

# Nasal Route: A Breakthrough for Drug Delivery

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## Abstract

Development and discovery are the two important parameters of evolution. With the progress of pharmaceutical science and technology, the empirical route of nose still remains one main attraction for the formulation of scientists. The nasal route has the capability to cover both topical and systematic delivery. The most important part of this route is that we can target the brain also. The extent to which a medicine may penetrate the Blood Brain Barrier is one of the factors that restricts the capacity of most treatments to treat illnesses of the Central Nervous System (CNS) (BBB). Tight junctions found in the endothelial cells of blood capillaries to the brain serve as a barrier to most medications and prevent them from passing through. The BBB successfully prevents hydrophilic substances from moving from the circulatory compartment to the brain tissue. Tight junctions between the cells prevent bulk passage across the capillary walls, unlike in other tissues. Nasal drug delivery strategies have emerged during the last few decades, some of which may be able to circumvent the difficulties in getting medications to cross the BBB. Various neuro-degenerative disorders like migraine, Parkinson's disease, Alzheimer's disease, etc. can be targeted with that particular path. This article will bring light on several features, strategies, and obstacles of this pathway. Also, there are several dosage forms and their evaluation is provided. During the preclinical studies, there are several models like can be designed in vivo evaluation of nasal dosage form. Among all others models, the dog model has so many advantages and well suited for performing any trial related intranasal drug delivery.

**Keywords:** Nasal drug delivery, Blood Brain Barrier, neuro-degenerative disorders, migraine, Parkinson's disease, preclinical studies, Alzheimer's disease.

## INTRODUCTION

With the current development of drug delivery routes, nasal route has taken special attention from the very earlier times of human civilization. [1-3] Our ancestors specifically tribal people were involved in the practice of our very own Ayurvedic process called 'Nasya Karma'. [4]

Though various kinds of drugs can be administered by this route, our ancestors were involved in basically with the drugs that are mainly psychotropic, or it can create hallucinations. They have administered through powdered dosage forms known as 'Snuffs'.

Latin America was also known for continuous practicing regarding the nasal route. Day by day, with the progress in this route, nasal route assuring very good systemic bioavailability of several drugs than the same taken through conventional oral route. But there are more hurdles, we must go. Such as, in the case of drugs having protein-peptide properties, it displays very little absorption as well as low bioavailability. By taking several approaches they are overcome, like absorption enhancer, inhibitory chemicals for enzymes.

A more novel approach is my formulating microsphere with bio-adhesive/bio-erodible polymers. As per our general considerations, we always choose parenteral for absolute bioavailability. But for pediatric patients or patients with several

neurodegenerative disorders are often found to be very hard rock to break, as they are prone to be not the selective candidate for conventional parenteral administration. In this kind of adverse situation, the nasal route can be a breakthrough for bypassing the parenteral administration. [5] As a route of administration, the nasal route is having some unique positive features such as [6]: -

- Wavering the hepatic first-pass metabolism.
- The bioavailability of plasma can be the same as already with Intravenous route (I.V)
- The nasal route specifically, the cavity of the nose is enriched with the network of blood transporters like capillaries, veins & arteries which engifting the best environment for systemic absorption.
- The patient compliance and ease of administration at its class best.

## ANATOMY & PHYSIOLOGY OF NOSE

### Anatomy

If we consider the structure of the nose, we can say it is situated in the middle of the beneath of two eyes that is a symmetrical position. The nose acts as a gateway (opening) of the respiratory tract and serves as an organ for the smell sensation. The gateway that allows the oxygen-enriched air to get inside which is suitable for respiration as well as the quality of air is maintained by filtration, applying temperature, by humidification, and expel out undesirable particulates from inhaled/sucked air. The two hollow space that is divided by the partition made of cartilage, which is known as the septum. The outer holes are basically called nostrils. The canopy of mouth and the ground of and the ground of the nose is constructed by palatine bone. Generally, the opening constructed by palatine bone. Generally, the opening portion is known as a solid palate. It acts as a valve that prevents the refluxing of food outside the nose. It is very difficult to study the structure of the nasal cavity because of its intricacy. The progressive part of the inside and outside part of each nostril is known as the vestibule. Backside of the vestibule and every external partition is basically three preferments flowing generally from frontside to backside. Each preferment is basically known as nasal concha or turbinate, draping over the cushion of air. On the side and the upper portion of the concha is the olfactory area of the nasal cavity is responsible for responding. The pathway surface of respiration is humidified with mucous integument with prime capillaries called cilia, which act as to contain lumber mucus helps in adhesion of dust mites, carbon, and bacteria. The skull structure made of bones contain sinus pockets on each side. The integument of mucus constructed the area which is responsible for the sensation of smell known as olfactory region. It also consists of several nerves that act as the organ which regulates the organ for sense or natural reflex manager. Spindles like dendrites coming outside from the nerve cells to the cavity is encapsulated by very small wetness of water. The smell sensation is a chemical process occurred by the solvation of small entities with nasal moisture that elite nervous cells (Figure 1).

### Physiology of nasal cavity

The main action nasal cavity is to permit the airflow or wind to get into the place. The structural matter. The olfactory organ is responsible for the sensation of smell. Nasal mucosa considering Conchae extends the alley and inception of inhaled air occurs. The exposure between raw infiltrated air and nasal mucosa causes the spinning movement of inhaled air. These bound particles before getting into the lungs. Olfactory systems work by effluvious response of the body. Bowman's glands help in the emanation of the mucus. The special pigments which are expelling out creates a pale yellow colour of mucus. They by solvation of the inhaled objects, aromatic response of nose. Paranasal sinuses are responsible for reverberate articulation and secrete the mucus into the nasal aisle. Various functions of the sinus are still under discovery. Nasolacrimal Ducts are responsible for tear production to the mucosal layer.

### Physiology of nasal mucosa

The nasal mucosa gives defense mechanism that boosts the power of the immune system to protect from foreign invaders. It protects/ bypass lungs from allergy forming substances and infectious pathogens. The adhesive mechanism of the nasal mucosal layer attaches dust particles. The inter-subject variability occurs due to the alteration of the defense/immune system. Production of IgE (immunoglobulin type E) is initiated by B cells which plays a major responsibility in Type-I hypersensitivity reaction.

### Epithelial cell

This wall act as a protective surface layer from foreign allergens and also mucus glands and cilia for expelling out unwanted substances or particulate matter from the nasal cavity. Current studies also show their bigger roles/ responsibility if the physical barrier has not the capability to expel out the pathogenic trespasser cell of the nasal mucosa. The main content of the epithelium is antigen-binding proteins. The main job of these cells is to inaugurate pathogens to the T-lymphocyte cells which causes massive destruction to them. The APCs (Antigen Presenting Cell) entraps the antigen and show an immune response. The factors given by epithelial cells give synergistic inflammatory responses like cytokines. The allergy formers with a strong association with epithelial cells build a great wall of defense. Epithelial cells also help in processing of IgE to show the activity against various allergen.

### Endothelial cell

They are responsible for allergic responses by creating an affinity of leukocyte from blood to the site of inflammation.

