IJBPAS, April, 2023, 12(4): 1536-1550

ISSN: 2277–4998

International Journal of Biology, Pharmacy and Allied Sciences (IJBPAS)

'A Bridge Between Laboratory and Reader'

www.ijbpas.com

NASAL DRUG DELIVERY SYSTEM: PRINCIPLE AND PRACTICES

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Received 8th May 2022; Revised 16th June 2022; Accepted 27th Aug. 2022; Available online 1st April 2023

https://doi.org/10.31032/IJBPAS/2023/12.4.7022

ABSTRACT

The intranasal route of drug delivery is reliable in so many ways. This route of drug delivery not only has less side-effect compared to other dosage forms but also has more bioavailability. There is no degradation of drug by enzymes as in case of oral route. It offers better patient comfort and preference as it is needleless and pain free which can aslo be favourable in case of diseases that require long term treatment. Lipophilic drugs can be administered via transcellular aided route. This route is preferable for local as well as systemic delivery of drug. The distribution of dose is enhanced and has a possibility of crossing the blood brain barrier (BBB) which is beneficial for treatment of CNS disorders. This route has a significant potential to deliver various therapeutic substances like small molecules, large molecules, lipophilic drugs, and stem cells to the brain.

Keywords: Intranasal route, bioavailability, lipophilic, transcellular, enzymes, local, systemic

INTRODUCTION

Delivery of drug via nasal route may be considered as a favourable route for drug administration due to significant advantages over other routes. In case of oral route, drug has to undergo first-pass metabolism and there is acidic or enzymatic degradation of drug. Hence, the bioavailability and efficacy of the drug is reduced. This can be overcomed by nasal route as it provides greater surface area, permeable endothelium membrane, elevated total blood flow and absence of first-pass metabolism **[1-3]**. The nasal route also provides direct access to systemic absorption. Lipophilic drugs is absorbed from the nasal tissue pretty well as the

nasal epithelium acts as a lipid sieve which allows the lipophilic drug to penetrate. Intranasal route is suitable for self-medication **[1]** whereas in case of parenteral route drug must be administered by trained practitioner. The patient will experience discomfort while injecting as it causes pain. Parenteral route of drug administration causes inflammation that might last for sometime or might last longer. There is increased side effect as of more systemic exposure unlike nasal route. In case of intranasal drug delivery system onset of action is fast and rapid absorption takes place **[1, 2, 4]**. It has reduced side effect. Hence, nasal drug delivery system may be an ethical approach for future advancement of medicinal research that will lead to development of dosage forms for different drugs.

ANATOMY OF NASAL CAVITY [1-3, 5, 6]

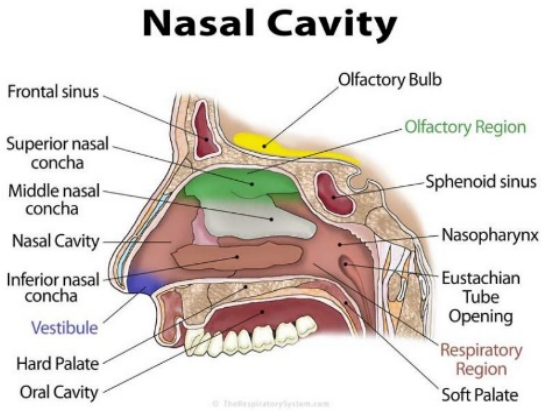

Figure 1: Structure of nasal cavity [2]

The septum separates the nasal cavity into two equal conduit. The bony posterior part of septum comprises the perpendicular plate of the ethmoid bone and the vomer. Hyaline consist the anterior part. The cribriform plate of the ethmoid bone and sphenoid bone, the frontal and nasal bones forms the roof of the nasal cavity. The hard palate in front and a soft plate behind comprises the floor of the cavity or the upper part of the mouth. The hard palate is composed of the maxilla and palatine bones. The soft palate consists of involuntary muscle. The medial wall forms the septum. Lateral wall is formed by the maxilla, ethmoid bone, and inferior conchae. The posterior wall is produced by the pharyngeal posterior wall. The respiratory, olfactory, and vestibular are the three portions in which the nasal cavity

is divided. The respiratory region is the most vascular and takes up the most space. The pseudostratified columnar ciliated epithelium lines it. This region is made up of four different types of cells. They are- goblet cells, ciliated and non-ciliated cells, columnar cells, and basal cells. At nostril aperture is the vestibular region. The vestibular region comprises of the nasal hairs, squamous epithelial cells and ciliated cells. The olfactory area is lined with olfactory cells and is found in the upper part of the cavity. The cavity continues to paranasal sinuses. The paranasal sinuses are the air-filled area in bones of face and cranium. The primary sinuses are- maxillary sinuses in the lateral walls, frontal and sphenoidal sinuses in the roof, and ethmoidal sinuses in the upper half of lateral walls.

