*ejpmr, 2022, 9(11), 125-132*

SJIF Impact Factor 6.222

EUROPEAN JOURNAL OF PHARMACEUTICAL AND MEDICAL RESEARCH

www.ejpmr.com

Review Article

ISSN 2394-3211

EJPMR

# REVIEW OF MECHANISM OF ACTION OF DRUG ABSORPTION THROUGH OLFACTORY REGION

**Dr. Ashu Sharma[1*], Dr. Ravindra Kumar[2], Dr. Atul Bhardwaj[3], Dr. Arun Gupta[4]**

[1]PG Scholar, PG Dept. of Panchkarma, CBPACS, Khera Dabar, New Delhi-110073.
[2]Assistant Professor, Department Of Panchkarma, Shri Dhanwantri Ayurvedic Medical College & Research Centre, Semri, Mathura (Up)-281401.
[3]Assistant Professor, Department of Shalakya Tantra, CBPACS, Khera Dabar, New Delhi-110073.
[4]HOD, PG Dept. of Panchkarma, CBPACS, Khera Dabar, New Delhi-110073.

***Corresponding Author: Dr. Ashu Sharma**

PG Scholar, PG Dept. of Panchkarma, CBPACS, Khera Dabar, New Delhi-110073.

**Article Received on 12/09/2022** **Article Revised on 02/10/2022** **Article Accepted on 23/10/2022**

## ABSTRACT

Nasal route offer a better route for delivery of drugs for local, systemic circulation and central nervous system as it circumvents the first pass metabolism, easy to use, can be used in those patients in which neither intravenous nor the oral route is preferred .This article outlines the relevant aspect of nasal anatomy, histology, physiology and pathways for transportation of nasal drugs transgressed through the olfactory area.

**KEYWORDS**: Nasal drug delivery system, Mucociliary clearance(MCC),Histology of nose, olfactory epithelium(OE).

## INTRODUCTION

Intra nasal delivery of drug is very effective and reliable alternative to oral and parenteral route. Nasal route can be used to treat local, systemic and CNS disorders. Now a days the efficacy of drugs in systematic and CNS using nose as a portal for drug delivery is receiving much more attention as it circumvents the first pass metabolism thus allowing direct drug delivery to the systemic circulation. It also circumvents the Blood Brain Barrier (BBB) which is the major obstacle in the treatment of CNS disorder like Parkinson Disease, Alzheimer Disease, Seizures[1] etc. In this era when the scientific community is endeavouring to quest for various drug delivery options for neurological disorder the use of nasal cavity to deliver the drugs into central nervous system become more effective as neuroprotective drugs are unable to cross the Blood Brain Barrier, in order to treat such disease many attempts were made to advent drugs to cross BBB but such modification in drugs, barrier integrity may leads to destruction of BBB which allow entry of undesirable molecules to the CNS. So the use of nasal cavity to deliver the drugs into CNS is blowing its own horn in favour of investigating the role of nasal drug delivery option.

### Advantages of nasal drug delivery system[2]

1. Circumvents hepatic first pass metabolism.
2. The drugs shows poor stability in g.i.t. fluids shows better effect when given by nasal route.
3. Polar compounds are suited for this route of delivery which shows poor oral absorption.
4. Suitable route for self-medication.

### Limitation[3,4]

1. Mechanical loss of dosage form may occur due to improper administration of drug.
2. Conditions which causes dysfunction of Mucociliary Clearance (MCC) can affect therapeutic efficacy of drug.
3. Time for drug absorption is limited due to MCC.
4. Certain surfactants used as chemical enhancers may affect the health of nasal mucosa.
5. Due to relatively small area available for the absorption the quantity of drug is limited.

### Anatomy of Nasal Vault

It is pyramidal structure of osteo cartilaginous framework covered by muscles and skin. Total area of both Nasal cavity is ~150-160 $cm^2$. It is divided into two cavities right and left by nasal septum. Each nasal cavity consists vestibule, and a mucosa lined portion (Respiratory & olfactory), the nasal cavity proper.[5] Each nasal cavity consists of medial wall, a lateral wall, a roof and a floor. Lateral wall having turbinates and meatii.

