



A REVIEW ON: DRUG DELIVERY THROUGH NASAL ROUTE

Roshani A. Sawarkar¹, Shrikant D. Pande², Nikita Jain³, Dipti Padole⁴, Tusharkumar Ingle⁵

¹²³⁴⁵M. Pharm, Vidyabharti college of Pharmacy, Amravati, C. K. Naidu Road, Camp, Amravati, Maharashtra, India

Abstract: Today, there is a lot of interest in the use of the nasal route for the delivery of difficult-to-deliver medications including tiny polar compounds, vaccines, hormones, peptides, and proteins. The nasal cavity is ideally suited for systemic drug delivery because of its high permeability, high vasculature, low enzymatic environment, and avoidance of hepatic first pass metabolism. Due to the need for quick and/or precise therapeutic targeting of the brain, numerous drug delivery methods for nasal application of liquid, semisolid, and solid formulation are being researched. These disorders include Parkinson's disease and Alzheimer's disease. The distribution of biotechnological products such as proteins, peptides, hormones, and DNA plasmids for DNA vaccines to provide increased bioavailability is ideally suited for it. This study aims to cover various aspects of nasal absorption, bioavailability barriers, techniques to enhance nasal absorption, current advancements in nasal dosage form design, and applications of nasal drug delivery system.

Keywords: Mucociliary clearance, nasal route, nasal drug delivery, mucoadhesion.

1. INTRODUCTION

Because the nasal mucosa is permeable to more compounds than the gastrointestinal tract, lack of pancreatic and gastric enzymatic activity, neutral pH of the nasal mucus, and less dilution by gastrointestinal contents have all been considered as potential administration routes to achieve faster and higher levels of drug absorption [1,2]. Several medications now have improved systemic bioavailability when administered orally rather than through the nasal route, according to recent studies. In the Ayurvedic systems of Indian medicine, nasal therapy is a recognised kind of treatment and is also known as "NASAYA KARMA" [3]. Nasal medication administration has been given new life despite being used for thousands of years. For medications like proteins and peptides that are effective at low dosages and have no minimal oral bioavailability, it is a viable delivery strategy. The mucociliary clearance process in the nasal cavity causes peptides and proteins to migrate quickly away from the absorption site, which contributes to the low degree of absorption of these substances via the nasal route. [4] The nasal route is convenient for self-medication and avoids the hepatic

first pass elimination associated with oral delivery. Over the past few decades, pharmaceutical scientists and physicians have paid more and more attention to the viability of medication delivery through the nose. Animal models have been used to test a variety of drug candidates, from tiny metal ions to massive macromolecular proteins. It has been proven that administering some hormones and steroids via the nose caused a more thorough absorption. [5,6]. This shows the potential benefit of using the nasal route for both local effects and systemic pharmaceutical administration. Nasal medication administration has been used for a long time to achieve both topical and systemic effects. Topical application has led to the development of a wide range of various drugs, including corticoids, antihistamines, anticholinergics, and vasoconstrictors, for the treatment of congestion, rhinitis, sinusitis, and related allergy or chronic disorders. Recent years have seen an increase in research on the nasal route, particularly on nasal application for systemic medication administration. [7]. There are currently only a few nasal delivery devices available on the market to deliver therapies into the nasal cavities, including pressurised MDIs, dry powder inhalers, aqueous nasal sprays, nasal gel pumps, and multiple- or single-dose formulations of nasal drops. Nowadays, intranasal administration is used to treat conditions such as osteoporosis, nocturnal enuresis, migraine, smoking cessation, acute pain alleviation, and vitamin B12 deficiency. Cancer treatment, epilepsy, anti-emetics, rheumatoid arthritis, and insulin-dependent diabetes are some more examples of therapeutic areas in development or with potential for nasal delivery. This review article offers a concise overview of the benefits and drawbacks of nasal medication delivery systems, as well as information on the anatomy of the nasal cavity, the mechanism of nasal absorption, potential obstacles to nasal absorption, and possible solutions.[8]

2. ANATOMY AND PHYSIOLOGY OF NOSE

The nose serves as the body's main respiratory tract entry, allowing air to enter to support breathing [9]. A cartilaginous wall known as the nasal septum divides the nasal cavity, which is 120–140 mm deep and extends from the nasal vestibule to the nasopharynx. The nose's overall capacity is between 16 and 19 ml, and its surface area is roughly 160 cm² [10]. The nose acts as a conduit for warm, humid air to enter the lungs. It is the main organ for removing particles from inspired air, and because it makes inspired air contact with the mucous-coated membrane, it also acts as the body's first line of defence against infection. Vestibular, turbinate, and olfactory areas are the nose's three principal structures. (Figure 1). The nasal cavity's smallest portion is located in the anterior, or vestibular, area of the nose. Most of this area is covered by vibrissae, making it capable of filtering out airborne particles with an aerodynamic particle size greater than 10 μm. The surface lining in the vestibular region transitions from skin at the beginning of the passage to a stratified squamous epithelium [3, 11]. There are superior, middle, and inferior parts of the turbinate area, a significant vascular portion of the nose (Figure 1). Columnar pseudo-stratified epithelium lines the inside. It is made up of basal cells, ciliated and non-ciliated cells that secrete mucus (Figure 2). The non-motile microvilli that cover the ciliated and non-ciliated cells increase the surface area of the cells, making this the location with the best medication absorption. Mucociliary clearance is predominant because ciliated cells are covered in about 100 motile cilia that are in charge of transporting mucus. After the drug (in the form of particles or a

solution) reaches the mucociliary area, it will be removed from the nasal cavity and have limited access to the absorption site [12, 13, 14].

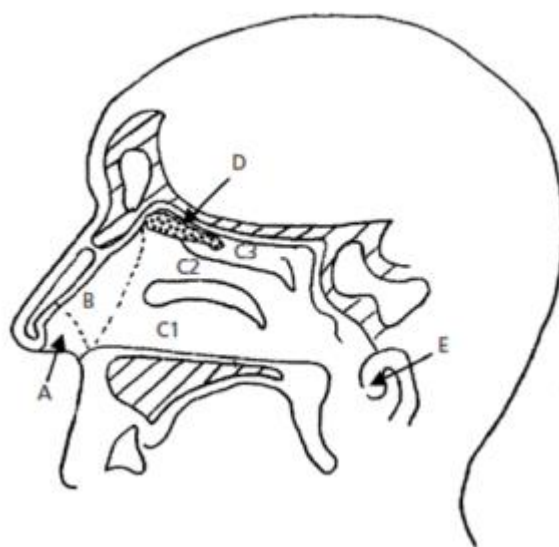


Figure 1. Sagittal section of the nasal cavity showing the nasal vestibule

respiratory system: inferior, middle, and superior turbinates (C1, C2, and C3), atrium (A), olfactory region (D), and nasopharynx (E). Reprinted from reference with permission. [15]