RESPIRATORY FUNCTION OF NOSE

The air enters the nasal cavity. The inhaled air is first warmed. The warmed air is moistened and then is filtered. The nasal cavity comprises of three nasal chonchae. This increases surface area and spreads the inhaled air all over nasal surface. Humidification increases so does warming and filtration in nasal cavity due to large surface area. Warming of inhaled air takes place due to high vascularity of mucosa. Hairs at the anterior portion of the nose filters and cleans the air by trapping large particles and small particles like dust and bacteria as it sticks to the mucus present. Mucus protects the epithelium and prevents from drying. When air passes by the nasal cavity it gets saturated and humidified.

SENSE OF SMELL [4]

When superior nasal concha, the upper part of septum and roof of the nose is combined olfactory area is formed which is located in small part of nasal mucosa. Special receptors are located in the upper part of nasal cavity in the region of cribriform plate of ethmoid bones and superior conchae. The odour stimulates the receptors and impulse is generated. The impulse generated is then carried by olfactory nerve to the brain. Then smell is sensed.

PATHWAY

Bipolar first order neurones are seen in olfactory epithelium nerve cells. Each receptor cell produces one axon, which combines with axons produced by other receptors to form the olfactory nerves. The neurodermal sheath surrounds the unmyelinated olfactory nerves. Nerves enter the olfactory bulb through the cribriform plate of the ethmoid bone. The key place for olfactory intelligence is the olfactory bulb. The glomeruli make up the bulb. Synapses between axons and dendrites of mitral cells and tufted cells produce the glomeruli structure. Each glomerulus has around 26,000 receptor cells, and each glomerulus sends impulses to mitral cells and tufted cells. Second-

order neurons are these cells. The olfactory tract is formed by the axons of these nerve cells. Signals are received by the olfactory bulb **[7]**.

MECHANISM OF DRUG ABSORPTION

For the drug to be absorbed, it has to pass through the mucus. It is easy for tiny uncharged particles to pass the mucus but large uncharged particles find it hard as it may bind with protein known as mucin present in the mucus thereby interfering in the diffusion rate **[1-8]**. The mechanisms involved in the absorption of drug via nasal route are-

- Para cellular transport
- Transcellular transport

Paracellular transport

In case of paracellular transport, movement of molecules or particles takes place across the epithelium by passing through the little spaces in between the cells. This is a slow and passive process and is basically an aqueous route of transport **[2-4]**. The smaller the particle, the better is the bioavailability **[2, 3]**. The tight junctions in between the cells allows the passage of particles upto certain size. There is a contrary relation between absorption via intranasal route and molecular weight of water soluble compounds. Hence, the passage of larger particles is difficult. Drugs with molecular weight greater than 1000 Daltons show lesser bioavailability **[1-3]**.

Transcellular transport

The movement of the particles takes place via lipoidal route across the cells **[2, 4]**. Lipophilic drugs are transported via this route **[1]**. Drugs are also transported by active transport through carrier-mediated means or via openings of tight junctions **[2, 3]**.

INTRANASAL DRUG DELIVERY TO BRAIN

Delivery of drug from nose to brain is achievable by the olfactory region. Drug can be administered directly from nasal cavity to the brain by three mechanisms- one intracellular transport mediated route and two extracellular mediated route **[4]**. The intracellular transport route is a time taking process. It takes time for the drug to reach olfactory bulb whereas the other two extracellular mediated route allows fast entry of drug for absorption. In case of first extracellular transport route, the administered drug crosses the gas between the olfactory neuron and then continues to the olfactory bulb. The drug is passed along trigeminal nerve in order to cross the blood brain barrier in case of the other extracellular mediated route. The drug reaches the olfactory bulb of trigeminal region and further travels to the other area of brain by the process of diffusion which is aided by perivascular pump guided by

arterial pulsation. The olfactory region connects nose to brain directly and is used to deliver drug molecules targeting CNS in case of diseases like depression, migraine, Alzheimer's disease, Parkinson's disease **[9]**.

