# Intranasal Drug Delivery: An Enthralling Route

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***Abstract***

*The most common and well-liked medication delivery method is discovered to be nasal. The nasal route has the potential to provide systemic availability for medicines that are now only available via intravenous delivery, such as peptide and protein therapies. The anatomy and physiology of the nose, as well as the variables that influence drug absorption over the BBB and into the CNS system, are examined. As per previous findings we know, by using permeation and absorption enhancers and other excipients in the formulation, certain medicaments that are poorly soluble are efficiently absorbed via the nasal epithelium. Strategies for improving drug absorption via nasal administration using nanoparticles was considered, the benefits and drawbacks of employing the nasal drug delivery system have been postulated.*

**Key words:** Nasal mucosa, drug delivery, Intranasal administration, and nasal devices.

## 1. Introduction

In spite of outstanding developments going on in brain research, brain and CNS disorders like meningitis, Parkinson ‘s disease, migraine, Alzheimer ‘s disease, and schizophrenia is steadily increasing. Yet, the lack of effective drug delivery in therapeutic doses to treat central nervous system (CNS) diseases continues to be the world's leading cause of disability, necessitating long-term care. [(1)] The preparation of CNS drugs is presently constrained by the facts that drugs in therapeutic dose have to cross the blood brain barrier (BBB). The BBB is a strong barrier avoiding the migration of most drugs from blood to brain. [(2)] The BBB is localised at [(3)] the choroid plexus epithelium, cerebral capillary endothelium and the arachnoid membranes, and is important to maintain the homeostasis of CNS, and by permitting the effective nutrient interchange among the blood and the tissue of the brain, whereas preventing the entry of xenobiotics may harm neurological function.

Because of a complex system of tight junctions (TJs) across neighbouring cells and non-fenestrated capillaries, as well as sluggish pinocytotic action, it prevents both paracellular and transcellular transit of ionised, large molecular weight, and hydrophilic molecules in the blood circulation. [4] The nasal route has gained a lot of popularity in recent years as a simple and accurate approach for systemic drug delivery. [5] The nasal mucosa is extremely vascular, with many blood arteries that aid in medication absorption. [6] Because of the lack of pancreatic, gastric enzymatic activity, and interference from gastrointestinal contents, it is permeable to more medicines than the gastrointestinal system. [7] Absorption and penetration enhancers, mucoadhesive agents, enzyme inhibitors, and hydrogel systems have been added to nasal drug formulations to improve the residence duration in the nasal mucosa. [8] Lipophilic medicines are said to be absorbed well through the nasal cavity in many situations, with pharmacokinetic profiles comparable to those seen after an intravenous administration and bioavailability of up to 100%. So, with large absorption surface area and high vascularization influence to fast permeability and absorption. In times of emergency, the substitute route for parenteral administration can be nasal route. [9] It is shown that the administration of certain drug substances ranging from tiny metal ions, hormones, steroids, and big macromolecular proteins, through nasal route has been tested in various animal models and have showed results in complete drug absorption. [10] Currently, nanotechnology-based drug delivery systems are being given high priority for drug delivery through intranasal route to the brain. As a novel approach for bypassing the low bioavailability of numerous pharmaceutical drugs, drug delivery systems by nano-size have been systematically studied through the past few decades. [11] Now a days, treatments for CNS diseases or imaging agents are very reliant on nanoparticles, as they play a capable role in drug delivery to CNS. It is shown that the nanodrug substances is shown to cross the BBB and penetrate deeply to the diseased brain tissue actively and efficiently. [12]

**2. Anatomy and physiology of Nose:**

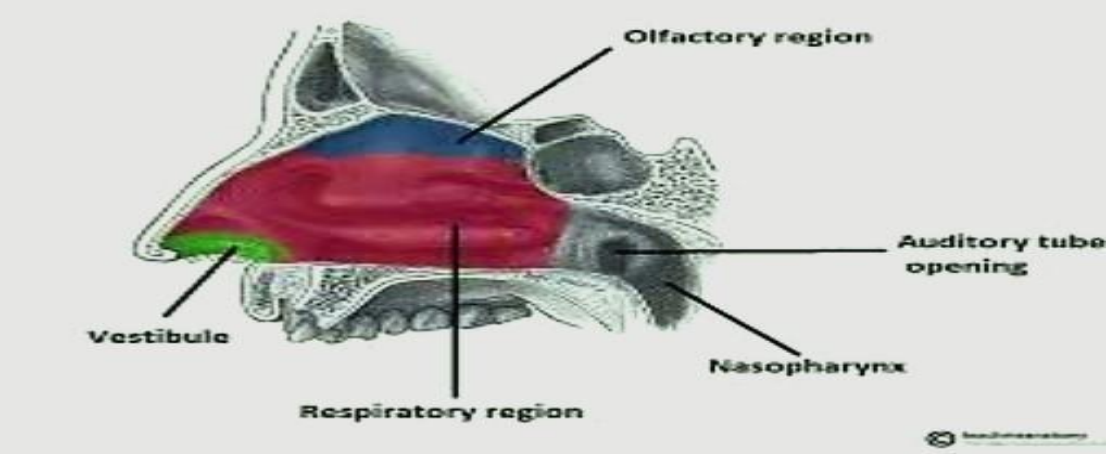


**Figure No. 01: The anatomy and physiology of the nasal cavity**

The nasal cavity of human occupies around 150cm$^2$ and has the total volume capacity of 15ml. Human nasal cavity is separated into two nostrils by nasal septum. The surface area is around 75cm$^2$ and the

volume occupied by each cavity is around 7.5ml. Three main regions are present in our nasal cavity they are: The vestibular region, respiratory regions and olfactory region. Role of these regions are summarised below.

