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An Overview of Intranasal Drug Delivery System

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Abstract

Nasal drug delivery has a long history that begins with the topical administration of medications meant for localized effects. The Indian medical system known as Ayurveda recognizes nasal therapy, also known as "Nasya karma," as a legitimate kind of treatment. The review focused on nasal drug delivery systems since they have higher systemic bioavailability when administered via the nasal route as opposed to the oral route. When compared to other drug delivery methods, the primary advantages of nasal delivery include: prevention of first pass metabolism; high permeability of certain drugs in nasal epithelium; quick drug absorption across this membrane; rapid onset of action; improved patient compliance and comfort; and sustained and prolonged action. Nasal administration is a beneficial long-term therapeutic option in addition to parenteral therapy. In this review was concentrated on anatomy and physiology of nose, factor affecting nasal drug absorption, nasal drug delivery dosage forms, novel nasal drug formulations, evaluation of nasal formulations.

Keyword-Anatomy, Intranasal drug delivery, Novel nasal formulations, Factors, Bioavailability.

I. Introduction

Nasal drug delivery has a history in the topical administration of medications meant for localized effects in earlier times. Ayurvedic medicine, commonly known as "Nasya karma," recognizes nasal therapy as an appropriate kind of treatment. The nasal route was introduced in the early 1980s as a potentially effective systemic drug delivery option to replace other traditional drug delivery methods. With a highly vascularized epithelium and a porous endothelium membrane, the nasal route is a dependable, easy, and easily accessible method of absorbing substances into the systemic circulation. This prevents the need for hepatic first pass elimination. Also, dose reduction, a faster initiation of pharmacological activity, a quicker attainment of therapeutic blood levels, and less side effects are all made possible by intranasal drug delivery. Potential exists in the nose's low metabolic environment. Moreover, nasal administration provides non-invasiveness, self-administration, patient comfort, and patient compliance—factors that are barriers in intravenous drug therapy—while minimizing the lag time connected with oral drug delivery.[1] A nasal drug delivery device can be used topically or systemically. Vaccines, hormones, proteins/peptides, and small and big macromolecules can all be administered through the nasal passage. A few nasal delivery systems that are now available for purchase and have been utilized in experimental investigations include thermoreversible mucoadhesive gels, gels, microemulsions, sprays, powders, and gels. Nowadays, nocturnal enuresis, osteoporosis, migraine, and vitamin B12 insufficiency are all being treated with nasal administration systems. Other therapeutic areas that are being developed or may be delivered via the nose include rheumatoid arthritis, cancer treatment, antiemetics, epilepsy, and insulin-dependent diabetes.[2] Nasal administration appears to be a promising method for getting beyond the blood-brain barrier (BBB) barriers such that direct drug delivery can occur. [1]

Anatomy, Physiology and Histology

The nasal cavity's primary uses in humans and other animal species are for breathing and olfaction, however after it filters, warms, and humidifies the breathed air before reaching the lowest airways, it also provides a crucial defensive role. Hairs and a mucus layer that serve to trap inhaled germs and debris line the inside of the nasal cavity. [3] The nasal cavity is a region that lies below the cerebral compartment and skull base and above the hard palate and oral cavity.[4] The passage of the nasal cavity, which extends from the nasal vestibule to the nasopharynx, is around 12–14 cm deep. The area of an entire surface of the human adults have a 150 cm^2 nasal cavity and a 15 ml total volume. [1] The nasal spetum separates the nasal cavity into two regions in the middle. The two chambers have an anterior nasal aperture that opens to the facial side and a posterior nasal aperture that opens to the rhinopharynx.[5]

The nasal cavity is separated into three regions: vestibular region, respiratory region and olfactory region