The olfactory region is a non-ciliated, pseudostratified columnar epithelium that makes up around 8% of the nasal epithelium's overall surface area. Drug delivery to the brain and cerebrospinal fluid depends on it (CSF). The epithelial cells are covered in a layer of mucus that is 5 m thick and catches foreign objects. Mucin, water, salts, proteins such albumin, immunoglobulin, lysozyme, and lactoferrin, and lipids make up the mucous secretion [16] The pH of the nasal secretions ranges from 5.0 to 6.5. [17] Because the nasal mucosa is highly vascularized and permeable, researchers were interested in using the nasal route for the systemic distribution of drugs [18]. Breathing and olfaction are the two main uses of the nasal cavity in humans and other animal species. But, after it filters, warms, and humidifies the breathed air before reaching the lowest airways, it also provides an essential defensive role. The passage of the nasal cavity, which extends from the nasal vestibule to the nasopharynx, is around 12–14 cm deep. The nasal cavity of an adult person has a total surface area of around 150 cm² and a volume of roughly 15 ml. [19] The nasal vestibule, inferior turbinate, middle turbinate, superior turbinate, olfactory area, frontal sinus, sphenoidal sinus, and cribriform plate of the ethmoid bone are just a few of the locations that may be found within each of the two nasal cavities. The nasal associated lymphoid tissue (NALT), which is mostly located in the nasopharynx, is also present in the nasal cavity. The mucus-coated nasal cavity is lined with hairs that serve the purpose of trapping inhaled contaminants and microorganisms. Furthermore, mucociliary clearance, immunological functions, and endogenous chemical metabolism are also crucial duties of nasal structures. [20]. The mucous membrane that covers the nasal cavity can be divided into two regions: the nonolfactory region, which includes the nasal vestibule, is covered with skin-like stratified squamous epithelium cells, and the respiratory region, which has a typical airways epithelium covered in numerous microvilli, creating a large surface area available for drug absorption and transport [21]. The middle septum divides the nasal cavity into two symmetrical halves, each of which extends

posterior to the nasopharynx and opens at the face through nostrils. The nasal vestibule, atrium, respiratory region, and olfactory region are the four symmetrical parts that make up each half and are characterised by their anatomical and histological features.

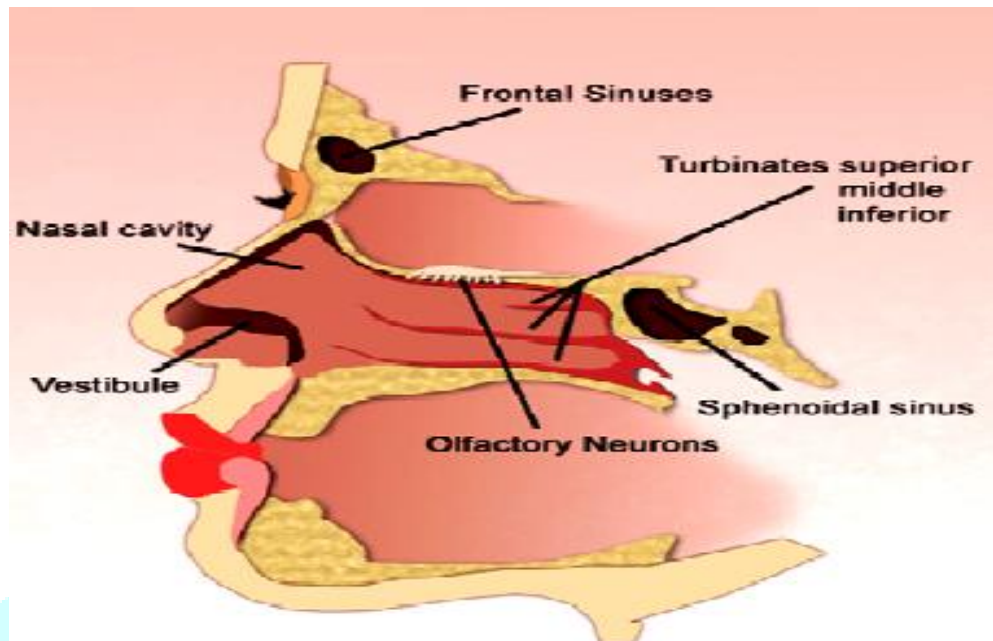


Fig 2: Schematic of a sagittal section of nasal cavity

the nasal :vestibule The nasal vestibule occupies the majority of the anterior nasal cavity and measures 0.6 cm² in size, right within the nostrils [22]. This region contains vibrissae, or nasal hairs, which filter the inhaled particles. A stratified squamous and keratinized epithelium with sebaceous glands covers this nasal region histologically.

Atrium: The atrium is the space that lies between the nasal vestibule and the pulmonary region. Its front region is made up of a stratified squamous epithelium, while its posterior region is made up of pseudostratifiedly organised columnar cells that exhibit microvilli.

Respiratory region: The respiratory section of the nasal cavity—also known as the conchae—is its largest portion. It is separated into superior, middle, and inferior turbinates, which protrude from the lateral wall. The epithelium, basement membrane, and lamina propria make up the nasal respiratory mucosa, which is regarded as the most crucial part for systemically distributing medications. Goblet cells, basal cells, pseudostratified columnar epithelial cells, and mucous and serous glands make up the nasal respiratory epithelium. On their apical surface, many epithelial cells are coated with microvilli, and the majority of them also have tiny projections known as cilia.

Region of the nose ; The olfactory area is located at the top of the nasal cavity and extends briefly along the septum and lateral wall. Only the neuro-epithelium of the CNS is directly exposed to the outside world. The olfactory epithelium is similarly pseudostratified to the respiratory epithelium and contains specialised olfactory receptor cells crucial for scent perception [23, 24].

Mucus membrane of nose and its composition: The nasal mucus layer is just 5 m thick and is divided into two separate layers: an exterior layer that is viscous and dense and an inside layer that is fluid and serous. In all, the mucus layer in the nose is composed of 95% water, 2.5–3% mucin, and 2% of electrolytes, proteins, lipids, enzymes, antibodies, sloughed epithelial cells, and bacterial products.

Epithelial cells: These cells primarily serve two purposes: 1. They act as a physical barrier against the entry of allergens and microbial pathogens, and 2. They cooperate with mucus glands and cilia to produce and remove mucus and foreign objects from the nasal cavity [25].

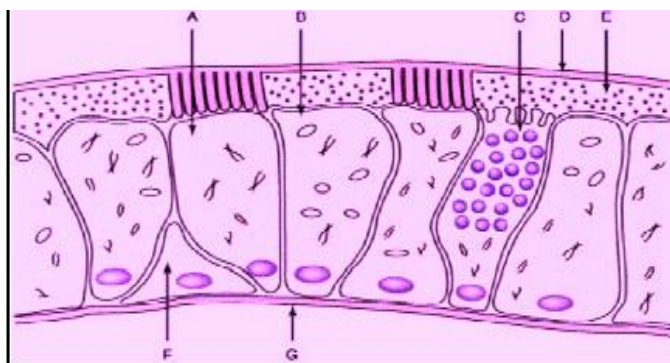


Figure 3: Cell type of the nasal epithelium

Blood supply to nasal cavity: The nasal cavity's vascular system receives abundant blood flow to perform essential tasks as heating and humidification, olfaction, mucociliary clearance, and immunological processes. Because of how the nasal vascular bed is constructed, it is simple to perform a quick exchange of fluid and dissolved excipients between blood vessels and nasal tissue. The nasal mucosa's capillary flow was estimated to be 0.5 ml/g/min. Maxillary artery branch known as the sphenopalatine artery. Ophthalmic artery branch called anterior ethmoidal artery. the vestibule of the nasal cavity is supplied by branches of the facial artery. [26]

3. ADVANTAGES [27]

- 1) The gastrointestinal tract's normal drug breakdown is not present.
- 2) There is a drop in hepatic first pass metabolism.
- 1) It is possible to obtain rapid medication absorption and speedy effect.
- 3) Using an absorption enhancer or another method can increase the bioavailability of bigger medication molecules.
- 4) For smaller medication molecules, the bioavailability through the nose is good.
- 5) Nasal drug administration can deliver medications to the systemic circulation that are not absorbed when taken orally.
- 6) Current studies indicate that the nasal route is a parenteral route alternative, particularly for protein and peptide medicines.
- 7) More practical for patients than parenteral medicine, especially for those receiving long-term therapy.
- 8) The nasal route is used to provide medications with poor GI fluid stability.
- 9) Polar substances with low oral absorption may work well with this delivery method.

