WORLD JOURNAL OF PHARMACEUTICAL RESEARCH
SJIF Impact Factor 7.523
Volume 6, Issue 9, 103-130. Review Article ISSN 2277– 7105

NASAL DRUG DELIVERY SYSTEM: A ROUTE FOR BRAINE TARGETTING

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Article Received on
27 June 2017,

Revised on 17 July 2017,
Accepted on 07 August 2017

DOI: 10.20959/wjpr20179-9096

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ABSTRACT

Present review highlights the potential of nasal mucosa as an administration route for targeting the central nervous system, the brain. Targeted drug delivery seeks to concentrate the medication in the tissues of interest while reducing the relative concentration of medication in the remaining tissues. Thus improving efficacy of the drug and reducing side effects. The nasal mucosa when compared to other mucous membranes is easily accessible and provides a practical entrance portal for small and large molecules. Intranasal administration offers rapid onset of action, no first-pass effect, no gastrointestinal degradation or lung toxicity and non-invasiveness application and also improves bioavailability. It is thought that olfactory route of drug transport, by pass the blood-brain barrier and allows the direct transport of drug from the nose to the brain. This review provides an overview of strategies to improve the drug delivery to brain via nasal mucosa and recent advances in this field.

KEYWORDS: Nasal Delivery, Brain targeting, Blood-Brain barrier (BBB), Central nervous system (CNS), Cerebrospinal fluid (CSF).

1. INTRODUCTION

Earlier the Nasal route has been used for the delivery of drugs in the treatment of local diseases. Nasal therapy has been recognized form of treatment in the Ayurvedic system of Indian medicines.[1] The early 1980s saw the introduction of nasal route as a promising systemic delivery alternative to other conventional drug delivery routes.[2] The delivery of

drugs to the brain has been fraught with issues of low bioavailability. The Central Nervous System which is made up of brain and the spinal cord do not have adequate access to the blood compartment due to a Blood Brain Barrier and others barriers. The lipophillic substances with molecular weight less than 600 Daltons are well known to permeate the BBB, which implies that the more lipophillic the molecules of drug the better is the permeability of the drug. The low metabolic environment of nose has potential to overcome the limitation of oral route and duplicate the benefit of intravenous administration. Nasal route has also been considered for the administration of vaccines. The interest in intranasal route for therapeutic purposes arises from the anatomical, physiological and histological characteristics of the nasal cavity, which provides rapid systemic drug absorption and quick onset of action. The main purpose for this type of study is to design a prolonged release dosage form to be used for targeted and controlled release of drug delivery.

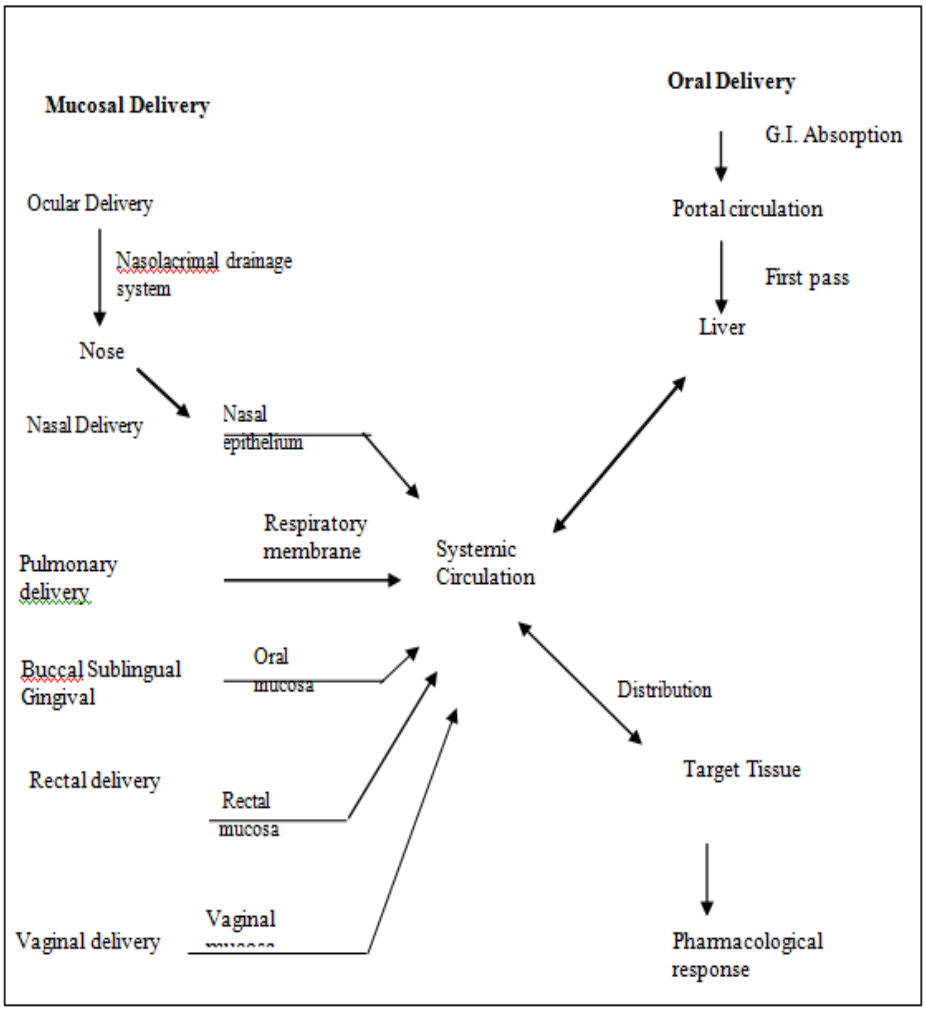

Fig.1: Various mucosal routes as potential pathway to bypass the hepatogastrointestinal first pass elimination associated with oral administration.