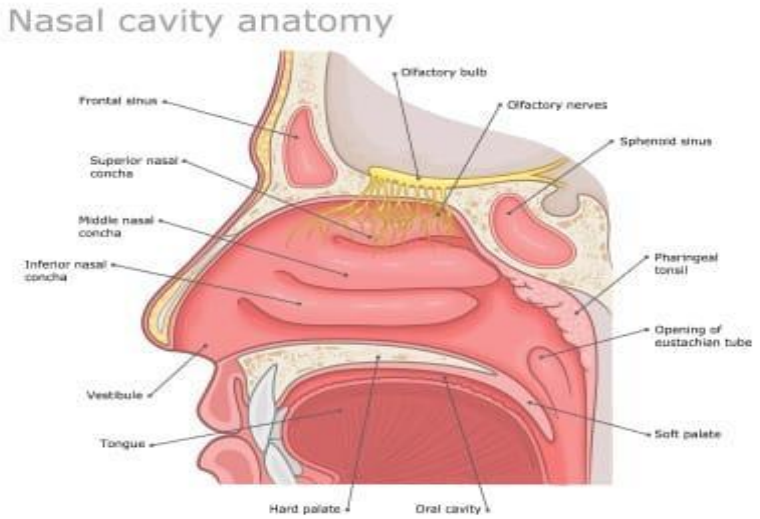

Figure 1: Nasal Cavity Anatomy [6]

1. Vestibular region-

The most anterior area, the vestibular region, which is located just at the nostril apertures. With a surface area of about 0.6 cm^2, it has nasal hairs that act as filters for inhaled particles. Squamous epithelial cells are the predominant cell type in this region; ciliated cells are rare, if present at all. The cellular structure and small surface area of this region make it very difficult for medications to be absorbed. [7]

2. Respiratory region-

The largest and most vascularized region is the respiratory region. The nasal cavity's lateral walls give rise to the superior, middle, and inferior nasal turbinates, which are located in the respiratory region. Because these turbinates are present, the airflow through the nasal passages is turbulent, which improves the interaction between the inhaled air and the mucosal surface. It is believed that the primary location of medication absorption into the systemic circulation is the respiratory area. The mucosa is made up of a lamina propria and an epithelium that are positioned on a basement membrane. The respiratory region is covered with pseudostratified columnar epithelium in the posterior section and squamous epithelium in the anterior part. There are roughly 300 microvilli on each respiratory epithelial cell.[8]

3. Olfactory region-

The olfactory organ is unique in the CNS, since it is the only part in direct contact with the environment and hence exposed to volatile odorants and airborne (toxic) substances. The olfactory mucosa is located within the recesses of the skull, just under the cribriform plate of the ethmoid bone, approximately 7 cm from the nostril, at the top of the nasal cavity, lying partly on the nasal septum and partly on the superior turbinate. A modified (pseudostratified) respiratory epithelium is the olfactory epithelium. It consists of basal cells, which can differentiate into neuronal receptor cells and replace these every 40 days, olfactory sensory neurons, and sustentacular cells, also known as supporting cells, which encase the receptor neurons and provide mechanical support and maintain the proper extracellular potassium levels required for neuronal activity.[9]

Factor Affecting Nasal Drug Absorption

[A] Nasal physiological factors

1. Blood flow

The nasal mucosal membrane has a high concentration of blood vessels and is important for controlling body temperature and humidity inhaled air, blood vessel dilation and constriction will affect how well drugs are absorbed.[10]

2. Mucociliary clearance (MCC)

The purpose of the mucociliary clearance system is to keep foreign objects and particles out of the nasal cavity so they can't enter the lungs below. [11]

The MCC system has been compared to a "conveyer belt," with cilia acting as the driving power and mucus serving as a sticky fluid to gather and eliminate unwanted particles. Under normal circumstances, mucus moves through the nasal cavity of humans at a speed of 5 mm/min, with a transit time of 15–20 minutes. The numbers that fall outside of these references ranges are abnormal and reflect impaired MCC.[12]

3. Enzymatic degradation

Drugs are administered by the nose to avoid the first pass effects on the liver and gastrointestinal tract. The drug is degraded significantly in the nasal cavity lumen and during transit through the nasal epithelial barrier because of the presence of enzymes such as lactose dehydrogenase, oxidoreductase, hydrolase, acid phosphatase, and esterase that are dependent on cytochrome P450. The cytochrome P450 isoenzyme was responsible for the metabolism of drugs such decongestants, progesterone, nicotine, alcohol, and cocaine. Proteolytic enzymes, namely proteases and aminopeptidases, are thought to be the primary obstacle preventing the absorption of protein and peptide medications, including desmopressin, insulin, and calcitonin. Drugs delivered via nasal inhalation may have different pharmacokinetic and pharmacodynamic profiles due to the presence of these enzymes in the nasal mucosa.[13]