### Mucus gland

Mucus glands secretes mucus for self-protection as well as to maintain the moisture inside the nasal wall.

### Cilia

Cilia is a hairy structure belonging epithelium, which with its systematic movement secretes mucus from the nasal pathway to the throat cavity. Temperature has a simple direct relation with the activity of cilia and promotes either nasal congestion or runny nose.

### Basal blood vessels

The basal vein with less encapsulation helps to increase the temperature of the inhaled air in the respiratory module. These vessels are directly responsible for congestion in the nasal pathway. The nerves surrounded by nerves that acts as a regulator of the congestion reflex.

### Nerves

Trigeminal and Maxillary nerves regulate the stimulation of nasal mucosa. The touch, pressure, and temperature are regulated by the trigeminal part whereas, the sympathetic and parasympathetic reflexes controlled by the maxillary nerve which includes the constriction and dilation of blood transporter. The mast cells are responsible for allergic or sensitivity reactions.

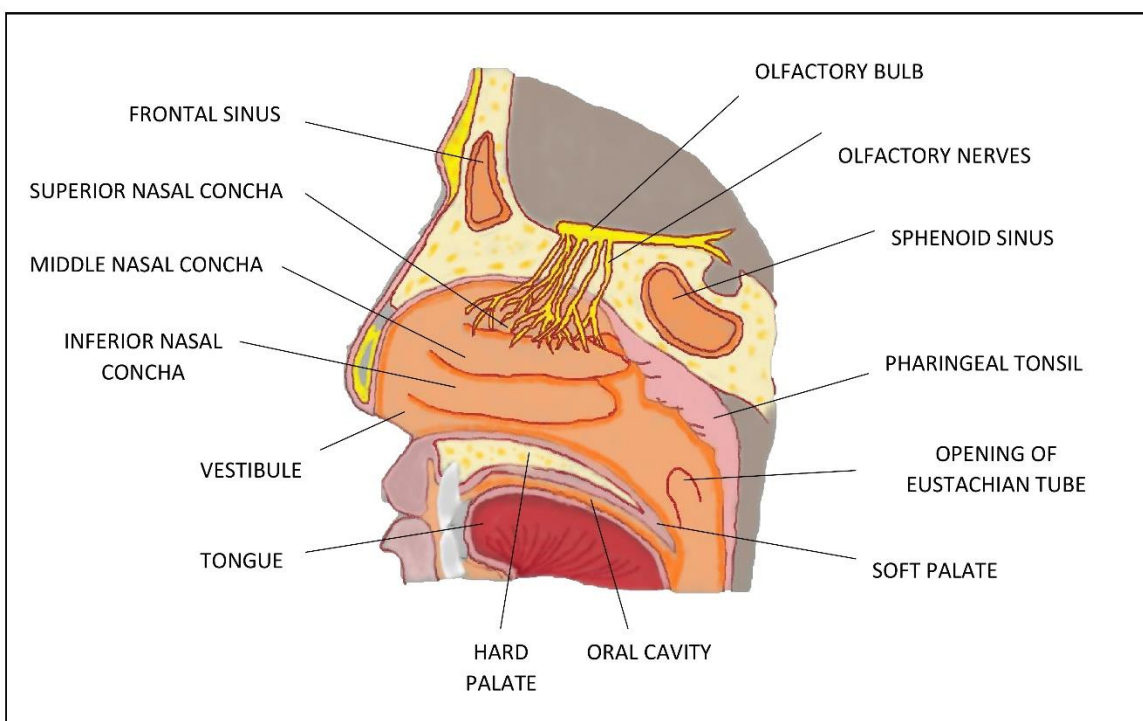


Figure 1: Anatomy and Physiology of Nose

Figure 1 depicted that the anatomy and physiology of nose. This diagram also represents the nasal routes with the proper labelling.

#### MECHANISM OF NASAL ABSORPTION

The major aim of the nasal drug delivery system is the captivation of the drug from the nasal chamber is the leaks it through mucous layer. The size of the particle plays a vital role with the permeability of the drug. It is very obvious that the particles which have very small size can pass the membrane whereas the particles which have big size can't easily cross the membrane. The mucus layer which contains a specialized protein mucin attracts the solute and influences the overall diffusion. Several exogenous factors either environmental or biological can also change the overall edifice of the mucus coating. [7] When a drug is passing through the mucus deposit, various systematic procedures are involved which overall influences the captivation. The various methods which are responsible for dispersion of active drugs are transcellular or simple diffusion which occurs around the crust of mucosa (Figure 2). The vesicles perform the transcytosis which helps in paracellular transport by maneuver drug between cells. Hypothetically, there are several mechanisms but major are paracellular and transcellular pathways. Paracellular conveying is deliberate and acquiescent. Intranasal captivation shows antithetical relation with molecular weight of water-disintegrable complexes. Very low bioavailability has been observed with drugs of molecular weight more than 1000 Daltons. [8] Another way of haulage engages transport via lipoidal track that is also called as the transcellular method which is accountable for the conveyance of the lipophilic drugs which displays rate reliance on their lipophilicity. Drugs also overlap cell sheath by the pathway of active transport through germinal of constricted convergence (Figure 2). [9] Therefore, we can derive mathematical manifestation of the effective permeability coefficient  $P_{eff}$  under steady-state conditions across excised mucosa, as equation 1:

$$P_{eff} = (dc/dt)_{ss} V / (A CD)$$

Where,  $(dc/dt)_{ss}$  is the time-dependent change of concentration in the steady-state, A is permeation area, V is the volume of the receiver compartment and CD is the initial concentration in the donor compartment. [10-11]

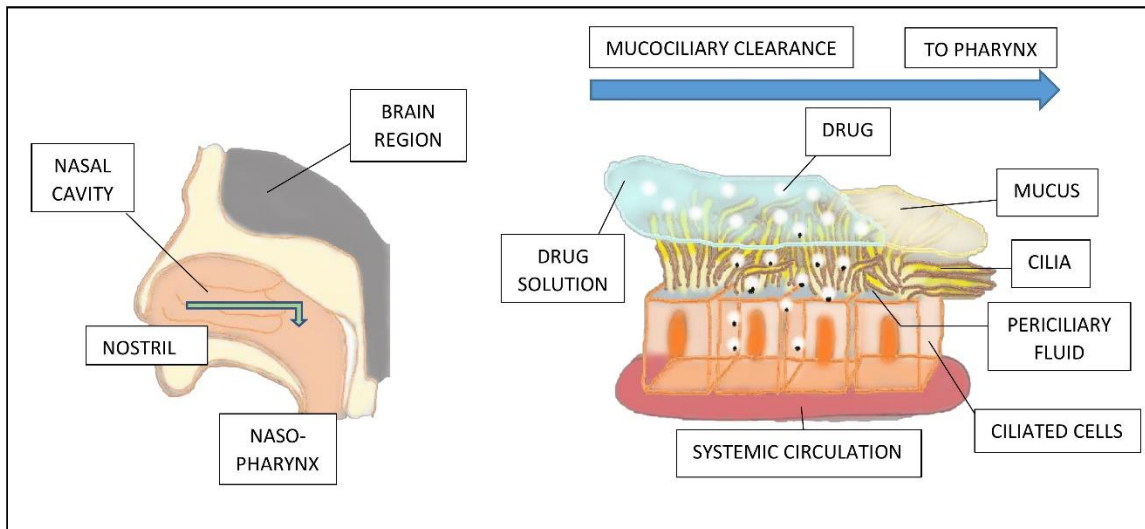


Figure 2: Mechanism of Nasal Absorption

Figure 2 depicted the drug absorption in nasal route with proper labelling.

