction.

Table 1: Structural features of various regions and their impact on the permeability of nasal cavity. (5)

Region	**Structural Features**	**Permeability**
Nasal vestibule	Contains nasal hairs (vibrissae) Has thick, keratinized skin cells Contains sebaceous (oil) glands	Least permeable; the keratinized cells resist moisture and protect against harmful substances.

Atrium	Has a mix of stratified squamous cells (in front) and pseudostra tified cells with tiny hair-like structures (microvilli) in the back. The narrowest part of the nasal cavity.	Less permeable; small surface area and the presence of thicker cells limit flow.
Respiratory region (inferior, middle, and superior turbinates)	Made up of ciliated columnar cells with microvilli (300 per cell) Large surface area Has many glands for mucus production Rich blood supply for warming and humidifying air.	Most permeable; large surface area and good blood supply allow for efficient airflow and moisture.
Olfactory region	Contains special nerve cells for detecting smells Receives branches of facial nerves Connects directly to the brain's fluid spaces (cerebrospinal fluid)	Highly specialized for smell; permeability not specifically defined but allows for sensory functions.
Nasopharynx	Upper part has ciliated cells Lower part has flat, squamous cells Drains mucus from the nasal cavity	Provides a pathway for drainage; permeability varies depending on the specific cell type present.

3.1] Barriers To Nasal Absorption:

1. Low bioavailability:
2. Low membrane transport:
3. Enzymatic Degradation:

1. Low bioavailability:-

Lipophilic Drugs: These drugs are usually well absorbed through the nasal cavity.

Polar Drugs: Polar drugs, especially large ones like peptides and proteins, are not absorbed as effectively. This is mainly because they have low permeability through the nasal membrane.

Molecular Weight: Polar drugs with a molecular weight under 1000 Daltons can typically pass through the membrane using the paracellular route (between cells).

Larger peptides and proteins can also cross the nasal membrane, but only in small amounts, using an endocytotic transport process (a method where cells engulf substances).(40) (3)

2. Low membrane transport:

Rapid Clearance: One major issue for low drug absorption is the fast removal of the formulation from the nasal cavity due to the mucociliary clearance mechanism. This is especially true for drugs that are not easily absorbed.

Clearance Time: For non-mucoadhesive liquid and powder formulations, the half-life of clearance is about 15 to 20 minutes.

Formulation Placement: Placing the formulation in the front part of the nasal cavity can reduce clearance and improve absorption, unlike when it’s deposited further back.

Nasal Sprays vs. Drops: Most nasal sprays target the front part of the nasal cavity, while nasal drops can reach a larger area further back.

Bioadhesive Excipients: Using bioadhesive ingredients in formulations can help slow down mucociliary clearance, enhancing absorption.(40)(41)

3. Enzymatic Degradation:

One reason that peptides and proteins don’t move well through the nasal membrane is that they can be broken down by enzymes. These enzymes are found in the nasal cavity and in the cells that line the nose. They can cut up the peptides and proteins before they can be absorbed. To help get around this problem, researchers might use enzyme inhibitors, which block these enzymes, or try to saturate the enzymes with other substances so they can’t break down the peptides and proteins as effectively.(3)(41)

3.2] STRATEGIES TO IMPROVE NASAL ABSORPTION :-

(16)

1. To improve the nasal residence time.
2. To enhance nasal absorption
3. To modify drug structure to change physiochemical properties.

3.3] Different Factors Affecting Nasal Drug Absorption:-

- **Biological Factors:-**

1. Structural Features: The nasal cavity has five sections: the vestibule, atrium, respiratory area, olfactory region, and nasopharynx. The structure and type of cells in these areas affect how well drugs can be absorbed. Using absorption enhancers with drugs can improve their permeability.

2. Biochemical Changes: The nasal mucosa has many enzymes, including peptidases and proteases, which can break down drugs. This can create a situation similar to a "first-pass effect," where the drug is metabolized before it reaches systemic circulation. The metabolism of substances like nasal decongestants and nicotine involves the cytochrome P450 enzyme system. Proteases and peptidases are particularly responsible for breaking down peptide drugs, reducing their absorption. To combat this, enzyme inhibitors like bacitracin and puromycin are used.(17) (9)

- **Physiological Factors**

1.Blood Supply and Neuronal Regulation: The nasal mucosa is highly permeable due to its rich blood supply. Parasympathetic stimulation increases blood flow, which can enhance drug absorption, while sympathetic stimulation decreases it.