4. Molecular permeability

The primary factor influencing drug absorption via the nasal route is the permeability of the nasal membrane. Drugs that dissolve in water, especially those with large molecular weights like proteins and peptides have low membrane permeability. Thus, small amounts of substance like peptides and proteins are mostly absorbed through the endocytotic transport pathway. The primary method by which water-soluble, high molecular weight medications penetrate the nasal mucosa is by passive diffusion via aqueous pores.[14]

[B] Physicochemical properties

1. Molecular weight and size

The molecular weight, molecular size, hydrophilicity, and lipophilicity of the chemical all affect drug permeability. Knowing the molecular weight (MW) of a substance allows for a direct prediction of its bioavailability. These big compounds have a bioavailability that typically falls between 0.5% and 5%. Drug LT 300 Da's physicochemical characteristics have little effect on how well it permeates the membrane; it largely does so through the aqueous channels. On the other hand, the rate of penetration is quite sensitive for molecules with MW 300 Da. [15]

2. Solubility and Dissolution rate

When it comes to powders and suspensions, drug solubility and dissolution rates have an important role on affecting nasal absorption. Before being absorbed, the particles that have been filed in the nasal cavity must be dissolved. No absorption takes place if a medicine is removed or stays in the form of particles. [16]

3. Stability

Medication stability studies that are biological, chemical, and physical play a significant role in every step of the process of creating novel medication formulations. Drugs delivered by nasal cavity may have less biological stability because of drug metabolism by defense enzymatic systems. A range of approaches, primarily the use of prodrugs and enzyme inhibitors, may be taken to get beyond this challenge.[12]

4. Polymorphism

An essential factor to take into account in the development of nasal drugs products is the examination and analysis of the polymorphic forms of drugs supplied in particle form. It is well recognized that polymorphism impacts how well drugs dissolve and are absorbed through cellular membranes.[17]

[C] Effect of drug Formulations

1. Formulation (concentration, pH, osmolarity)

Drug penetration may be impacted by the formulation's pH and the nasal surface. Because nasal secretions contain lysozyme, which kills certain bacteria at acidic pH levels, the nasal formulation's pH should be adjusted to 4.5–6.5 to prevent irritation of the nasal passages. Lysozyme becomes inactive in an alkaline environment, making tissue vulnerable to microbial invasion. Apart from preventing discomfort, this also leads to effective medicine penetration and inhibits the growth of microorganisms. Due to damage to the nasal mucosa, concentration gradient is crucial to the drug's ability to penetrate the nasal membrane and be absorbed. Examples of this include studies on nasal perfusion, where it has been demonstrated that the absorption of L-tyrosine increases with medication concentrations. Salicylic acid absorption is discovered to. In nasal perfusion tests, it has been demonstrated that the absorption of L-Tyrosine increases with drug concentration. Salicylic acid is observed to be less absorbed at higher concentrations. This decrease is most likely the result of lasting damage to the nasal mucosa. The drug's nasal absorption Is influenced by the dosage form's osmolarity. Examples of this include studies on nasal perfusion, which demonstrate that the amount of L-tyrosine absorbed increases with drug concentration. Salicylic acid is observed to be less absorbed at higher concentrations. The persistent injury to the nasal mucosa is probably the cause of this deterioration. The drug's nasal absorption is influenced by the osmolarity of the dose form. Nasal absorption is influenced by the formulation's sodium chloride content. A concentration of 0.462 M sodium chloride results in maximal absorption. In addition to increasing bioavailability, the larger dose causes toxicity to the nasal epithelium.[18]

2. Viscosity

The longer the drug remains in touch with the nasal mucosa due to a higher viscosity of the pharmaceutical formulation, the longer the time it takes for penetration to occur. Simultaneously, more viscous formulations may affect the medication's porosity by interfering with conventional processes like ciliary beating and mucociliary clearance.[19]