1.2 Advantages of Nasal Drug Delivery System

- Absorption of drug is rapid via highly vascularised mucosa.
- Bypass the BBB.
- Unsuitable drug candidates for oral route can be successfully given via nasal route.
- Non-invasive and easy for administration.
- Direct transport into systemic circulation and CNS is Possible.
- Degradation of drug observed in GIT is avoided.
- Side effects are reduced due to low dose.
- Patient convenience and compliance is improved
- Hepatic first pass metabolism is prevented.
- Convenient route for the patient on long term therapy.
- Onset of action is rapid.
- A self-administration is possible.[3,4]

1.2 Disadvantages

- Residence time of drug reduces due to the mucociliary clearance.
- It is not applicable to all drugs.
- Due to the lack of adequate aqueous solubility it shows insufficient absorption.
- Depending on aqueous solubility of drug it require high volume of dose (25-200ml).
- Some drugs can cause nasal irritation.
- Some drugs may undergo metabolic degradation in the nasal cavity.
- It is less suitable for chronically administered drugs.
- Those medications that needed sustained blood levels shouldn't be thought about for nasal delivery as there is no standard approach of formulating sustained release type nasal dosage forms.

1.3 Limitation[5,6]

- The histological toxicity of absorption enhancers used in nasal drug delivery system is not yet clearly established.
- Relatively inconvenient to patients compared to oral delivery systems since there is a clear stage of nasal irritation.
- Nasal cavity provides smaller absorption surface area when compared to GIT.

1.4 Profile of an 'ideal' drug candidate for nasal delivery[7]

An ideal nasal drug candidate should possess the following attributes:

- Appropriate aqueous solubility to provide the desired dose in a 25–150ml volume of formulation administration per nostril.
- Appropriate nasal absorption properties.
- No nasal irritation from the drug.
- A suitable clinical rationale for nasal dosage forms, e.g. rapid onset of action.
- Low dose. Generally, below 25mg per dose.
- No toxic nasal metabolites.
- No offensive odors/aroma associated with the drug.
- Suitable stability characteristics.

2. OVERVIEW OF NASAL MUCOSA

2.1 Nasal passage

The nasal passage, which runs from the nasal vestibule to the cavum, includes a depth of roughly 12-14cm. There are three distinct functional zones in the nasal cavity; namely vestibular, respiratory and olfactory areas. The vestibular area serves as a baffle system and its surface is covered by a common pseudostratified epithelium where the long hair may provide the function of filtering airborne particles. The respiratory area has a surface lined by a pseudostratified columnar epithelium and is normally covered by a dense layer of mucus that is constantly moving toward the posterior apertures of the bodily cavity by a robust system of motile cilia. The olfactory airway lies above the middle turbinate between the nasal septum and the lateral wall of the main nasal passage. The airway here is only about 1-2mm wide and is contiguous to the cribriform plate above. This region is generally free of inspiratory airflow.[8]

The nasal passage is composed of a horizontally skin-lined vestibule with the passage being directed upward and backward and is separated by a cartilaginous, bony nasal septum. The lateral wall is convoluted with strategically placed turbinatess that mold the air stream to their configurations and changing dimensions.[9]

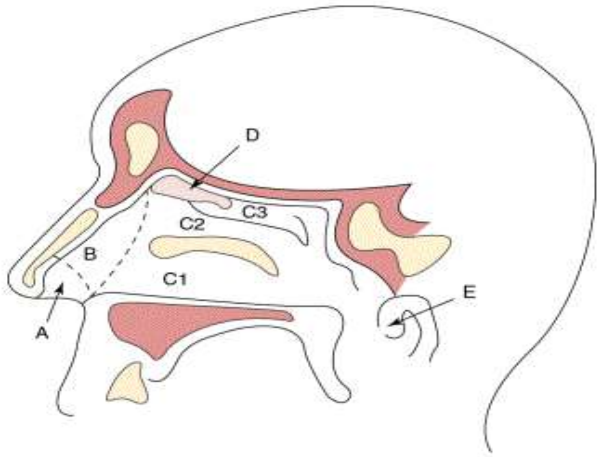

Fig.2: Schematic diagram of sagittal section of the nasal cavity A. nasal vestibule, B. atrium, C1. Respiratory area: inferior turbinate, C2. Middle turbinate, C3. Superior turbinate, D. olfactory region, E. nasopharynx.

2.2 Nasal epithelium[8]

The nasal membrane can be classified into olfactory and non-olfactory epithelia. The olfactory epithelium is a pseudostratified columna in type, and consists of specialized olfactory cells, supporting cells and both serous and mucous glands, the non-olfactory epithelium is highly vascular tissue covered by a ciliated pseudostratified columnar epithelium.

Numerous groups of microvilli can be seen microscopically among the groups of cilia. All microvilli are of short club like appearance and there are approximately 500 microvilli are called goblet cell. Another type of epithelial cell is observed in the free surface of the mucus membrane. They are rounded or elonged in shape and rough on the surface. These cells are defined as squamous cell.

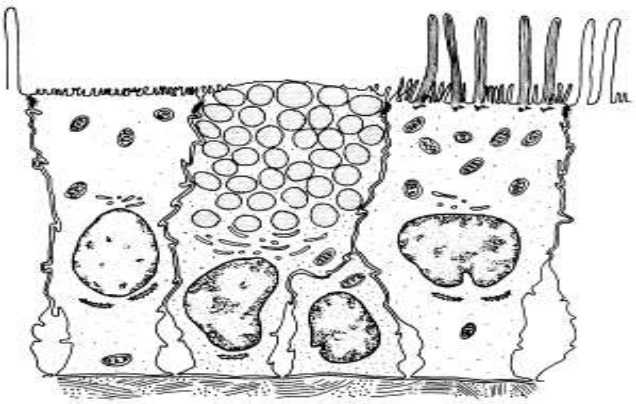

Fig.3: Transmembrane electron microscopic view of various cell types in the nasal epithelium.

2.3 Nasal secretions

The composition of the nasal secretions is complex and consists of a mixture of secretary materials from the goblet cells, nasal glands, lacrimal glands and a transuadate from plasma. In a clean, noninfected, non-allergic and non-irritated nose, the mucosa is covered by a thin layer of clear mucus, which is secreted from the mucus and serous gland in the nasal mucosa and sub mucosa. A total of approximately 1500-2000ml of mucus is produced daily, which contains 90- 95% water, 1-2% salt and 2-3% mucin. The mucus has a two-layer composition: the watery (sol) layer is located immediately adjacent to the mucosal surface, and the mucus (gel) layer, which is more superficial. Normal nasal secretions contain about 150mEq/L of sodium, 40mEq/L of potassium and 8mEq/L of calcium as well as about 600mg% of protein, including 57 mg% of albumins and 133 and 50mg% of immunoglobulin A (IgA) and G (IgG) respectively.[8]

In addition to mucous glycoproteins, nasal secretions contain a variety of other proteins, lysozomes, enzymes, IgA, IgE, IgG and albumins, kallikrein like substances, protease inhibitor, prostaglandin as well as serum proteins like gamma A-globulin, gamma g-globulin, albumin and siderophilin.[10]

The functions of mucus include

- Acts as a retainer for the substances in the nasal duct.
- Behaves as an adhesive.
- Has water holding capacity.
- Transports particulate matter.
- Exhibit surface electricity activity.
- Protect the mucosa.
- Acts as mesh with permeability.
- Allows heat transfer.