2.Nasal Secretions: The nasal cavity produces about 1.5-2 liters of mucus daily, which can affect drug permeability in several ways:

3.Viscosity: Thick mucus can hinder ciliary movement, impacting drug clearance and contact time.

4.Solubility: Drugs must dissolve in nasal secretions to be absorbed effectively.

5.Diurnal Variation: Nasal secretions vary throughout the day, affecting drug absorption rates, especially at night.

6.pH Levels: The pH in the nasal cavity varies (5.5–6.5 in adults), and drugs are more likely to permeate when the pH is lower than the drug's pKa, as this keeps the molecules in an uncharged form. The ideal pH for formulations is between 4.5 and 6.5.

7.Mucociliary Clearance (MCC): This is the body's way of clearing substances from the nasal cavity. It typically clears substances in about 21 minutes. Increased contact time with the mucous membrane enhances drug absorption, while increased MCC can reduce it.

8.Pathological Conditions: Conditions like the common cold or rhinitis can affect mucus production and ciliary function, which in turn affects drug absorption.

9.Environmental Conditions: At moderate temperatures (around 24°C), MCC can slow down, while warmer temperatures can increase ciliary beat frequency.

10. Membrane Permeability: The permeability of the nasal membrane is crucial for drug absorption. Large, water-soluble drugs like peptides and proteins often have low permeability, which limits their absorption through the nasal route.(38)

- **Physicochemical Properties of Drugs:-**

1. Molecular Weight and Size: Drug absorption depends on molecular weight, size, hydrophilicity, and lipophilicity. For compounds under 1 kDa, bioavailability can be predicted based on molecular weight, typically ranging from 0.5% to 5%. Compounds under 300 Da can easily permeate through membranes, while those over 300 Da show more variable permeability.

2. Solubility: A drug's solubility is crucial for absorption through biological membranes. Since nasal secretions are watery, drugs must be water-soluble for effective dissolution. Water-soluble drugs are absorbed via passive diffusion, while lipophilic drugs may require active transport.

3. Lipophilicity: Increased lipophilicity generally enhances drug permeation through the nasal mucosa, which is primarily lipophilic. Excessive hydrophilicity can reduce bioavailability, making prodrugs beneficial for improving absorption.

4. pKa and Partition Coefficient: According to the pH partition theory, non-ionized (unionized) drugs are absorbed better than ionized ones. The relationship between pKa and nasal absorption is constant, and higher lipophilicity leads to greater tissue concentration and improved absorption rates.

5. Polymorphism: This refers to the different physical forms of a drug, which can affect its dissolution and absorption. It is essential to consider polymorphism during the development of nasal drug formulations.

6. Chemical State of Drug: The chemical form in which a drug is presented affects its absorption. Modifying a drug to include a bio-cleavable lipophilic component (prodrug) can improve absorption but requires careful evaluation of toxicity.

7. Physical State of Drug: The size and shape of drug particles are critical for nasal drug products. Particles smaller than 5 microns may be inhaled into the lungs, while those in the 5–10 micron range are ideal for deposition in the nostrils.(18) (38)

- **Physicochemical Properties of Formulation:-**

1. Physical Form: The type of formulation affects nasal drug absorption. In studies, powder forms have shown to be more effective than liquid forms in delivering drugs like insulin. Viscous formulations can help reduce nasal drip but may not significantly increase bioavailability.

2. pH: The pH of the formulation should be between 4.5 and 6.5 to ensure optimal absorption, reduce irritation, and prevent bacterial growth. The nasal surface pH is around 7.39, while nasal secretions have a pH of 5.5–6.5 in adults and 5.0–6.7 in infants and children.

3. Osmolarity: The formulation's tonicity influences nasal mucosa. Isotonic solutions are preferred, but studies show that absorption can peak with certain salt concentrations, affecting cell size and drug uptake.

4. Volume and Concentration: There isn't a direct link between the volume applied and absorption rate. However, studies have shown that increasing drug concentration can improve effectiveness up to a certain point, after which higher concentrations may reduce efficacy.