Nasal Drug Delivery System Dosage Forms

The drug being used, the suggested indication, the patient demographic, and, last but not least, marketing preferences all play a role in the dosage form selection process

[A] Liquid Nasal Formulations:

Since many chronic and allergy disorders are associated with dry particles and mucous membrane dryness, liquid solutions are preferred because of their convenient, helpful, and humidifying properties. The main issues with the water-based dosage forms were microbiological stability, irritation, and allergic rhinitis because they required preservatives, which compromised mucociliary function. The most advanced method for administering medications intranasally that need precise dosage is through the use of unit/bidose devices for liquid formulations.[20]

The following describes the various liquid dosage forms that are available.

1. Instillation and rhinyle catheter

A simple way for a physician or trained assistant to deposit drug in the nose is to insert the tip of a fine catheter or micropipette to the desired area under visual control and squirt the liquid into the desired location. Catheter delivery where 0.2 ml of a liquid desmopressin formulation is filled into a thin plastic tube with a dropper. One end of the tube is positioned in the nostril, and the drug is administered into the nose as drops or as a "liquid jet" by blowing through the other end of the thin tube by the mouth.[21]

2. Compressed air nebulizers

Nebulizers are nasal delivery systems that distribute medication formulations in gaseous form into the lungs. It is a device that fills the nasal cavity with compressed air and delivers a medication formulation. With this device, the medication formulation can be more specifically targeted to the respiratory system, resulting in a quicker onset of action and a decrease in adverse effects. This gadget cannot be used to deliver drugs through systemic channels.[22]

3. Squeezed bottles

Decongestants are mainly administered by squeezed nasal bottles. They are made out of a simple jet outlet and a smooth plastic bottle. A specific volume is atomized as a result of the instrument's air being forced out of the tiny nozzle while pushing the plastic container. Air is sucked into the bottle again by cathartic pressure. This process typically results in the liquid becoming contaminated with bacteria and drawing in nasal secretions. Accurate dosing and liquid deposition from squeezed nasal bottles are strongly correlated with the manner of delivery. The formulation's drop size has an extra effect on the dose because to variances between applications that are smoothly pressed and those that are not. The dosage is therefore challenging to control. Bottles that were squeezed with vasoconstrictors.[23]

4. Meter dose pump spray

Meter dosage pump sprays are used to deliver the majority of pharmaceutical nasal preparations that contain solutions, emulsions, or suspensions that are available on the market. In contrast to squeezed bottles and continuous valve sprays, they enable the application of a predetermined dose with a standard spray pattern and great dosing precision.[24]

The hand operated pump mechanism is the basis for meter dosage pump sprays. Giving local effects is crucial. Examples of this include topical decongestants and antihistamines. The actuator, valve, and pump may be contained in this container. The formulation's surface tension and viscosity determine the metered dose pump spray's dosage. [25]

5. Nasal drops

Among all formulations, nasal drops are among the easiest and most practical delivery methods. The primary constraints are the potential for contamination during usage and the impreciseness of the amount delivered. Nasal drops can be administered via squeezed bottle or pipette. Though there are certain drawbacks such as microbial growth, mucociliary dysfunction, and non-specific loss from the nose or down the back of the throat, these formulations are typically advised for the treatment of local ailments. For instance, nasal congestion is treated with ephedrine nasal drop (0.5% w/v). [26]

[B] Powder dosage formulations

If the lack of medication stability prevents the development of solution and suspension dosage forms, this dosage form might be created. The greater stability of the formulation and lack of preservative are the benefits of the nasal powder administration form. Although the solubility, particle size, aerodynamic characteristics, and nasal irritancy of the active medication and excipients determine the appropriateness of the powder formulation. [27]

1. Insufflator

The equipment used to provide drugs for inhalation is called an insufflator. It can be assembled using a straw or tube that holds the medication, and occasionally a syringe as well. [28]