#### OBSTACLES TO NASAL ABSORPTION

Nasal drug delivery ponders as the most economical and effective pathway for the formulators due to the simplest tactics and efficacy. Curative value and poisonous effects are controlled by several following aspects. [12]

##### Poor Bioavailability

From our normal concept, it is very obvious that lipophilic drugs have the largest tendency of absorption in comparison with polar drugs. The bioavailability is highest i.e. 100% in the case of intravenous route which is approximately the same as in the case of lipophilic drugs. e.g., Though the  $T_{max}$  (Maximum time needed for absorption) is same for Fentanyl while the bioavailability is 20% less in nasal route than the parenteral route. The low membrane permeability is the most significant and blessed element restricting the nasal absorption of polar medicines and particularly big molecular polar drugs, such as peptides and proteins. Medications may cross either the transcellular route through which simulated concentration gradients are exploited, the transceiving or transportation mechanisms of the receptors are mediated or vesicular transported or by the paracellular path through the tight junctions between cells. Polar drugs below 1000 Da usually go through the membrane on the latter path. The shipping of mucus is strongly linked to the cilia on respiratory epithelial cells. At the back, the cilia are twisted and moving in the pericellular fluid only underneath the viscous mucus. This means that the mucus of the viscous membranes is bent. The cilia carry the mucus at a velocity of ~1000 strokes per minute, and formulations administered on the human breathing epithelium have been discovered to be removed from the nasal cavity with a half-time clearance of approximately 15 minutes. The mucociliary clearance mechanism can readily transfer the medicine away from the entry point in the nose cavity into the esophagus in polar drugs which are not easily transported across the nasal membrane that limits the absorption. For instance, we take nasal spray of sumatriptan (Imigran®; GlaxoSmithKline, <http://www.gsk.com>) which displays bioavailability of 15.8%. If we compare between nasal administration with oral dosage form, we can easily observe that very small amount of drug is absorbed through nasal route so the bioavailability of nasal dosage is relatively very low with comparison with conventional oral dose. But there are some exceptions. The hydrous solution of Sumatriptan which easily expelled out from nasal cavity shows better relief than tablet though very small amount of drug is absorbed through this route. So, we can conclude that nasal route is a very potential route of drug delivery. [13]

##### Poor membrane conveyance

The overall fast removal of the administered oral cell structure owing to the mucociliary removal system is another significant variable in minor membrane transportation. In particular, these drugs are not readily taken throughout the nasal membrane. The half-life of the removal is in the range of 15-20 minutes for both liquid and powder formulations not mucoadhesive. [14]

#### Enzymatic drug mortification and prospective efflux

A few medicinal enzymes, including oxidase Phase I, conjugative phase II and proteolytic enzymes, have been recognized in the Nasal Mucus. Recent surveys proved a comparable population, communities and distributed of CYP enzymes by cattle nasal olfactory, respiratory mucous membranes and brain tissue. [15] The most significant function, however, for the shipment of nasal drugs are proteolytic enzymes. These proteins include exopeptidases that are limited to cell hydrolysis at / near the N- or C-terminal or endopeptidases, which are hydrolyzed within a cell bond. [16] Aminoproteinases, diaminopeptidases, postpropyl enzymes, angiotensine converting enzymes, endopeptidases - 24.11 (a metalloproteinase), and thioproteinase are included in these exopeptidases and endopeptidases. [17] During and after DNA intake, the existence of membrane-like and cyto-cytosolic aminopeptidases shows that both proteins and peptides may be degraded. The proteins that cause substance degradation are still not clear. It can be assumed that, based on the exposure to protein or peptide medicines, intracellular proteases are accountable. With regard to nasal enzyme activity and allocation, it shows in the olfactory region that there are likely more enzymes and enzyme activity for the disablement of toxic odor vapors. In laboratory animals (for example rodents) the high metabolic capacity of mucosa shows its roles in toxic detoxification. [18]

But, in terms of drug metabolic status, their ability and their prospective functions in people have not yet been proven. However, these enzymes can play a major role in the metabolization of ciblated medicines. Brain supplies due to absence of olfactory classification, and delayed permeation to the brain of medication. P-gp has not been proved in relation to nasally administered drug clinically important restrictions. It should be noted, however, that P-gp is regional in the nose, with a greater level of olfactory mucovascular activity and overexpression in certain chronic inflammation, which can affect drug delivery. [19]

#### Physicochemical problems drug applicants & formulations

A careful study of physical chemical characteristics of a drug molecule for the nasal route involves biopharmaceutical analysis of nasal absorption. Molecular Weight, partition coefficient, chemical stability, solubility and surface charges are the prime parameters. Although crucial for the absorption of oral medicines, these features take an significant part in the absorption of nasal medications given that the dwelling period of the nasal drug is comparatively brief owing to the concentration in mucocilia. The function of physical chemicals in nasal absorption was widely discussed. [19-20]

Not just to select suitable medication applicants, but also to ensure that the drug remains soluble and stable during the absorption phase, the physicochemical characteristics of nasally administered drug have a significant effect. If the oral mucosa is to absorb a medicine effectively, it should be comparatively water soluble, secure, small molecular in weight (about 500 Daltons), unionized and without a ground load. [20]

#### IMPROVED NASAL DRUG ABSORPTION PROGRESS TO DATE

Many methods to overcome nasal drug absorption problems have been employed or supported. Includes common approaches:

- Hindrance of clearance inhibition using mucoadhesive;
- Improvement in intake by absorption enhancer;
- Alteration of physicochemical characteristics by active component using medicines and other policies;
- Inhibition of metabolism with inhibitors of enzymes;
- Micro-/nano-particular formulation development;
- Design and feasibility of supply equipment;
- Using techniques for the testing and improvement of the intake of oral drugs ex vivo and in vitro study;

It is essential to study processes of drug permeation throughout the nasal epithelium before debating these approaches. Understanding the processes concerned is essential in the design and optimization of policies for absorption improvement. [21-22]

## NOSE TO BRAIN TARGETING

To present, most drugs for the treatment of CNS and associated brain disorders are used systematically and are a condition for crossing the blood-brain barrier (BBB). BBB is the main obstacle for the implementation of the medicine in the brain. BBB is the sensitive network of endothelial ships that separate the brain from the circulatory system. It preserves the brain against the introduction of toxins and bacteria. This barrier cannot be crossed by hydrophilic, loaded molecules or by peptides, while lipophile medicines such as antidepressants, anxiolytics and many enzymes are readily passable over endothelial cells. [23]