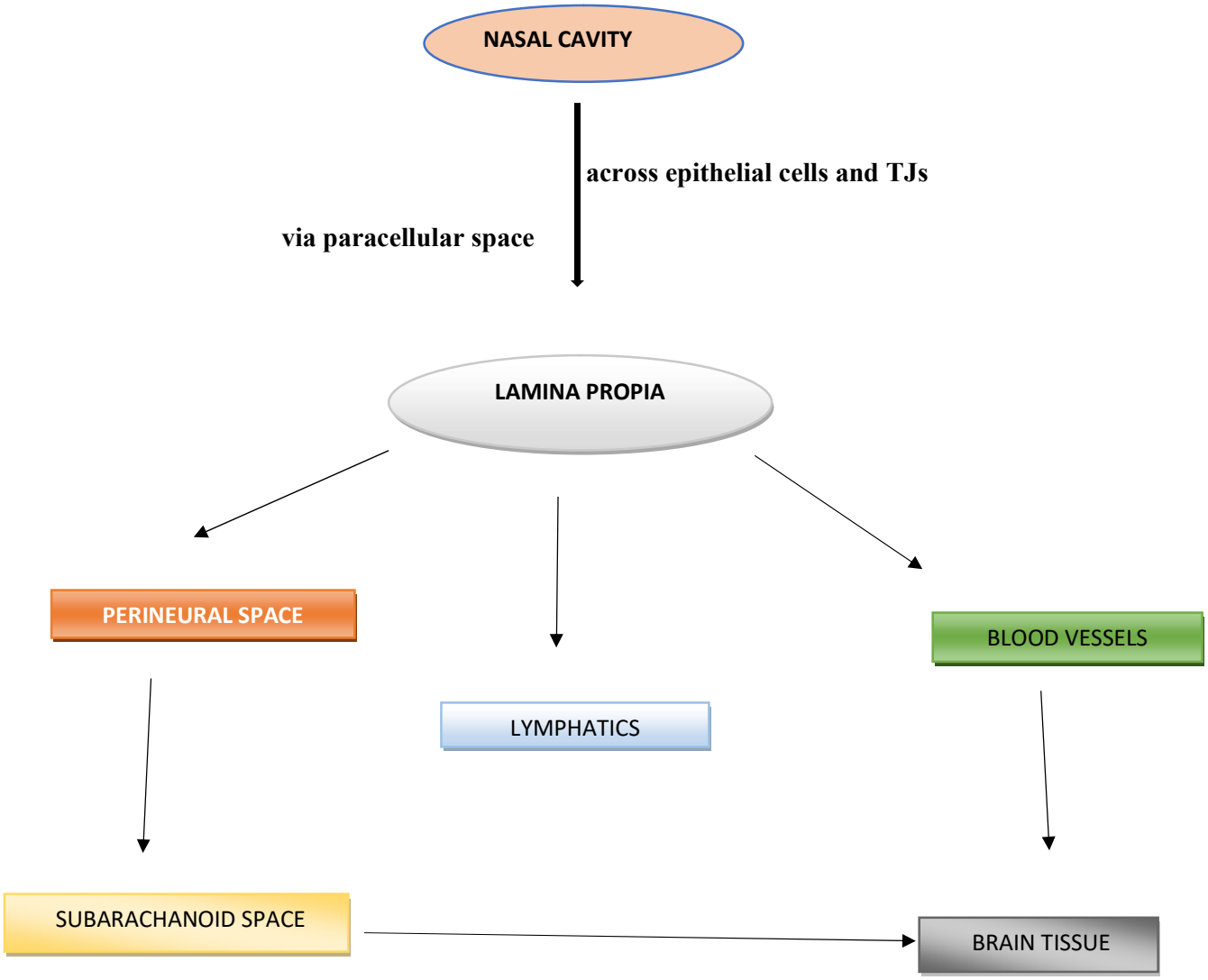

Figure 2: Nose to brain drug delivery

INTRANASAL DRUG DELIVERY TO THE CNS

The transport of drug to the brain is significantly reduced as there is a blood brain barrier that protects the CNS from several harmful substances. Due to the unpassable nature of the blood brain barrie due to tight junctions present, drug delivery to CNS is quite a challenge. The BBB prevents the entry of substances depending on characteristics of particles like it's molecular size, lipophilicity and specificity for variety of ATP-dependent transport routes. On the interior side of the BBB P-glycoprotein efflux are found. This decreases the exposure of drug to CNS as it

rejects the drug again to the bloodstream. However, constant researches are made for the possibility of drug penetration across BBB for advancement in drug delivery system **[10]**.

