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AN OVERVIEW STUDY ON NASAL AND INTRANASAL DELIVERY SYSTEM OF DRUG

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ABSTRACT

Researchers and scientists make an incredible attempt to deliver the active medicaments in the various dosage forms for getting an effective therapeutic action. Several routes for drug administration are available presently with their promising effects and acceptance by the patients. Among this various drug delivery systems, nasal and intranasal route of drug delivery is found to be more promising as it is minimizing the shortcomings of oral and parenteral route. It is the only drug delivery systems which delivered the active medicament to the brain. It is found more valuable to treat the brain related disorders by administering the drug through the intranasal route. Hence, this delivery system is having a large surface area and found effective at low concentration of drug doses with the ease of drug administration, convenient and better patient compliance.

INTRODUCTION

In the current scenario, there are a several sort of dosage forms are available in the market for the administration of the pharmaceutical products to urge a faster therapeutic effectiveness. Each and every dosage form is having a plenty of advantages and that they are found to be more effective to deliver drug and complete their therapeutic purposes. Oral route is the most acceptable, easiest way and suitable route of drug administration for all kind of population due to their ease of manufacture and administration and enhance bioavailability. Inadequate absorption through the GI tract and hepatic metabolism effect cause the necessity to seek out an alternate route of drug delivery like parenteral route, transdermal route, subcutaneous route, etc. Among all the route of drug administration, nasal route of drug administration found more useful for the delivery of the drugs which are active in low doses and having less oral bio-availability like proteins and peptides. The history of development of nasal drug delivery dates back to earlier topical applications of drugs intended for local effects [1]. In the first 1980s the introduction of the nasal route comes out as a most promising systemic delivery which substituted the other conventional drug delivery routes. Nasal therapy, has been recognized sort of treatment within the Ayurvedic systems of Indian medicine, it's also called "NASAYA KARMA". In addition, nasal mucosa is found to be highly permeable for more compounds than the alimentary canal because of the absence of gastric juices, pancreatic and gastric

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enzymatic activities, and interference by gastrointestinal contents. [2] This method of nasal delivery seems to be a positive way to circumvent the obstacles for blood brain barrier (BBB) allowing the direct entry of drug within the bio phase of central nervous system (CNS) active compounds. Development of multiple sorts of formulation are used to administer drug by nasal route, which incorporates nasal spray, nasal drop, nasal powder, nasal gels & nasal insert. [3]

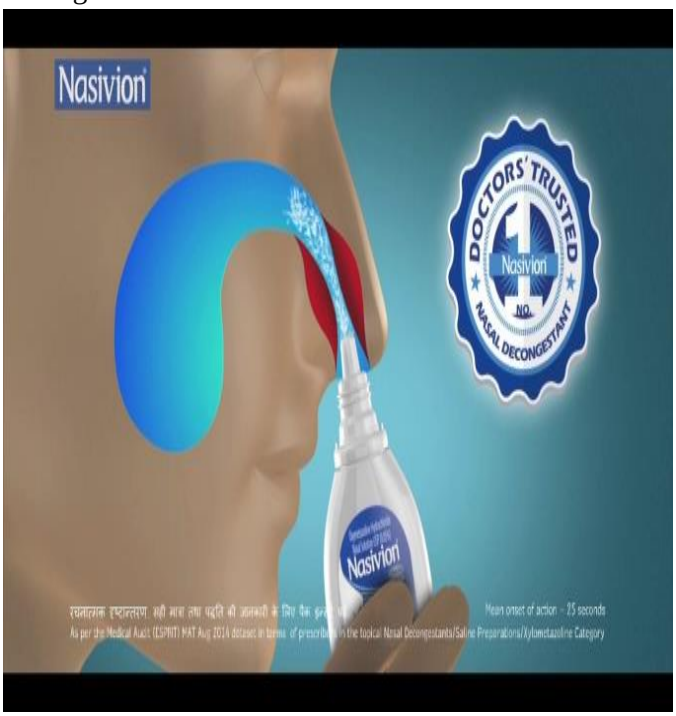

Figure: 1 showing nasal formulation.

DEFINITION

Nasal drug delivery system can be defined as the method of administration of the drug through the nasal route.