2.4 Nasal mucocoiliary clearance

Nasal mucociliary clearance is traditional defense mechanism of the cavity that clears mucus secretion moreover as substance adhering to the nasal mucous membrane (bacteria, allergens etc) and drains them into cavum for ultimate discharge into the digestive tube.[11]

There are approximately five ciliated cells for each mucous cell, with an average of 200 cilia extending from every ciliated cell on the surface of pseudo stratified columnar epithelium.[12] An individual cilium is approximately 5µm in length and 0.2µ in diameters, which moves at a frequency of about 20 beats/sec. Nasal clearance proceeds at an average rate of about 5-6mm/min.[13]

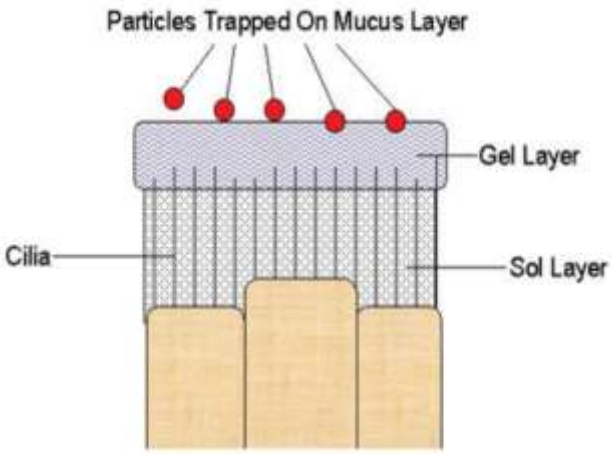

Fig.4: Mucocilliary clearance of the nose.

2.5 Nasal pH

The normal pH of the nasal secretions in the adult ranges approximately from 5.5 to 6.5, whereas in infants and young children it ranges from 5.0 to 6.7. During acute rhinitis, acute sinusitis and in the more acute phases of allergic rhinitis, the pH of the nasal secretion was found to be on the alkaline side and then shifted back to acidity, when the stage of clinical resolution was reached. The cause of nasal pH can be altered by the influence of cold or heat. Cold air produces a drift towards alkalinity, whereas heat yields a drift towards acidity. Greater drug permeation is typically achieved at a nasal pH scale that's less than the medication pKa as a result of beneth such conditions the penetrant molecules existing as a unionized species. As result of the pH scale of the cavum will alter the pH scale of the formulation and vice-versa, the perfect pH scale of a formulation ought to be inside 4.5-6.5.

2.6 Nasal blood flow

The nasal mucosa is highly vascular. The surface of epithelium is supplied with a dense network of erectile carvernous tissue, which is particularly well developed over the turbinates and septum. The arterial supply to the nose is derived from both the external and the internal carotid arteries. The terminal branch of the maxillary artery, which is a branch of the external

carotid, supplies the sphenopalatine artery, which in turn supplies blood to the lateral and medial wall of the nasal chamber. The anterior and posterior ethmoid branches come from the ophthalmic artery, which is a branch of the carotid artery. These vessels supply the anterior portion of the nose.

Constriction of the blood vessels would decrease blood flow and blood content in the nasal mucosa, whereas vasodilation would yield the opposite response. The penetration of the drug through the sinus mucosa is partly influenced by the blood flow in the region under normal and pathological conditions.

2.7 Nasal Pathophysiology

Diseases such as common cold, rhinitis, atropic rhinitis, and nasal polyposis are usually associated with mucociliary dysfunction, hypo and hyper secretions and irritation of the nasal mucosa, which can influence drug permeation and subsequently the therapeutic efficacy of the drugs administered nasally. In some subjects with a severe nasal allergy, an excessive response of the secretary system to irritants could wash away the drug solution administered into the nasal cavity before the nasal membrane absorbs the drug.

2.8 Nasal enzymes

Nasal mucus acts as enzymatic barrier to delivery of drugs because of the presence of a large number of enzymes. They are cytochrome p-450 dependent monooxygenases, lactate dehydrogenase, oxydoreductases, hydrolases acid phosphatase and esterase, NAD+ dependant formaldehyde dehydrogenases and aldehyde dehydrogenase; leucine amino peptidase, phosphoglucomutase, glucose-6-phosphate dehydrogenase, aldolase, lactate dehydrogenase, isocitric dehydrogenase, glutamic pyruvic transaminase and steroid hydroxylases. These enzymes are responsible for the degradation of drugs in the nasal mucosa and results in creation of pseudo-first pass effect, which hampers the absorption of drugs. In spite of these hurdles, the nasal route is still considered to be superior to the oral route. The level of amino peptidase present is much lower than that in the gastrointestinal tract. Various approaches have been used to overcome these degradations. These include the use of protease and peptidase inhibitors such as bacitracin, amastatin etc. apart from using enzyme inhibitors, efforts are focused on designing prodrug to increase stability and permeation of compounds.[8]

Although enzymes are known to exist in the nasal tissues, they do not appear to have a significant effect on the extent of absorption of most compounds except peptides. For example, nasal bioavailability in animal and man of progesterone, testosterone, estradiol, naloxone, propranolol and butorphanol is almost 100% of that of the intravenous administration. The above drugs have an oral bioavailability ranging from 20-30% for propranolol to 0% for other mentioned drugs. These low oral bioavailabilities are due to extensive metabolism of the compounds in gastrointestinal tract. Nasal administration of these compounds results in complete absorption because the level of the enzyme in the nasal tissue (mg/g) is very low and can be easily saturated with drug.[14]

3 Mechanism of Nasal absorption

The absorbed drug from the bodily cavity passes through the secretion layer. It's primary step in Absorption. Small, unchanged medicine simply meet up with this layer however gaint, charged medicine notice issue to cross it. The principle protein of the mucus is mucin. It has the tendency to bind to the solutes and hinders diffusion of drug molecules. Structural changes in the mucus layer are possible as a result of environmental changes like change in pH, temperature. Many absorption Mechanisms were proposed earlier but only two mechanisms have been predominantly used, such as[15]

(a) First mechanism: It is also known as the para cellular transport. It involves an aqueous Route of transport but slow and passive. There is an inverse correlation between intranasal Absorption and the molecular weight of water soluble compounds. Drugs having molecular Weight greater than 1000 Daltons shows poor bioavailability.