FACTORS INFLUENCING INTRANASAL DRUG DELIVERY

Some important factors that impact drug absorption-

A) Physiochemical properties of a compound/drug

i) pH

The pH of the prepared formulation should be 4.5-6.5 which is equivalent to the nasal secretion to avoid any kind of nasal irritation. This aids in improving drug permeation and also prevents growth of bacteria.

ii) Molecular size

In case of lipophilic drugs, the molecular weight is directly proportional to drug permeation **[2]**. Some lipophilic drugs like testosterone, naloxone, buprenorphine are almost totally absorbed via intranasal route. On the other hand in case of hydrophilic drug molecular weight is inversely proportional to drug permeation. The compounds with molecular weight ≥300 is highly sensitive to permeation **[3, 4]**.

iii) Viscosity

When the formulation is highly viscous in nature, the contact time between the drug and the nasal mucosa increases. So, there is better chance of increase in permeability of the drug **[2, 3]**.

iv) Enzymatic degradation of drug

Proteins or peptides might undergo enzymatic degradation when they pass through the lumen of the nasal cavity which lessens the bioavailability decreasing the therapeutic efficacy of the drug **[2-4]**.

v) Chemical form

A drug can exists in different form like salt or ester. This significantly alters the rate of absorption. It was observed that in-situ absorption of carboxylic acid esters of L-tyrosine via nasal route was greater than that of simply L-tyrosine **[2]**.

B) Environmental pH

The ionised lipophilic particle passes via aqueous paracellular path whereas non-ionised lipophilic particles cross the nasal epithelial via transcellular route **[4]**.

C) Drug distribution

When the drug is administered to the anterior part of the nasal cavity, there is exposure of the drug for longer time and hence there is better chances of drug absorption. Drug is deposited in the posterior portion of the nasal cavity and drug is eliminated by the mucociliary process hence showing low bipavailability **[4]**.

INTRANASALN DOSAGE FORM

1. Nasal drops

Simple and convenient. However, lacks precision in dose while administering in patients **[1]**.

2. Nasal spray

Nasal sprays deliver more precise doses than nasal drops as controlled by metered dose pumps and actuators. Solutions as well as suspensions can be formulated into nasal sprays. It can deliver exact doses from 25 -200 micro litre **[1]**.

3. Nasal gels

Nasal gels have high viscosity. Solutions and suspensions can be formulated to this dosage form. Due to it's high viscous nature there is no dripping of the formulation and there is no anterior leakage. Soothing excipients are added to it which prevents any kind of nasal irritation. The taste of the drug hardly matters to the patient as there is reduced chances of swallowing **[3]**.

4. Nasal powders

Some drugs are not stable when prepared as solutions or suspensions. This dosage form is usually prepared when there is low stability of drug. Nasal powders can be applied locally and there are no added preservatives which are some of the advantage. However, might cause some nasal irritancy. There is no metered delivery of the drug due to lack of metered dose pumps.

DRUGS DELIVERED VIA NASAL ROUTE

Some drugs can be administered intranasally. They are mentioned along with their uses in the table below-

Table 1: Drugs delivered via nasal route [1, 10]

DRUG NAME	DOSAGE DEVICES	USES
Busereli n formulation	Nasal spray, ointment	Treatment of prostate cancer
Anti-histaminics	Nasal spray, nasal drop	Used in case of runny nose and relieves congestion, itchiness and sneezing
Calcitonin	Nasal drop	Treat osteoporosis in women
Adrenal corticosteroids jelly	Nasal drop, nasal spray, aerosol, Sub mucosal injection solution	Treat rheumatoid arthritis, reduces swelling and pain caused by inflammation
Cocaine	Nasal spray, nasal drop, insufflator, gaugepacktail	Local anesthetic in case of surgery and diagonostic process
Dopamine	Nasal spray	Therapy of Parkinson's disease
Gentamicin	Nasal spray	Treatment of sinusitis and destroys bacteria from sinus cavities
Hyoscine	Nasal spray, nasal drop	Prevention and treatment of motion sickness
Insulin	Metered pump spray, metered erosolized spray, fixed volume aerosol spray, nasal spray, nasal drop, cotton pledget	Treatment of diabetes
Isosorbide dinitrate	Nasal spray	Prevent angina(chest pain)
Naferelin acetate	Spray, injection, snuff	Used in case of endometriosis
Nitroglycerin	Injection, spray	To relieve from chest pain, to treat hypertension when given parenterally
Oxytocin	Nasal spray, nasal drop, aerosol activated spray, injection	Used for psychiatric effect, post traumatic stress disorder and autism
Progesterone	Nasal spray, nasal solution	Treatment of amenorrhoea, cure abnormal uterine bleeding
Xylometazoline	Nasal spray, nasal drop	Relieves congestion due to common cold, sinusitis, allergies
Levomenthol	Nasal ointment	To relieve congestion