2. Dry powder inhaler (DPI)

A device that administers medication to the lungs in the form of dry powder is called a dry powder inhaler (DPI). Devices that produce an aerosol directly from medication powder with a size of 1 to 5 μm or mixes with excipients are included in the dry powder platform. The active pharmaceutical ingredient (API) is carried by the excipients used in DPI. DPIs have been used to treat diabetes mellitus, but they are most frequently used to treat respiratory conditions such emphysema, COPD, bronchitis, and asthma. [29]

[C] Meter dose inhalers

A metered dosage inhaler is a medication delivery tool intended to deliver tiny medicine droplets, often with a particle size of less than 5μm. The device is filled with the formulation, and an actuator releases the necessary dosage. MDIs use propellants such as hydrofluoralkanes and chlorofluorocarbons. The main drawback of the MDI is that the patient needs to learn how to use it. A further issue with MDI is the limited amount of medication that can be inhaled. 10% to 20% of the dosage that is exhaled usually ends up in the lungs. [30]

[D] Nasal gels

In order to extend the duration of the formulation's contact with the nasal mucosa for experimental testing, the use of nasal gels as carriers for systemically delivered medications has been studied. Syringes have been used to administer the formulations. Precompression pumps that enable precise dosing have been created with regard to the gel's viscosity. A nasal adapter that has been particularly made is needed as an actuator when using it for nasal delivery. Because the formulation has low spreading capabilities due to its viscosity, the deposition of the gel in the nasal cavity depends on the route of administration. It only fills a small distribution area in the nasal cavity when applied directly, requiring particular application procedures. [31]

[E] Novel NASAL Formulations

1. Microspheres

Microspheres are spheres made of polymer that range in size from 1 to 1000 μm. Microspheres can interact with mucin and lengthen the formulation's residence duration in epithelial cells because of their large surface area. Drugs are shielded from chemical and enzymatic breakdown in vivo by microparticle carriers. Reduced dosage frequency may arise from the drug's accommodation and prolonged release via particulate bioadhesive systems. When mucous layer comes into touch with mucoadhesive microspheres, they have the capacity to swell and create viscous gels, which helps to keep the medication at the site of absorption for longer. Additionally, mucoadhesive particles may facilitate drug absorption by loosening the tight connections between epithelial cells.[32] According to Gungor and colleagues, the primary cause of the brief contact period that permits drug absorption via the nasal mucosa in nasal drug delivery is quick mucociliary clearance. In order to increase drug absorption through the nasal cavity and overcome the quick mucociliary clearance, mucoadhesive nano- and microparticles have been developed. [33]

2. Liposomes

A liposome is a synthetic microscopic vesicle with one or more concentric phospholipid layers surrounding a core aqueous compartment. Moreover, these vesicles allow the incorporation of hydrophilic, hydrophobic, and amphiphilic molecules, opening up a wide range of potential uses. [34]As comparing to other nanocarrier systems, liposomes have been studied for their potential as drug carriers in nasal delivery for local or systemic effects. It has been claimed that covering liposomes with polysaccharides like chitosan results in improved targeting, controlled drug release, and other desirable properties. [32] The influenza vaccine has also been shown to benefit from liposomal drug delivery methods, and non-peptide medications like nifedipine liposomes can be used in a variety of formulations. Obtained levonorgestrel intranasally as a liposome suspension, which resulted in a quick start of action and continuous administration. Positive outcomes were also observed when acyclovir in a liposomal gel was delivered by nasal gel. Using a liposomal gel allowed for direct absorption via the nasal mucosa in addition to promoting extended contact between the drug and the absorptive region. By contrasting liposomal formulations with free medication suspended in gel, these conclusions were drawn.[3]

3. Nanoparticles

Nanoparticles are solid colloidal drug carriers with a diameter of 10–1000 nm. The drug molecule is encapsulated in polymers that can be natural, synthetic, or semi-synthetic. Chitosan is one of the polymeric carriers for nanoparticulate drug administration that has some advantages over others because of its biodegradability, biocompatibility, ease of formulation, variety in application, and low toxicity. [35]

When using nanoparticles for intranasal medication delivery, controversial outcomes are discovered. Actually, there aren't many studies where the medication transport via the nasal cavity isn't markedly improved by nanoparticle formulations. The fact that particles are likely ingested by M-cells in the nasally related lymphoid tissue and subsequently carried into the lymphatic system and blood stream may account for the low bioavailability observed. However, other research indicates that the nanoparticle approach might be the best choice for administering nasal vaccines. [3]