5. Viscosity: Higher viscosity formulations increase the contact time between the drug and nasal mucosa, which can help improve drug permeation.(19) (39)

4. FORMULATION APPROACHES:-

1. Nasal gels
2. Nasal Drops
3. Nasal sprays
4. Nasal Powder
5. Liposome
6. Microspheres
7. Nanoparticles

1. Nasal Gels:-

Nasal gels are thick solutions or suspensions that have a high viscosity, making them more gel-like than liquid.

Advantages:

- Less Dripping: The thickness of the gel helps it stay in the nose and reduces dripping down the throat.
- Less Bad Taste: Because it doesn't drip back as much, you taste it less.
- Less Leakage: The gel consistency prevents it from running out of the nose.
- Less Irritation: Gentle ingredients in the gel can make it more comfortable and less irritating to use.(23) (24)

2. Nasal Drops:-

Nasal drops are a basic and easy-to-use option for delivering medicine through the nose.

Advantages:

- Easy and Convenient: They're simple to use and don't require special devices.
- Efficient Delivery: Nasal drops can sometimes deliver certain substances, like human serum albumin, more effectively to the nostrils than nasal sprays.

Disadvantages:

- Less Accurate Dosing: It's hard to control the exact amount with drops, so they might not be suitable when precise dosing is important.(23) (25)

3. **Nasal Sprays:-**

Nasal sprays can be made as either solutions (fully dissolved) or suspensions (small particles mixed in liquid).

Advantages:

- Accurate Dosing: Metered-dose pumps allow each spray to deliver a precise dose, usually between 25 to 200 micrometers.
- Customizable Design: The drug particle size, shape, and thickness of the spray affect the choice of pump, making it adjustable to meet specific needs.(23) (26)

4. **Nasal Powder**

Nasal powders are used when liquid forms, like solutions or suspensions, aren't possible because the drug isn't stable in liquid.

Advantages:

- No Preservatives Needed: Powders don't require preservatives, which some people prefer.
- Better Stability: The powder form keeps the drug more stable over time.
- Local Treatment: Powder can target specific areas in the nose.

Considerations:

- The effectiveness of nasal powder depends on factors like how well the drug dissolves, the size and shape of the particles, how well it moves through the air, and whether it causes any irritation in the nose.(23)

5. **Liposomes:-**

Liposomes are tiny, bubble-like carriers that can deliver drugs through the nose.

Formulation Options:

- Liposomal nasal solutions can contain only the drug or include other safe ingredients to help with delivery.

Administration Methods:

- They can be given as a spray, in a solution for a nebulizer, or as a fine powder.
- Sometimes, they are combined with harmless carriers like lactose to help them reach the right area.

Size of Particles:

- The particles in these formulations are very small, typically less than 50 microns, allowing them to travel more easily in the respiratory tract.(23)

6. **Microspheres:-**

Microspheres are tiny particles that are being used more often in nasal products because they help the drug stay in the nose longer.

How They Work:

- These powder-like particles swell and form a gel when they come in contact with the moist nasal lining.
- This gel sticks to the nasal tissue, which keeps the drug in place longer, allowing for better absorption and effectiveness.

Ideal Particle Size:

- For nasal delivery, microspheres should be between 10 and 50 micrometers to work effectively without irritation.(23)

7. **Nanoparticles:-**

Nanoparticles are tiny, solid particles that range in size from 1 to 1000 nanometers. They are made of large molecules and can be used in medicine, either to help vaccines work better (as adjuvants) or to carry drugs.

How They Work:

5. NASAL DRUG DELIVERY DEVICES :-

- The active drug can be held in the nanoparticle in different ways: it might be dissolved, trapped, coated on the surface, or attached chemically.

Advantages and Limitations:

- Due to their small size, nanoparticles can sometimes pass through the mucosal lining in the nose, though only the smallest ones can squeeze through the tight spaces (3.9-8.4 Å) between cells. However, they pass through in limited amounts because these spaces are very tiny.(23)

The mechanics of creating particles for nasal aerosols were thoroughly discussed by Vidgren and Kublik in 1998. This overview will focus on the technology that affects how particles are delivered and highlight new devices.