Fentanyl acetate	Powder, solution, diluent for reconstitution aqueous spray nasal spray	Used to treat breakthrough pain in case of cancer patients
Nafarelin acetate	Nasal spray, solution	Treat symptoms of endometriosis such as menstrual cramps, pelvic pain and painful intercourse
Sumatriptan	Nasal spray, solution	Treat migraines
Zolmitriptan	Nasal spray, solution	Treatment of migraine headache
Diamorphine hydrochloride	Powder, solution, diluent for reconstitution aqueous spray nasal spray	Used in case of emergency to relief pain, narcotic analgesic

ADVANTAGES OF NASAL DRUG DELIVERY

- It has better patient compliance compared to parenteral route as it is totally needle free and is suitable for self-medication **[2, 4]**. There is no need of assistance of trained professional for drug administration **[2]**.
- Due to rich vascularization and large surface area of the nasal cavity there is more absorption of the drug **[7]**. Absorption of the drug takes place rapidly and soon the action of drug begins **[2]**. So, this route can be a possible replacement of parenteral route in emergency in case of some drugs.
- Penetration of lipophilic drugs and particles with low molecular weight is possible via this route **[2]**.
- Increased bioavailability of drug as compared to the oral route as there is no enzymatic degradation of drug. Also first pass metabolism is absent **[2, 11]**.
- There is a possible chance of drug delivery to CNS through olfactory area crossing the BBB. Vaccines can be delivered directly to the lymphatic tissue via this route of drug delivery **[1, 2]**.
- Lower side effects as the drug is less exposed to systemic circulation **[2]**.
- Is easy when it comes to long term treatment when compared to parenteral route **[1, 2]**.

DISADVANTAGES OF INTTRANASAL DRUG DELIVERY

- There is damage of musocal lining when drug is administered often via this route **[3]**.
- Common cold and allergies might reduce the absorption of the drug **[2, 11]**.
- Some patients suffer from allergies depending on the drug composition **[2, 3]**.
- The amount of drug reaching the CNS is limited as of the BBB that is

impenetrable due to tight junctions present.

PARAMETERS FOR IDEAL DRUG USED FOR NASAL DELIVERY

Some important parameters required for ideal drug used for nasal delivery is expressed with the help of diagram below.

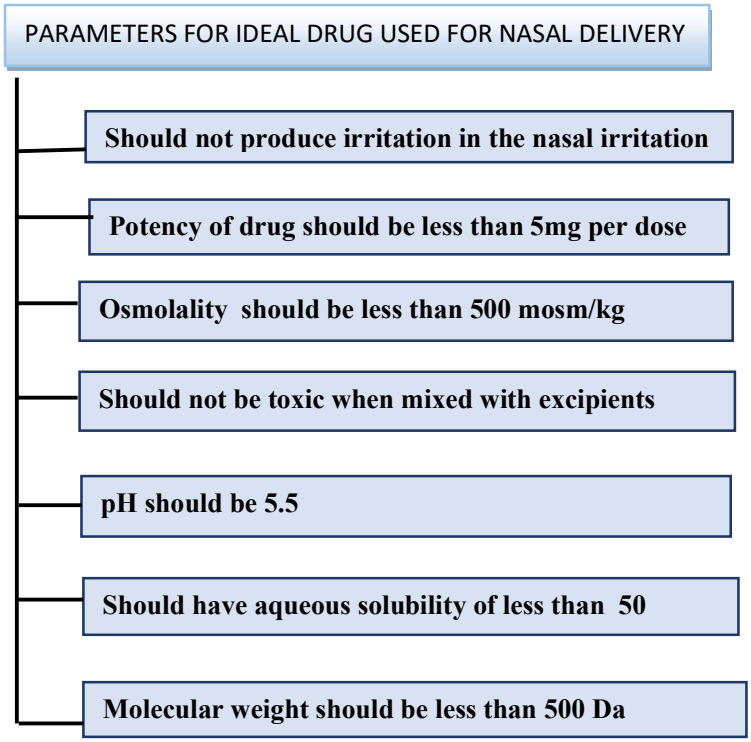

Figure 3: Parameters for ideal drug used for nasal delivery [2, 12]

APPROACHES TO IMPROVE DRUG ABSORPTION

Drug absorption can be improved by incorporating enhancers.