Nasal cavity can be ramified in different regions as elucidated hereafter.

### Vestibular region

It is the part of nasal cavity which is lined by keratinized squamous epithelium with interspersed sebaceous glands and hair follicles. Its surface area is around 0.6 $cm^2$.

**Respiratory region**

It acquires lower two-thirds of the nasal cavity.It is highly vascular and lined by pseudostratified ciliated columnar epithelium which contains plenty of goblet cells. It has largest surface area at ~130cm$^2$ in Adults.[6]

**A. Olfactory region[7]**

This particular area is limited to Upper one-third of lateral wall, corresponding part of the nasal septum and the roof of nasal cavity form the Olfactory region. Here, mucous membrane is paler in colour by virtue of presence of a pigment known as 'Lipofuscin' . Its surface area is around ~10cm$^2$.

The olfactory mucosa has three primary components (Figure-1):

1. Olfactory Epithelium
2. Basement membrane
3. lamina propria

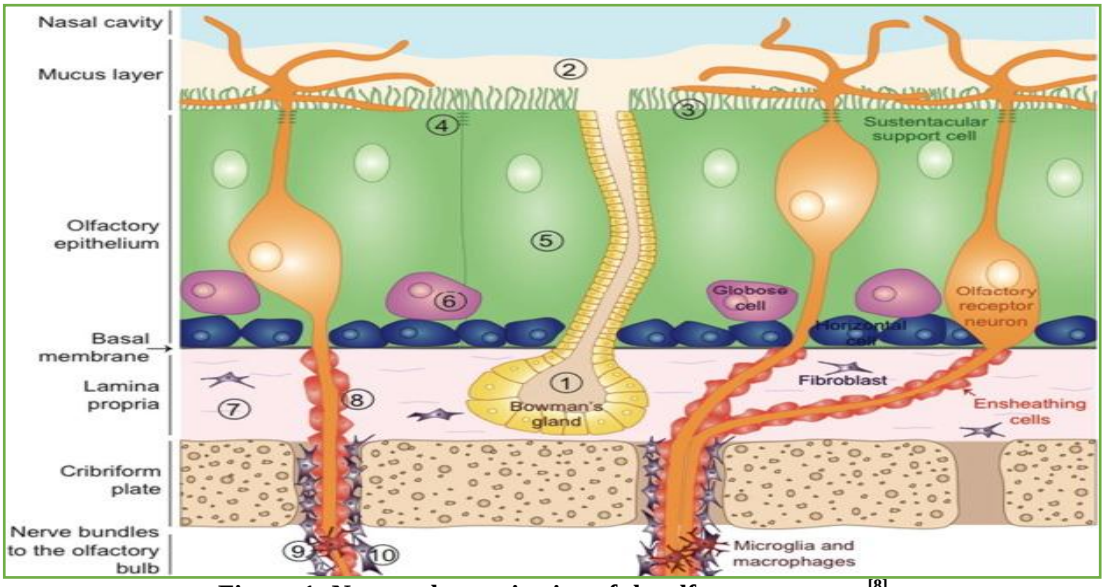



**Figure-1: Neuronal organization of the olfactory mucosa.[8]**

1. Olfactory Epithelium: Composed of five principal cell types

a) Olfactory receptor neurons

Olfactory receptor neurons are actually bipolar neurons (sensory cells) each having a thin dendritic rod that contains specialized cilia, providing the transduction surface for odorous stimuli.[9] These cilia extending from the olfactory vesicle having a long central process that forms the fila olfactoria. These cells are interspersed with sustentacular cells, with each receptor cell having 5-6 cilia.[10]

b) Sustentacular cells

These are scattered among the receptor cells and have numerous microvilli and secretory granules, which empty their contents onto the mucosal surface.[11] It contains xenobiotic metabolising enzymes & this enzyme is also present in duct cells of Bowman's gland, Basal cells and little bit amount in the Olfactory receptor neurons.[12]

c) Basal cells[13]: Two types of cells namely Horizontal Basal Cells and Globose basal cells are present in this structure.