Advantages [4]

- It provides high drug permeability, especially for lipophilic and low relative molecular mass drugs.
- It provides the direct contact site with lymphatic tissues for vaccines.
- Drug degradation within the alimentary canal is absent and drugs with poor stability in G.I.T. fluids are given by nasal route.
- Hepatic first pass metabolism is avoided and it provides large area for the absorption of a drug.
- Rapid drug absorption at the site of the action with quick onset of action will be achieved.
- It prevents the risk of overdose of medicaments, avoidance to polluted environment and gastrointestinal conditions.
- As it is a non-invasive, reducing the risk of communicable disease transmission.
- Convenient for the patients, especially for those on long run therapy, in comparison with parenteral medication.
- Hydrophilic compounds exhibit poor oral absorption could also be particularly fitted to this route of delivery.

Limitations

- The histological toxicity of absorption enhancers utilized in nasal drug delivery system is not yet clearly established.
- Relatively inconvenient to patients in comparison to oral delivery systems since there is an opportunity of nasal irritation.
- There is a risk of local side effects and irreversible damage of the cilia on the nasal mucosa, both from the substance and from constituents added to the dosage form.
- Chemical enhancers like surfactants may result in the disruption and even dissolve membrane in high concentration.
- Mechanical loss of the dosage form into the other parts of the respiratory tract like lungs due to the improper technique of administration.
- Smaller absorption surface compared with GIT and Delivery volume in cavity is restricted to 25–200µl.
- High relative molecular mass compound cannot be delivered through this route (mass cut off ~1kda).

IDEAL DRUG CHARACTERISTICS FOR NASAL DELIVERY [5-6]

Based upon an overall review of the literature on the nasal route of drug administration, an ideal nasal drug candidate should possess the following qualities

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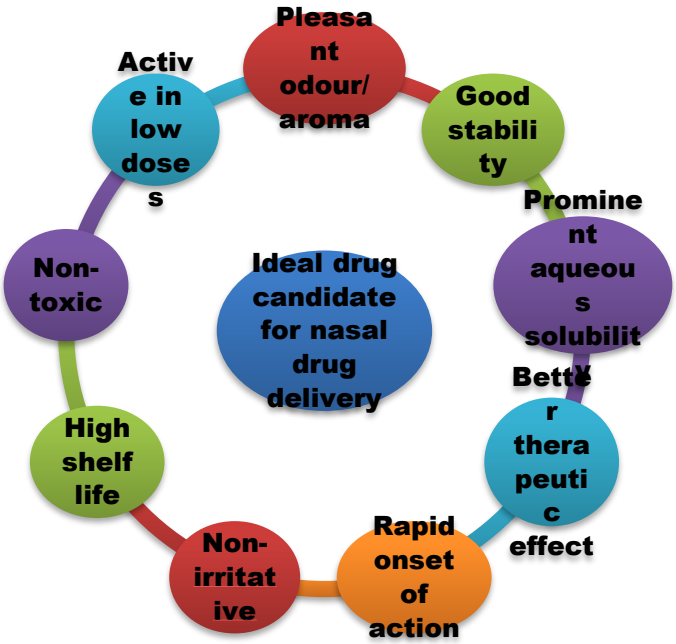

Figure: 2 Ideal drug characteristics for nasal drug delivery.

Mechanism of drug absorption from nose [1]

The principal step in the absorption of a drug from the nasal cavity is the passage through the mucus. Fine particles can easily go through the mucus layer except the larger particles which may find some barriers to get transported. Mucus contains a protein mucin having a potential to bind with solutes and thus affect the diffusion process. Structural changes can occur within the mucus layer due to environmental or physiological changes but a small unchanged particle can easily pass through this layer.