4. LIMITATIONS [28,29]

- 1) It is still unclear if absorption enhancers utilised in nasal medication delivery systems are hazardous to tissues.
- 2) Less convenient for patients than oral administration methods since there is a chance of nose discomfort.
3. The nasal cavity has a lesser absorption surface area than the gastrointestinal system.
- 4) Both the drug and any ingredients added to the dose form have the risk of local adverse effects and severe cilia damage to the nasal mucosa.
- 5) When employed in high concentrations as chemical enhancers, some surfactants can destabilize and even disintegrate membranes.
- 6) Due to incorrect delivery methods, the dose form could physically leak into other respiratory tract organs, including the lungs.

5. JUSTIFICATION FOR NASAL DELIVERY'S DEVELOPMENT

Drugs that are active at low dosages and have no or very limited oral bioavailability can be delivered effectively via the nasal route. With its accessibility and suitability for self-medication, the nasal route avoids the hepatic first pass elimination that is brought on by oral administration. There are two categories of medicines for nasal delivery available today. Decongestants, topical steroids, antibiotics, and other over-the-counter (OTC) medicines are among the first group of low molecular weight and hydrophobic medications used to treat sinus and nasal mucosa. The second group of medications includes a handful that can exert systemic effects thanks to adequate nasal absorption. Due to their instability, chemicals that are typically supplied by injection are good candidates since they are almost ever absorbed after oral administration.[30, 31]

6. MECHANISM OF DRUG ABSORPTION THROUGH NASAL MUCOSA

The passing through of mucus is the initial stage in the drug's absorption from the nasal cavity. This layer is easily penetrated by small, unaltered particles. It could be more challenging for massive or charged particles to pass, though. The primary mucus protein, mucin, has the capacity to adhere to solutes and obstruct diffusion. Environmental modifications might also cause structural changes in the mucus layer (i.e. pH, temperature, etc.). Many pathways exist for medication absorption via the mucosa once it has passed through the mucus. [30]. They include paracellular transport by cell-to-cell migration, transcytosis by vesicle carriers, and transcellular or straightforward diffusion through the membrane. Drug absorption is hampered by probable metabolism before it reaches the systemic circulation and by the cavity's brief length of occupancy. Although other processes have been suggested, the two that follow have received the most attention. first paracellular pathway (1) Inter - cellular spaces, (2) Transcellular pathway, and (1) Tight connections (3) Transcytosis, (2) Passive Diffusion, (2) Active Transport (modified) [31] The aquatic route of transport, sometimes referred to as the paracellular pathway, is a component of the first mechanism. This path is passive and sluggish. This method allowed for the absorption of insulin, mannitol, and propranolol. Intranasal

absorption and the molecular weight of water-soluble compounds are inversely associated via logarithmic scaling. [31]. The second mechanism, also known as the transcellular process, includes transport via a lipoidal pathway and is responsible for the movement of medicines that are lipophilic and exhibit rate dependence. Medicines can also enter cells through tight junctions or by carrier-mediated active transport. For instance, the natural biopolymer chitosan, derived from shellfish, relaxes the tight junctions between epithelial cells to promote the transfer of drugs [32, 33].

BLOOD BRAIN BARRIER

The Blood Brain Barrier (BBB) serves as a physiological link between the peripheral and central neurological systems (CNS). It serves two purposes: to protect brain tissue and to control blood flow exchanges. A barrier called the Blood-Brain Barrier (BBB), which is selectively permeable and controls how many big and tiny chemicals may enter the microenvironment of the neurons, is present in the brain. It accomplishes this accomplishment with the help of many cellular transport channels dispersed throughout the membrane. Among them are:

- Amino acid transporters
- Glucotransporter 1 (GLUT1)
- Nucleoside and nucleotide transporters

The BBB is highly selective allowing the passages through simple diffusion of only certain molecules such as water, carbon dioxide, and oxygen; Only highly selective drugs can cross this barrier. Water soluble drug with very less permeability can cross. The Endothelial layer tightly bound with each other consist of astrocyte cell, pericyte cell, and capillary endothelial cell. All these three cells together form a solid barrier.

Pathways for Nose-to-Brain Delivery of Drug:

For the in vivo administration of neurotherapeutics, the BBB serves as a formidable barrier. Direct medication delivery from the nose to the brain via two pathways—the olfactory and trigeminal nerve pathways—is an attempt to get beyond this barrier. The BBB must be present because it safeguards the brain from chemicals or infections that are circulated in the blood. The flow of potential therapeutic chemicals into the brain is also hampered, on the other side. 98% of tiny compounds and all big molecules having therapeutic effect, according to estimates, cannot enter the brain across the BBB.

The delivery of medicinal chemicals to the brain to treat CNS Disorders has been researched for drug transport through the olfactory mucosa. As previously mentioned, it has the considerable benefit of avoiding the BBB and lowering systemic exposure. Nose-to-Brain delivery mechanisms are not entirely known, however several recent investigations have pointed to some important potential paths. One method is the direct delivery of medications to the brain via neuronal networks like the Trigeminal Nerve Pathway and Olfactory Nerve Pathway. The brain can also cross the BBB by virtue of indirect medication delivery via the lymphatic and vascular systems. Nose-to-brain medicine delivery is employed to get over the barriers. [34]

7. DETERMINANTS OF NASAL DRUGS ABSORPTION

Nasal physiology, physicochemical properties of medicines, and formulation features are all factors that affect absorption.

I. Biological Elements

- Structural elements
- Biochemical alterations
- Pathological circumstances • Physiological parameters • Blood flow • Nasal secretions • pH of the nasal cavity • Mucociliary clearance and ciliary beat frequency
- Humidity and environmental conditions, including temperature

I. Physicochemical Properties of Drugs

- Molecular weight
- Size • Solubility
- Lipophilicity
- Pka and Partition coefficient

II. Physicochemical Properties of Formulation [35]

- Dosage form
- Viscosity
- pH and mucosal irritancy
- Osmolarity
- Volume of solution applied

III. Device Related Factors [35]

- Particle size of the droplet/powder
- Size and pattern of disposition

I. BIOLOGICAL FACTORS

The first physiological element is mucociliary clearance, which includes the joint action of the mucus layer and cilia and moves the less viscous lower layer of mucus towards the nasopharynx while the more viscous upper layer remains mostly immobile. The nasal mucosa also contains a wide variety of metabolic enzymes. While the degree of activity of these enzymes is lower than that seen in the GIT and liver, it can nevertheless reduce the bioavailability of medications given orally. Together with pathological disorders like rhinitis and the common cold, medications can also be absorbed from the nasal cavity differently depending on the pH of the cavity.