- Horizontal basal cells (HBCs) lie deepest in the olfactory epithelium(OE) and closest to the basement membrane, and they maintain a flat morphology. They are relatively quiescent and are thought to divide only occasionally to give rise to Globose basal cells(GBCs). When there is damage to the OE Then HBCs divides more frequently to give rise to multiple cell types. This also potentially accelerates tissue repair. HBCs were suggested to give rise to OECs.[14]
- GBCs lie above the HBCs and have a rounder morphology and are assumed to give rise to ORNs and sustentacular cells.

d) Microvillar cells[15]

These cells are most superficial among all cells present in the olfactory epithelium having flask-shape with large round nuclei. Having neck from which a tuft microvilli project that extends into the mucus layer of the epithelium, there is a thin axon-like cytoplasmic process extends toward the basement membrane. Microvillar cells are chemoreceptors in the olfactory mucosa. In addition microvillar receptors are the type of receptors present in the Jacobsen's organ and, this accessory olfactory organ is vestigial in humans.

e) Finger like microvilli cells[16]

These cells are straight and strong and characterized by a specific core structure consisting of microfilament bundles while the microvilli of the microvillar cell were had no core structure and are meandering. These cells

were seen after the resection of olfactory bulb when cilia mat disappeared.

2. Basement Membrane-
This membrane differentiate olfactory epithelium from Lamina propria and associate with the Basal cells.

3. Lamina propria
It is situated underneath the epithelial layer(s). It contains 20 olfactory nerve bundles[17] along with blood vessels, Bowman's glands (mucus secreting glands), olfactory ensheathing cells[18], Lymphatics and Nerve supply (Olfactory axon bundles, Maxillary branch of trigeminal nerve and autonomic nerve fibres).

Bowman's glands are under the control of the parasympathetic nervous system and produce nasal secretions.

Olfactory ensheathing cells encloses the olfactory axons. These cells are responsible for phagocytosis of degenerated axons of olfactory nerves.

**B. Cribriform Plate**

This is sieve like (structure) part of ethmoid bone situated between anterior cranial fossa and the nasal cavity, separated at midline by crista galli. It contain multiple foramina through which olfactory nerve fibres passes.

**C. Olfactory Bulb**

Lies inferior to the basal frontal lobe. It is composed of six layers[19] and synapsis (Figure-2). These layers (from outside to centre of bulb) are.

a) Olfactory nerve layer
b) Glomerular layer
c) External plexiform layer
d) Mitral cell layer
e) Internal plexiform layer
f) Granule cell layer