The nasal delivery system can be considered as one of the main non-invasive routes of delivery. Apart from DDS, another immediate transportation approach for the drug from nose to brain is to place the medicine on the olfactory epithelium or nose area, which is internalized by trigeminal nerves in order to carry more medicines into their brain through olfactory/trigeminal pathways. In order to achieve this, scientists have researched and developed numerous efficient and effective new nasal drugs distribution systems. This includes pressurized olfactory devices, nebulizers, atomizers, pressurized meter dose inhalers and bidirectional breath powdered equipment. [24] There has been also evidence of an immediate nose for the transport of drugs into the brain by humans, mainly as regards pharmacodynamic impacts on CNS, such as impacts on event-related potential during a subject's oddball task in nasal and intravenous delivery paths contrasting drug administration. [25-26]

## INFLOWING FACTORS OF NASAL DRUG ABSORPTION

Various variables influence the intrinsic bioavailability of drugs administered by the oral pathway. The physicochemical properties, the nasal cavity's anatomic and physiologic properties and the sort and features of chosen nasal drugs are affected by these variables. Multiple circumstances can affect the nasal absorption. They are,

Physicochemical properties of drug

Molecular Size [5][27]

The molecular dimension of the drug impacts the nasal absorption of the medicine. Lipophilic drugs are directly related to the permeation of the MW, whereas water-soluble substances represent a reverse relation. The permeation level for MW compounds of more than or equal to 300 Daltons is extremely molecular-sensitive.

The nasal membrane permeability for drugs seems to rely on the magnitude of the drug molecules. In a thorough assessment of various drugs with a molecular weight ranging from 160 to 34000 Da, the impact of molecular sizes was explored. [28] The findings indicate that the molecular weight of nasal absorption reduces exponentially. For rats and people, the same pattern was observed. The molecular weight of the nasal rate limiting was 1000 Da as against 300 Da for the oral route. In other research, rat have exposed with oral intake of various water-soluble compounds, including p-aminohippuric acid, potassium cromolyn, inulin and dextran with distinct molecular weights. [29] The findings showed a strong linear correlation between the logarithm of percent absorbed and the log of molecular weight, indicating aquatic channels' involvement in water-soluble molecules' respiratory intake. [30] It is been also found that there is an overall impact of nasal absorption with the molecular weight of polydisperse polyethylene glycols (PEGs, 600,1000 & 2000) in rats. [31] Higher the molecular weight, lesser is the absorption.

Chemical Form

In determining absorption, the chemical type of a drug is essential. Converting the drug to salt or ester can also change its absorption, for instance. Huang et al., observed the impact on absorption of the drug structural alteration. [32] In-situ nasal absorption of L-tyrosine carboxylic acid esters has been found to be much higher than L-tyrosine.

Polymorphism

Polymorphism happened when one drug can exist in more than one crystalline form. It is very common that polymorphism can alter the dissolution rate and solubility of drugs. This can also change the absorption via physiological sheath. [33]

## Particle Size

The oral cavity has been revealed to contain particulate dimensions above 10 $\mu$ m. Particles 2 to 10  $\mu$ m in the atmosphere may be maintained and ions below 1  $\mu$ m exhale. [32-33]

## Solubility & Dissolution Rate

Drug solubility and rate of dissolution are key considerations in the determination of powder and suspension nasal absorption. The nasal cavity stored ions must be disbanded before they are absorbed. No absorption happens when a drug stays as droplets or has been removed. [33]

## FACTORS FOR FORMULATION

### Formulation pH

In order to optimize systemic absorption, both the pH of the nasal cavity and the pKa of a certain drug must be taken under contemplation. When delivering products with a pH range of 4.5 to 6.5 nasal irritation is minimized. It is also essential to remember quantity and intensity. The amount of shipment is restricted to the nucleus of the nose. A maximum restriction of 25 mg / dose has been proposed and a quantity of 25-200  $\mu$ L / nostril.

Maintenance of pH is much important in case of nasal formulation preparation. The reasons are following:

- To prevent nasal mucosal inflammation
- In nasal passage, to avoid the development of disease bacteria
- To keep excipients such as preservatives functional
- Maintain excipient features such as preservatives
- Support ordinary ciliary physiological motion

The nasal secretions that cause some bacteria to be removed in acidic pH are lysozyme. Lysozyme is blocked under alkaline conditions and the tissue of the nose is prone to microbial infection. Therefore, it is advisable to take into account the physiochemical characteristics of the drug at a pH of 4.5 to 6.5 when taking drug products unionized.

### Buffer Capacity [34]

In general, tiny amounts of nasal formulations varying from 25 to 200 $\mu$ L are administered. Nasal secretions can therefore change the pH of the given sample. The level of the unionized drug accessible to absorb may be affected. A sufficient buffer capacity may therefore be necessary to keep the pH present.

### Osmolarity [35]

Tonicity of formulation preparation may affect drug absorption. The decline in the existence of hypertonic alternatives has been noted for epithelial cells. Hypertonic saline solution is responsible for constraining bustle of cilia. Low pH has an impact comparable to hypertonics. Suzuki et al.,1999 have shown that a drug holder like hydroxypropyl cellulose can improve the absorption of low-molecular weight drugs but does not have the same effects for high-molecular peptides.

### Solubilizers [36]

Aqueous drug solubility is a nasal drug delivery constraint in equilibrium. Conventional solvents or co-solvents, such as glycols, tiny amounts of drugs, transcutol, medium chain glycerides and labrasol, may be used to improve drug solubility. Other options

include the application, in conjunction with lipophilic absorption boosters, of surfactants or cyclodextrins such as HP- $\beta$ -cyclodextrin as a biocompatible solubilizer and stabilizer.

#### Preservatives [37]

The majority of nasal formulations are consisting with water which are very prone to microbial growth should be added with preservative. Generally, Parabens, benzalkonium chloride, phenyl ethyl alcohol, EDTA and benzoyl alcohol are used. Van de Donks et al., 1980, demonstrated the rapid and irreversible impact on ciliary motion of mercury comprising preservatives and should not be used for nasal devices.

#### Antioxidants [38]

Antioxidants usually do not trigger nasal discomfort or drug uptake. As portion of the formulated design programmed, chemical / physical interactions of antioxidants and preservatives should be regarded with medication, excipients, manufacturing machinery and packaging elements. Sodium metabisulfite, sodium bisulfite, butylated hydroxyl toluene, and tocopherol are commonly used antioxidants. Significant clinical improvement has been found with the use of antioxidant with fluticasone furoate rather than single use of fluticasone furoate.

#### Humectants [39]

Many allergic and chronic conditions are often linked to crusts and mucus washing. In order to prevent dehydration, adequate intranasal moisture is crucial. Thus, particularly in gel-based nasal products, humectants can be introduced. Nasal infection is prevented by humectants and is unlikely to impact drug absorption. Glycerine, sorbitol and mannitol are common instances. The use of sorbitol or glycerine have shown improvement in the permeation of apomorphine.

#### Drug Concentration, Dose & The Volume of Dose [40-42]

Drug levels, drug and quantity are three interrelated parameters that affect the efficiency of the nasal service. In nasal perfusion studies, nasal absorption of L-Tyrosine increased with drug level.