(b) Second mechanism: It involves transport through a lipoidal route. It is also known as the Trans cellular process. It is responsible for the transport of lipophilic drugs that show a rate Dependency on their lipophilicity. Drug also crosses the cell membranes by an active transport route via carrier-mediated means.

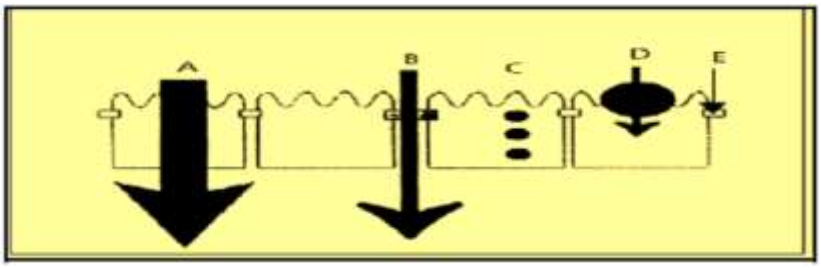

Fig.5: Drug transport pathways across the epithelium (A), Paracellular transport (B), Transcytosis (C), Carrier mediated transport (D), and Intracellular tight junction (E)

For example: chitosan, a natural biopolymer from shellfish is known to open the tight junctions between epithelial cells and facilitate drug transport.

4. PATHWAYS FOR REACHING THE DRUG TO BRAIN AFTER INTRANASAL ADMINISTRATION

Intranasal drug delivery appears to be a rapidly developing field. However, the exact mechanisms that can lead to efficient drug delivery to the brain following intranasal administration are not completely elucidated. An accumulating amount of evidence demonstrates that drug can reach the brain following intranasal administration via several direct and indirect pathways. The drug that is deposited in the nasal cavity can escape enzymatic degradation and the normal rapid clearance by the mucociliary system, undergo uptake to the cells of the olfactory or the trigeminal nerve pathways, or be absorbed into the systemic circulation. The olfactory pathway consists of the olfactory epithelium, olfactory tract, anterior olfactory nucleus, piriform cortex, amygdala, and hypothalamus. It has been suggested that drugs can reach the CNS via extracellular or intracellular transport along olfactory nerves, and that this pathway can be the major route for brain delivery of certain drugs following intranasal administration. Branches of the trigeminal nerve innervate the respiratory and olfactory epithelia of the nasal cavity. Thus, the trigeminal pathway, which is often overlooked by the researchers, can be an important direct pathway of drug delivery to the brain.[16,17,18,19] Three branches of the trigeminal nerve (ophthalmic division, maxillary division, and mandibular division) merge at the trigeminal ganglion, enter the CNS in the pons, and terminate in the spinal trigeminal nuclei in the brainstem. Therefore, cross-talk between the trigeminal and olfactory routes of brain drug delivery is possible. In addition to these direct pathways, drug can enter the brain indirectly, via blood vasculature and/or lymphatic system. The nasal mucosa is highly vascularized, and the blood vessels (lined with continuous and fenestrated endothelium) allow passage of drugs (in free or maybe even in particle-encapsulated form), following nasal drug administration in nano-drug delivery systems. The drug that has been absorbed into the systemic circulation has to cross the BBB in order to reach the CNS. It is possible that the BBB is breached (temporarily or for prolonged periods of time, in small or big regions of the brain) in certain pathological conditions.[20,21] Therefore, efficiency of this indirect pathway of drug delivery to the brain following intranasal administration can differ in individual patients, or depending on the applied disease model in preclinical in vivo studies.[22]

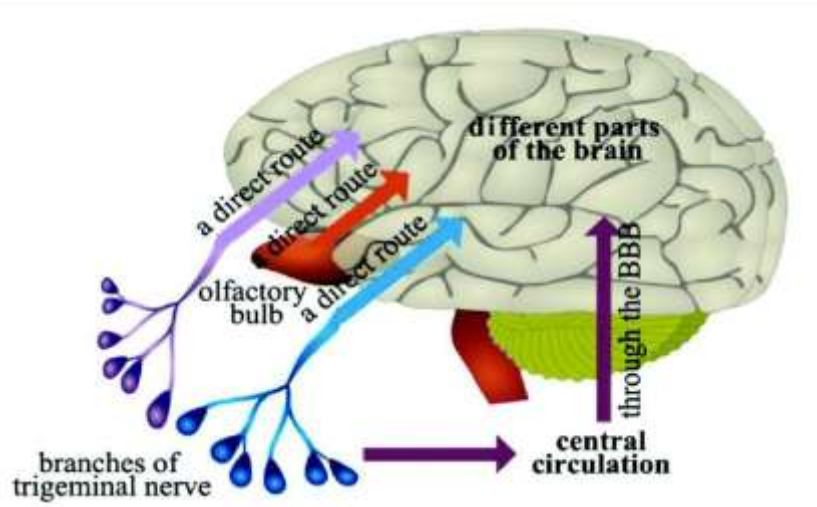

Fig6: Pathways for reaching the drug to brain afrter intranasal administration.

5 FACTORS INFLUENCING THE ABSORPTION OF MEDICINE THROUGH NASAL EPITHELIUM

1) Physicochemical Properties of the drugs

- Drug molecular weight and size.
- Drug solubility and dissolution rate.
- pka and partition coefficient.
- Chemical form.
- Physical state: particle size and morphology.

2) Formulation properties of drugs

- Drug conc., Dose, Volume of administration.
- Physical form of formulation.
- Formulation pH.
- Formulation osmolarity.
- Formulation excipients.

- Solubilizers.
- Buffer components.
- Antioxidants.
- Flavor/taste.
- Preservatives.
- Humectants.
- Gelling/Viscofying agents.