**2.1 The Vestibular region**

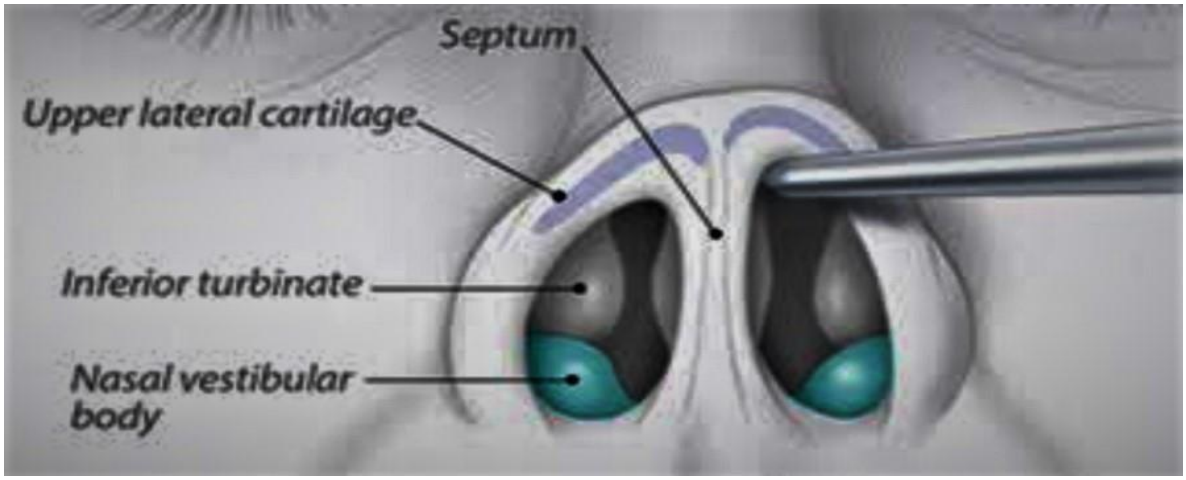


**Figure No.02: Different parts in nasal cavity**

The vestibular region is present at the opening of nasal passage near to the mouth. It avoids the entry of micro-organism or air borne particles. When the drug is administered in this region drug absorption is negligible. The main function of the septum is to provide support and structural strength for the nose and to regulate for smooth airflow through the nasal cavities. The surface of the nasal cavity is lined by the mucosa which secretes mucus which keeps the nasal cavity moist [(13)].

**2.2 The Respiratory region:**

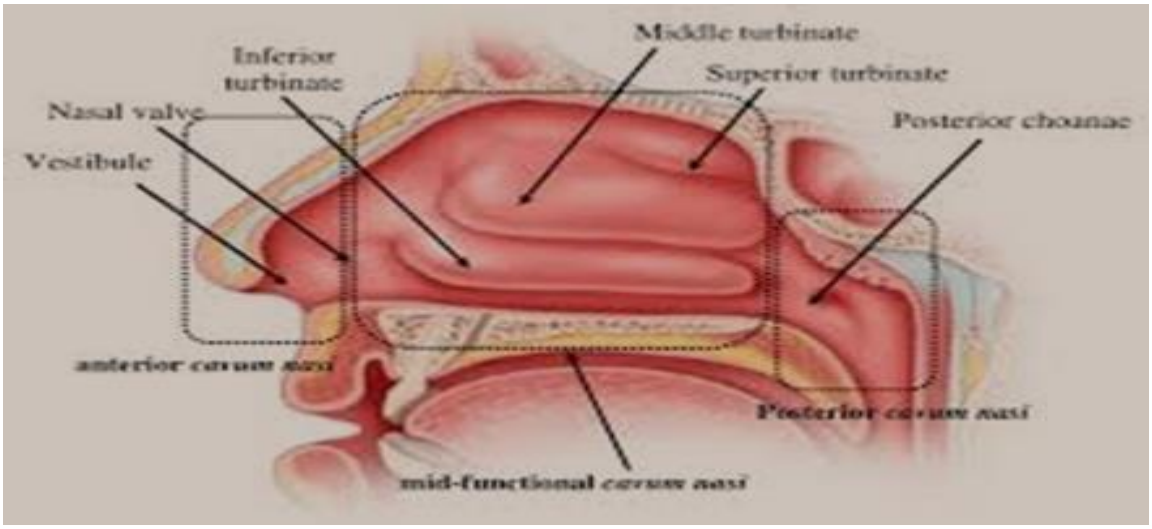


**Figure No. 03 Different regions of respiratory region in the nasal cavity.**

The respiratory region is believed to be larger and with high degree of vasculature. It consists of superior, middle, and inferior nasal turbinates or conchae which protrude through the lateral wall of each nasal cavity in the respiratory area. These turbinates cause turbulent air flow from the nasal passages, indicating that the mucosal surface and inhaled air are in better contact. The respiratory area, which is believed to be the primary site of drug absorption, is where the majority of the drug is absorbed. Two layers of mucous membranes or mucosa line the nasal airways: the luminal surface epithelium and the underlying connective tissue, or lamina propria. The connective tissue matrix surrounds a layer of blood and lymphatic vessels, nerves, glands, and mesenchymal cells. Squamous epithelium covers the front portion of the respiratory area, while a pseudo stratified columnar epithelium covers the posterior section. The respiratory epithelium cells are enclosed by about 300 microvilli per cell. [14]

**2.3 Olfactory region:**

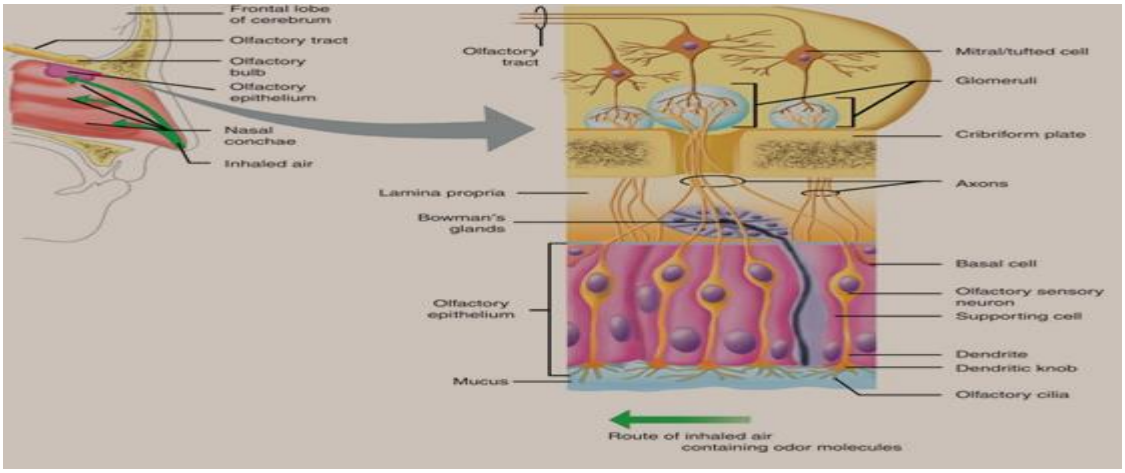


**Figure No. 04. Various parts of olfactory region in the nasal cavity.**

The olfactory mucosa is located in the upper region of the nasal cavity and is made up of the olfactory epithelium and the underlying lamina propria, connective tissue containing fibroblasts, blood vessels, Bowman's glands and bundles of fine axons from the olfactory neurons. The upper region of the nasal cavity consists of superior, middle and inferior turbinates, olfactory mucosa that exists on the nasal cavity's roof and these superior turbinates which is a structurally modified to check odour-producing substances (odorants). Olfactory receptor consists of epithelium layer which mainly consist of millions of nerve cells which also detects the smell. The olfactory epithelium is pseudostratified and comprises of olfactory receptor neurons, supporting and sustentacular cells [15] which are analogous to the basal cells and the glial cells of the brain. The receptor cilia and microvilli are covered by thin watery mucus made with the supporting cells and Bowman's glands. Upon inhalation, odorants are inhaled into this region in which they dissolve and later bind to the receptors of microvilli and cilia. The olfactory epithelium occupies just around 5% of the total nasal cavity area in humans. It has a surface area of around 10 $cm^2$ and is essential for drug delivery since it bypasses the BBB, allowing therapeutic medicines to reach the CNS. For systemic medication, distribution of blood flow through nasal mucosa is necessarily important. [16]