II. PHYSICOCHEMICAL PROPERTIES OF DRUGS

Various physicochemical characteristics of drug can also affect nasal absorption of the drug.

Molecular Weight

Quantity and size of molecules For hydrophilic substances in particular, the molecular weight affects how much of the medicine is absorbed. For effective medication delivery up to 1000 Daltons, the nasal route is ideal. Unless penetration enhancers are used, absorption decreases dramatically if the molecular weight is more than 1000 Daltons. According to a study, there is a strong linear link between the log of the amount of

medicine taken by the nose and the log of the molecular weight of water-soluble compounds, indicating that aqueous channels are involved in the absorption of water-soluble molecules through the nose. The nasal cavity is said to be coated with particles larger than 10 microns. Particles that are 2 to 10 μm can be retained in the lungs and particles of less than 1 μm are exhaled.

Solubility and Dissolution

Drug absorption via biological membranes is significantly influenced by the solubility of the medication. If the medication is not adequately soluble in the necessary carriers, it not only restricts the drug's absorption but also the formulator's capacity to create a product. A medicine should have the required aqueous solubility for enhanced dissolution since nasal secretions are more watery in nature. Prior to absorption, particles lodged in the nose must be dissolved. One could not notice medication absorption if the drug's particles stay in the nostrils or if they are flushed out of the nasal cavity.

Chemical Form

The chemical form in which a medicine is delivered to the nasal mucosa can affect how well it is absorbed. For instance, changing a drug's form into a salt or ester might change how well it is absorbed. This behaviour is linked to the rise in lipophilicity that occurred after esterification, which raised the pace and volume of nasal absorption.

Partition Coefficient and pKa

Nasal absorption has a constant quantitative connection with the partition coefficient. Unionized species are better absorbed when compared to ionised species, and this is also true for nasal absorption, according to the pH partition hypothesis. The amount of absorption is pH dependant, increasing at a pH below the pKa and decreasing after the pKa. According to their research, the lipophilicity of the permeant generally causes the nasal absorption to rise. When the medications' lipophilicity or partition coefficient increases, investigations show that the drug concentrations in the cerebrospinal fluid (CSF) also rise.

III. FORMULATION ASPECTS

Drug Concentration, Dose and Dose volume

Three connected factors that affect the effectiveness of the nasal delivery method are drug concentration, dosage, and dose volume of administration. In trials using nasal perfusion, it was shown that L-Tyrosine nasal absorption increased with drug concentration. Increased doses were often associated with increased nasal absorption or pharmacological efficacy. It's vital to pay attention to how the dosage varies. There could be a limit to how much nasal absorption can be enhanced if the medication is increasing by increasing formulation volume. A formulation can only be held in the nostrils for a certain amount of time before draining out of the nasal cavity. With a maximum dose volume of 0.20 ml, the optimal dose volume range is 0.05-0.15 ml.

Physical Form of Formulation

Nasal medication absorption is influenced by the formulation's physical shape. The formulation's viscosity is a crucial factor in formulation development. The systemic nasal medication distribution will often be less effective with a more viscous formulation. The use of viscous substances may result in a somewhat more

prolonged impact in desmopressin nasal administration. More viscous formulations, such as gels, would seem to be more suited for locally acting medications.

Formulation pH

The pH of the formulation and the nasal surface both have an impact on how effectively a medicine penetrates. For the following reasons, the pH of the nasal formulation is crucial:

- To prevent irritation of the nasal mucosa.

- To enable the medication to be absorbed by the body while in a unionised state.
- To preserve the functionality of excipients like preservatives.
- To maintain normal physiological ciliary activity.
- To stop the growth of harmful germs in the nose channel.
- Nasal secretions include lysozymes, which are necessary for the acidic pH bacterial eradication. Lysozyme is rendered inactive in an alkaline environment, leaving the nasal tissue open to microbial infection. Thus, maintaining the formulation's pH between 4.5 and 6.5 is advised.

Buffer Capacity

Nasal formulations are often given in modest doses of 25 to 200 l, with 100 l serving as the most typical dosing volume. As a result, nasal secretions may change the dose's given pH. The amount of unionised medication that is accessible for absorption may change as a result. As a result, maintaining the pH may call for an acceptable formulation buffer capacity.

Osmolarity

The formulation's tonicity may influence how well a drug is absorbed. In the presence of hypertonic solutions, epithelial cell shrinkage has been noted. The activity of cilia is similarly decreased or eliminated by hypertonic saline solutions. The effects of hypertonic solutions and low pH are comparable. The recommended formulation is often one that is isotonic.

Gelling / Viscosity Agents or Gel Forming Carriers

To lengthen the nasal residence time, some formulations need to be gelled or made viscouer. The therapeutic effect of nasal preparations may be prolonged by increasing the solution viscosity. High molecular weight peptides were not affected in the same way as low molecular weight medications by the use of drug carriers like hydroxypropylcellulose. From a safety (nasal irritancy) perspective, it is frequently advised to use a combination of carriers.

Solubilizers

Nasal medication administration in solution is always restricted by a drug's aqueous solubility. To increase the solubility of therapeutics, one can use conventional solvents or co-solvents such glycols, tiny amounts of alcohol, Transcutol, medium chain glycerides, and Labrasol. Another approach is to combine lipophilic absorption boosters with surfactants or cyclodextrins, such as HP— Cyclodextrins, which operate as a biocompatible solubilizer and stabiliser. In these situations, their effect on nasal irritancy should be taken into account.

Preservatives

Preservatives are essential in the majority of aqueous-based nasal formulations in order to stop the development of microbes. Some of the preservatives that are frequently utilised in nasal formulations include parabens, benzalkonium chloride, phenyl ethyl alcohol, EDTA, and benzyl alcohol.

Antioxidants

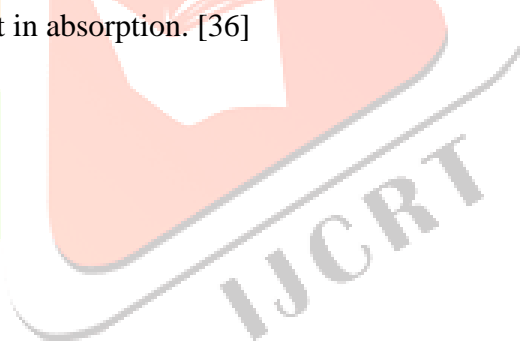
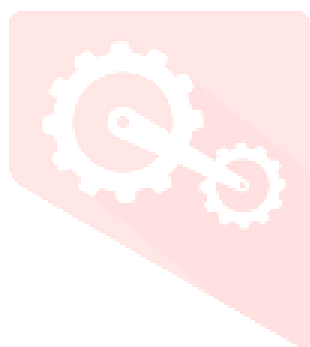
Using antioxidants to stop pharmaceutical degradation may be essential, depending on the stability profile of a specific drug in the formulation chosen. Antioxidants like butylated hydroxytoluene, sodium bisulfite, sodium metabisulfite, and tocopherol are frequently used.

Humectants

Dehydration could be avoided with enough intranasal moisture. In order to avoid nasal irritation and because they're unlikely to affect medicine absorption, humectants might be used, particularly to gel-based nasal treatments. Glycerin, sorbitol, and mannitol are a few of the frequently utilised humectants.