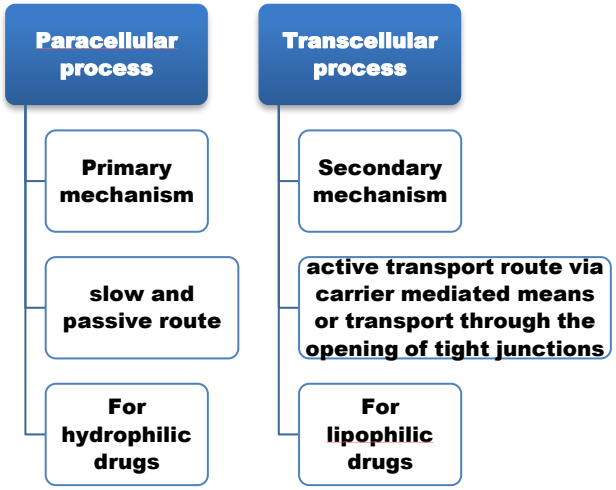

Figure: 3 Mechanism of drug absorption

BARRIERS

Nasal drug delivery system is consider as a profitable route for the formulation aspects by a formulator because of its simple and approaching formulation strategies. Intranasal administered drug products shows therapeutic efficacy and toxicities due to the influence by the number of factors. Following factors are acting as a barrier to the absorption of drugs through nasal cavity.[7]

Table no.:1 Barriers for the nasal absorption of the drugs

Barriers	Mechanism
Low bio-availability	Lipophilic drugs are generally well absorbed from the nasal cavity as compared to polar drugs. The pharmacokinetic profiles of the lipophilic drugs are often similar to those obtained after an injection and bioavailability approaching 100%. The factor which is responsible for limiting the nasal absorption of polar drugs and particularly large relative molecular mass polar drugs like peptides and proteins is the low membrane permeability. Polar drugs having molecular weights below 1000 Da will generally able to pass through the membrane using the latter route. Larger peptides and proteins are shown to be able to pass the nasal membrane using an endocytotic transport process but only in low amounts.
Low membrane transport	Another important factor to be considered is low membrane transport which can causes the rapid clearance of the administered formulation from the nasal cavity because of the mucociliary clearance mechanism. This can be especially for drugs that are not easily absorbed across the nasal membrane. The utilization of bio adhesive excipients within the formulations is an approach to overcome the rapid mucociliary clearance.

Enzymatic Degradation	Another contributing factor to the low transport of especially peptides and proteins across the nasal membrane is the possibility of an enzymatic degradation of the molecule either within the lumen of the nasal cavity or during passage across the epithelial barrier. The utilization of enzyme inhibitors and/or saturation of enzymes could also be approaches to overcome this barrier.

APPROACHES FOR IMPROVING DRUG BIO AVAILABILITY

Various strategies used to improve the availability of the drug in the nasal mucosa are explained below:

Nasal enzyme inhibitors

Enzyme inhibitors are used for eliminating the nasal metabolism of active substance, mainly for the formulation of proteins and peptide molecule, enzyme inhibitors like peptidases and proteases are used. The retention enhancers like salts and fusidic corrosive subsidiaries additionally shows chemical hindrance action to broaden the assimilation and bioavailability of the medication. The other chemical inhibitors regularly utilized for the enzymatic action are tripsin, aprotinin, borovaline, amastatin, bestatin and boroleucin inhibitors.

Permeation enhancers

The permeation enhancers are mainly used for the enhancement of absorption of the active medicament and it acts via one of the following mechanisms: by inhibiting enzyme activity, by reducing mucus viscosity, by decreasing mucociliary clearance and by solubilizes or stabilizes the drug.

Prodrug approach

Prodrug approach is primarily implied for streamlining positive physicochemical properties, for example, dissolvability, taste, smell, steadiness, and so on. Prodrug is normally alluded as promoiety, which is utilized to cover the undesired utilitarian gatherings with another practical gatherings. It is for the most part valuable for improving the nasal bioavailability particularly for the proteins and peptides to fortify the membrane porousness close by expanded enzymatic stability. The prodrug experiences enzymatic change to discharge the dynamic medicament, when it crosses the enzymatic and membrane barrier.

Structural modification

Adjustment of medication structure without changing pharmacological action is one among the worthwhile approaches to improve the nasal assimilation. The physical and compound adjustment of medication particle has been usually used to alter the physicochemical properties of a medication, for example, atomic size, sub-atomic weight, pka and dissolvability are ideal to improve the nasal retention of medication. Model, compound adjustment of salmon calcitonin to ecatonin (C-N bond replaces the S-S bond) indicated preferable bioavailability over salmon calcitonin. It is valuable to changes and expands the helpful adequacy of the medication moiety. [8]