**3. Blood circulation pathway in nasal cavity**:

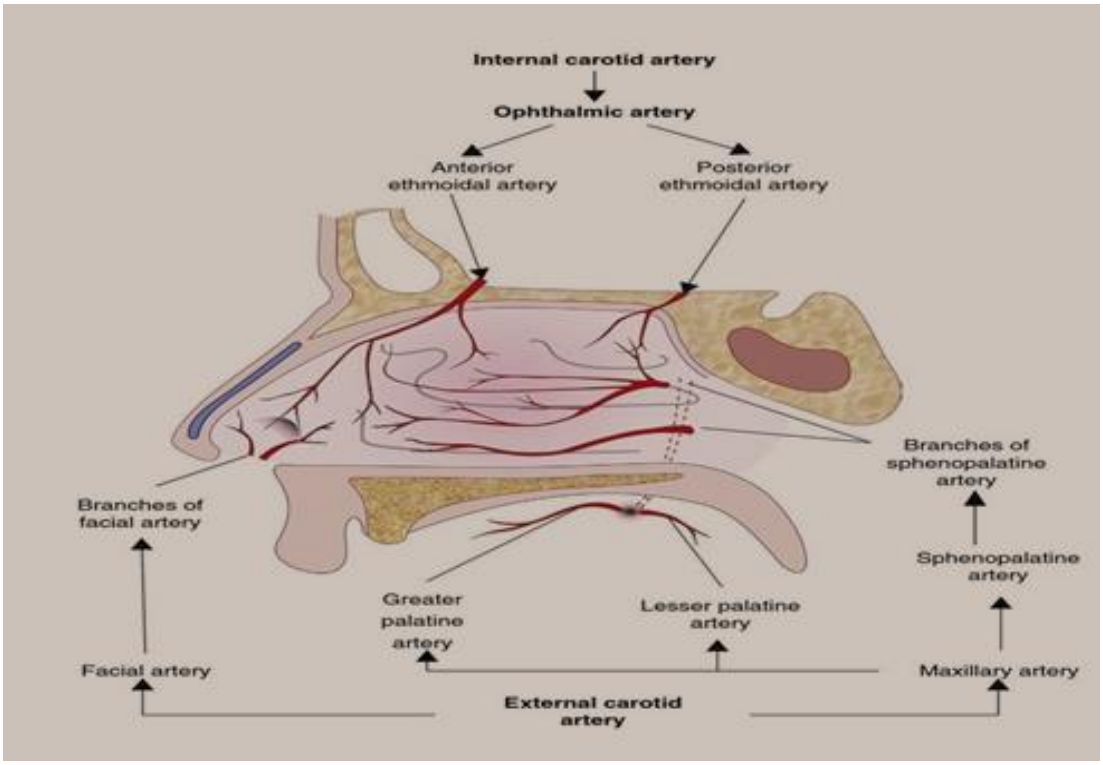


**Figure No. 05: Various pathway of blood supply in the nasal cavity.**

Heating and humidification, olfaction, mucociliary clearance, and immunological activities are the primary functions of the vasculature of the nasal cavity, which is densely packed with blood cells. There is a visible exchange of fluid and dissolved chemicals between the blood vessels and nasal tissue in the vascular area of the nasal cavity. [17] The blood supply to the olfactory area comes from the anterior and posterior ethmoidal branches of the ophthalmic artery branch, which is located in the carotid artery branch. These blood veins supply the front portion of the nasal cavity. After the drug(lipophilic) being administered through nasal route it enters via three different paths The first path is systemic way, which involves the drug entering into the bloodstream and then passes the blood brain barrier to reach the brain. The second path which involves the drug being absorbed into the bloodstream and then passing the blood brain barrier to reach the brain. The olfactory area and the trigeminal neural route are the other two paths, these two paths carry drugs straight from the nasal cavity to the CNS. Trigeminal nerve receptors in the nasal cavity are responsible for chemoperception as well as drug transport into the brain. From different areas of the nose superficial lymphatic vessels run with the veins, and deep lymphatic vessels travel with the arteries. Lymph drains from the anterior half of the nasal cavity, including both the medial and lateral walls, to join that of the external nasal skin to drain into the submandibular lymph nodes. The rest of the nasal cavity and paranasal sinuses all drain to the upper deep cervical lymph nodes, directly or through the retropharyngeal lymph nodes. The dorsal of the nasal floor probably drains to the parotid lymph nodes. Lymph nodes which have a specific relevance in intranasal drug administration. This lymphatic tissue may detect infections that have been entered through the nasal cavity. Drugs penetrate the olfactory areas by different paths. The first path involves drug delivery directly to the primary neural cells of the olfactory epithelium,

followed by intracellular axonal transport through the olfactory bulb and then reaching brain tissues. The second path is through olfactory sustentacular epithelial cells, where drug permeates via transcellular or paracellular routes, and then enters into the CNS. The third path is pinocytosis which is carried through olfactory neurons. So different paths are used by drugs to cross the olfactory lobe to enter brain [(18)]

**4. The Drug absorption mechanism from nasal route:**

The first stage of drug absorption is through mucus layer, where tiny drug molecules are absorbed faster when compared to larger drug molecules. Drugs uses diffusion paths for its pharmacological mechanisms such as paracellular transport which is between the cells and transcellular transport which is across the cells,

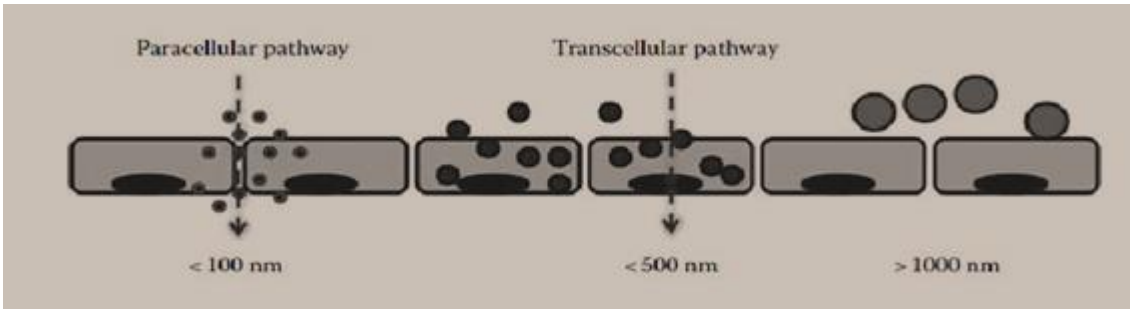


**Figure No. 06: Transport of drugs through different pathways**

Paracellular route is the first mechanism where aqueous drugs are absorbed slowly and through diffusion. Drugs having more than 1000daltons shows poor bioavailability when compared to drugs with less molecular weight with high bioavailability and absorption. **(19)** Transcellular route is the second mechanism, where drugs depending upon its lipophilicity crosses the biological membranes. Lipophilic drugs penetrate cell membranes by active transport via a carrier-mediated pathway or by opening tight junctions. For example, cyclodextrin, a natural biodegradable polymer, opens junctions between epithelial cells to allow medication delivery. For example, nasal oestradiol marketed recently by Servier in Europe has used cyclodextrin to solubilise the drug and thus enhance permeation. [(20)]