4. Nanoemulsions

According to a thorough analysis of the most recent studies on nanoemulsions for nose-to-brain transport, intranasal administration is typically an alternative to oral medication. As the chemical is intended to reach the brain, many medications actually have problems when taken orally. Occasionally, parenteral therapy outperforms CNS distribution through the nasal mucosa, according to in vivo testing. Also the antipsychotic medication risperidone, which is a member of the benzisoxazole derivative class, was one of the most obvious examples of a nanoemulsion that entered the brain through the nasal mucosa. One problem with oral preparations is their poor absorption. [36]

5. Cubosomes

Cubosomes are extremely stable nanoparticles that are produced from the lipid cubic phase and have an outer corona made of polymers to stabilize them. A single lipid bilayer that creates a continuous periodic membrane lattice structure with pores created by two interwoven water channels makes up bicontinuous lipid cubic phases. [37]

6. Nasal inserts

When administering medications in small dosages, the nasal drug administration method is a helpful method. A nasal drug delivery system makes it simple to apply medication and practice self-administration. Nasal inserts are a compact, lightweight device. Novel, bioadhesive, solid dosage forms for extended systemic drug delivery via the nasal route are called nasal inserts. The idea behind the dosage form is to prevent the nasal cavity from feeling like a foreign body by imbibing nasal fluid from the mucosa after administration and forming a gel there. They are made up of an implanted medication in a hydrophilic matrix that resembles a sponge. [38]

Evaluation of nasal formulations

There are several methods for calculating the drug's diffusion via the nasal mucosa from the formulation. There are two approaches for examining the drug's diffusion profile:

(A) In vitro diffusion studies

The glass used to construct the nasal diffusion cell. The 60 ml total capacity water-jacketed recipient chamber has a flanged top measuring approximately 3 mm. The lid features three openings, one for a thermometer, one for sampling, and one for a donor tube chamber. The donor tube chamber has a total capacity of 60 ml and a flanged top measuring approximately 3 mm. The lid features three apertures, one for a thermometer and one for sampling. The donor chamber measures 10 cm in length and 1.13 cm in diameter. The sheep's nasal mucosa was isolated from the underlying bone tissues and immersed in distilled water with a small amount of genatamycin injected. The donor chamber tube is connected to the muscle surface once all blood has been removed. The recipient chamber's diffusion medium is barely touched by the donor chamber tube because of its positioning. Samples (0.5 ml) are drawn from the recipient chamber at pre-arranged intervals and put into ampoules having an amber tint. The experiment is conducted with the temperature kept at 37□.[39]

(B) In vivo nasal absorption studies

1. Rat model

Rats are surgically prepared for an in vivo nasal absorption investigation in the following manner: To anesthetize the rat, an intraperitoneal dose of pentobarbital sodium. A polyethylene tube is used to cannulate the trachea after a neck incision. A second tube is placed into the nasal cavity's posterior area via the oesophagus. In order to prevent the medication solution from being drained from the nasal cavity through the mouth, the nasopalatine tract channel is blocked. The cannulation tubing or a nostril are the two ways that the medication solution enters the nasal cavity. Blood samples are taken via the femoral vein. Due to the obstruction of all potential drainage outlets, the medication can only be absorbed and delivered into the systemic circulation by diffusion or penetration across the nasal mucosa [1]

2. Rabbit model

The rabbit is a useful animal model for research on nasal absorption since it has various benefits.

1. It enables pharmacokinetic research, same like with big creatures (such as monkeys)
2. It can be easily maintained in laboratory settings, is widely available, and is reasonably priced.
3. There is enough blood (about 300 ml) in the sample.

To permit frequent l-2 ml blood sample. As a result, it makes it possible to fully characterize a drug's absorption and determine its pharmacokinetic profile.