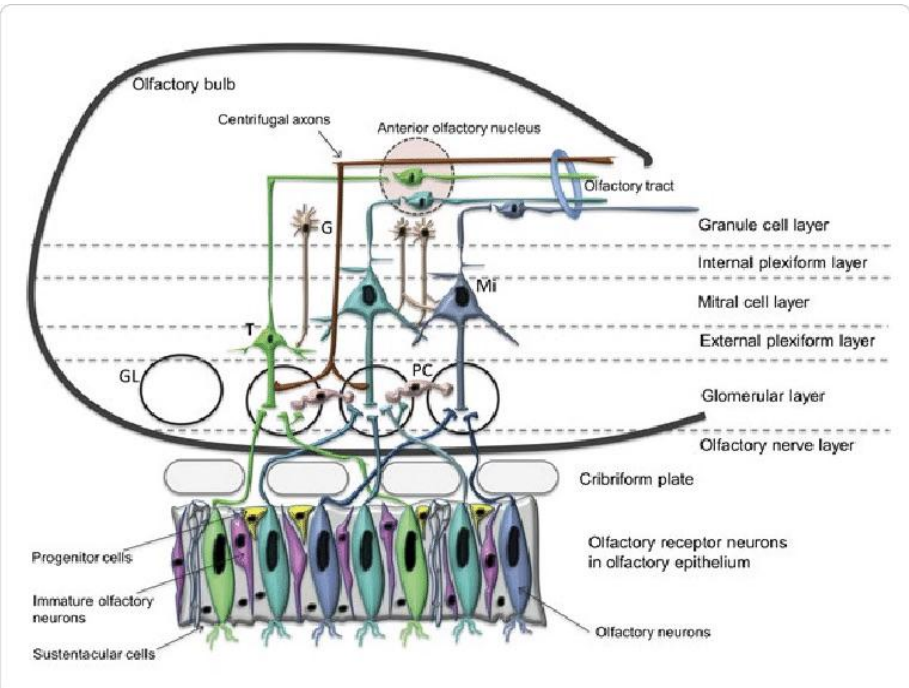



**Figure-2: Schematic diagram of the olfactory neuroepithelium (OE) and the olfactory bulb (OB).[20]**

The OE consists of cells at different stages of differentiation, including the proliferating progenitor cells (yellow colour), the postmitotic immature olfactory neurons (pink colour) and the olfactory sensory, OSN (also known as olfactory receptor neurons, ORN). Axons from the OSN enter the Olfactory Bulb after passing through the cribriform plate (at the base of the skull), here they form the olfactory nerve layer. The OB shows the laminar organization, the major cell types and the basic neuronal circuits. Granule cells (across different layers) and the periglomerular cells are Interneurons in the glomerular layer (GL). Tuffed and mitral cells are the Efferent neurons of the olfactory bulb.

a) Olfactory nerve layer

- Formed by the axon fibres from olfactory receptor neurons.

b) Glomerular layer

- It is outermost layer consisting of olfactory nerve fibre, dendrites of mitral cells, and periglomerular cells.
- Periglomerular cells provide lateral inhibition of neighbouring glomeruli (while allowing excitation of a specific mitral cell dendritic tree) by contacting among multiple mitral cell dendrites within the glomeruli.[21]

c) External plexiform layer

- This layer is composed of Passing dendrites of Mitral cells (Secondary olfactory neurons) and tufted cells.

d) Mitral cells

- This layer have mitral cell (possessing cell body) and dendrites of Granule cells.

e) Internal plexiform layer

- Having Axons of Mitral cells.

f) Granular cell layer

- The granule cell layer contains Granule cells (round neurons that lack axons). Long dendritic processes of the granule cells inhibit mitral cells and tufted cells while Small distal processes make contact with the exiting mitral cell axons.

**Central projections of olfactory tract**

For olfactory information from periphery to the rest of the brain (Figure-3)

Olfactory receptor neurons have to targets olfactory bulb then from here the information is further carried out by axon of mitral and tufted cells. The axons of mitral cell form a bundle, these bundles unites to form lateral olfactory tracts, These tract projects to the accessory olfactory nucli, entorhinal cortex, olfactory tubercle portion of amygdaloid.[22]