**5. Advantages and Limitations of Nasal Route**

**5.1 Advantages of Nasal route.**

1. Ease of administration.
2. Onset of action is rapid.
3. Dose required is less
4. Accuracy of dose is maintained
5. Less time with rapid action and quick relief
6. Non-invasive, self-medication no skill is required
7. Drugs which are not absorbed through oral route can be administered by this route
8. Nasal route is considered as a substitute route to parenteral route
9. Most of the drugs which undergo degradation by GIT fluids are completely absorbed when given by nasal route.
10. When compared to other dosage forms like oral route, nasal route shows better bioavailability for those drugs which are poorly soluble.
11. Permeability of the drug is better through nasal epithelium as it is thin and highly vascular.

12. Absorption enhancers are added to improve bioavailability of larger drug substances [21]
13. Drugs undergoing oxidation, reduction, hydrolysis and decomposition upon exposure to GIT can be administered by this method.
14. Nasal route is proved to be convenient in comparison to parenteral route for patient with extended therapy.
15. Drug enters directly to brain bypassing BBB. [22]
16. Metered device is easily handled no special training is required.
17. Avoid manual contamination.
18. No first pass metabolism of the drug through liver.
19. Method of preparation is easy.
20. Less number of excipients are used in formulation to avoid nasal irritation.
21. Can be used for both local and systemic action.
22. Easy of transportation
23. Cost is economic not expensive
24. Better Patient compliance and acceptance
25. Drugs with low molecular weight is taken

**5.2 Limitations of Nasal route:**

1. Mucus layer act as a physical barrier thereby drug diffusion is limited.
2. High concentration of drug solution causes nasal irritation.
3. Drug administration is difficult in pathological conditions like nasal congestion due to allergy and cold conditions. [23]
4. Only specified dosage of drug solution can be administered intranasally.
5. Increased administration of the drug solution causes damage to nasal mucosal membrane. [24]
6. The histological toxicity of absorption enhancers that are used in nasal drug formulation is not clearly reported.
7. Patient shows discomfort towards nasal administration. [25]

**6. Factors influencing the nasal drug absorption:**

There are numerous factors that influence in the development of nasal drug delivery system. These factors usually change the effectiveness of the dosage forms in therapeutic action to great extent.

**6.1 Factors related to drug:**

**1. Molecular size/ weight:**

Absorption of the drug through nasal route which mainly depends upon the molecular size. Aqueous drugs show less absorption than lipophilic drugs as it has direct affinity towards permeation. The drugs having molecular weight less than 300Da show better absorption and above it is sensitive.

**2. Enzymatic degradation in nasal cavity:**

Nasal cavity has several enzymes which converts the drug and helps in absorption. Enzymes like exopeptidase and endopeptidases play a significant role in drug absorption. This exopeptidase helps in cleave peptides at their N and C terminal whereas endopeptidases which acts on internal amide bonds. Drugs having peptides and proteins links have less bioavailability across the nasal cavity. Therefore, avoid catalytic degradation of the drug in the nasal lumen or through epithelial barrier passage. [26]

**3. Polymorphism:**

Polymorphism plays a great impact in the drug dissolution rate, solubility, absorption and bioavailability through biological membranes. It has significant role in case of stability and drug purity

and study should be carried out for nasal drug formulations.

**4. Dissolution Rate and Solubility:**

The solubility of drug plays a significant role in the drug delivery through nasal route. Drugs in solution form are absorbed faster than drugs in powder form. Drugs which are polar in nature are soluble in water than in organic phases and vice versa with the nonpolar drugs. Dissolution rate depends upon solubility of the drug substances in the surrounding medium.

**5. Lipophilicity:**

Drugs which are lipophilic in nature are better absorbed through nasal mucosa. It crosses the biological membranes faster than aqueous drugs through transcellular route, since the biological cell membranes are lipoidal in nature and more permeable to lipid soluble substances. Lipid soluble drugs diffuse into cell cytoplasm transversely. So lipophilic drugs are better absorbed through nasal route and the results are observed in animal models.

**6.Partition Coefficient and pKa:**

Partition coefficient is an important measure for drug permeability, because it is an indication of drug ability to cross epithelial membranes. It is an important step for passive diffusion of the drugs. Based on pH partition theory, unionised drug absorbs better when compared with ionised drug, this holds good for nasal route administration. So, the distribution of the drug depends on the pH and the concentration of the ionized drug. [(27)]

**6.2Factors related to formulation**

**1. Viscosity:**

Viscosity is internal resistance of the fluid. If the viscosity of the drug solution in the formulation is increased by the use of viscosity agents, then the contact time of the drug with nasal mucosa is increased that enhances the drug permeation through the nasal cavity.

**2. pH of formulation:**

Some drugs are pH dependent and shows good absorption at particular pH. So, to avoid nasal irritation, drug solution in the formulation is prepared at pH ranging from 4.5-6.5. The surface area of the nasal cavity depends upon the dose volume. Drug in unionised form is well absorbed by the nasal mucosa than in ionised form. To avoid bacterial infection in the nasal cavity the pH of the drug solution is maintained.

**3. Buffer capacity:**

To prevent degradation of the drug in the formulation, pH is adjusted by addition of the appropriate buffering agents. Usually, small volumes are preferred for nasal administration which ranges from 20-200µl. So nasal secretions change the pH of the administered drug dose solution.

**4. Role of absorption enhancers:**

Drugs which show less membrane permeability, drug with low lipophilic in nature and drug undergoing deterioration by enzymes in nasal mucosa. So, to avoid such functions absorption enhancers are added. The absorption enhancers decrease mucociliary clearance, open tight junctions and helps in stabilization of the drug. [(28)]

**5. Osmolarity:**

The high concentration of the drug solutions causes nasal discomfort and mucosal damage. So, the osmolarity depends upon the total concentration of the penetrating drug molecules and with nonpenetrating drug molecules through nasal epithelium. To avoid dehydration and tonicity of the nasal mucosa, osmotic agents are incorporated in the formulation. Preferably isotonic solutions are prepared for nasal administration. [(29)]

**6. Biological factors:**

**Structural features:** There are three regions in the nasal cavity that is nasal vestibule, respiratory region and olfactory region. These structures help in the olfaction respiration and helps drug permeation. To increase drug permeability through nasal mucosa absorption enhancers are used.