Particulate drug delivery

Particle designed having an important role in absorption enhancement. Microspheres, nanoparticles and liposomes are all systems which are acting as a carrier for the encapsulation of an active drug moiety. They provide the good result by increasing an absorption efficacy, stability and reduced poisonous effect of an active ingredient. Systems can be designed to be mucoadhesive to enhancing the retention time and facilitate sustained release.

a. Microspheres are the most conspicuous particulate medication conveyance framework which predominantly expands the ingestion and bioavailability of medication by holding fast to the nasal mucosa and increment the nasal living arrangement time. b. Liposomes are ampiphilic in nature and are very much portrayed for great penetration of medications through the organic layers, consequently the water dissolvable medications are conveyed to nasal medications. Cationic liposomes are having acceptable saturation limit than adversely charged anionic liposomes. [9]

Bio-adhesive polymers

For the improvement of the nasal residence and for increasing the bioavailability of the drug, bio-adhesive polymers are used. They improve the retention time of the drug inside the nasal cavity by making an adhesive force between formulation and nasal mucosa, which leads to minimization of mucociliary clearance of formulation. [10]

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To advance the nasal residence time

Mucociliary clearance acts to evacuate the remote bodies and substances from nasal mucosa as fast as could be expected under the circumstances. One way to deal with postpone the clearance is to apply the medication to the foremost piece of the nasal depression, an impact that is to a great extent controlled by the sort of dose structure utilized. Another rewarding method to expand the nasal obstruction time is utilizing biodegradable microspheres as a bearer for conveyance of medication. Biodegradable microspheres swell within the sight of water, accordingly expanding the thickness. This wonder prompts increment the nasal private time.

By enhancing nasal absorption

It is probable to significantly improve the nasal absorption of polar drugs by giving them in combination with an absorption enhancer that promotes the movement of the drug across the nasal membrane.

In situ gel

These are the details which get changed over into gel upon instillation into nasal pit by the impact of boosts incorporates temperature, pH and ionic fixation. Thick consistency of the gel makes the definition hard to deplete by the impact of ciliate development. [11]

FACTORS AFFECTING NASAL DRUG ABSORPTION

1) Physiochemical properties of drug.

◎ Molecular size.

The permeation of medication under 300 Dalton isn't altogether affected by the physicochemical properties of the medication.

◎ Lipophilic-hydrophilic balance (HLB).

As lipophilicity continues expanding it builds saturation through the nasal mucosa. Lipophilic mixes will in general promptly cross biological membrane through the transcellular course since they can parcel into the lipid (bilayer) of the cell layer and diffuse into and transverse the cell in the cell cytoplasm.

◎ Enzymatic degradation in nasal cavity.

A few enzymatic that are available in the nasal mucosa may influence the shelf life of medications. For instance, proteins and peptides are exposed to degradation by proteases and amino peptidase at the mucosal layer. Peptides may likewise shape edifices with immunoglobulin (IgS) in the nasal depression prompting an expansion in the atomic weight and a decrease of porousness.

◎ Chemical Form.

Synthetic structure is the significant parameter in medicate absorption since transformation of the medication into a salt or ester structure may change its absorption.

◎ Polymorphism.

Polymorphism is known to affect the dissolution rate and solubility of drugs and their absorption through biological membranes. So, it is of vital importance that polymorphic stability and purity of drugs for nasal powders and/or suspensions should study.

2) Nasal Effect

◎ Environmental pH.

The pH of the definition, just as that of nasal surface can influence a medication's penetration. To keep away from nasal disturbance, the pH of the nasal plan ought to be acclimated to 4.5-6.5.

◎ Mucociliary clearance.

The retention of medication is impacted by the habitation (contact) time between the medication and the epithelial tissue. The mucociliary clearance is conversely identified with the residence time and in this way contrarily relative to the absorption of medications directed.

◎ Effect of states of being.

Intranasal pathologies may influence the nasal mucociliary transport process or potentially limit with respect to nasal assimilation. There are times when the mucosa is squashing, bleeding, or dry. One might be experiencing rhinorhea, sinitis, or nasal contamination. In individuals experiencing extreme nasal hypersensitivities, an unnecessary nasal discharge can wash away the definition before the medication gets an opportunity of getting ingested through the mucosa or before acting locally. [12]

◎ Nasal Blood Flow.

Nasal mucosal layer is wealthy in vascular and assumes an indispensable job in the warm guideline and humidification of the breathed in air along these lines the medication assimilation will rely on the vasoconstriction and vasodilation of the veins.