Enhancers

Using absorption enhancers improves the rate at which drug penetrate the nasal mucosa. They act by following any one of the following process.

- Stabilizing the dug
- Reducing mucociliary clearance
- Opening of tight junctions
- Interference in enzyme activity
- Reducing viscosity of the mucus
- Permeation enhancers should posses few absolute qualities. There should be no permanent damage to the tissues. It should be non-toxic and non-irritant **[3]**. The change made while enhancing drug permeation should be reversible. It should be compatible with other excipients and must be effecient when used in small amount.

Enhancers can be chemical as well as physical enhancers **[3]**. The chemical enhancers destroy nasal mucosa. This change is irreversible. Physical enhancers

affect nasal clearance by forming a gel. This change is reversible.

Permeation enhancers can be classified as-

Table 2: Classification of enhancers [1, 3, 10, 13]

Classification	Mechanism of action	Example
Surfactants	Disruption of membrane takes place	Sodium lauryl sulphate, saponin, Cetylpyridinium chloride, Polyoxyethylene-9-lauryl ether
Chelating agent	Opening of tight junctions	Salicylates, ethylene diamine tetra acetic acid, sodium citrate, citric acid
Enzyme inhibitors	Enzyme inhibition	Amastatia, bestatin, fusidic acids, boroleucine, bile salt
Fatty acids	Disrupts membrane	Sodium laurate, oleic acid, lauric acid, caprilic acid, phosphotidylcholine, Methyloleate
Bile salts	Sodium glycocholate, sodium taurocholate, fusidic acid derivatives, sodium glycol deoxycholate	Opening of tight junctions, inhibition of enzyme activity, disruption of membrane, mucolytic activity
Bioadhesive materials	Starch, chitosan, carbopol, microspheres	Opening of tight junctions, decrease in nasal clearance
Miscellaneous	Cyclodextrins	Opening of tight junctions, disrupts membrane

DRUGS USED FOR NOSE TO BRAIN DELIVERY [14]

Zolmitriptan

Zolmitriptan is a particular agonist for serotonin receptors. It has symptomatic antimigraine properties. The medicine decreases cranial artery dilatation and inflammation by stimulating receptors in the brain. In the market it is sold as tablet (ZOMIG), an oral disintegration tablet (ZOMIG-ZMT), and a nasal spray (ZOMIG-ZMT) (ZOMIG nasal spray). Oral zolmitriptan has a slow beginning of action, causes nausea and headaches, has a short half-life, provides insufficient pain relief, and has a limited absorption. After 15 minutes of treatment, the medicine in the form of a nasal spray showed a faster beginning of action and alleviation from headache.

Venlafaxine

Venlafaxine is used to treat major depressive disorder and anxiety. It is a serotonin and norepinephrine reuptake inhibitor. The drug is available in the form of immediate and controlled-release pills and capsules (Efeexor, Effexor XR). The oral therapy of this drug has a slow beginning of action, lower bioavailability, and half-life elimination as well as adverse effects such as high blood pressure, weariness, headache, sexual dysfunction, dizziness and mouth dryness. As a result, there is a requirement to control the efficacy of drug concentration in the brain via alternative channels in order to treat depression.

Sumatriptan

The drug is used in the treatment of migraine. It is commercially available as tablets, intranasal spray and subcutaneous injection. There are various kind of limitations in case of these dosage forms,

few are low bioavailability in case of oral administration, hepatic first pass effect, protein binding (14-21%). However, researches are being made to overcome these barriers to achieve more effeciency in drug delivery of sumatriptan via nasal route.

Interferon beta

Interferons are anti-inflammatory cytokine. It has antiviral, mmune regulatory and also has antitumor activity. There are two classes of interferons. They are- type I and typeII. Type I comprises of IFNα and IFNβ and type II comprises of IFNγ. Type I is used in the treatment of conditions like multiple sclerosis (MS), arthritis, cancer and hepatitis as they modulate immunological activity. Presently, IFNβ is delivered by subcutaneous injections or intramuscular route. These routes have side effects like necrosis and inadequate delivery to CNS. Studies were made by the researchers that explained that drug could be administered intranasally directly to the CNS more efficiently. So, it was concluded that delivery of drug via intranasal route was more efficient than the other route and has potential to bypass BBB targeting CNS.