Currently, liquid formulations dominate the nasal drug market, but there are also nasal powders and devices available, with more being developed. This includes an overview of the main types of liquid and powder delivery devices, their key features, and examples of popular products and new drug-device combinations in clinical trials.(27) (28)

5.1] Devices for liquid formulations :

Liquid nasal formulations are mostly made up of water-based solutions, but suspensions and emulsions can also be used. These liquids are convenient for treating nasal issues because they help add moisture, which can relieve dryness and crusting caused by chronic nasal diseases.

Spray Pumps and Preservatives:

Traditional spray pumps often need preservatives to keep the liquid stable and safe from bacteria.

Some preservatives, like benzalkonium chloride, may irritate the nose and reduce ciliary movement, but recent studies show that it is safe and well-tolerated for long-term use.

Certain liquid formulations, especially those containing peptides and proteins, can be unstable when dissolved.

Nasal Drops and Vapors:

Nasal drops delivered with a pipette and vapors are among the oldest methods of nasal delivery.

For example, breast milk has been used to treat nasal congestion in infants, and menthol vapors have been used to revive people who fainted.

While drops have mostly been replaced by metered-dose spray pumps for regular use, single-dose pipettes are still common for over-the-counter products like decongestants and saline. The benefit of these pipettes is that they don’t require preservatives.

Nasal Drops for Specific Conditions:

A nasal drop formulation of fluticasone in single-dose pipettes was introduced in the EU to treat nasal polyps. This method aims to deliver the medication more effectively to the area where polyps develop.

Limitations of Nasal Drops:

However, using nasal drops can be challenging since patients often need to tilt their heads or extend their necks for the drops to work properly. This can lead to discomfort and poor compliance, especially for those with conditions like rhinosinusitis who may have headaches in these positions.(29)

Delivery of Liquid with Rhinyle Catheter and Squirt Tube:-

A simple method for delivering medication into the nose is to use a fine catheter or micropipette. A physician or trained assistant can insert the tip into the desired area and squirt the liquid directly. This technique is commonly used in animal studies where the animals are sedated but can also be used in humans with care to avoid irritating the sensitive nasal membranes. However, this method is not suitable for self-administration.

Harris et al. described a variation of this method using a thin plastic tube. In this technique, 0.2 ml of a liquid desmopressin formulation is placed in one end of the tube, which is inserted into the nostril. The drug can be delivered as drops or a “liquid jet” by blowing through the other end of the tube with the mouth.

Despite the cumbersome process and the risk of inconsistent dosing, desmopressin is still available in some countries using this rhinyle catheter, along with a nasal spray and a tablet form for treating conditions like primary nocturnal enuresis, Von Willebrand disease, and diabetes insipidus.(30) (29)

Squeeze Bottles:-

Squeeze bottles are commonly used for delivering over-the-counter (OTC) products, such as decongestants. When you squeeze the bottle, the liquid inside is forced out through a small opening, creating a fine spray.

How They Work:

The amount of medication and the size of the particles can change depending on how hard you squeeze the bottle.

When you stop squeezing, nasal mucus and germs can sometimes get pulled back into the bottle.

Precautions:

Squeeze bottles are not recommended for use by children due to the risk of improper handling and potential contamination.(31) (29)

Metered-dose spray pumps:- have been the main method for delivering nasal medication for about 40 years. These pumps usually release 100 microliters (ranging from 25 to 200 microliters) with each spray and are known for providing consistent doses and spray patterns during testing. The size of the particles and the shape of the spray can change based on the pump design, the medication's formulation, the size of the nozzle, and how hard the pump is pressed.

Traditionally, these spray pumps replace the liquid with air, which requires the use of preservatives to keep the medicine from getting contaminated. However, due to concerns about preservatives, manufacturers have developed systems that eliminate their need. These newer systems use methods like collapsible bags, movable pistons, or compressed gas to replace the liquid without requiring preservatives. This design also allows the pump to be used upside down, which is helpful for patients who are bedridden and need to administer medication while lying down.

Another approach is to filter the air replacing the liquid through an aseptic filter, and some designs have a ball valve at the tip to prevent contamination. While these preservative-free systems can be more complex and costly, studies have shown that preservatives are generally safe and tolerated well, making the demand for preservative-free systems less critical than once thought.