**7. Biochemical changes:** The nasal mucosa contains a number of enzymes that serve as a barrier and provide a pseudo-first-pass effect in drug delivery. The enzymes comprise of oxidative, conjugative, peptidases and proteases. The function of these enzymes is to degrade the drugs that are present in the nasal mucosa. The protein delivery and peptides are been hindered by the protease and peptidase enzymes in nasal cavity. So, enzyme inhibitors are used to overcome these type degradations.

**7. Physiological factors**

**1. Neuronal regulation and blood supply:**
Nasal mucosa is vascular and extremely permeable region. Parasympathetic stimulation increases the blood supply in the nasal cavity causes congestion and with sympathetic stimulation blood supply is decreased and gets relaxed, thereby fluctuations is seen in the amount of drug permeated. Thus, increased drug permeable is because of parasympathetic stimulation.

**2. Nasal secretions:**
Nasal secretions are derived from goblet cells and nasal glands. Normal person produces mucus more than a litre per day. The solubility of drugs in nasal secretions, the viscosity of nasal secretions, and the pH of the nasal cavity all influence drug permeability through the mucosa. Diurnal variation is observed in allergic rhinitis and also nasal secretions is affected by circadian rhythm and alters the drug permeation at night and clearances rates are reduced.

**3. Mucociliary clearance:**
When drug solution is administered through nasal route, mucociliary clearance takes 720 mins from the nasal cavity. It's a common nasal cavity defensive mechanism that clears the nasal mucosa of adherent particles and drains into the nasopharynx. Drug penetration rises with longer contact time between the drug and the mucus membrane, resulting in reduced mucociliary clearance, whereas drug permeation decreases, resulting in higher mucociliary clearance.

**4. Pathological conditions:**
Irritation in the nasal mucosa, mucociliary disorder, hyper or hypo nasal secretion occurs due to infections such as rhinosinusitis, nasal polyps, asthma, nasal allergy, this in turn reduces the drug permeation through nasal mucosa.

**5. Environment conditions:**
Depressant effect is observed on mucociliary clearance as it is dependent on different factors such as pollutant concentration, temperature of 20°c and the duration of exposure in the environment. With rise in temperature, it is predicted that the ciliary beat frequency is increased.

**6. Membrane permeability:**
The drug substances with high molecular weight and polar in nature similar to peptides and proteins show less membrane permeability but it is absorbed more in anterior part of nasal cavity. Drugs less than 300 Daltons are easily permeable through nasal epithelium when compared with drugs having more than 1000daltons. [30]

**8. Strategies for nasal drug delivery:**

There are number of strategics involved in developing the formulation for drug absorption through nasal drug delivery. The mechanism involved to enhance bioavailability are by following ways. a) by incorporating permeation enhancers to increase nasal absorption., b) reduction of nasal metabolism by enzyme inhibitors c) developing mucoadhesive dosage formulations to increase residence time and d) prodrug approach. To improve medication bioavailability via the nasal route, any of the approaches can be employed singly or in combination. When developing a nasal drug delivery system, certain factors such as dose, dosage regimen, duration of therapy, adverse reactions, therapeutic indication, toxicity of medicines and excipients, cost, and the various categories of patients to be treated are thought to be important in ensuring the safety and effectiveness of nasal formulations.

- **Permeation enhancers:**

  Drug substances with high molecular weight and poorly soluble drugs are less absorbed through nasal mucosa so as to improve absorption, permeation enhancers are incorporated in nasal formulations to increase permeability and bioavailability. It also inhibits enzyme activity, decreasing the membrane viscosity, increase membrane fluidity and opening the tight junctions. Permeation enhancers are added in small proportion as it causes nasal irritation. Ex.

  Bile salts, fusidic acid derivatives and cyclodextrin.

- **Enzyme inhibitors:**

  Proteins and peptides are poorly absorbed due to enzymatic activity of protease and peptidase present in the nasal mucosa, so to reduce the enzyme activity and increase absorption enzymatic inhibitors are added. Ex. bestatin, boroleucin and trypsin inhibitors and absorption enhancers like derivatives of fusidic acid and bile salts are been incorporated to enhance absorption and bioavailability.

- **Pro drug approach:**

  To increase the physicochemical properties like solubility, taste, odour and stability etc, prodrug approach is adopted. To avoid pre-systemic biotransformation, chemical decomposition of drug substances and to overcome pharmacokinetics problems prodrug approach is developed. In this approach, the enzymatic transformation is required for prodrug to release the parent compound. ex. conversion of ester derivatives of acyclovir to parent molecule is due to the presence of respiratory carboxylesterase in respiratory epithelium.

- **Nasal mucoadhesive drug delivery system:**

  Mucoadhesive drug delivery refers to a type of drug delivery method that attaches to biological tissue that is coated with mucus. This drug delivery system is selected to improves the intimate contact, retention time, increase permeability, bioavailability and prolong the drug absorption through nasal mucosa. ex. lecithin. To improve bioavailability of drugs like antibiotics, vaccines, DNA, proteins and other molecules mucoadhesive drug delivery system are administered nasally. [(31)]

- **Particulate drug delivery system:**

  To improve bioavailability of nasal formulations, particulate systems are used which includes like microspheres, liposomes, nanoparticles etc.

- **Microspheres:**

Microspheres are multiparticulate drug delivery systems that are designed to achieve extended or controlled drug administration in order to enhance bioavailability, permeability, stability, and to target the medication to particular sites at a predefined pace. Albumin microspheres, which absorb water and produce a transparent coating that clears slowly from the nasal canal, and are employed in nasal medication delivery systems to extend residence duration.

- **Liposomes:**

  Liposomes are the carriers of both hydrophilic and lipophilic drugs in intranasal drug administration. The hydrophilic drugs are confined in the aqueous core, whereas the lipophilic drugs migrate to the phospholipid bilayers that surround it. Following intranasal administration, drugs are transported to the CNS through olfactory region and crossing the BBB, where systemic absorption of the drug takes place. [32]

Nano particles are wide class of materials having less than 100nm in size. In this system drug is dispersed in the polymeric material and released by different mechanism for drug absorption. The nanoparticles are used as carrier in the intranasal drug delivery system for drugs which are poorly soluble, less absorption, less permeability through biological membranes. Ex: nano particles such as dextran, degradable starch, microcrystalline cellulose (MCC), chitosan, hydroxypropyl cellulose (HPC), poly (lactic-co-glycolic acid) carbomer, hydroxypropyl methylcellulose (HPMC) gelatin polymers and wax-like maize starch. Drugs are incorporated in nanoparticulate system to release into host system by different mechanism, that is from particle surface, diffusion through swollen polymer matrix and through erosion of polymer. [33] Some marketed drug molecules and drug carrier systems being delivered by direct nose to brain drug delivery route are listed below.