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3) Delivery Effect

◎ Drugs distribution and deposition.

The anterior portion of the nose is an area of low permeability while posterior portion of the nose where the drug permeability is generally higher, provides shorter residence time. Deposition of the formulation in the anterior of the nose provides a longer nasal residence time.

◎ Viscosity.

Higher viscosity of the formulation leads to promote the contact time between the medicaments and the nasal mucosa which results in the increment of the permeation time. Simultaneously, highly viscous formulations interfere with the normal functions like ciliary beating or mucociliary clearance and thus alter the permeability of drugs which affects the absorption of the drug.

◎ Osmolarity.

Optimum osmolarity needed to be maintain as it may leads to the shrinkage of the nasal epithelial mucosa and alters the permeation of drugs.

◎ Buffer Capacity.

Nasal poducts are generally taken in small volume ranging from 25-20 µL because the nasal secretions may alter the pH of the administrated dose which leads to affects the concentration of unionized drug available for absorption.

◎ Drug Concentration, Dose and Dose Volume.

Drug concentration, dose and volume of administration are three interrelated parameters that impact the performance of the nasal delivery performance. Nasal absorption of L-Tyrosine was shown to increase with drug concentration in nasal perfusion experiments. [13]

NASAL DRUG DELIVERY SYSTEM DOSAGE FORMS

The selection of delivery system depends upon the drug being used, proposed indication, patient population and marketing preference.

Table. 2 Nasal Formulations

A. Liquid Nasal Formulations- [14] Liquid preparations are preferably found more useful because of their humidifying effect, convenience and usefulness, since many allergic and chronic diseases are often connected with dry particles and drying of mucous membranes. Microbiological stability, irritation and allergic rhinitis are the major problems associated with the water-based dosage forms because they needed preservatives to impair mucociliary function. **Unit/Bidose systems** for liquid formulations are state of the art for the intranasal administration of drugs requiring exact dosing.

1. Instillation and rhinyle catheter- Catheters are used to deliver the drops to a specified region of the nasal cavity easily. The formulation was placed in the tube and one end of the tube kept positioned in the nose, and the solution was delivered into the nasal cavity by blowing through the other end by mouth. It is the simple way to instilled the formulation into the nasal cavity and acceptable by the patients.	
2. Compressed air nebulizers- Nebulizer is a device which is used to administer the medicament in the form of a mist inhaled into the lungs. The compressed air is filled into the device, so it is called compressed air nebulizers. The common technical principal or mechanism for using all the nebulizers is to use oxygen, compressed air or ultrasonic power, as means to break up medical solutions/ suspensions into small aerosol droplets, for direct inhalation from the mouthpiece of the device.	

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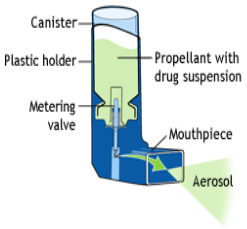
3. Metered-dose pump sprays-

Most of the pharmaceutical nasal preparations in the market containing solutions, emulsions or suspensions are delivered by metered-dose pump sprays. Nasal sprays, or nasal mists, are used for the nasal delivery of a drug or drugs, either locally to generally alleviate cold or allergy symptoms such as nasal congestion or systemically. Although delivery methods vary, most nasal sprays function by instilling a fine mist into the nostril by action of a hand-operated pump mechanism. The three main types available for local effect are: antihistamines, corticosteroids, and topical decongestants. Metered- dose pump sprays include the container, the pump with the valve and the actuator.



4. Squeezed bottle-

Squeezed nasal bottles are mainly used as delivery device for decongestants as it includes smooth plastic bottle with a simple jet outlet. While pressing the plastic bottle the air inside the container is pressed out of the small nozzle, thereby atomizing a certain volume. By releasing the pressure again air is drawn inside the bottle. This procedure often results in the hampering of the sterilization conditions, more chances of contamination of the medicated liquid resulting in the deterioration of efficacy of formulations.