Clonazepam

IT is a derivative of benzodiazepine. It can be used as sedative, hypnotic, muscle relaxant and anticonvulsant. It acts by inhibiting transmission of neurotransmitter. It is available in the market in the form of tablets (Klonopin or Linotril) and injections. Clonazepine mucoadhesive microemulsion was prepared by adding polycarbophil to CME (clonazepine microemulsion). Efficient targeting of the brain was observed when the delivery of CMME was via intranasal route. More researches and experimental studies are made to design the formulations with low side effects and better therapeutic effect.

Bromocriptine (BRC)

The drug is a derivative of ergoline and dopamine D2 receptors. It is used to retard and lessen the motor fluctuations related to long term levodopa treatment in case of Parkinson's disease (PD). It retards apoptosis in case of Parkinson's disease. It retards formation of free radicals and acts as antioxidants. Presently, the drug is available in tablet form (Sicriptin). It was found that the drug could not cross the BBB via oral route with decreased bioavailability and reduced absorption due to first pass metabolism. Studies were made for the delivery of BRC to brain via nanolipidiccarriers. Still, one major drawback is that it requires surgical supervision for the delivery via such medium. Direct delivery of drug from nose to brain allows targeted drug delivery with reduced systemic side effects.

Growth hormone-releasing neuropeptide (hexarelin)

Growth and reproduction of cells is instigated by growth hormone in case of animals and human beings. Administration of GHRP is challenging due to drawbacks like low permeability via G.I. mucosa, enzymatic degradation and hepatic first pass metabolism directing to reduced bioavailability of the drug to the targeted site. The mentioned drawbacks can be overcomed by delivering drug via intranasal route.

Didanosine (2',3'-dideoxyinosine,ddI)

The drug is a reverse transcriptase inhibitor and is used in the treatment of HIV. It is available as tablet and capsule form. There are several drawbacks in case of oral delivery like low bioavailability, enzymatic degradation, first-pass metabolism and reduced permeability. Hence, the drug can be administered intranasally. Experimental studies on rats were conducted and it was observed that ddI travels to CNS via nasal route more efficiently than other route. Other drugs that can be administered from nose to brain are erythropoietin, duloxetine, estradiol, risperidone, rivastigmine, deferoxamine, buspirone HCL.

SOME PATENTS RELATED TO NASAL DRUG DELIVERY

There are number of patents has been filed which are related with nasal drug delivery system. All these patents are listed in **Table 3**.

Table 3: Patents related with nasal drug delivery system

Patent number	Year of patent granted	Inventor	Brief about patent	Reference
US9550036B2	2017	John D Hoekman, Michael Hite, Alan Brunelle, Joel Relethford, Rodney J.Y.Ho	Delivery device delivers drug in the form of powder, liquid or suspension, aided by a propellant system. Hydrofluoroalkane propellant passes to a diffuser and then to the compound chamber, drug is aerosolised from a pressurised canister. The aerosolised drug then passes via nozzle for delivery to the olfactory area of nasal cavity.	15
US8381729B2	2013	Lutz Freitag, Anthony Wondka, Gregory Kapust, Robert Bryan, Michael Khenansho, Anthony Gerbe	Method and devices to impart oxygen supply and ventilation to patient: Ventilation system comprises of a special gas supply, catheters, access devices and breath sensing techniques.	16
US4919132A	1990	Martin G Miser	Apparatus for supplying gas to the patient: oxygen or anesthetic gas is supplied via face mask involving a bendy reservoir bag comprising a valve assembly connected to the end of a bag.	17
US9561177B2	2017	Fintan KEEGAN, Robert Gerard Bell, Roger Crystal, Michael Brenner Weiss	Nasal drug products and methods of their use	18

US20020054856 A1	**2003**	**Richard Jones**	**Nicotine mucosal spray: the drug product is composed of nicotine solution of concentration less than 10mg/ml. It helps to get rid from smoking tobacco.**	**19**
US6284765B1	**2001**	**James L.Caffrey**	**(+)naloxone and epinephrine combination therapy: novel composition of (+)naloxone and epinephrine delivered via atomizer for treatment of nasal congestion and asthma attack.**	**20**
US20150005356 A1	**2017**	**Nigel Ten Fleming**	**Composition of epinephrine delivered via nasal mucosa for treatment ofanaphylaxis, bronchospasm or cardiopulmonary resuscitation(CPR)**	**21**