Absorption Enhancers

It is advised to use absorption enhancers when a nasal medication finds it challenging to retain the necessary absorption profile. Based on their acceptance by regulatory bodies and their effect on the physiological operation of the nose, absorption enhancers are chosen. If a medicine has low membrane permeability, a high molecular size, no lipophilicity, or is degraded by enzymes, absorption enhancers may be necessary. After a good enhancer has been found, its ideal concentration has to be tested. Generally speaking, larger doses of enhancers are likely to cause nasal discomfort and nasal mucosa damage. Conversely, lesser enhancer doses would often lead to a reduced or absent enhancement in absorption. [36]



www.ijcrt.org	Sodium dodecyl sulfate (SDS), Polyoxyethylene-9-lauryl ether
Surfactant	Phosphatidylcholines
Complexing and Chelating agents	Ethylene diamine tetraacetic acid(EDTA)
Cyclodextrins and derivatives	α -, β -, γ -cyclodextrin, DM β -, HP β -cyclodextrin
Fusidic acid derivatives	Sodium Tauradihydrofusidate (STDHF)
Bile salts	Sodium taurocholate, Sodium glycocholate
Dry microspheres	Degradable starch microsphere, Dextran microspheres

TABLE NO.2 The various compounds investigated as enhancers in nasal drug delivery research are mentioned in Table 2

8.VARIOUS DOSAGE FORMS ADMINSTRATED BY NASAL ROUTE

The medicine being utilised, the planned indication, the patient demographic, and marketing preferences all have a role in choosing the dose form.

A. Nasal liquid formulations

The most popular dose forms for nasal medication delivery are liquid formulations. They mostly rely on formulations for the aqueous state. As many allergic and chronic disorders are frequently associated with crusts and drying of mucous membranes, their humidifying action is handy and helpful. Because the necessary preservatives affect mucociliary function, the main downsides of the water-based dosage forms are their lack of microbiological stability, irritation, and allergic rhinitis [37].

1. Rhinyle catheter and instillation

The drops are simply delivered to a specific area of the nasal cavity using catheters. Put the solution in the tube, keep it in place with one end in the nose, and blow through the other end with the mouth to transfer the solution into the nasal cavity. [37, 38]

2. Nebulizers that use compressed air

A nebulizer is a tool for delivering medication as a mist that is breathed into the lungs. Nebulizers that use compressed air are those that fill with compressed air. All nebulizers have a similar technological principle in

that they either employ oxygen, compressed air, or ultrasonic power to disperse medicinal fluids or suspensions into tiny aerosol droplets for direct inhalation by the use of mouthpiece of the device [39]

3. A squeezed bottle

In order to distribute decongestants, squeezed nasal bottles are often employed. A smooth plastic container with a straightforward jet outlet is among them. A particular amount of air within the plastic bottle is atomized when it is pushed, as air is forced out of the little nozzle. A vacuum is created within the bottle by releasing the pressure once more. By using this technique, nasal secretions are frequently sucked within and the liquid is contaminated by bacteria. [40]

4. Metered-dose pump sprays

Metered-dose pump sprays are used to administer the majority of pharmaceutical nasal treatments on the market that comprise solutions, emulsions, or suspensions. For further information on nasal administration, see nasal sprays and nasal mists. Nasal sprays and nasal mists are used to administer medications through the nose, either locally to treat common cold and allergy symptoms such as nasal congestion or systemically. Although there are many delivery mechanisms, the majority of nasal sprays work by using a hand-operated pump mechanism to inject a fine mist into the nose. Antihistamines, corticosteroids, and topical solutions are the three primary categories with regard to local impacts. Sprays with metered dosages come with a container, a pump with a valve, and an actuator.

A. Powder Dosage Forms

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 [42]. 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. The medication is commonly held either in a capsule for manual loading or a proprietary form from inside the inhaler. Once loaded or actuated, the operator puts the mouthpiece of the inhaler into their mouth and takes a deep inhalation, holding their breath for 5-10 seconds. There are a variety of such devices. The dose that can be delivered is typically less than a few tens of milligrams in a single breath since larger powder doses may lead to provocation of cough. [43]

B. Pressurized MDIs

A metered-dose inhaler (MDI)

Less typically utilised in nasal medication administration are dry powders. The absence of preservatives and the formulation's increased stability are two of this dosage form's main benefits. The administration of powders might cause a prolonged interaction with the nasal mucosa compared to solutions.

1. insufflators

Insufflators are tools used to administer drug substances for inhalation; they may be built using a tube or a straw that carries the drug ingredient and occasionally a syringe as well. Due to inadequate deaggregation of the particles, the realised particle size of these systems is frequently higher than the particle size of the powder particles, which has a significant coefficient of variation for initial deposition regions. A lot of insufflator devices use pre-dosed powder in capsules.

Asthma, chronic obstructive pulmonary disease (COPD), and other respiratory illnesses are most frequently treated with it. For the treatment of asthma and COPD, the drug in a metered dosage inhaler is often a bronchodilator, corticosteroid, or a combination of the two. Mast cell stabilisers, such as, are other drugs that are less often utilised but are nonetheless given by MDI (cromoglicate or nedocromil). The advantages of MDIs include their mobility, compact size, availability over a broad dosage range per actuation, dose constancy, dose accuracy, protection of the contents, and that they are rapidly available for use. More than 99% of the dosage given by MDIs is generally made up of propellants. The formulation, which contains the drug either dissolved or suspended in the propellant, is released in a single metered dose upon device activation. An aerosol containing micrometer-sized pharmaceutical particles is produced when the volatile propellant breaks up into droplets, which are quickly evaporated afterward. [44]

C. Nasal Gels

High-viscosity thickened liquids or suspensions are what nasal gels are. There was not much interest in this method prior to the recent invention of precision dosage devices. A nasal gel's benefits include the reduction of post-nasal drip due to its high viscosity, the reduction of taste impact due to decreased swallowing, the reduction of anterior formulation leakage, the reduction of irritation due to the use of soothing/emollient excipients, and targeted delivery to mucosa for better absorption. [45] Due to the formulation's limited spreading capabilities and viscosity, the deposition of the gel in the nasal cavity depends on the method of administration. It only spreads out narrowly in the nasal cavity, where it is applied directly, without the use of specific application methods. Recently, the first nasal gel with vitamin B12 was released.