B. Powder Dosage Forms-

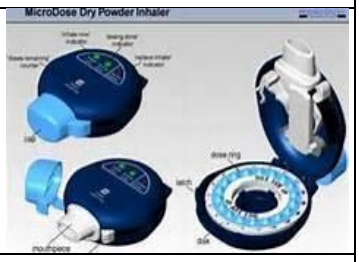
Dry powders are less frequently used in nasal drug delivery. Major advantages of this dosage form are the lack of preservatives and the improved stability of the formulation. Compared to solutions, the administration of powders could result in a prolonged contact with the nasal mucosa.

1. Insufflators-

Insufflators are the devices used to deliver the drug substance for inhalation; it can be designed as having straw or tube containing the drug substance and syringes. The achieved particle size of these systems is often greater than the particle size of the powder particles due to insufficient disaggregation of the particles and results in a high coefficient of variation for initial deposition areas. Many insufflator systems work with pre-dosed powder doses in capsules.

2. Dry powder inhaler-

Dry powder inhalers (DPIs) are devices through which a dry powder formulation of an active drug is delivered for local or systemic effect via the pulmonary route. Dry powder inhalers are bolus drug delivery devices that contain solid drug, suspended or dissolved in a non-polar volatile propellant or in dry powder inhaler that is fluidized when the patient inhales. These are commonly used to treat respiratory diseases such as asthma, bronchitis, emphysema and COPD and have also been used in the treatment of diabetes mellitus.



C. Pressurized MDIs-

A metered-dose inhaler (MDI) is a device that delivers a specific amount of medication to the lungs, in the form of a short burst of aerosolized medicine that is inhaled by the patient. The medication in a metered dose inhaler is most commonly a bronchodilator, corticosteroid or a combination of both for the treatment of asthma and COPD. The advantages of MDIs are their ease of transport, portability and small size, availability over a wide dosage range per actuation, dose consistency, dose accuracy, protection of the contents and that they are quickly ready for use.[5]

D. Nasal Drops-

Nasal drops are one of the most simple, promising and convenient systems developed for nasal delivery. More patient compliance is obtained with this dosage forms. The main disadvantage of this system is the lack of dose precision. It has been reported that nasal drops deposit human serum albumin in the nostrils more efficiently than nasal sprays.

E. Nasal Sprays-

Nasal sprays are developed for providing the accurate delivery of the drug medicament. Both solution and suspension formulations can be formulated into nasal sprays. Due to the availability of metered dose pumps and actuators, a nasal spray can deliver an exact dose from 25 to 200 µL.

F. Nasal Gels-

Nasal solutions or drops are having demerits that they get wiped out, so to overcome these problem nasal gels are formulated as it is having high-viscosity thickened solutions or suspensions. The advantages of a nasal gel include the enhance retention time, the reduction of post-nasal drip due to high viscosity, reduction of taste impact due to reduced swallowing, reduction of anterior leakage of the formulation, reduction of irritation by using soothing excipients and target delivery to mucosa for better absorption. [10]

NOSE TO BRAIN DELIVERY

An olfactory region of the nasal cavity remains directly attached to the frontal cortex (especially olfactory bulb) *via* olfactory nerves. Alongside the middle and the largest region of the nasal cavity i.e the respiratory region remain supplied with the trigeminal sensory neurons and blood vessels. As the drug is administered into the nasal cavity, firstly it passes through the mucociliary clearance in the vestibular region. [10] Later, the drug molecule reaches to the internal portion of the nasal cavity where it comes in contact with the blood vessels and neuronal network (olfactory and respiratory epithelium). The drug entered into the systemic circulation and distributed throughout the body as per the relative volume of distribution through the blood vessels. This systemic bioavailability remains as the minor route of drug transport to the brain in which the drug entered the brain *via* BBB. The primary route of brain drug delivery is the direct neuronal pathway, in which the drug follows intracellular and extracellular transport mechanism to enter into the different regions of the brain *via* olfactory and trigeminal sensory neurons. The exact pathways or mechanism of drug transport from the nasal cavity to the brain is still an uncleared and difficult issue for the scientists although; it was hypothetical to follow the combined way to enter into the brain. [15]