#### Role of Absorption Boosters [43-44]

Added absorption improvers may be needed if the drug shows bad membrane permeability, big molecular size, insufficient lipophilicity, and amino-peptidased enzyme degradation. The improvement impact can increase osmolarity and pH. For example, surfactants, glycosides, cyclodextrin and glycols are enhancement substances. Improve absorption through a number of distinct processes, including increased fluidity of the membrane, increased blood flow of the nose, reduced mucus viscosity, and inhibition of enzymes.

### PHYSIOLOGICAL FACTORS

#### Effect of Deposition on Absorption [44]

The deposition of the formulation in the anterior part of the nose offers a larger period of nasal dwelling. The previous part of the nose is poor permeability and the rear part of the nose with a greater drug permeability offers longer stay.

#### Circulation of blood through nasal route [45]

A vasculature-rich nasal mucosal membrane performs an important part in thermal regulation and moisturisation of the breathed air. Vasoconstriction and vasodilatation of blood vessels will determine the circulation in the blood and thus the drug absorption.

#### Mucociliary Clearance Effect [46]

Drug absorption is affected by the moment between the drug and the epithelial tissue. Mucociliary removal is inversely related to the moment of stay and, consequently, inversely linked to drug absorption. The mucociliary clearance relates inversely to

the period of residency and, consequently, to drug absorption. The use of bioadhesive polymers or an increase of the viscosity of the product can also achieve a longer stay in the nasal cavity.

#### Action of Enzyme [47]

Various enzymes current in the nasal mucous membrane could influence drug stabilization. Proteins and peptides, for instance, have been degraded in the mucosal membrane by proteases and amino peptidase. The amount of aminopeptidase in the gastrointestinal system is considerably smaller. Peptides can also create immunoglobulin clusters (Igs) that boost molecular weight and decrease permeability of the nasal cavity.

#### Effect of Pathological Status [48]

The nasal mucociliary method and/or the ability for nasal absorption could be affected by intranasal diseases such as allergic rhinitis, diseases, or previous nasal surgery. In the freezing, the intranasal drug's efficacy is frequently affected. Insulin-dependent diabetes decreases nasal clearance. Nasal disorder may also change the pH of the mucosa and consequently influence absorption.

### SYSTEMS OF NASAL DRUG DELIVERY

#### Nasal Drops and Sprays

Nasal drops are among all formulations one of the most simple and comfortable shipping processes. The primary limit is the absence of accuracy in the dosage given and the danger of contamination during use. [49] A pipette or a squeezed tube can be supplied to the nasal drops. [34-39] These are generally suggested for local circumstances, but difficulties include microbial development, mucociliar dysfunction and unspecified nose or neck reduction. [49] A piston and a tube working actuator are the nasal spray devices. Relatively more precise nasal sprays than drops produce accurate amounts (25-200  $\mu$ l) per spray. [34] Several trials show that a coherent dose of reproducible plum geometry is generated through nasal sprays. Properties of formulation, such as thixotropy, surface tension and viscosity may affect droplet volume and dosage precision. The most used form of dosage for nasal administration of drugs is liquid preparation. They are focused primarily on aqueous formulations of the state. Their moisturizing impact is practical and practical, given that many allergic and chronic diseases are often linked to crusts and mucosal membrane processing. [50] The significant drawbacks connected with the water-dose formations are microbiological strength, discomfort and allergic rhinitis, because the necessary preservatives affect the mucosal structure. [51]

#### Instillation and rhinyle catheter [52]

Drops are readily supplied to a certain area of the nasal cavity with catheters. The formula was placed on the nose on the one side of the pipe and the remedy was supplied through the other by the mouth into the nasal cavity.

#### Compressed Air Nebulizers [49-50]

Nebulizer is a medicine that is breathed into the lungs in the shape of a brist. The condensed water fills into the machine and is therefore referred to as forced water nebulizers. For all nebulizers the common technical principle is either to use oxygen, compressed air or ultrasound energy as a means of breaking up medical solutions / suspensions in small droplets, for direct inhalation from a device's mouthpiece.

#### Squeezed Bottle [53]

The most commonly used for the supply of decongestants is squeezed nasal containers. A soft metal container with a straightforward gas inlet is included. The wind in the container is pushed out from the tiny punch while the plastic bottle is pushed and a certain quantity atomized. Air is taken into the jar by pulling the stress again. This operation usually ends in micro-organism and nasal secretion contaminating the liquid.

#### Metered-dose Pump Sprays [51-52]

A metered-dose pump spray is provided with many of the pharmaceutical nasal preparations that contain alternatives, emulsions, or suspensions on the market. Nasal sprays or nasal mists are used for the shipment of a drug or drugs locally to relieve the general signs of pain or allergies such as nasal congestion. Although the techniques of the shipping variable, most nasal sprays work through the instillation of a good nebula in the nose by hand pumping. The three principal kinds of local effects accessible are: antihistamines, corticosteroids, and topical decongestion. The container, the valve's pump, and the actuator include measured volume pump sprays.

#### Powder Dosage Forms [53]

Dry powder is less commonly used in the shipment of nasal drugs. The main advantages of this dosage form are the absence of preservatives and an improved formulation stability. The administration of powders in comparison with alternatives could lead to long-lasting interaction with the nasal mucosa.

#### Insufflators [52]

The insufflators are equipment for inhaling the drug; they can be built using a straw or pipe containing the drug substance and, at times, containing the syringe. Compared to the particle size of the dust material, the parts obtained by these processes are often improved owing to inadequate de-aggregation of the solids and lead to a elevated variety factor in original fields of deposition. Many insufflator devices operate in capsules with pre-dosed dust.

#### Dry Powder Inhaler [54]

Dry powder inhalers (DPIs) are instruments by which the effective drug's dry powder structure is supplied via pulmonary routes to local or intrinsic effects. Dry powder inhalers are bolus inhalers containing a strong medicine capped or placed in a non-polar unstable propellant or the inhaler of dry powder, fluidized when the child inhales.

#### Pressurized MDIs [55]

A metered dose inhaler is a tool that supplies a certain quantity of medication to the lungs as a brief explosion of exhaled aerosol medicine. Asthma, chronic obstructive lung illness like COPD and other breathing conditions are the most frequently used delivery system for treatment. The drug in a metered dose inhaler is mainly a bronchodilator, corticosteroid, or a mixture for both asthma and COPD therapy. Mast tissue stabilizers, such as cromoglicate or nedocromil are also less frequently used but also MDI administered medicines. MDIs benefit from its portability and its tiny volume, accessibility over a broad spectrum of doses per actuation, sample consistency, dosage precision, packaging safety and readiness to be used rapidly. In general, more than 99% of the dose is provided by propellants in MDIs. The instrument act produces a previous sample of the mixture containing the drug, either submerged in the propellant or held in it. The breakdown into droplets of the volatile propellant, accompanied by fast evaporation of these droplets, ends in a micrometer-sized medication particle aerosol which is then breathed.