The medication solutions are inhaled orally as nebulizers with measured doses, nasal sprays, and drops. The volume and concentration of the medicine in the formulation affect how much of the active component is delivered. After intranasal administration of 0.8 mg/ml of nitroglycerine in normal saline, the therapeutic nitroglycerine levels of 3 ng/ml in central venous blood, 1.7 ng/ml in arterial blood, and 0.4 ng/ml in peripheral venous blood were reached in less than 2 minutes. Several researchers have reported on the impact of formulation factors on nasal absorption, including the dosage of the active component, the pH of the solution, and its osmolarity. The Latin term *in situ*, which may be translated literally as "In position," is also used to refer to the phase transition system. Prior to distribution in the body, *in situ* gel is a drug delivery method that is in solution form; however, after administration, *in situ* gelation occurs to create a gel. There are several different ways to provide *in situ* gel, including orally, intravenously, recto-rectally, vaginally, topically, and nasally. [45]

9. APPLICATIONS

1. Delivery of non-peptide pharmaceuticals

In the absence of a permeation enhancer, low molecular weight (below 1000 daltons) small nonpeptide lipophilic medications are efficiently absorbed via the nasal mucosa. When nasal turbinates are present, the highly vascularized nasal membrane epithelium, which has a huge surface area, is easily accessible for medication absorption. Medicines having a high pre-systemic metabolism, such progesterone, estradiol, propranolol, nitroglycerin, and sodium chromoglyate, can be quickly absorbed through the nasal mucosa with a systemic bioavailability of around 100% [46, 47]. Due to the direct passage of venous blood from the nose into the systemic circulation, these medications can enter extensive circulation few minutes after dosage. In fact, many pharmaceuticals that are administered intranasally are frequently absorbed more quickly and effectively than those via oral administration, resulting in a rapid absorption. Non-peptide medicines that are being explored for nasal administration and have demonstrated high bioavailability by this route include:

- 1) Corticosteroids for the adrenals
- 2) Sex hormones, including testosterone, norethindrone, progesterone, and 17 beta-estradiol.
3. Supplements: vitamin B

hydralazine, an Angiotensin II antagonist, nitroglycerin, isosobide dinitrate, propanolol, and colifilium tosylate are four examples of cardiovascular medications.

- 5) Sympathomimetics: Ephedrine, epinephrine, and phenylephrine; Xylometazoline, dopamine, and dobutamine; Autonomic Nervous System. c. Nicotine, metacholine, and other parasymphomimetics Scopolamine, atropine, and ipatropium are types of parasympholytics. Prostaglandins
- 6) Stimulants of the central nervous system: cocaine, lidocaine
- 7) Narcotics and decongestants: bupemorphine and naloxone
- 8) Antihistamines (histamine) and disodium cromoglycate (meclizine)
- 9) Ergotamine, tartrate, and dierogotamine are antimigrant medications.
- 10) Gentamycin, cephalosporins, and phenicillin
- 11) Enviroxime and phenyl-p-guanidine benzoate are antivirals.
- 12) Inorganic substances, include inorganic salts, colloidal silver, gold, and carbon.

2. Delivery of peptide-based pharmaceuticals

Due to their physico-chemical instability and vulnerability to hepato-gastrointestinal (HG) first-pass elimination, peptides and proteins often have a low oral bioavailability. Examples include calcitonin, insulin, and other pituitary hormones [48]. These peptides and proteins are hydrophilic polar molecules with relatively large molecular weight that are poorly absorbed through biological membranes, with bioavailabilities reached at concentrations of around 1% to 2% when given as simple solutions. Sufactants, glycosides, cyclodextrin, and glycols are some of the key absorption enhancers we use to promote bioavailability in order to solve this issue. For these biotechnological compounds, nasal administration is proven to be the most effective method.

3. Delivery of Drugs to Brain through Nasal Cavity:

Due to the need for quick and/or precise medication targeting to the brain, this delivery technique is advantageous in treating illnesses like Parkinson's disease, Alzheimer's disease, or pain. The percentage of drugs that enter the central nervous system (CNS) following nasal administration will rise as nasal delivery systems for the brain advance. It is possible for some substances to cross the blood-brain barrier and reach the brain through the olfactory area, which is situated in the upper distant regions of the nasal passages. The intranasal administration of neurotrophic factors such NGF, IGFI, FGF, and ADNF to the central nervous system (CNS) has shown promising effects in increasing the drug's bioavailability in the brain, according to recent research. AVP, CCK analogue, MSH/ACTH, and insulin have all been used in human studies to show that these are delivered directly to the brain from the nasal cavity.

4. Delivery of Vaccines through Nasal Route:

The first line of defence against microorganisms entering the body is the mucosal sites. Nasal mucosa filter pathogens from inspired air by compaction and mucociliary clearance. In humans, the nasal cavity and nose-associated lymphoid tissue (NALT), also known as Waldeyer's Ring, serve as an effective immune system site. Nasal secretions are primarily composed of immunoglobulins (IgA, IgG, IgM, and IgE), protective proteins like complement, neutrophils, and lymphocytes in the mucosa [49,50,51]. The following are the main justifications for using the nasal route for vaccination delivery:

- 1) The nasal mucosa is the first site of contacts with inhaled pathogens,
- 2) The nasal passages are rich in lymphoid tissue,
- 3) Creation of both mucosal and systemic immune responses,
- 4) Low cost, patient friendly, non-injectable, safe.

According to some reports, nasal administration of vaccines induces local immune response in the nasal lining in addition to systemic immunological response, forming an extra barrier of defence [49]. Injecting the vaccine directly into the nasal cavity encourages the formation of both local and IgG-specific secretory IgA antibodies, adding another first line of defence that aids in eradicating the pathogen before it can establish itself. Recently, nasal vaccines made with chitosan and recombinant Bacillus anthracis protective antigen (rPA) have been used to treat illnesses including anthrax and influenza[52,53]. Because the majority of bacteria that cause common illnesses like measles, pertussis, meningitis, and influenza enter the body through the nasal mucosal surfaces, nasal vaccinations are a useful option for protecting against these diseases. Nasally given vaccinations, particularly if based on attenuated live cells or adjuvanted via an immunostimulator or delivery method, can cause mucosal and systemic (i.e. humoral and cell-mediated) immune responses.

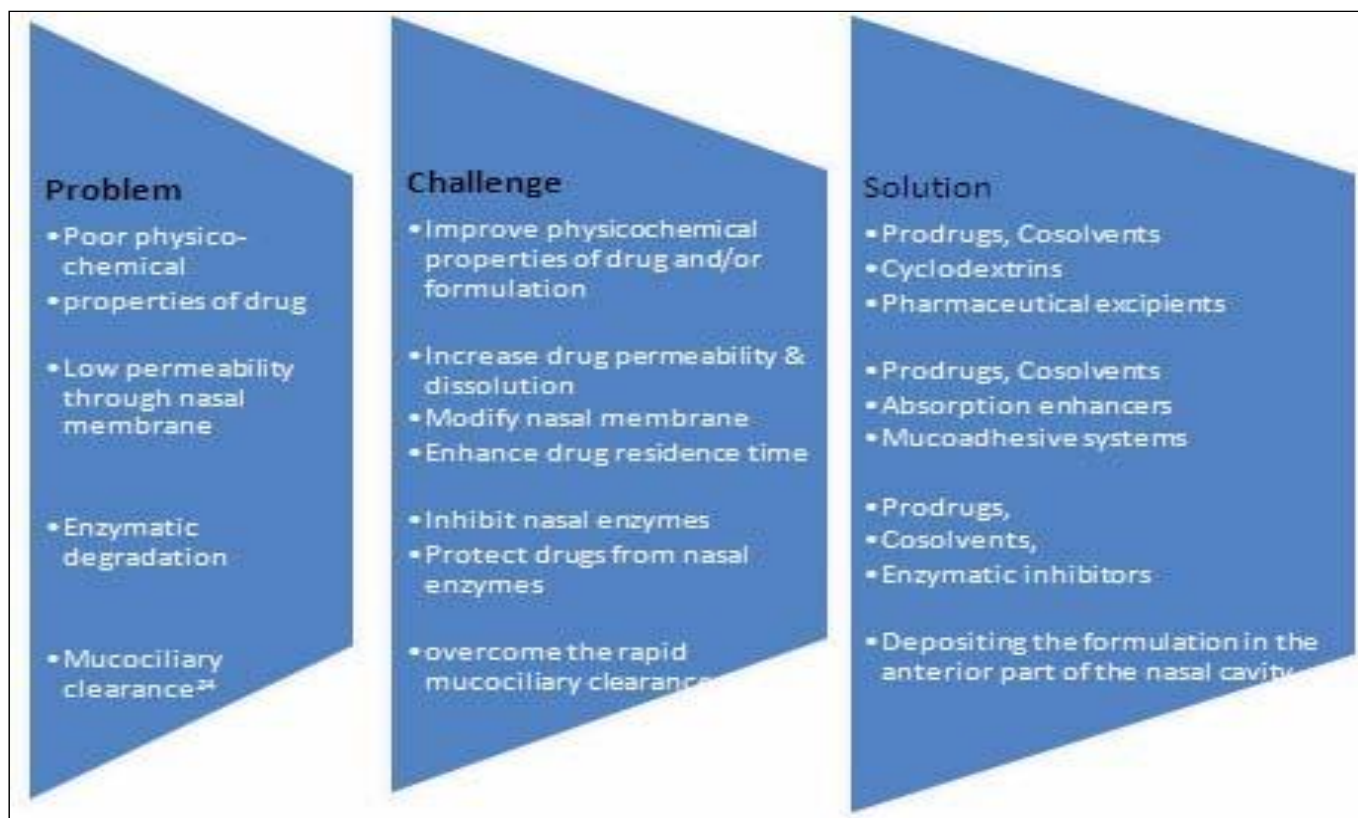
5. Delivery of diagnostic drugs:

The delivery of diagnostic tools for the diagnosis of a variety of bodily diseases and disorders is another crucial function of the nasal drug delivery system. Because the intranasal route allows for a more rapid and less toxic systemic drug release into the bloodstream, it is better for treating medical conditions. For the purpose of determining a patient's kidney function, phenol-sulfonphthalein is a diagnostic tool. Diabetes patients were given a "Secretin" diagnosis for pancreatic disorders. Additionally, the diagnostic tool Pentagastrin determined the secretory function of gastric acid. As compared to parenteral drug administration,

the nasal drug delivery system is a viable alternative mode of administration for a number of systemically acting medicines with low bioavailability. It also offers advantages in terms of enhanced patient acceptance and compliance. Because it requires rapid and/or precise targeting of drugs to the brain and is an effective way to induce an immune response against a variety of diseases like anthrax, influenza, etc., by administering the vaccines through the nasal mucosa, this delivery system is advantageous in conditions like Parkinson's disease, Alzheimer's disease, or pain. In the near future, we anticipate the introduction of novel nasal products for the treatment of chronic conditions like diabetes, growth deficiency, osteoporosis, infertility, and endometriosis as well as intranasal products for the treatment of crisis conditions like erectile dysfunction, sleep induction, acute pain (migraine), panic attacks, nausea, heart attacks, and Parkinson's disease. A thorough consideration of the properties of the drug formulation and delivery system, as well as an awareness of how they interact with one another, are necessary for the successful use of these attributes. [54]

10. CHALLENGES AND OPPURTUNITIES FOR NASAL DELIVERY SYSTEMS:

The mentioned potential benefits of nasal delivery cannot be completely used by currently available nasal delivery tools like spray pumps and pipettes. The front section, which is bordered by skin and is not the target of either topical or systemic medications, receives a significant portion of the dosage. Medications delivered along the nasal cavity's floor may have an unpleasant taste, irritate the nose, and decrease patient acceptability. Last but not least, insufficient and inconsistent deposition in the distant area housing the sinus and middle ear openings, as well as the olfactory region, poses a significant obstacle for prolonged use of nasal administration of medications and vaccinations. This is especially true for the new, costly, and sophisticated medications that necessitate a precise dosage, great patient compliance, and consistent results of bioavailability to ensure their efficacy and safety. The majority of nasal products are presently liquids that are administered using metered spray pumps. Solubility, stability, and dosage volume are potential limitations for liquid formulations. In contrast, it is simpler to alter the size and surface characteristics of powders and they are more stable. According to certain research, cutaneous discomfort is lessened and powders are absorbed more quickly. Nasal devices are medical devices that administer medications to the nose, and they are being developed by Bioactis Ltd. ("Bioactis"; CEO, Ryoichi Nagata, MD, PhD). [55]



Current approaches for nasal permeation enhancement:

Low drug solubility, quick enzymatic decay in the nasal cavity, limited membrane penetration, and rapid MCC all have an impact on how bioavailable medications given via the nasal route are. To get around these constraints, a number of strategies have been proposed.

Prodrugs:

Intranasal medications are often supplied as solutions or powder formulations that must be dissolved before absorption. Drugs that are lipophilic are weakly water soluble but quickly pass through biomembranes. They should be given in this manner as a prodrug with enhanced hydrophilic character to enable the creation of an aqueous nasal formulation with an appropriate concentration. The prodrug has to be changed into the parent medication as soon as it enters the bloodstream. In order to create suitable nasal formulations, Kao et al. created a number of prodrugs of L-Dopa and found that their solubility greatly improved when compared to the parent drug.[56] With testosterone, which is similarly not very water-soluble, similar outcomes were seen. [57]The capacity of extremely hydrophilic polar medicines to traverse biomembranes, however, may be compromised. The penetration across the membrane may thus increase if they are supplied as prodrugs with enhanced lipophilic nature [58]. Moreover, several studies have improved the enzymatic stability of medications using the prodrug strategy. Acyclovir's L-aspartate—ester prodrug, for instance, was reported by Yang et al to be less labile to enzymatic hydrolysis and more permeable than its parent medication [59]. The possible use of prodrugs as a potent method to boost the bioavailability of peptides when delivered intranasally has also been proposed. Prodrugs might shield peptide medications from nasal enzymatic breakdown. [60,61]

Co-Solvents:

The use of cosolvents is a different strategy to using prodrugs to promote drug solubility[59]. Glycerol, ethanol, propylene glycol, and polyethylene glycol are the co-solvents most frequently employed in intranasal

formulations, and they may also be the most crucial since they are nontoxic, appropriate for use in pharmaceuticals, and nonirritating to the nasal mucosa.