4. Rabbits (approx. 3 kg) are either anaesthetized or maintained in the conscious state depending on the purpose of study. In the anaesthetized model, intramuscular injection of a combination of ketamine and xylazine is given to anasthetized rabbit. The rabbit's head is held in an upright position and nasal spray of drug solution is administered into each nostril. The body temperature of the rabbit is maintained at 37°C during experiment with the help of a heating pad. The blood samples are collected by an indwelling catheter in the marginal ear vein or artery. Depending on the goal of the research,3-kilogram rabbits are either kept conscious or put under anesthesia. In the model under anesthesia, A rabbit is anesthetized and given an intramuscular injection of a ketamine and xylazine mixture. The medication solution is sprayed into each nostril of the upright-posted rabbit while its head is held in place. Using a heating pad, the rabbit's body temperature is kept constant at 37°C during the experiment. An indwelling catheter is used to take blood samples from the marginal ear vein or artery.[1]

Ex vivo nasal perfusion model

The surgical setup is identical to that of the in vivo rat model. A funnel is positioned between the nose and reservoir during the perfusion experiments in order to reduce the amount of medication solution lost. A peristaltic pump is used to circulate the medication solution through the rat's nasal cavity while it is kept in a reservoir at 37°C. The perfusion fluid flows back into the reservoir after exiting the nostrils (via the funnel). T8here is constant stirring of the medication solution in the reservoir. The residual drug concentration in the perfusing fluid is measured to assess the amount of drug absorbed. Studies on ex vivo nasal perfusion can also be conducted using rabbits as the animal model. The rabbit is given parenteral uretliane-acepromazine anesthesia. The neck is cut midline, and the trachea is cannulated using a neonatal endotracheal tube made of polyethylene. After isolation, the oesophagus is ligated. Flexible tygon tubing is placed into the proximal end of the oesophagus and advanced to the posterior region of the nasal cavity after the distal end is sutured shut. The nasopalatine tract, which joins the nasal cavity to the mouth, is sealed with adhesive to prevent medication solution from draining from the nasal cavity. Using a peristalstic pump, the medication is pumped within an isotonic buffer solution.[40]

In vivo bioavailability studies

A study on in-vivo bioavailability is carried out on male rabbits in good health. Three groups, each with six rabbits, participated in the study and fasted for twenty-four hours. One group was given care with traditional preparation, a second group maintained as a control (i.e., not given any test materials), and a third group that received the test formulation. Throughout the trial and during the fasting period, water is provided freely. The rabbits' marginal ear veins were utilized to draw blood samples, and a sample of roughly 2 ml was collected in heparinized centrifuge tubes at 0.5, 1, 2, 3, 4, 5, 6, 7, and 8 hours following the medication's administration. The blood samples are kept at -20°C until analysis by centrifuging them at 3000 × g for 15 minutes in order to extract the plasma. The medication can be extracted from plasma according to earlier reports, and the HPLC equipment can then be used for analysis.[39]

Pharmacokinetic analysis

The plasma concentration vs. time plot is used to calculate pharmacokinetic parameters. These plots can be used to determine the area under the curve (AUC), the peak plasma concentration (Cmax), and the time required to reach the peak concentration (Tmax). The semilogarithmic plot of plasma concentration vs. time yields the elimination rate constant (Kel). The formula for calculating the elimination half-life (t1/2) is $t1/2 = 0.693/Kel$.[40]

II. Conclusion

When compared to parenteral administration, the INDD system offers a benefit in terms of patient compliance and may be a potential delivery method for medications with low bioavailability. This method of administration is particularly suitable for treating a number of neurodegenerative disorders, such as Parkinson's and Alzheimer's, which call for the quick and precise delivery of medication to the brain. Numerous factors influence the development of a medicine with a drug delivery system. Let's hope that in the near future, intranasal products will most likely include medication for treating acute pain, sexual dysfunction, and sleep induction. (migraine), anxiety attacks, nausea, heart attacks, and Parkinson's disease. Additionally, new nasal

products for the management of chronic conditions including diabetes, growth deficit, osteoporosis, endometriosis, and fertility treatments will be sold. Careful consideration of the features of the drug formulation and delivery system, as well as a thorough comprehension of how they interact, are necessary for the effective application of these traits.

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