3) Biological factors

- Nasal blood flow.
- Enzymatic activity in the nose.
- Physical condition of the nasal mucosa.
- Volume of administration.
- Site of deposit of formulation in the nose.

5.1 Physicochemical properties of drugs

Various physiochemical characteristic of drug have an impression on nasal absorption of the drug.

i) Relative molecular mass and size

Extent of the absorption of the drug depends on relative molecular mass notably for hydrophilic compounds. Nasal route is appropriate for economical delivery of medicine up to 1000 Daltons. Absorption reduces the significantly if the molecular weight is greater than 1000 Daltons except with the use of penetration enhancers. It has been reported that a good linear correlation exists between the log percentage drug absorbed nasally and the log molecular weight of water-soluble compounds suggestion the participation of aqueous channels in the nasal absorption of water-soluble molecules.

It has been reported that particle size greater than 10µm are deposited in the nasal cavity. Particles that are 2 to 10µm can be retained in the lungs and particles of less than 1µm are exhaled.[23]

ii) Solubility and Dissolution

Drug solubility could be a major issue determinative absorption of drug through biological membranes. It limits a formulator's ability to formulate a product if the drug isn't sufficiently soluble within the desired vehicles. As nasal secretions square measure a lot watery in nature, a drug ought to have applicable liquid solubility for increased dissolution. Particles deposited in the nostrils need to be dissolved prior to absorption. If the drug remains as particles in nostrils, or if they are cleared away from the nasal cavity, one may not observe absorption of the drug.

iii) Partition coefficient and pKa

Jiang et. al. conducted a study to find out the quantitative relationship between the physicochemical properties of drugs and their nasal absorption, using diltiazem hydrochloride and paracetamol as model drug. The result showed that a quantitative relationship exist between the partition coefficient and nasal absorption constant. As per the hydrogen ion concentration (pH) partition theory, unionized species square measure absorbed higher compared with ionized species and it holds true within the case of nasal absorption. The extent of absorption is pH dependent, being higher at a pH lower than the pKa and decreases beyond the pKa.

In general, the authors found that nasal absorption will increases with the lipophilicity of permative. Various studies indicate that the drug concentration in the cerebrospinal fluid (CSF) rise with an increase in lipophilicity or partition coefficient of the drugs. The nasal absorption of weak electrolytes such as salicylic acid and aminopyrine was found to be highly dependent on their degree of ionization. Although for aminopyrine, the absorption rate increased with the increase in pH and was found to fit well to the theoretical profile, substantial deviations were observed with salicylic acid. The authors concluded that perhaps a different transport pathway, along with the lipoidal pathway, existed for salicylic acid. Similarly when the absorption of benzoic acid was studied at pH 7.19 (99.9% of the drug existed in ionized form) it was found that >10% of drug was absorbed indicating that the ionized species also permeates through nasal mucosa. Based on all of this observation, the authors discount partition coefficient as a major factor governing nasal absorption and supported that other transport pathway for hydrophilic drug might be of importance.

iv) Chemical form

The chemical type during which a drug is given at the mucous membrane necessary in determinant its absorption. For example, conversion of drug into salt or ester form can alter its absorption. Huang et. al. studied the structural modification of drug on absorption. It was determined that in situ nasal absorption of carboxylic acid ester of L-tyrosine was considerably bigger than that of L-tyrosine. This development is related to the rise in lipophilicity following esterification that increases the speed and extent of absorption.

v) Physical state: particle size and morphology

Particle size and morphology of drug particles constitute important properties for particular nasal drug products. Particle size and morphology are related to the rate of drug dissolution

and should be controlled to obtain suitable drug dissolution properties in the nostrils. Too fine particles, below five microns may be inhaled into the lungs and should be avoided for the nasal products. Generally, particles in the 5-10 micron range are deposited in the nostrils.

5.2 Formulation properties of drugs

The formulation properties that affect absorption of drugs are.

i) Drug concentration, dose and dose volume

Drug concentration, dose and dose volume of administration are three interconnected parameters that impact the performance of nasal delivery system. Nasal absorption of L-tyrosine was shown to extend with drug concentration in nasal insertion experiments. However, in another study, painkiller was found to soak up at a relentless rate as a operate of concentration.

Several studies have reportable in impact of drug dose on nasal absorption, e.g. calcitonin, desmopresin, secretin. In general, higher nasal absorption or therapeutic effect was observed with increasing dose. It is important to note how the dose is varied. If the drug is increasing by increasing formulation volume, there could be a limit on what extent nasal absorption is often magnified. The nostril can retain only a limited volume, beyond which a formulation wile drain out of the nasal cavity. The ideal dose volume range is 0.05-0.15ml with an upper limit of 0.20ml.

ii) Physical form of formulation

Nasal drug absorption depends on the physical form of the formulation. A powder form was found to be more effective than liquid formulations in delivering insulin in rabbits. Resta et al who compared the powder reported a similar finding and solution dosage forms of sodium cromoglycate in humans suffering with allergic rhinitis. Their data show that both powder and solution forms were effective for treatment and suggested that the powder form was somewhat better than solution because powder is readily washed out with the nasal secretions.

Another important parameter in formulation development is a viscosity of the formulation. Generally a more viscous formulation will provide less efficient systemic nasal drug delivery. Harris et al studied the nasal delivery of desmopressin and reported that although the addition of viscous agent to nasal formulations may produce a somewhat more sustained effect. It would seem logical that more viscous formulations e.g. gel should be more appropriate for

those drugs which cause unpleasant taste in the mouth via a nasal drip of solution or spray formulations. Nasal drip would be minimized from viscous formulation.[24]

iii) Formulation pH

The pH of the formulation as well as that of nasal surface can affect a drug's permeation. The pH of nasal formulation is important for the following reasons:

- To avoid irritation of the nasal mucosa.
- To permit the drug to be obtainable in unionized kind for absorption.
- To forestall the expansion of unhealthful microorganism within the nasal passage.
- To sustain normal physiological ciliary movement.
- To maintain functionality of excipients such as preservatives.