Enzymatic inhibitors:

Enzymatic barriers during nasal are provided by the nasal mucosa and mucus layer. It is frequently necessary to dissolve intranasal drugs, which are frequently provided as solutions or powder formulations. Lipophilic drugs are only moderately soluble in water, yet they cross biomembranes swiftly. To enable the development of an adequate concentration of an aqueous nasal formulation, they should be administered in this way as a prodrug with improved hydrophilicity. After the prodrug has entered the bloodstream, it has to be converted into the parent drug. Kao et al. produced a number of prodrugs of L-Dopa in order to develop acceptable nasal formulations and discovered that their solubility was significantly better than that of the parent medication. [56]. With testosterone, which is similarly not very water-soluble, similar outcomes were seen. Drug delivery, because they have a wide variety of enzymes. Various approaches have been used to avoid enzymatic degradation, including the use of proteases and peptidases inhibitors. For example, bestatine and comostate amylase are used as aminopeptidases inhibitors and leupeptine and aprotinin as trypsin inhibitors probably involved in the degradation of calcitonin [61]. Furthermore, bacitracin, amastatin, boroleucin and puromycin [61-63] have been used to avoid enzymatic degradation of drugs such as leucine enkephalin [64, 65] and human growth hormone. Finally, enzymatic inhibition can also be achieved using certain absorption enhancers (bile salts and fusidic acid). It is demonstrated that disodium EDTA, an absorption enhancer, reduces enzymatic degradation of beta sheet breaker peptide used for the treatment of Alzheimer's disease. The nasal mucosa and mucus layer serve as enzymatic barriers during nasal. Intranasal medications are typically offered in solutions or powder formulations, and it is frequently essential to dissolve them. Drugs that are lipophilic pass biomembranes quickly while having a modest water solubility. They should be taken in this fashion as a prodrug with increased hydrophilicity, allowing for the creation of a sufficient concentration of an aqueous nasal formulation. The prodrug has to be changed into the parent medication after it has circulated throughout the body. To create suitable nasal formulations, Kao et al. created a number of L-Dopa prodrugs and found that their solubility was much higher than that of the parent drug.

Permeation enhancers:

Both small and big hydrophilic medicines may not have adequate bioavailability when administered through the nasal epithelium. Combining their administration with absorption enhancers, which cause reversible changes in the epithelial barrier's structure, can increase their permeability. [66]

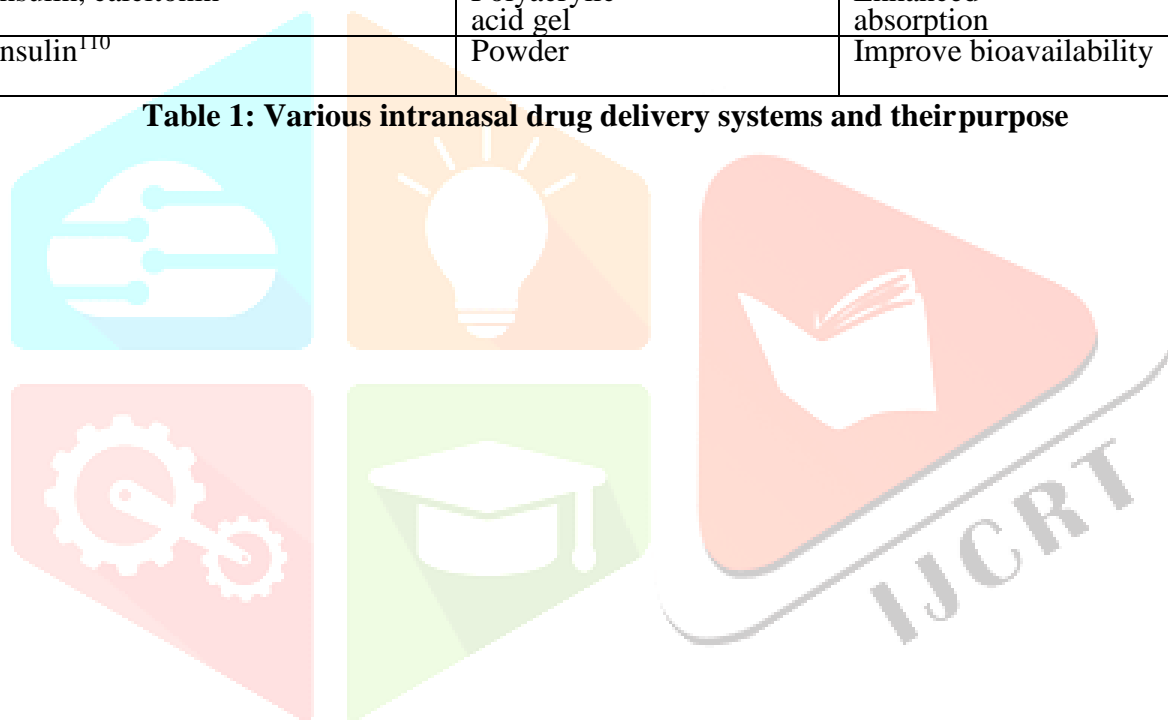
11. VARIOUS INTRANASAL DRUG DELIVERY SYSTEMS AND THEIR PURPOSE

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Drug	Delivery system	Purpose
Pentazocine ⁶⁷	Microspheres	Avoiding first pass effect
Ketorolac Trimethamine ⁶⁸	Microspheres	Avoid gastric complications
Sildenafil Citrate ⁶⁹	Microspheres	Avoid first pass metabolism
Metoclopramide HCl ⁷⁰	Microspheres	Permeation enhancement
Propranolol HCl ⁷¹	Microspheres	Open tight junction without cell damage
N ⁶ Cyclopentyladenosine ⁷²	Microspheres	Selective brain targeting
Propranolol HCl ⁷³	Microspheres	Avoiding first pass effect
Ondansetron ^{74,75}	Microspheres	Avoiding first pass effect and improve therapeutic efficacy
Domperidone ⁷⁶	Microspheres	Selective brain targeting
Sumatriptan Succinate ⁷⁷	Microspheres	Avoid hepatic first pass metabolism and brain targeting
Clonazepam ⁷⁸	Microspheres	Brain targeting
Clonazepam ⁷⁹	Microemulsion	Brain targeting
Valproic Acid ⁸⁰	Microemulsion	Enhanced bioavailability with brain targeting
Clobazam ⁸¹	Microemulsion	Brain targeting
Lomotrigone ⁸²	Microemulsion	Brain targeting
Lorazepam ^{83,86}	Microemulsion	Brain targeting
Sumatriptan ⁸⁷⁻⁹²	Microemulsion	Enhanced the bioavailability
Zolmitriptan ⁹³	Microemulsion	Enhanced bioavailability
Zolmitriptan ⁹⁴	Microemulsion	Enhanced bioavailability & rapid onset of action
Eucalyptus oil ⁹⁵	Microemulsion	Enhanced bioavailability with brain targeting
Nimodipine ⁹⁶	Microemulsion	Enhanced solubility and brain targeting
Nobiletin ⁹⁷	Microemulsion	Improve bioavailability in the brain
Tacrine ⁹⁸	Microemulsion	Targeting to brain
Zolmitriptan ⁹⁹	Microemulsion	Targeting to brain

Diazepam ¹⁰⁰	Microemulsion	Rapid absorption
Raltitrex ¹⁰¹	Microemulsion	Targeting to brain tissue
Sildenafil Citrate ¹⁰²	Microemulsion	Improve bioavailability with shorter T _{max}
Insulin ¹⁰³	Microemulsion	Enhanced the Bioavailability
Midazolam ¹⁰⁴	Microemulsion	To investigate the pharmacokinetic & pharmacodynamic profile
Tetanus toxoid ¹⁰⁵	Liposome	Improved immun response
Insulin ¹⁰⁶	Liposome	Increased insulin permeability
Desmopressin ¹⁰⁷	Liposome	Enhancement of antidiuresis
Diphenhydramine ¹⁰⁸	Liposome	Increased drug retention in the nasal cavity
Insulin, calcitonin ¹⁰⁹	Polyacrylic acid gel	Enhanced absorption
Insulin ¹¹⁰	Powder	Improve bioavailability

Table 1: Various intranasal drug delivery systems and their purpose



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