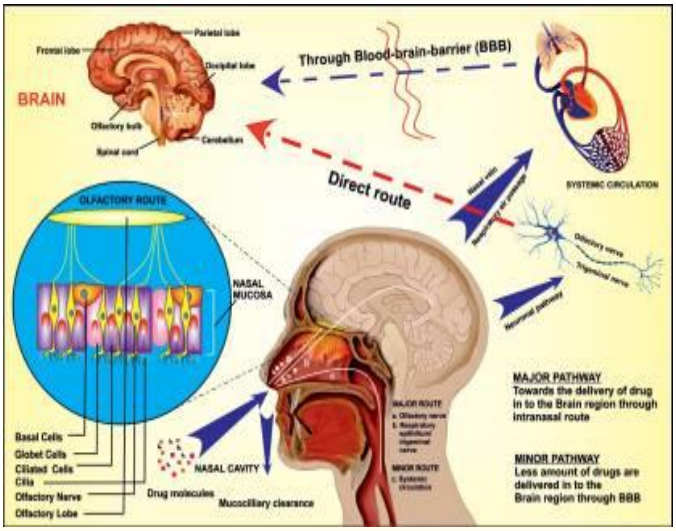


Figure: 4 Drug transport from the nasal cavity to the brain primarily through the neuronal pathway *via* olfactory and trigeminal sensory neurons and secondly through the systemic circulation.

Models for testing direct nose-to-brain delivery

Models of nasal drug delivery can be used for detecting and testing nasal drug absorption and permeation, for PK/PD studies, toxicological and electrophysiological studies, and also for assessment of drug transporter interaction and the nasal barrier. Models used for testing direct nose to brain delivery are depicted in the following table no.3.[16]

Table no.: 3 Models used for testing direct nose to brain delivery

Models	Description
In vivo models (characterization of nasal absorption and pharmacokinetic profile)	For efficiently studying the nasal delivery systems, adequate in vivo models are essential. It is important to study the anatomy of the nasal cavity of the animal before selecting appropriate animal model for an in vivo nasal absorption studies. Mouse and rat models are very useful for preliminary studies of nose-to-brain drug absorption, while rabbit, dog and sheep models are more frequently used for pharmacokinetic studies.
In vitro models (permit permeation and	Mainly two cell lines (RPMI 2650 and CaCo-2) are used to assess nasal absorption and permeability. It should be noted that these cellular models provide information on the transport across the cells or par cellular, but concurrent factors such as mucus, mucins, clearance, anatomical and physiological

diffusion studies)	factors involved in keeping the nose functional may also affect the absorption.
Ex vivo models (to study the nasal perfusion)	Determination of toxic effects of excipients and transmucosal transport of drugs are usually performed ex vivo using nasal mucosa from experimental or slaughtered animals. The well-known ex vivo nasal perfusion model for drug permeability is the Ussing chamber which is simple, very easy to monitor and maintain viability of tissues throughout the study. On the basis of permeability study, it is possible to quantify passive diffusion, active transport, efflux transport as well as identify and characterize (compound)-specific carrier-mediated routes of transport. [12]

PHARMACEUTICAL EXCIPIENTS [1]

In nasal formulations pharmaceutical excipients are selected accordingly to their functions and they are shown in the table no.4

Table no.: 4 Excipients used for the formulation of nasal and intranasal drug delivery system.

Excipients	Role	Examples
API	An agent providing a pharmacological activity and therapeutic effect.	Anti-allergic drugs, antihistamines, antipsychotic drugs.
Solubilisers	Aqueous solubility of drug is always a limitation for nasal drug delivery in solution. It was added into the nasal formulation for the purpose of proper drug mixing and solubilising of all the ingredients.	Conventional solvents or co-solvents such as glycols, small quantities of alcohol, Transcutol.
Antioxidants	An antioxidant was added in a small quantity which may be required to prevent drug oxidation.	Sodium bisulfite, butylated hydroxy toluene, sodium metabisulfite and tocopherol.
Humectants	It is added to prevent the formation of crusts and drying of mucous membrane occurs due to an allergic and chronic diseases.	Glycerin, sorbitol and mannitol.
Preservatives	Most nasal formulations are aqueous based so they need preservatives to prevent microbial growth and protect the degradation of the products.	Parabens, phenyl ethyl alcohol, benzalkonium chloride, EDTA and benzoyl alcohol.
Buffer	In the formulation buffer capacity may be required to maintain the pH in-situ to prevent the concentration of un-ionized drug available for absorption results into the delayed of its therapeutic effectiveness.	Citric acid, tartaric acid
Surfactants	Surfactants are added into nasal dosage forms for the modification of the permeability of nasal membranes, which may facilitate the nasal absorption of drug.	Tween 80, Sodium laurylsulphate
Penetration enhancers	Chemical penetration enhancers are widely used in the nasal drug delivery to penetrate or permeate the drug to the site of action which enhances its pharmacological activity.	Solvents,Alkyl methyl sulphoxides, Pyrrolidones , 1-Dodecyl azacycloheptan-2-one
Gelling agents	Gelling agents are used to increase the viscosity of the solutions which can act by prolonging the therapeutic effectiveness of the nasal preparations.	Hydroxypropylcellulose, HPMC,etc
Bioadhesive polymers	Bioadhesive polymers are the compounds which are capable of interacting with biological material through interfacial forces and being retained on such material for a longer period of time. They are also known as mucoadhesive polymers if the biological material is mucus membrane.	Cellulose derivatives, chitosan, pectin, starch.