#### Nasal Gels [56]

Nasal gels are alternatives or suspensions with high viscosity thickening. There was little concern in this scheme until the latest growth of accurate dosing systems. Nasal gel's benefits include reducing post-nasal flow owing to elevated viscosity, reducing flavor effect owing to decreased swallow, reducing pre-formulation leakage, reducing discomfort through the use of soothing excipients and targeting of mucosa to increase intake. The deposition of the gel in the nasal cavity relies on how the product is administered because the product has bad diffusion capacity owing to its viscosity. In the facial canal, it is put straight in the facial canal with no unique implementation methods. Recently, the first vitamin B12 nasal gel was launched on the market for generic drugs.

#### ASSESSMENT OF DOSAGE FORM [57]

##### Appearance, Color, and Clarity

The content (i.e., formulas) of the container and the container closure system (e.g., components of the bowl, inside the container) should be indicated as an indication of the drug product completeness according to their respective descriptions. If a colour

connected with the formulation is (originally available or from degrading procedures that occur during shelf life), the supplier shall establish a quantitative exam of the drug product with suitable recognition requirements.

#### Priming and Repriming in Various Orientations

Studies should be conducted on the multiple-dose of pulmonary and inhalation-spraying goods, in order to characterize, in multifocal (straight and reversed or straight and horizontal) and after distinct phases of non-use, priming and repressing needed for the item. It is important to evaluate SCU and other relevant parameters. It is necessary to provide the previous data:

- An estimated period before the drug item should be repressed in order to supply the labeled quantity of drug.
- The number of sprays to activate or repress the device.
- Introductory sprays and sprays near the label claim number should be used for multiple orientation studies. In order to promote the suggested tag claims, priming and repressing data will be used.

#### Rest Time Effect

For multidose spray medications, research to determine the impact of increased rest period on first unit spray, accompanied by second and fifth sprays, is suggested. Only before the survey is initiated, units should be prepared. The homogeneity of the medicines provided for the first, second and third sprays (no priming) should be determined after rest for increasing periods of time (i.e., for 6, 12, 24, 48 hours). Testing of the systems in separate directions (i.e., straight and reversed or straight and horizontal) should be done. To shorten the research duration, tests on distinct samples with gradually shorter rest times can be carried out simultaneously.

#### Temperature Cycling

A cyclic stress temperature analysis should be carried out to assess impacts of elevated and small temperature differences during the delivery and processing of drug products for nasal spray, inhalation suspension and inhalation injection products. The studies can consist of 12-hour cycles with a minimum of four weeks of temperatures ranging from freezer temperatures (-10 to -20 ° C) to 40 ° C. With suitable reasoning, alternative circumstances and length can be used. Periodically, the specimens should be evaluated for suitable parameters at the start of a predetermined number of runs, opposed to the control medicinal item. Parameters for testing cycling research should include, as relevant, allocation of droplet volume, particle size distribution, dimensional assessment, shape, colour, transparency, testing, SCU, motor parts ' sterility and capabilities. Instead of sterility tests, a validated container boundary validity experiment can be used to evaluate sterility and show that the container closure system maintaining the continuity of the micro space obstacle. In terms of the presence of nasal spray and medicinal products for inhalation, the product decolouration, the distortion of pump parts and the pumping, and drug attachment to the container, the closed and/or filter parts should be taken into consideration as appropriate.

#### In Vitro Dose Proportionality

Studies should address the in vitro dose proportionality between the strengths by defining the distribution of SCU and particle-/droplet-size for nasal and inhaled spray drug products with multiple strength suspension formulations.

#### Cleaning Instructions

For nasal and inhalation spray drug products, in-use studies should be performed to determine the frequency of cleaning and related instructions to be included in the labeling.

#### Strength of the device

The strength of the device should be taken under evaluation for products related to nasal & inhalational spray drugs and they should commit the following:

- A study should be conducted in order to establish the product performance properties for the SCU and the distribution of particle/droplet size across the nominal number of sprays in devices that can be used repeatedly with replaceable reservoirs.
- To determine suitable substitution times for the instrument, the use limits for error in the critical system systems should be investigated.
- Different processing scenarios, like descending, trembling, trembling, etc, should examine the efficiency features of the instrument.

See the records of the Center for Devices and Radiological Health (CDRH) for further data on research on instrument robustness.

#### Dose Orientation Effect

Studies on the relative efficiency of instruments in SCU and particle/droplet distributions in different dosage orientations should be conducted for oral and inhalation foam medicines.

#### Variable Flow Effect

The impact of the different flow rate on inhalation spray medicines should be investigated and addressed as follows:

- A study should be undertaken to determine the SCU and the sized particle/droplet distribution according to different testing flow rates at a constant volume, in the case of breath-activated drugs or those intended for marketing with an expansion or holding chamber, spacer or the like. There should be a complete amount of 2 liters. This research evaluates the tolerance of the machine to a wide variety of stream prices caused by clients of a distinct era, sex and illness.
- The activation intervals for the flow rate of delivery quantity and the respective particle/droplet type allocation should also be assessed in additional research for breath-activated products.
- A separate study is encouraged to assess, with a specified flow rate, the effect of the increasing waiting periods (e.g., 0, 5, 10 seconds) between actuation and start of inflow on the SCU and the particle/droplet size distribution for drug products with an expansion or holding chamber, spacer or similar component.

#### Near container explosion (Tail Off Features) profiling of sprays

A study is needed for the profiles of nasal or inhalation drug products to determine the distribution of the size of each single spray, whether in SCU and droplet (solution) profiles (suspension) after a point where there is no spraying more (i.e. the container is empty). Pump shipping tests for problem formulations can be substituted with SCU tests. These surveys assist to determine whether the goal load and any suggested container overfill is warranted, because the top of properties can differ depending on pump layout, container geometry and structure.

#### Storage effect on the distribution of particle size

The stabilization tests on the main stabilization lots should determine the impact of processing moment and circumstances on grain volume with respect to suspended spray medicinal goods. If stabilization surveys have an impact on the allocation of particulate mass over system lives then the daily maintenance protocol must include device life-testing of particulate mass allocation.

#### Plume Geometry

Penetration anatomy should be defined for allergic spray medicinal goods. The plume geometry does not differentiate between the nuclei of the drug substances and the water product bubbles or show any density gradient, but rather the whole plume structure. Similar nasal pulverized medication products may be compared by distinct producers or if certain modifications to an already authorized medicinal product are implemented, by the plume geometry characters.

## Efficiency of preservatives and maintenance of sterility

If preservatives have been used in the design, a microbiological test for the microbial problem test of the drug designed with a level of preservation equivalent or below the minimum quantity indicated should demonstrate a minimum level of microbiological efficacy. See the stabilization guideline for information on this characterization. In order to determine the appropriate microbiological quality during the reservoir life and during the time the reservoir is used, studies should be carried out on inhalation spray pharmaceutical products measured on an equipment basis. These tests could evaluate the capacity to avoid the application and/or to inhibit the development characteristics of the product by the container clamping scheme.

## Nebulizer characterization specified characterization

Research to determine the amount supplied and the particle/droplet length allocation in accordance with the specified working parameters and range for a given nebulizer should be carried out for inhalation solution and suspension medications.

## Photostability

If warranting instant containers, i.e., a design in the main container may obtain air contact, Photostability tests should be conducted under suitable sample circumstances. In the lack of extra products (e.g., metal overwrap), these tests should be performed.