- **Nano-/ micro-particulate systems:**

**Table No.01: Drug molecules and drug carrier systems being delivered by direct nose to brain drug delivery route.** [34]

| | | | |
|---|---|---|---|
| Venlafaxin | Polymeric nanoparticles | Slow onset of action, poor oral bioavailability | Quick onset of action, enhanced brain uptake |
| Ropinirole | In situ gel | Low oral bioavailability, limited uptake across BBB | High brain uptake, high targeting efficiency |
| Insulin | Solution | Cognitive deficits | Improved memory |
| Olanzapine | Nanoemulsion | High hepatic metabolism, high P-glycoprotein efflux | High bioavailability, high therapeutic efficiency |

**9. Development in the Nasal dosage forms**

**1. Nasal drops:** They are very simple, effective and convenient system developed for intranasal delivery. It is recommended for local treatment for allergic reactions and also to act on microbial growth and mucosal dysfunction. Accuracy of the

dose is not maintained so it is not recommended for prescription products.


**Figure No. 07: Nasal drops device**

**2. Nasal Spray:** Nasal sprays are usually formulated in the form of suspensions and solutions. It is administered through metered dose pumps with actuators to deliver the specified dose. Nasal sprays are better over nasal powders as it results in nasal irritation. [35]


**Fig-8: Nasal spray device**

**3. Nasal powders:** Nasal powders are better in drug stability. It requires less excipients, no preservatives and maintains greater drug stability in the formulation. Nasal powders depend upon the particle size, solubility of the active ingredients and excipients. Main disadvantage is nasal irritation so local application of drug preferred. [36,37]

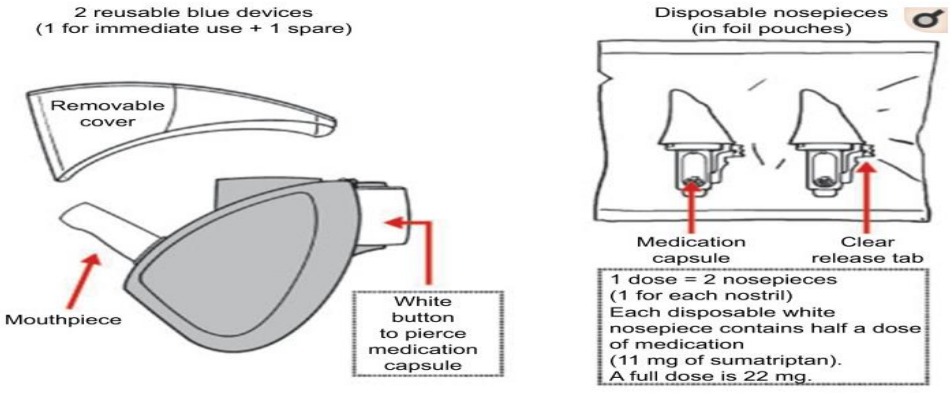


**Figure No. 09: Nasal powder device**

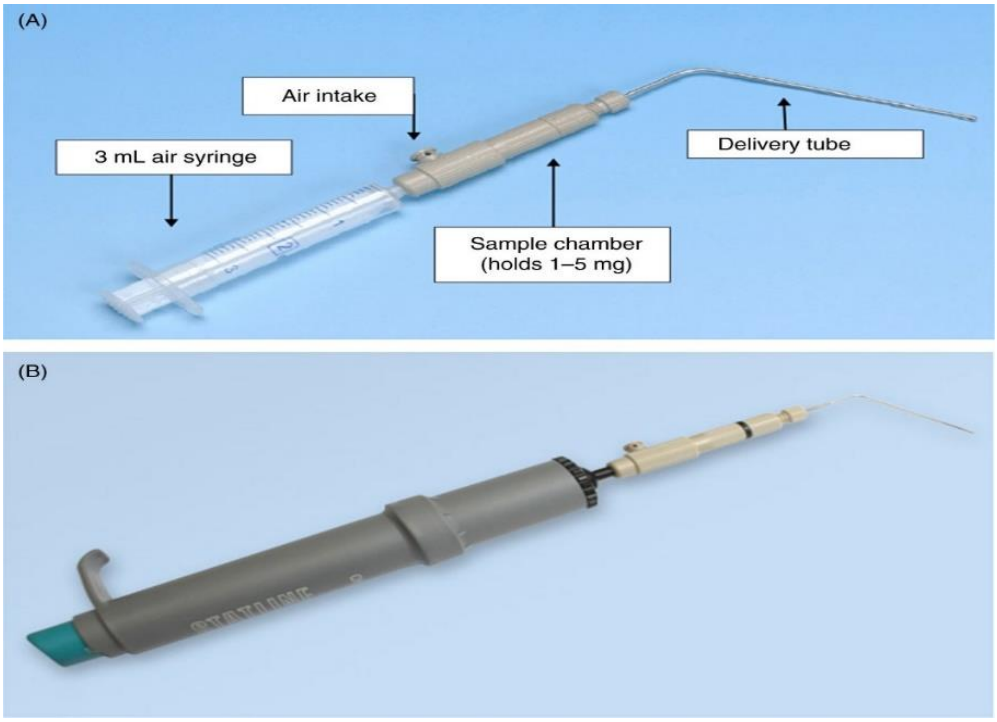


**Figure No. 10: showing (A) Penn-Century Dry Powder Insufflator—Model DP-4 connected with commercial syringe, (B) Dry Powder Insufflator Air Pump Assembly**

- **Nasal Gel**: Nasal gels are preferred now a days due to its high viscosity, retention time with mucosal membrane, taste reduction, avoid dose dripping, less irritation, increase in adherence to nasal mucosa thereby drug absorption is increased. [38]