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PHARMACEUTICAL APPLICATIONS [13]

Intranasal route of drug delivery system has been used for treating numerous disease condition like asthma, influenza diseases, allergic conditions and many more severe diseases and its provide a fast relief to a patients. Some of applications are listed in the table no.4.

Table no.: 5 Pharmaceutical applications of intranasal drug delivery system.

Systems	Examples
Local delivery	For the natural treatment of topical nasal disorders the drug is administered through nasal route.Among the most common examples are antihistamines and corticosteroidsfor rhinosinusitis, and nasal decongestants for cold symptoms.
Systemic delivery	An intranasal administration of drugs is a successful way for systemic availability as compared to oral and i ntravascular routes. Examples:analgesics (morphine), cardiovascular drugs as propranolol and carvedilol, ho rmones such as levonorgestrel, progesterone and insulin,anti-inflammatory agents as indomethacin and keto rolac, and antiviral drugs (acyclovir). Some examples which are available in the market include zolmitriptan and sumatriptan.
Nasal vaccines	Nasal mucosa is the first site of contact with inhaled antigens and hence, its use for vaccination, especially f or the treatment of respiratory infections, has been extensively evaluated.Examples of the human efficacy of intranasal vaccinesinclude those against i nfluenzaA and B virus, proteosoma-influenza, adenovirus-vectored influenza.
CNS drug delivery by nasal route	The delivery of drugs to the brain from the nasal route may occur via Olfactory neuroepithelium. Drug deliv ery through nasal route into CNS has been reported beneficial for several serious disorders such as Alzheimer's disease.

Research boundaries

It was observed that not even single IN therapy is available in the market for the treatment of the brain disorders also after the entire successful preclinical and clinical trial results, The contraindication may be due to the variability in the physiological responses and *in vivo* pharmacokinetic and Pharmacodynamic behaviors. Various factors are involved in the formulation such as use of various kind of excipients, characteristics of the drug, formulation parameters and experimental conditions which may affects the drug bioavailability in the brain. [17] Therefore, it is a requirement to develop a suitable delivery device which directly targets the drug to the olfactory region of the nasal cavity which facilitates the absorption of the drug through neuronal channels. The major reason behind these contradictory results might be the non-uniformity of the experimental practices. Furthermore, the etiology, pathophysiology and target site of various brain disorders is not exactly clearly specified, and the mechanism of the drug action inside the brain is also not sure which causes the delayed in the development of a promising system. [18,19]

CONCLUSION

Intranasal drug delivery delivery system having a numerous advantages over the other routes of drug administration. Intranasal route provides a huge surface area, non- invasive, permeable endothelial membrane, high supply of blood flow, bypassing the hepatic metabolism and more accessibility. In the upcoming years, various approaches are made to prevail over the limitation of this drug delivery system. This drug delivery system having a novel approach to deliver the drug to the affected site of a brain which is hardly possible by other routes. Nasal formulations are beneficial and show efficacious results in case of asthma patients and patients having respiratory tract infections. It can be used for all kind of patients. This drug delivery received an excellent deal of attention for its convenient, promising, and reliable way of systemic administration for drugs, chiefly for those drugs which are ineffective orally and administered by injections. Hence, this delivery system must gain more acceptance and popularity in the pharmaceutical market because it's offers high advantages, more patient compliance and shows faster pharmacological activity.

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