Lysozymes are found in nasal secretions, which is responsible for destroying certain bacteria at acidic ph. under alkaline conditions, lysozyme is inactivated and the nasal tissue is susceptible to microbial infection. It is therefore advisable to keep the formulation at pH of 4.5 to 6.5 keeping in mind the physicochemical properties of the drug as drugs are absorbed in the unionized type and additionally to avoid nasal irritation.

iv) Formulation osmolarity

Drug absorption is suffering from tonicity of the formulation. Shrinkage of the epithelial cells has been observed in the presence of hypertonic solution. Hypertonic saline solution also inhibits or ceases ciliary activity. Low pH has similar results as that of hypertonic solutions. Typically associated isotonic formulation is preferred.

V) Formulation excipients

Solubilizers

Aqueous solubility of a drug is always a limitation for nasal drug delivery in solution. Conventional solvents or cosolvents such as glycols, small quantities of alcohol, medium chain glycerides and labrasol (saturated polyglycolized C8-C10 glycerides) can be used to enhance the solubility of drugs. Other options include the use of surfactants or cyclodextrins that serve as a biocompatible solubilizer and stabilizer in combination with lipophillic enhancers. In such cases, their impact on nasal irritancy should be considered.

Buffer component

Nasal formulations are generally administered in little volumes starting from 25 to 200µl being the foremost common dose volume. Hence, nasal secretion may alter the pH of the administered dose. This can have an effect on the concentration of unionized drug offered for absorption. Therefore, associated adequate formulation buffer part is also needed to keep up the pH.

Antioxidants

Depending upon the stability profile of a given in the formulation chosen, it may be necessary to use antioxidants to prevent degradation. Commonly used antioxidants are sodium metabisulphite, sodium bisulphate, butylated hydroxytoluene and tocopherol. Usually antioxidants are used in small quantities and they may not affect drug absorption or cause any nasal irritation. Chemical/physical interactions of antioxidants and preservatives with drugs, excipients, manufacturing equipment and packaging components should be considered as a part of formulation development program.

Flavor/taste

Some drugs may present problems with regard to aroma and taste. Taste becomes a problem if a substantial amount of the formulation drips into the back of throat. The choice of such agents will depend on drug being developed.

Preservative

Most nasal formulation are aqueous based and need preservatives to prevent microbial growth. Parabens, benzalkonium chloride, phenyl ethyl alcohol, and benzoyl alcohol are some of the commonly used preservative in nasal formulations. Van De Donk et. al. has shown that mercury-containing preservatives have a fast and irreversible effect on ciliary movement and should be used in nasal systems. Preservatives are based in small quantities and are not likely to affect drug absorption.

Humectants

Many allergenic and chronic diseases are often connected with crusts and drying of mucous membranes. Certain preservatives/antioxidants among the other excipients are also likely to cause nasal irritation especially when used in higher quantities. Adequate intranasal moisture is essential for preventing dehydration. Therefore, humectants are often values added aren't

probably to have effect on drug absorption. Some common humectants uses embody glycerin, sorbitol and diuretic drugs.

Gelling/viscofying agents

Some formulations need to be gelled or made more viscous to increase nasal residence time. According to a study by Pennington et al. increasing the solution viscosity may provide a means of prolonging the therapeutic effect of nasal preparations. Suzuki et al showed that a drug carrier such as hydroxypropylcelulose was effective for improving the absorption of low molecular weight drugs but did not produce the same effect for high molecular weight peptides. Use of combination of carries is often recommended from a safety (nasal irritancy) point of view.

5.3 Biological factors

i) Nasal blood flow

The blood vessels in the nasal mucosal membrane play an important role in the thermal regulation and humidification of the inhaled air. The nasal membrane is provided by rich vasculature and a dense network of erectile cavernous tissue that is especially well developed over the turbinates and septum. The extremely vascular nature of the membrane makes it a decent membrane for drug absorption.

The nasal vascular bed is so designed that a rapid exchange can be made for fluid and dissolved substances between blood vessels and nasal tissue. The nasal blood flow is affected by many external and physiological factors like close temperature, humidity, presence of vasoactive medicine, trauma and inflammation additionally some psychological factors like fear, anxiety and frustration.

ii) Enzymatic activity in the nose

The nasal epithelial tissue includes a defensive catalyst barrier against the entry of xenobiotics. Biotransformation of foreign compounds within the nasal tissue layer of animals has shown intensive cytochrome P450 dependent metabolism.

Many compounds are known to be metabolized by the nasal P450 dependent monooxygenase system, e.g. nasal decongestant, anaesthetics, alcohol, nicotine. Along with the P450 monooxygenase system, several other enzymes exist in the nasal secretions e.g. lactate dehydrogenase, oxydoreductases, hydrolases, acid phosphatadase and esterases, which are

responsible for metabolism of certain drugs. This can affect drug delivery for both systemic as well as local drugs. Sometimes it may be necessary to add enzyme inhibitors to reduce enzymatic drug loss.

iii) Physical condition of the nasal mucosal

The condition of the nasal mucosal can have an important effect on drug absorption. In individuals laid low with many nasal allergies, associated excessive nasal secretion will wash away the formulation before the drug features a probability of obtaining absorption through the membrane or before acting domestically. These situations may have to be taken into account during the drug development process.

iv) Volume of administration

The optimal formulation volume for nasal administration is 25-200µl per nostril. Large volume will drain out of the nose. The most practical volume is 100µl per nostril. During the development process, it may be important to study the volume effect on drug absorption.

v) Site of deposit of formulation in the nose

Deposition of formulation within the anterior portion of the nose provides a biigger nasal duration and permits additional contact time between drug and also the mucus membrane. Depositing a formulation in the posterior part of the nose will allow a faster ciliary clearance of the formulation. The porousness of the posterior nasal passage is mostly on the top of the anterior passage. Slow absorbing drugs should be deposited in the anterior part of the nose and fast acting drug in the posterior part of the nose.

6. DRUG DISTRIBUTIONS AND DEPOSITION

Drug distribution within the nasal cavity is a very important issue that affects the potency of nasal absorption. The mode of drug administration may affect this distribution, which in turn can help to determine the absorption efficiency of a drug. Significant differences were observed in drug distribution with such different nasal delivery system as nose drops, plastic bottle nebulisers atomized pumps and metered dose pressurized aerosol. Among the systems evaluated, the system that gave a constant dose and a very good mucosal distribution was found to be best.