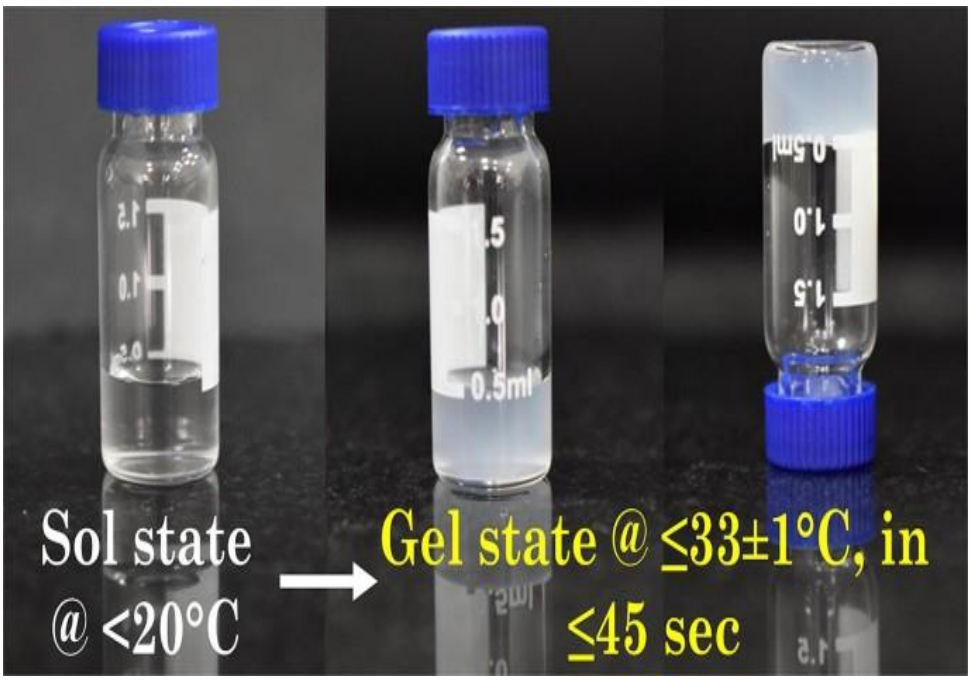


**Figure No. 11: Nasal gel**

- **Nasal Inserts:** Lyophilization or gelsification is used for preparation of nasal inserts. They are solid dosage forms that are employed for late systemic drug delivery via nasal route. Drug dosing is easy with greater potential for systemic administration. The mechanism involved in administration of nasal inserts is, when nasal mucosa comes in contact with nasal inserts it forms nasal fluid and converts into gel in the nasal cavity and gets adhere due to bio adhesive property thereby sustained drug delivery is achieved. Ex. Epistasis. [39]

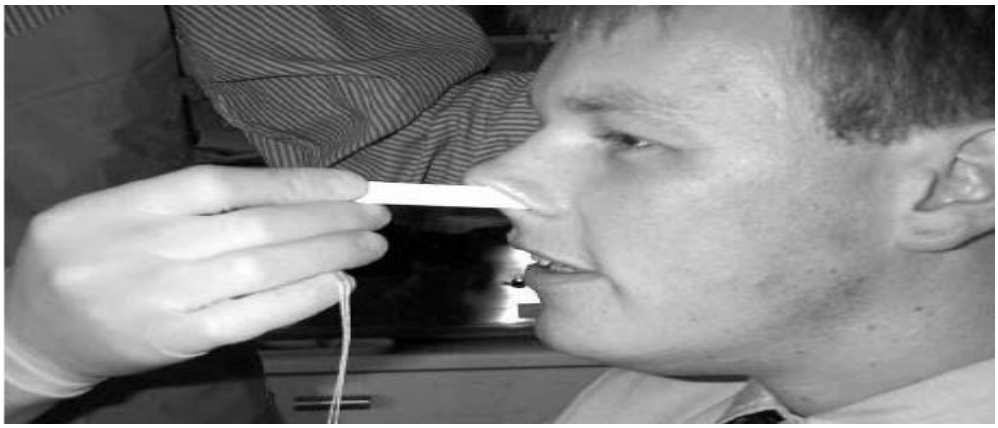

**Figure No. 12: Nasal insert**

- **Nano emulsions:** Nano emulsions occur as colloidal in nature in the particulate system, having a sub-micron range size, which is used for carrying drug molecules. The size ranges around 10 to 1000 nm. These are type of carriers that appear as solid spheres having amorphous and lipophilic surface enclosing a negative charge. the size specificity can be enhanced by magnetised nanoparticles. In drug delivery system these increase therapeutic efficacy of the drug via by decreasing adverse reactions. ex. It can be used in RES, ERT in the liver and vaccination. [40]
- **Micro-emulsions**: Micro emulsions are the preparations which are clear, stable, isotropic mixtures of oil, water and surface-active agents, and more often in combination with a co-surfactant. Recently these preparations showing greater potential in drug delivery system. Due to its thermodynamic stability, improved drug solubilization and bioavailability. [41]

**Table 2: Various CNS drugs formulations targeted to brain by intranasal route** [34,41]

| Sl. No. | Drug | Formulations | Category | Disease |
|---|---|---|---|---|
| 01 | Bromocriptine | Chitosan-loaded nanoparticles CS-BRC-NPs | Dopamine$D_2$ agonist | Parkinson's diseases |
| 02 | Deferoxamine | Nasal solution | High-affinity iron chelator | Cerebral Ischemia |
| 03 | Rivastigmine | Chitosan-loaded nanoparticles CS-RHT-NPs | Acetylcholinesterase (AChES) inhibitor | Alzheimer's disease |
| 04 | Sumatriptan | Micellar nanocarrier and micro emulsion | Selective5-HT1D agonist | Migraine |

**10. Preparation of nasal spray:**

Therapeutically active ingredients (AIP) are dissolved, dispersed, or suspended in solutions or combinations of excipients (ex. buffering agents, emulsifying agents, viscosity modifiers, preservatives) in non-pressurized dispensers that release a spray containing a specific dosage of the medication. The spray pump allows you to control the dosage. The nasal dispenser spray may be set to provide a single dosage or several dosing metered sprays of active ingredient mixtures. For local and systemic effects in the nasal cavity, nasal sprays are best suited. In terms of formulations, production, stability, container closing mechanism, and finished medicinal product, nasal sprays are identical to other medication formulations. The pump's metering and spray-producing (e.g., orifice, nozzle, jet) mechanisms have been changed such that their size and composition may be altered for consistent drug formulation distribution. Pressing is required for administration of the nasal spray through actuator and its orifice. Overall drug product constitutes formulation and the container closure system. There are different types of container closure system to facilitate the administration without altering the dosing performance of the drug product. Nasal sprays can be formulated in form of solutions and suspensions.

**10.1Active Pharmaceutical ingredient:**

Ideal characteristics of nasal drug candidates:

1. Onset of action is very rapid
2. Less dose preferably less than 25mg per dose
3. It should be inert, non-toxic, non-irritant.
4. Should have good absorption properties
5. Good stability characteristics
6. No physical chemical interactions

1.

**10.2Excipients used in nasal spray formulation**

Different types of excipients used in preparing nasal formulations.

**1. Buffers:** Buffer solutions are added to maintain pH of the nasal formulations in order to avoid degradation of the drug by nasal secretions. Ex. Citric acid, sodium citrate.

**2. Solubilisers:** The limiting element for nasal medication administration in solution is, drugs that are soluble in aqueous phase. Solubilisers like solvents and co-solvents such as alcohols and polyethylene glycols are used to increase the solubility of poorly soluble drugs. Other compounds like cyclodextrin, surfactants are utilised to improve the drug absorption via biological membranes.