Recently, new pumps have been developed with side-actuation to deliver fluticasone furoate, a treatment for allergies. These pumps feature shorter tips to avoid contact with sensitive nasal tissues. Innovations also include designs that reduce the need for priming, as well as features like pressure points to improve dosing accuracy, dose counters, and safety locks. Additionally, some pumps can use a new breath-powered delivery system, called “Bi-Directional™,” to improve how the medication is deposited in the body.(32) (29)

Single- and Duo-Dose Spray Devices:-

Metered-dose spray pumps need to be primed and usually contain extra liquid to ensure accurate dosing for multiple uses. While they're good for medications taken daily over a long time, they aren't ideal for drugs that require precise dosing, especially those with narrow therapeutic windows. For expensive medications or vaccines that are used only once or occasionally, single-dose or duo-dose spray devices are better.

One simple type of single-dose spray device is the MAD from LMA, which connects a spray tip to a standard syringe. This device has been used in studies to deliver topical steroids and vaccines. Another example is the Accuspray™ by Becton Dickinson, which is used for the FluMist influenza vaccine, approved for both adults and children in the U.S.

These devices typically consist of a vial, a piston, and a swirl chamber. The medication is sprayed out when it’s pushed through the swirl chamber. Users hold the device with their second and third fingers, using their thumb to activate it. Some models have pressure point mechanisms to ensure consistent spraying.

Currently, nasal migraine medications like Imitrex and Zomig, as well as FluMist, are delivered using these devices. Because these devices are filled in a sterile environment, they don’t need preservatives, but they do require some extra liquid, leading to waste similar to multi-dose sprays. For example, to deliver 100 microliters, the device is filled with 125 microliters. Duo-dose designs use about half that volume.(27)(29) (33)

Nasal Pressurized Metered-Dose Inhalers (pMDIs):-

Most nasal medications are delivered using spray pumps, but some can also be delivered as nasal aerosols from pressurized metered-dose inhalers (pMDIs). After the ban on chlorofluorocarbon (CFC) propellants, the number of pMDI products for both pulmonary and nasal use dropped significantly, and they were taken off the U.S. market in 2003. The older CFC pMDIs often caused nasal irritation and dryness because they released particles at a very high speed, which created an uncomfortable “cold Freon effect.”

The particles from traditional pMDIs traveled much faster than those from spray pumps (5,200 cm/s compared to 1,500 cm/s). However, newer pMDIs use hydrofluoroalkane (HFA) propellants, which have reduced particle speeds and irritation. The first nasal pMDI with HFA, delivering beclomethasone dipropionate (a topical steroid), has been approved for allergic rhinitis in the U.S.

Like spray pumps, nasal pMDIs target the front parts of the nasal cavity, where the medication is deposited in the anterior non-ciliated epithelium. Because the spray from pMDIs evaporates quickly, the problem of excess medication dripping out is less common.(29)

Mismatch between geometry of anterior nose and the spray plume:-

The pressure from a spray pump forces liquid through a swirl chamber and out of a circular nozzle. This creates a thin, spinning sheet of liquid that soon breaks up into droplets. The spray forms a hollow cone shape, with droplets mostly around the edges. Key factors that affect the spray pattern include the swirl strength, nozzle size, cone angle, and the length before the liquid breaks into droplets.

For example, one study found that with a 0.5 mm nozzle, a 30° cone angle, and a break-up length of 3.5 mm, the spray reaches a diameter of 4 mm at the break-up point. Another study showed a cone diameter of 2.34 cm at 1 cm from the nozzle for a 54.6° angle, and 2.52 cm at 3 cm for a 39° angle.

When using a spray pump inside the nostril, the wide, circular spray cone does not match the narrow triangular shape of the nasal valve opening. Most droplets end up hitting the front, non-ciliated nasal walls. Only droplets near the bottom and wider part of the triangle make it through the valve, especially if sprayed during a sniff. Similar issues occur with other devices like inhalers, nebulizers, and powder sprays, where the spray cone doesn’t fit well within the nose's narrow opening.(29)

Powered nebulizers and atomizers

Nebulizers use compressed air, oxygen, or nitrogen, or they use ultrasonic or mechanical energy to turn liquid medicine into a fine mist that can be inhaled through the nose or mouth. The small, slow-moving particles of mist from a nebulizer are thought to help the medicine reach deeper areas of the nose and sinuses. Studies have shown that breathing in medicine through a nebulizer can lead to better coverage in the upper part of the nose compared to a standard nasal spray. However, in tests, 33–56% of the mist ended up in the lungs. Because of this lung exposure, using nebulized antibiotics meant for the nose in patients with chronic sinus issues often caused coughing and increased the need for inhalers.(29)(27)