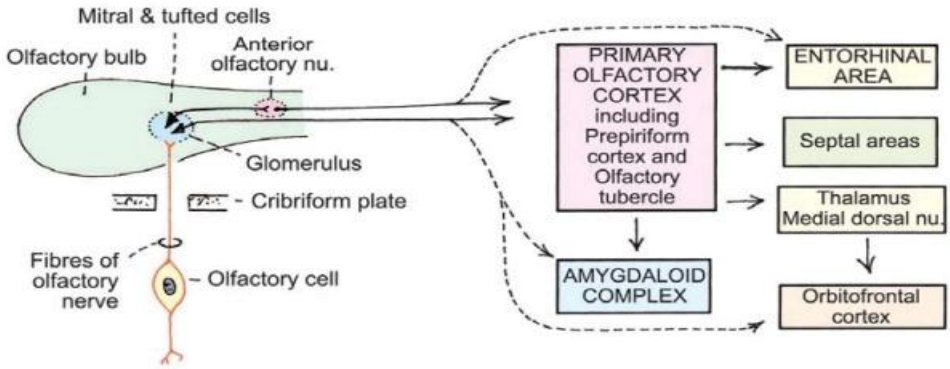


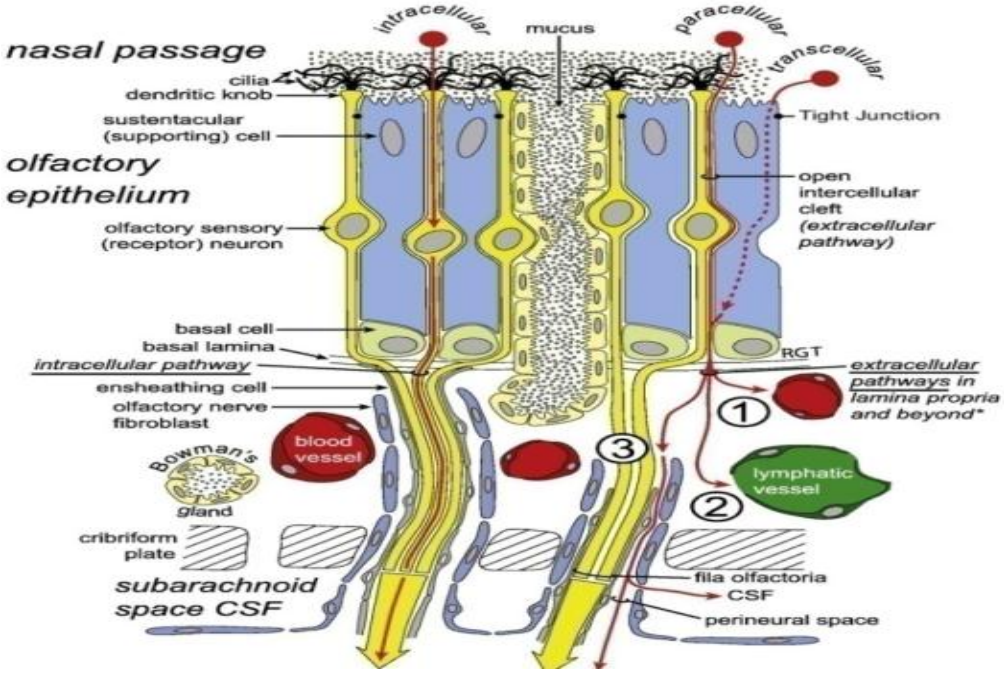

**Figure-3: Central projection of olfactory tract.[23]**

**Transport mechanism**

Molecular movement of drug constituents from olfactory region of nasal cavity to the brain (along both olfactory and trigeminal nerves to the origins of the nerves in the cerebrum and pons respectively). After reaching to the brain the drug got dispersed throughout the brain.

This drug transport mechanism occurs via two pathways[24]

**Pathways for nasal drug absorption**




(Figure-4)

Olfactory bulb[25]

1. Intracellular pathway: there are three intracellular pathways

A. Endocytosis into the neuron
B. Receptor mediated Endocytosis

2. Extracellular pathway: There are two extracellular pathways[26]

A. Paracellular
i. Perineural pathway
ii. Perivascular pathway
B. Transcellular

1. Intracellular pathways: it begin with endocytosis followed by exonal transport (to synaptic cleft in the olfactory bulb)

Endocytosis- It is the process of internalization of substance by the cells from external environment. By this process cells get nutrients for their growth and development, and some cells like wbc capture and destroy potential pathogen.

Steps of endocytosis-the plasma membrane fold inward or invaginates to form a cavity after that the cavity get filled with the extra cellular fluid disclose molecules.

These two end of the plasma membrane fuse together in order to completely encloses the internalized fluid of ECF, this fluid filled cavity known as vesicle.

This vesicle is then detached from the membrane and moved towards the *cis* face of the Golgi apparatus, here the drug molecule are packed in form of vesicle by the endoplasmic reticulum attached to the cis face of the Golgi and rest of the nutrients used by the cell then this drug molecule filled vesicle moved towards *trans* or maturing face of Golgi.

Following endocytosis and Golgi trafficking, the drug containing vesicle move toward the olfactory neurons exonal terminal and olfactory bulb.

After reaching to the nerve terminal the drug containing vesicle reaches close to the cell membrane then attach with the cell membrane.