**3. Preservatives:** Preservatives are included to almost all nasal formulations since they are watery in solution form. Parabens, phenyl ethyl alcohol, benzalkonium chloride, benzoyl alcohol, and EDTA are among the most common preservatives found in nasal compositions.

**4. Antioxidants:** To prevent oxidation of the drug when exposed to atmosphere antioxidants are added. Ex., sodium bisulfite, butylated hydroxytoluene, sodium metabisulfite and tocopherol. Antioxidants should not interfere with therapeutic /medication absorption or cause nasal irritation.

**5. Humectants:** To avoid dryness in the nose due to allergic and chronic disease, humectants are used. These humectants hydrate the nasal epithelium layers and thereby reducing the nasal irritation without affecting the drug absorption. Ex. glycerine, sorbitol and mannitol.

**6. Surfactants:** To increase the drug permeability across the nasal mucosa, surfactants are incorporated in the formulations which facilitates the drug absorption through nasal cavity. It also increases stability of the formulation.

**7. Bio adhesive polymers:** Polymers adhering to the biological membranes/mucosa for prolonged periods of time capable of interacting through interfacial forces is called bio adhesive/mucoadhesive polymers. The type of the polymer employed, the surrounding environment, edoema, and other physiological variables all influence bio adhesive polymers. To reduce the nasal irritation combination of carrier are used.

**8. Penetration enhancer:** Penetration enhancers are used to increase absorption, inhibiting enzymatic viscosity, reducing MCC and open tight junctions for drugs showing less permeability through biological membranes in nasal drug delivery. [42,43]

**11. Applications of intranasal approach for brain drug delivery.** [44,45,46]

**1. Intranasal administration used for drug delivery:**

Antihistamines and corticosteroids have been utilised as first-line prescription drugs to treat seasonal rhinitis and nasal congestion caused by allergic responses or infections in recent years for nasal drug delivery. Levocabastine is a good example of this type of administration.

**2. Intranasal systemic drug delivery:**

Intra nasal administrations have proven to be more effective for systemic drug delivery and are used to treat a variety of disorders such as migraine, headache, and infection emergency therapy. Several clinical investigations utilising cardiovascular medications such as nitroglycerine and propranolol shown that Intra nasal treatment increased exercise tolerance in patients with angina pectoris. Nyxoid® is for example the nasal formulation of naloxone approved in Europe. The replacement of hormones by intra nasal delivery is an important indication for Intra nasal application with systemic delivery. One example is the aqueous formulated 17-β-estradiol (Aerodiol®), which is used as an oestrogen therapy to reduce menopause symptoms in women.

**3. Intranasal application used for CNS drug delivery:**

The presence of multidrug efflux protein transporters reduces the amount of material reaching the CNS through the systemic route. The active P-

glycoprotein efflux pumps are located on the luminal side of the BBB and help to limit drug exposure in the CNS by expelling them back into the circulation. Intra nasal administration of medications is gaining popularity in the treatment of neurological illnesses such as Alzheimer's disease (AD) because it avoids the BBB and the systemic first-pass effect, making it a potential strategy as a drug delivery route. Nanotherapeutics and nanomaterials have been proven in studies to promote medication biodistribution in the brain for more effective glioblastoma treatment, not only by convection-enhanced delivery, but also through intranasal delivery. New delivery tactics, such as nanotechnology-based technologies and devices like bi-directional nasal insufflators that enhance distribution to the posterior section of the nose and reduce lung deposition, are being developed with vigour.

**4. Delivery of small molecules to CNS**

Li et al. formulated a microemulsion based ethyl laurate which is used for direct nose to brain delivery of diazepam and it was found that after administration of the drug there was a rapid onset of action attained within 2-3 min with considerable 50% bioavailability after nasal spray compared with intravenous injection.

**5. Toxicological challenges of Intra nasal applications:**

The active components and excipients in the formulation, as well as the medicine itself, must be examined for their safety. For larger molecules such as peptides and proteins, absorption enhancers are required there by enhancing the permeability of the nasal mucosa, and also, they boost the drug's bioavailability when delivered by Intra nasal administration.

**6. Delivery of macromolecules to CNS:**

Human studies have shown that proteins including arginine-vasopressin (AVP), cholecystokinin (CCK) analogue, adrenocorticotropic hormone (ACTH), and insulin can be transported directly to the brain via the nasal cavity. Clinical investigations in both healthy human volunteers and patients with cognitive abnormalities such as Alzheimer's disease have shown that extended intranasal insulin treatment improves memory and mood without causing systemic side effects.

**7. Delivery of stem cells:**

Stem cell technology have become a more appealing option for investigating and treating brain illnesses over the last two decades. Stem cells may be used to treat neurological illnesses by replacing dead or injured neurons or producing neurotrophic substances to help nourish host neurons. The therapeutic efficacy of intranasally delivered mesenchymal stem cells (MSCs) to the brains of 6-hydroxydopamine-lesioned rat models of PD was demonstrated by Danielyan et al. MSCs were injected into the olfactory bulb, cortex, hippocampus, striatum, cerebellum, brainstem, and spinal cord, resulting in the appearance of cells in the olfactory bulb, cortex, hippocampus, striatum, cerebellum, brainstem, and spinal cord. Intranasal administration is a non-invasive, safe, and promising alternative to traumatic surgical techniques for stem cell transplantation that allows for focused delivery of stem cells to the brain.

**8. Delivery of DNA plasmids to CNS:**

Nasal delivery of DNA plasmids showed that the plasmid concentration in the brain was 3.9–4.8 times higher than in the lungs and spleen. It was also discovered that 15 minutes after intranasal treatment, the plasmid DNA entered the brain. This shows that nasal administration could be a potential

route for delivery of therapeutic genes to the brain with reduced side effects in other organs.

**Table No. 03: Drugs with different devices [47]**

| Sl. No. | DRUGS | DELIVERY DEVICES |
|---|---|---|
| 01 | Adrenal corticosteroids jelly | Nasal drops, Nasal insufflators |
| 02 | Dopamine | Nasal spray |
| 03 | Insulin | Metered pump sprayer |
| 04 | Nitro glycerine | Metered dose spray |
| 05 | Oxytocin | Aerosol activated spray |
| 06 | Vaccines | Nebulizer aerosol |
| 07 | Xylometazoline | Nasal spray. |

## 12. Conclusion

Intranasal delivery has several advantages, the most notable of which is that it is quick and painless. It lowers systemic exposure and hence negative effects. It also skips the BBB, delivering the medication straight to the CNS. For the administration of particular medicines, it can be used instead of parenteral and oral routes. Given the present research interest in nasal delivery and the outstanding outcomes of clinical trials conducted throughout the world, it would not be unrealistic to expect a wide range of nasal therapies to enter the market in the near future. Furthermore, improved drug absorption through the olfactory area bypassing the BBB and reaching the CNS system. Intranasal administration of several drugs with different type of nasal formulations are targeted to CNS system by use of suitable nasal devices.

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