VibrENT pulsation membrane nebulizer :

A new nebulizer called VibrENT by PARI Pharma uses a pulsating mist created by a vibrating membrane to deliver medicine directly to the nose and sinuses for people with chronic sinusitis. The small, pulsing particles and a special breathing technique help reduce medicine going to the lungs and improve reach to the sinuses. In one test, breathing through the nose with an exit filter allowed 2.8% of the dose to reach the sinuses, with 10% ending up in the lungs. With a special technique to keep the soft palate closed, 4.9% of the dose reached the sinuses, while lung deposition was nearly eliminated.

When compared to a regular nasal spray, which had no lung deposition but limited sinus reach, the pulsating nebulizer showed promise in increasing sinus delivery. However, these tests were on healthy individuals, so it's unclear how effective this would be in people with blocked sinus passages. Also, this technique is more complex than other devices like OptiNose's Bi-Directional delivery, which uses exhaled breath to help prevent lung deposition and direct more medication to the sinuses. Additionally, although both methods showed "hot spots" of medication in certain areas, the study did not analyze exactly where within the nose the medicine was going.(29) (34) (28)

Aeroneb Solo vibrating mesh nebulizer:-

A recent study compared two nasal nebulizers: the Atomisor NL11S sonic/pulsating jet nebulizer and the Aeroneb Solo nasal mesh nebulizer, both with similar particle sizes (5.6±0.5 μm). The Aeroneb Solo system, designed to reduce lung deposition, delivered more medicine to the nasal cavity (27% vs. 9% of the dose). This higher deposition may be due to the shorter delivery time in this study (20 seconds) compared to a previous study of the PARI nebulizer, which ran for up to 10 minutes. Both devices showed peak deposition around 2 cm from the nostril (the nasal valve area) and near the floor of the nose. However, overall delivery efficiency was low, likely due to longer delivery times and nasal clearance processes.(35) (27)

Powder devices :

Powder medication formulations offer advantages like increased stability over liquids and potentially reduced need for preservatives. Powders adhere to the moist nasal mucosa, which supports absorption, and bioadhesive excipients or agents that slow ciliary action can enhance this effect. Factors such as moisture sensitivity, solubility, particle size, shape, and flow properties impact powder deposition and absorption.

Nasal powder devices function via three main principles:

1. Compressible compartment sprayers: Release a powder plume similar to liquid sprays.

2. Breath-actuated inhalers: User breathes in powder from a blister or capsule.

3. Nasal insufflators: User exhales into a mouthpiece, delivering powder through a nosepiece; includes Bi-Directional™ technology.(36)(27)

Breath-powered:-

Bi-Directional™ technology—a new nasal drug delivery concept

The Bi-Directional™ breath-powered technology is an innovative nasal delivery method designed to overcome limitations of traditional devices. It uses a mouthpiece and a specially-shaped nosepiece to create a sealed flow path through the nasal passages. When a user exhales into the mouthpiece, the pressure lifts the soft palate, closing off the nasal cavity from the rest of the airway and allowing the airflow to travel from one nostril to the other. This design improves drug delivery, reaching target sites deeper in the nasal cavity without affecting the lungs.

The device can be adapted for both liquids and powders, using manual or automatic triggers. Current designs in trials include a multi-dose liquid sprayer and a powder device with disposable drug chambers.(29)(28) (37)

6. CONCLUSION :-

Nasal drug delivery systems offer a promising alternative to traditional routes of administration, providing numerous advantages such as rapid absorption, bypassing the hepatic first-pass metabolism, and the potential for direct delivery to the central nervous system. Advances in formulation technologies and delivery devices have significantly enhanced the efficacy and patient compliance associated with nasal therapies. However, challenges remain, including formulation stability, mucociliary clearance, and variability in individual patient responses. Future research should focus on optimizing drug formulations, improving delivery devices, and exploring innovative approaches, such as nanocarriers and mucoadhesive agents, to further enhance the bioavailability and therapeutic outcomes of nasal drug delivery. By addressing these challenges, nasal drug delivery can play a pivotal role in the future of pharmacotherapy, particularly for chronic and acute conditions requiring rapid onset of action.

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