Nasal deposition of particles is related to the individual's nasal resistance to airflow. With nasal breathing nearly all particles having an aerodynamic diameter of 10-20µm are deposited

on the nasal mucosa. Deposition in both the poorly absorptive stratified epithelium of the anterior atrium and in the posterior nasopharyngeal region should be avoided; as such deposition leads to drug loss to stomach by swallowing. Insoluble particles deposited in the main nasal passage are likely to be carried back by the ciliary movement and dispatched to the stomach. If the drug is introduced as vapour or a soluble particle, it may readily pass into the lining secretions and then be absorbed into the blood. The site of drug deposition within the nasal cavity is dependent upon the types of delivery system and technique used in application.

7 ENHANCEMENT OF NASAL DRUG ABSORPTION

Several ways are wont to facilitate the nasal absorption of drugs.

7.1 Structural modification

The chemical modification of drug molecule has been usually accustomed modify the chemistry properties of a drug and even be utilized to enhance the nasal absorption of drug.

7.2 Salt or ester formation

The drug could be converted to form a salt for a better nasal permeability. For example, nasal absorption may be improved considerably by forming a salt with accumulated solubility in nasal fluid or ester with improved uptake by nasal epithelium.

7.3 Formulation design

It is yet another approach to enhance nasal delivery of drug and increase their nasal absorption. Bioadhesieve agents such as methylcellulose, carboxymethylcellulose, hydroxypropylcellulose, and polyacrylic acid have been used. This enhancement is probably due to the increase in drug residence time and higher local drug concentration in the mucus lining on the mucosal surface. The bioadhesive polymers swell by absorbing water from the mucus layer in the nasal cavity, thereby forming a gel-like layer in which the polymer bonds with glycoproteins in the mucus. Recent advances have resulted with glycoproteins in formulations such as erythrocytes loaded with propranolol as well as proliposomal delivery of propranolol by nasal route.

7.4 Use of absorption enhancers

Many researchers have claimed the discovery of enhancers, which eliminate all nasal absorption problems. When it becomes tough for a nasal product to attain its needed

absorption profile, the employment of absorption enhancers is suggested. The selection of absorption enhancers is based upon their acceptability by regulatory agencies and their impact on the physiological functioning of the nose. Absorption enhancers is also needed once a drug exhibit poor membrane permeableness, massive molecular size, lack of lipophilicity and protein degradation by aminopeptidase's. Once suitable enhancer is identified, its optimal concentration should be experimentally determined. Generally higher concentrations of enhancer's are likely to result in nasal irritation and damage to the nasal mucosa. On the other hand, lower enhancer concentration would generally provide lower or no improvement of absorption.

8. Ideal characteristic of absorption enhancers

The following characteristic should be considered in choosing absorption enhancers

- The enhancer should be pharmacologically inert at concentration used.
- It should be non-irritating, nontoxic and nonallergic.
- If the enhancer has any effect on the nasal mucosa, it should be completely reversible.
- The enhancer should be a potent absorption promoter therefore requiring only small amounts to be used.
- It should be compatible with the drug and formulation adjuvant.
- It should be able to remain in contact with the nasal mucosa long enough to achieve a maximal effect.
- The enhancer should not have any offensive odor or taste.
- It should be relatively inexpensive and readily available.

9. Mechanism of nasal drug absorption enhancers

Precise mechanism of enhancer effect is not known. However, it is generally believed that enhancers may show their actions via one or both of the following mechanisms.

Physiochemical effects

Some enhancers can alter the physiochemical properties of a drug in the formulation. This can happen by altering the drug solubility, drug partition coefficient, or by weak ionic interaction with the drug. This mechanism of drug absorption enhancement is desirable because it can be effective with the lowest potential of toxicity.

Membrane effects[25]

Many enhancers show their effects by affecting the nasal mucosal surface. It should be emphasized that these effects are not necessarily harmful. In most cases the enhancer's effects are transient with no lasting or pathological consequences. The final decision should take into consideration the benefit to risk ratio.

Generally, the absorption enhancers act via one of the following mechanism:

- Inhibit enzyme activity.
- Reduce mucus viscosity or elasticity.
- Decrease mucociliary clearance.
- Open tight junctions and.
- Solubilize or stabilize drug,

Table No.1: Various absorption enhancers

Sr. No.	Enhancers	Mechanism of Action
1.	Ethyl cellulose	1) Prolong the residence time of drug in nasal cavity 2) Sustain the release of drug due to high viscosity 3) Act as absorption enhancer 4) Effectively increase intranasal bioavailability 5) Strong mucoadhesive properties of ethyl cellulose increases residence time of drug in nasal passage.
2.	EDTA	Increases paracellular transport by removal of calcium thus affecting the permeability of the tight junction.
3.	Fatty acid salts	1) Act to create intercellular space by temporarily extracting calcium ions from the nasal mucosa. 2) Inhibit leucine aminopeptidase activity.

10. DELIVERY SYSTEM FOR INTRANASAL ADMINISTRATION AND DRUGS GIVEN BY NASAL ROUTE[26]

There are several types of drug delivery system, which have been long used for the delivery of drugs to nasal cavity such as nasal spray, nasal drops, insufflators, and saturated cotton pledge Examples of certain drugs along with their delivery system are mentioned below:

Table No.2: Delivery devices used in nasal drug delivery.

Drugs	Delivery Devices
Adrenal corticosteroids	Nasal spray, Nasal jellies
Antihistamines	Nasal spray, Nasal drops
Insulin	Metered pump sprayer, Nasal spray
Gentamicin	Nasal spray
Isosorbide dinitrate	Nasal spray
Nitroglycerine	Metered dose spray
Vitamin B12	Nasal Drops, Insufflators
Xylometazoline	Nasal Spray, Nasal drops
Oxytocin	Nasal spray, Aerosol activated spray, Nasal drops

11. NASAL FORMULATIONS

The nasal formulation along with the physicochemical properties of the drug and anatomical and physiological factors of the nasal cavity affect the nasal absorption of drug molecules.[27] Most conventional nasal formulation constitutes the nasal drops, which is simple and convenient system for nasal delivery. Although solutions are easy to use, the drug solution instilled in the nose is eliminated within 15 min, because of the mucocilliary clearance, thus leads to a low bioavailability especially for large hydrophilic drugs. The duration of the therapeutic effect is often short, and hence frequent dosing is necessary.