## Primary Package Stability (Unprotected)

If additional labels (e.g., foil overwrap for LDPE-containing item) is applied in the medicinal product for space climate processing, adequately stable data conducted at a minimum of 25 ° C and up to 40% RH, without safety packaging for relevant parameters, for these devices should be produced for a drug product marked for room temperature storage. The information can help to determine the peak item use duration after the safety packaging has been withdrawn. Both freshly produced drug products and close to the close of the suggested expiry date should be assessed.

## Special Evaluation test for Nasal Spray: [58-59]

## Colour, Clarity & Display

The container contents (i.e., the formulation) and the container closure system (for instance, pump components within the container) should be present as an indication of the integrity of the drug product as described in their respective descriptions. If the formulation is related to any color (whether originally present or from degradation procedures that occur during shelf life), then the manufacturer should set a quantifiable test with adequate recognition requirements for the drug product.

## Identification

In order to check the identity of the drug substance in the drug product, a specific identification test is suggested. Time-alone chromatographic retention is insufficient to guarantee the drug product's identity. If the medicinal material is one enantiomer, at least one of the techniques for this property should be particular.

## Drug Content (Assay)

A stability-indicating procedure should be used to determine the test of the medicated substance on the entire container. The test guarantees a consistent production (for example, formulation, filling, screening). Criteria of acceptance (assay limits as laid down in official books) must be narrow enough to guarantee compliance in other associated characteristics (e.g., uniformity of spray material). In order to tackle any degradation of the pharmaceutical product, drug adhesion to container compounds and closure elements, and the prospective impact of formulation evaporation and/or leakage, an appropriate test method should be developed.

## Impurities and Degradation Product

The rates of product and impurity degradation should be determined by the process(s) showing stability. Individual and complete degradation products and impurities should be established with the acceptance criteria. Refer to the suitable guidelines for identifying and qualifying thresholds. It is required to specify all associated impurities which appear at 0.1% or above. The impurities and degradation products specified are those which are, identified or not, individually and limited in the specification of the drug product.

## Preservative(s) and Stabilizing Excipient(s) Assay

A special test with the corresponding acceptance criteria (at the concentration of 0,10 percent or 1,0 milligram per day) for these components should be conducted if preservatives, antioxidants, chelates or other stabilizing excipients (e.g., benzalkonium chloride, phenyl alcohol, edetate) are applied to the formulation.

## Pump Delivery

A test should be conducted to assess the reproducibility of the pump in terms of the efficiency of the drug product and to assess the pump's metering capacity. A pump manufacturer, who should assemble the pump with accurate dimensions components, should ensure adequate output in the pump mainly. The applicant for the drug product should verify the supply of pump spray weight. Generally, acceptance criteria for pumping spray weight should regulate the weight of each spray up to  $\pm 15\%$  of its destination weight and its mean weight up to  $\pm 10\%$  of the target weight.

## Spray Content Uniformity (SCU)

The spray released from the nosepiece should be carefully evaluated among containers and batches of a drug product for the content of various sprays in a particular container. The exam should provide a general assessment of the results of a batch, assessment of the formulation, production method, and pump. The number of sprays should not exceed the number of sprays per dose per determination. The minimum number of sprays per nose indicated in the item labeling is one dose. The method should be checked for actuation parameters (e.g., stroke length, depressive force) to guarantee a reproducible in vitro dosage collection. The experiment can be done with units that have been prepared according to the labeling guidelines. As the true quantity and percent of the label demand, the quantity of drug substance supplied from the nose part should be expressed. This test is intended to show that the drug is compatible with the label statement of a suitable amount ( $n= 10$  is recommended for each batch of containers, by spray or a minimum dose), taken from the nosepiece. The primary objective is to ensure SCU within the same container and between several batch containers. The requirements for adoption are as follows:

- For more than 1 out of 10 containers, the amount of active ingredient for each determination does not exceed 80% to 120% of the marked claim, none of them exceeds 75% to 125% of the label claim and the mean does not exceed 85%-115% of the label claim.
- For more than 1 out of 10 containers, the amount of active ingredient for each determination does not exceed 80% to 120% of the marked claim, none of them exceeds 75% to 125% of the label claim and the mean does not exceed 85%-115% of the label claim.
- In the second level of batch testing, the amount of active ingredient per determination does not exceed 80–120% of the label claim for more than three of all 30 determinations, none of these 30 determinations exceeds 75–125% of the label claim and the mean is 85–115% of the label claim.

## Spray Content Uniformity (SCU) through container life

This test aims to determine whether the item offers the amount of fully labeled SCU admission requirements for medicinal products over the entire lifetime of the nasal spray unit. The test includes determining the SCU for the suitable number of containers ( $n= 5$  is suggested), from the start of unit life and at the requested amount claims sprays per container. The following acceptance criteria are recommended.

- A label claim amounts to not more than 1 in 10 determinations from five containers and not more than 80-120% of the label claim, neither of the determinations is beyond 75-125% of the label claim and the means of each of the start and end decisions are not less than 85-115% of the label claim.
- If 2 or 3 of 10 determinations do not exceed 80–120 percent of the etiquette claim, no label claim exceeds 75–125 percent, and the mean do not exceed 85–115 percent of the label claim for each start-and-termination decision, a further ten containers shall be sampled in the first quarter and the second quarter at the end of the etiquette.
- The second stage of batch testing involves a total of no less than 80–120 percent for the label's claim, no one of the 30 determinations exceeding 75–125 percent for each of the label's claims and no less than 85–115 percent for each of the start and end determinations.

### Spray Pattern and Plume Geometry

Spray pattern characterizations and plume geometry are essential for assessing the pump and dust performance. Different variables may influence the geometry of the spray pattern and feather, including the size and shape of the pump, the pump layout, the chamber size, and the formulation features. Spray pattern testing as a quality control for the release of a medicinal product should be done on a regular basis. However, during the product characterization, feather geometry should usually be determined and not regularly tested thereafter. To permit replication by agency laboratories, the suggested testing procedure for the spray pattern, including analytical sampling plans, should be detailed. For example, the spray distance to the nosepiece and the collection surface is to be indicated in the evaluation of the spray pattern, the number of sprays per spray pattern, as well as their position and orientation in relation to the nosepiece and the process of visualization, should be determined. The acceptance criteria should include the form (e.g., the uniform density ellipsoid) and the size of the pattern (for example, no axis is more than x millimeters and the ratio from the longest to the shorter axes is to be within a certain range, e.g., 1.00 to 1.20).

The spray pattern should be determined at distinct distances (e.g., two) from the nose-piece, preferably by an operation particular to the medicinal substance, in order to offer higher discriminatory testing. By developing a delicate detection procedure and supplying procedure 502 with particular analyst training, the variability in the experiment can be decreased.

### Distribution of Droplet Size

The requirements should include the appropriate control of the droplet size distribution of the feather supplied following spraying in certain experimental and instrumental conditions for both suspension and solution nasal sprays (i.e., 3 to 4 cut-off values). Sufficient details are needed in order to allow precise evaluation by agency laboratories (e.g., appliances and accessories, software version and algorithms of the calculation, sample positioning, laser trigger, measurement range and beam width) to adequately and validate dynamic feather droplets size analytical procedures.