CONCLUSION

The administration of drug via intranasal route can be advisable in many ways. One of the major benefit is that drug can bypass BBB. There is a possible chance of delivery of drug directly to CNS. Diseases related with deficiency of neurotransmitter and CNS disorder can be treated. Onset of action is rapid and can be used as an alternative to parenteral route in case of emergency. Drugs with high molecular weight can be administered. Administration of lipophilic drug is possible via trans cellular mediated route. Systemic delivery of drug is possible. First pass metabolism can be avoided and has better bioavailability. This route provides better patient comfort as bit is needle free unlike parenteral route. So, is more suitable in case of diseases that requires long term treatment **[2, 3]**. Drugs causing GI side-effectcs can be administered safely via this route. Delivery of various vaccines is possible. Delivery of vaccines against influenza, plague, tetanus and HIV is possible. Intranasal route attracts broad scope in future market as it is not only cheap and affordable but also indicates less side-effects.

REFERENCES

[1] Ghori, M. U., Mahdi, M. H., Smith, A. M., & Conway, B. R. (2015). Nasal drug delivery systems: an overview. American Journal of Pharmacological Sciences, 3(5), 110-119.

[2] Sabale, A. S., Kulkarni, A. D., &Sabale, A. S. (2020). Nasal in situ gel: novel approach for nasal drug delivery. Journal of Drug Delivery and Therapeutics, 10(2-s), 183-197.

[3] Upadhyay, S., Parikh, A., Joshi, P., Upadhyay, U. M., &Chotai, N. P. (2011). Intranasal drug delivery system-A glimpse to become maestro. Journal of applied

pharmaceutical science, 1(03), 34-44.

[4] Parvathi, M. (2012). Intranasal drug delivery to brain: an overview. Inter. J. Res. Pharm. Chem, 2(3), 889-895

[5] Ross And Wilson, Anatomy& Physiology in Health and Illness, 12th edition; 2014,Elsevier Ltd, Churchill Livingstone Elsevier, Page no.243-245

[6] Keller, L. A., Merkel, O., & Popp, A. (2021). Intranasal drug delivery: opportunities and toxicologic challenges during drug development. Drug Delivery and Translational Research, 1-23.

[7] C.C. Chatterjee's Human Physiology, CBS Publisher & Distributors PvtLtd, Eleventh Edition;1985,Page no.6-6 to 6-11

[8] Xu, J., Tao, J., & Wang, J. (2020). Design and application in delivery system of intranasal antidepressants. Frontiers in Bioengineering and Biotechnology, 8.

[9] Chapman, C. D., Frey, W. H., Craft, S., Danielyan, L., Hallschmid, M., Schiöth, H. B., & Benedict, C. (2013). Intranasal treatment of central nervous system dysfunction in humans. Pharmaceutical research, 30(10), 2475-2484.

[10] Thorat, S. (2016). Formulation and product development of nasal spray: an overview. Scholars journal of applied medical sciences, 4(8D), 2976-2985.

[11] Dhakar, R. C., Maurya, S. D., Tilak, V. K., & Gupta, A. K. (2011). A review on factors affecting the design of nasal drug delivery system. International journal of drug delivery, 3(2), 194-208.

[12] Marx, D., Williams, G., & Birkhoff, M. (2015). Intranasal drug administration—an attractive delivery route for some drugs. Drug Discov Dev, 299-320.

[13] Agarwal, V., & Mishra, B. (1999). Recent trends in drug delivery systems: intranasal drug delivery.

[14] Mittal, D., Ali, A., Md, S., Baboota, S., Sahni, J. K., & Ali, J. (2014). Insights into direct nose to brain delivery: current status and future perspective. Drug delivery, 21(2), 75-86.

[15] Pandey, A., Nikam, A., Basavraj, S., Mutalik, S., Gopalan, D., Kulkarni, S., & Mutalik, S. (2021). Nose-to-brain drug delivery: regulatory aspects, clinical trials, patents, and future perspectives. In Direct Nose-to-Brain Drug

Delivery (pp. 495-522). Academic Press.

[16] https://patentimages.storage.googleapis.com/ad/bf/27/c668a721a58e21/US8381729.pdf

[17] https://patents.google.com/patent/US4919132

[18] https://patents.google.com/patent/US9561177B2/en?oq=US9561177B2

[19] https://patents.google.com/patent/US20020054856A1/en?oq=US20020054856A1

[20] https://patents.google.com/patent/US6284765B1/en?oq=US6284765B1

[21] https://patents.google.com/patent/US20150005356A1/en