Nasal therapy would be significantly improved if the nasal residence time of the drugs could be increased. To prolong residence time at absorption site and thereby facilitate the uptake of the drug, a number of strategies have been investigated. For example the use of suspension, ointments, powders, has been reported to increase the contact time within the mucosa in comparison to solution.

11.1 Nasal Drops[28]

Nasal drops are one of the most straightforward and convenient systems developed for nasal delivery. The main disadvantage of this method is that the lack of the dose preciseness and so nasal drops might not be appropriate for prescription products. It has been according that nasal drops deposit human serum albumin within the nostrils a lot of expeditiously more efficiently than nasal sprays.

11.2 Nasal sprays

Both solution and suspension formulations can be formulated into nasal sprays. Due to the provision of metered dose pumps and actuators, a nasal aerosol container can deliver a definite dose from 25 to 200µm.[29] The particles size and morphology (for suspensions) of

the drug and viscosity of the formulation determine the choice of pump and actuator assembly.

11.3 Nasal Gels

Nasal gels are high-viscosity thickened solutions or suspensions. Until the recent development of precise dosing device, there was not much interest in this system. The advantages of a nasal gel includes the reduction of post-nasal because of high viscosity, reduction of taste impact due to reduced swallowing, reduction of anterior discharge of the formulation, reduction of irritation by exploitation soothing/emollient excipients and target to tissue layer for higher absorption.

11.4 Suspensions

The nasal absorption of the human metal internal secretion was found to be higher from suspension compared to the opposite dosage forms. This is often because of exaggerated concentration gradient for drug diffusion across nasal membrane.

11.5 Emulsions and ointments[30]

Only a restricted quantity of labor has been reported on the event of emulsion and ointment for nasal drug delivery. By their nature, they would seem to be more appropriate for locally acting drugs. However, their use for systemic drugs cannot be ruled out. Major disadvantages of nasal emulsion and ointments embrace poor acceptance by patients, developments efforts required are high, and issues in delivering precise doses from metered dose nasal actuators. The nasal drug delivery systems, however, have not been used extensively because of some drawbacks, such as low patient's compliance.

Several new preparations are developed for nasal route not solely to prolong the contact time of the vehicle on nasal mucosal surface however conjointly to block the drug clearance like,

- Microspheres.
- Liposome and proliposomes.
- Mucoadhesive drug delivery systems.

11.6 Microspheres

Drug delivery systems designed to provide a therapeutic agent in the needed amount, at the right time, at the proper location in the body, in a manner that optimizes efficacy, increases compliance and minimizes side effects. Microspheres increase the residence time in nasal

cavity. Several bioadhesieve microsphere systems (such as degradable starch microspheres, serum albumin microspheres) have been studied for administration of the insulin, human growth hormone, oxytocin and propranolol. It had been demonstrated that a significant improvement in bioavailability could be achieved when drugs were administered as bioadhesives microsphere without absorption enhancers.[31] Illum et al in their in vivo studies using formulations including bioadhesives microspheres for nasal administration in humans have reported that intranasal clearance from microspheres systems were 3 hours or longer while the half time for the clearance of control solutions or powders were approximately 15min.[32]

Starch microspheres are not only biodegradable but also show a high degree of swelling when in contact with aqueous media. It forms a gel like system, which prolongs residence time in the nose and contact with nasal mucus significantly.[33]

11.7 Lipopsomes and proliposomes[34]

The use of liposomes as nasal drug delivery system has been advocated by Vyas and Goswani as a result of the subsequent advantages:

- The component of the liposomes are themselves considered to be bioadhesives, there is no need to add bioadhesives material.
- Multilamellar liposomes may fuse in nasal mucosa and gradual fusion of the lamellae and membrane ends up in sustained and controlled discharged of drug.
- Liposomes due to their flexible nature do not abstract the nasal airways.

For the drug of very short biological half-life, the fast absorption is unfavorable to sustain the drug level within the circulation and therefore the large mucociliary clearance of the nasal tissue layer could cause poor absorption of certain drugs. In this respect, liposomes are also known to sustain the release of entrapped drugs and to decrease the mucociliary clearance of the drugs due to their surface viscosity. Therefore more effective and sustain absorption of drug would be attained by administering the drug containing liposomes intranasally.

In spite of positive expectation of the liposomes, however aqueous dispersion of liposomes has a variety of disadvantages including.

- Phospholipids hydrolysis.
- Phospholipids oxidation.
- Decomposition of encapsulated drug and.

- Aggregation, sedimentation and fusion of liposomes.

In order to overcome these disadvantages Payne et. al. introduced proliposomes, which offer an elegant alternative to conventional liposomal formulation. Proliposomes are prepared by adding drops of organic solution of drug and lipid onto microporous sorbitol with subsequent vaccum drying. Proliposomes have free flowing flow ability and immediately form a liposomal dispersion on adding water.

11.8 Nasal Powder

This dosage form may be developed if solution and suspension dosage forms cannot be developed e.g., due to lack of drug stability. Local application of drug is another advantage of this system. Many reports have appeared describing powder dosage forms as microspheres as colyophilized powder using bile salts, cyclodextrins, starch, cellulose and their derivatives for nasal delivery. However, the suitability of the powder formulation is dependent on the solubility, particle size, aerodynamic properties and nasal irritancy of the active drug and/or excipients.[35] Dry powder formulations are potentially superior to liquid formulations in that they do not support microbial growth and are more stable, eliminating the necessity of the refrigerated storage. Dry-powder nasal formulations are the most widely used in situ gelling formulations and have been historically used mostly for locally acting drugs. Their advantage over liquid formulations is as follows:

- They enable higher drug payload per dose delivered.
- They prolong absorption time in nasal cavity.
- They reduce temperature sensitivity during product distribution and storage.
- Superior stability of the formulation.[36]
- Absence of preservatives.

Ishikawa et al. proved that insoluble powder formulations improve nasal bioavailability predominantly by retarding drug elimination from the absorption website and appears to be effective for nasal general drug delivery.

A dry powder vaccine formulation containing whole inactivated influenza virus (WIIV) and a mucoadhesive compound suitable for nasal delivery was prepared. Powders containing WIIV and either lactose or trehalose were produced by lyophilisation. A micro-ball mill was used to reduce the lyophilized cake to sizes suitable for nasal delivery.

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