### Particle Size Distribution (Suspensions)

The specification should contain controls for the allocation of particle sizes of the drug substance parts in the formulation for suspension nasal sprays. The sensitivity and capacity to detect changes that could happen within the distribution should properly validate this Quantitative Process. The criteria of recognition should monitor the entire allocation and reflect the information gathered on the lots presented (e.g., clinical, pre-clinical, bio batch, main stabilization, manufacturing).

### Microscopic Evaluation (Suspensions)

In addition to particle size distribution tests for release and stability reasons, this experiment includes a qualitative and semi-quantitative microscopic examination of the suspension formulations. For instance, the review provides information on the presence of large particulate matter and changes in the morphology and extent of agglomerates and crystal growth in the drug substance particles. Moreover, if changes in the strong condition of a drug substance may impact bioavailability, efficiency, stability, or other characteristics of a drug product, the control and monitoring of modifications in stability observable is suggested for microscopic assessments or other suitable processes.

## Foreign Particulates

Validated tests and related approval criteria for overseas particulates shall be available for both solution and suspension nasal sprays. During the production of formulating parts, and in specific container and closure materials, foreign particulates may originate.

## Limitations of microbial

In addition to the maximum aerobic count, total yeast and mold counting, and freedom from indicator pathogens, the microbial value should be regulated by acceptable tests and acceptance criteria. The approval requirements must reflect the submitted batches' data (e.g., medical, preclinical, bio batch, primary stability and production), but should fulfill the prescribed criteria for appropriate microbial limits in USP < 1111 >, Non-sterile Pharmacopeia microbiological attributes, at least. Appropriate testing must demonstrate that the pharmaceutical material does not help microbial growth and that the microbiological value is preserved over the expiry span. Link to the protocol in USP < 61 > for a description of this sample.

## Efficacy of Preservatives

Stability checks should include microbial challenge studies conducted on the first three manufacturing lots of a medical product for nasal sprays that contain a preservative(s).

## Net Content and Weight Loss (Stability)

Products of nasal spray medications must have net product acceptance criteria and quality weight loss. The pharmaceutical material should be placed in straight, inverted and flat, horizontal positions to test this characteristic, since the orientation of storage has a vital part to play in any weight loss. All formulation sections of the container should be listed for their total net material. The net content will be according to the release specification in each of the 10 test containers. See the method in USP < 755 > Minimum Fill for a summary of this test.

## Reinforceable (Stability)

The pharmaceutical material should be tested for compounds such as nitrosamines, monomers, plasticizers, accelerators, antioxidants, or vulcanizing agents that leach from elastomers or plastics of the container shutting method. During research studies, adequate analytical protocols should be established for the detection, monitoring and quantification of leached components in the drug material. In addition, these approved protocols may be used during the entire delivery period to check the pharmaceutical product. Suitable acceptance criteria should be defined for the levels of liquid compounds in the formulation.

## pH

The apparent pH of a product should be tested for both solution and suspension nasal sprays, as well as an appropriate acceptability criterion. Under alkaline conditions, lysozyme inactivation and nasal tissue susceptibility to bacterial infections are contained under nasal secretions responsible for the destruction of certain bacteria at an acidic pH. Therefore, it is advisable to keep in mind the physicochemical properties of the drug at a pH of 4.5 to 6.5, since drugs are absorbed in a unionized shape.

## Osmolality

With an acceptable method and approval by the supplier, the osmolality of the product should be measured and controlled.

## IN-VIVO EVALUATION [60-61]

### Rat Model

Intraperitoneal injection of pentobarbital sodium is used as anesthesia for rats. There is an incision in the neck and a polyethylene tube canceling the trachea. The femoral vein gathers blood samples. [60]

### Rabbit Model

Rabbits anesthetically injected with a ketamine and xylazine combination. The head of the rabbit is kept upright and the drug solution is added to each nasal spray. The blood samples are taken from the marginal ear vein or artery by an inhabited catheter. [60]

### Dog Model

Intravenous sodium thiopental injection is anesthetizing the dog and sodium phenobarbital anesthetics are preserved. The ventilation is provided by a positive pressure pump via a smacked endotracheal tube. The blood sample from the juvenile vein is done. [60]

In dog models, Beagles have been used whose weight was near about 10 kgs and age was 1-2 years old. The main advantage of using dog models was that they were easy to handle and had malleable mold, also dogs contain large and open nostrils. The dogs used were trained for intranasal drug administration, therefore no anesthesia was required to be administered, which acted as an added advantage. However, if the drug to be administered is likely to produce irritation in the nasal canal, then prior anesthesia should be carried out. Dogs, like humans, can thrive well in a normal environment. They don't require any facilitated animal house. Also, the unavailability of proper or standard food may not affect the survival of dogs much. Thus, using dogs for experimental analysis is way more cost-effective. [61]

Despite all the aforementioned advantages, there exist certain negative aspects of using dog models in experiments. The anatomical build-up of dogs is very different from human beings. Although these two species have similar intranasal volume, size, and surface area value. This large surface area value provides for better absorption of intranasal drugs from the nostrils of dogs. Hence, we can infer that the dog model is well-suited for performing any trial related to intranasal drug delivery. [61]

### Sheep Model

Available for the practical examination of formulations for nasal delivery. Sheep breeding in the house is used because they are free from nasal infections. [60]

### Monkey Model

Sheep breeding in the house is used because they are free from nasal infections. The monkey is persuaded by intramuscular ketamine hydrochloride injections or by anesthetic intravenous Phenobarbital sodium injections. The monkey's head is kept upright and the drug solution is inserted into each eye. The blood samples were obtained in the vein by an internal catheter. [60]

## CONCLUSION

When compared to parenteral drug administration, the nasal drug delivery system is a viable alternative route of administration for a number of systemically acting medicines with poor bioavailability. It also has advantages in terms of enhanced patient acceptability 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. We anticipate that intranasal treatments for short-term conditions like erectile dysfunction, sleep induction, acute pain (migraine), panic attacks, nausea, heart attacks, and Parkinson's disease will soon be marketed alongside novel nasal treatments for long-term conditions like diabetes, growth deficiency, osteoporosis, fertility treatment, and endometriosis. The formulation of the medicine and the delivery system must be carefully designed, and their interactions with one another must be understood for these attributes to be successfully used.

## AUTHORS CONTRIBUTION

Mr. Souvik Chattopadhyay selected the topic and did the overall planning. Mr. Sourav Chakraborty, Mr. Subhas Chandra Maity and Mr. Sumon Sheel searched the literature and drafted the manuscript accordingly. Mr. Dipan Roy checked the similarity index after the completion of the writing. Mr. Souvik Biswas checked the manuscript continuously during the drafting and formatted it. Dr. Mrinmoy Nag guided the co-authors during the drafting of the manuscript. Mr. Sanjit Mandal checked the language and grammatical errors and lastly Mr. Amartya Sen edited all the pictures of the manuscript.

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## CONFLICT OF INTEREST

The authors declare that they have no conflict of interest.

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