After fusion of vesicle membrane with the cell membrane there is release of drug content outside the cell. Onto the post synaptic cells of the olfactory bulb. (this process known as exocytosis).

Sensory neurons are capable of endocytosis of variety of molecules ranges from aluminium lactate(294 Da)[27] to insulin(5.8 kDa)[28] to gold particles (50nm)[29], Evans blue labelled albumin(67.4kDa), wheat-germ-agglutinin horse reddish peroxidase WGA-HRP(80kDa).

Receptor mediated endocytosis-This is the another way of endocytosis, This mechanism is an exception as there is specific receptor activation stimuli should be there on molecules, therefore this mechanism is followed by very few particles. *Throne et al* in his study conclude that endocytosis of WGA-HRP was receptor mediated and also found that native HRP was poorly absorbed by the neuron. *Richard et.al* suggest that This may be due to the binding of a large, overwhelming number of lectins (like WGA-HRP) to cellular glycoproteins and carbohydrates is able to over-stimulate endocytosis. There is another study done by *Renner DB*, he found that nanogold labelled insulin internalisation in olfactory neuron was receptor mediated.[30]

2. Extracellular Pathway

A. Paracellular Transport (movement between cells)- The nasal epithelium comprised of different type of cells these are interconnected via tight junction. These Tight Junctions are integral protein extend to the paracellular space and restricting movement of solutes present in the extra cellular fluid.

Some intracellular space are openly allowing material to pass through while most passes through tight junction, which determining the permeability of any particular molecule. After intranasal drug administration, the drug molecules cross the nasal epithelia through the paracellular cleft &tight junctions.

Paracellular movement occurs between olfactory neuron cells and supporting cells the drug administered intranasally move from nasal cavity to the lamina propria. Lipophilic molecules and small hydrophilic molecules are not affected by TJs, though the size limit (for large hydrophilic) varies as per exact TJ protein composition.

i. Perineural pathway: After nasal administration of drug most part of this goes to the lamina propria through paracellular cleft from there it has three fate i.e drug is either absorbed by blood vessels and by lymphatics or diffuses into the perineural space between the olfactory neuron ensheathing cells (OECs) and the olfactory neuronal fibroblast (ONFs). This perineural space directly communicates with the subarachnoid space[31], and provides a transport of material between extracellular fluid from nasal lamina to the Cerebrospinal Fluid (CSF) of subarachnoid space. Through this pathway large part of the drugs coming in the lamina propria is delivered (faster than the axonal pathway) to the brain.[32] This pathway is same for trigeminal nerve also.

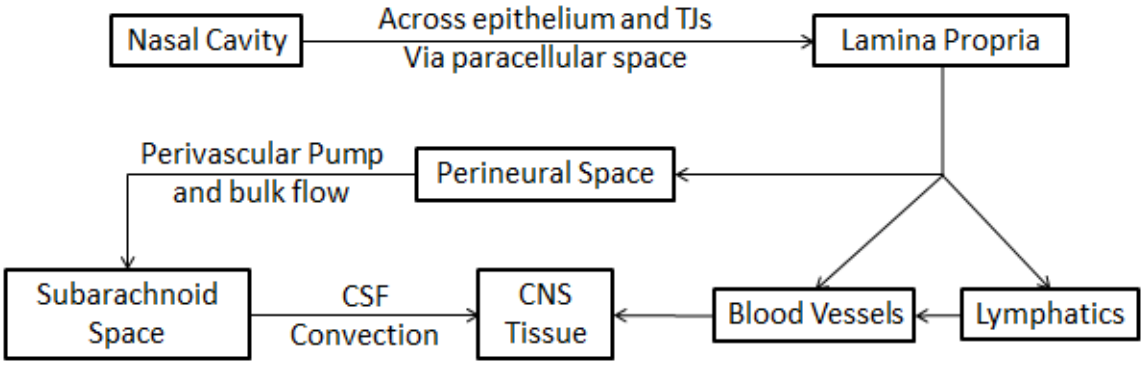
ii. Perivascular pathway: To explain this mechanism a Perivascular Pump theory in sheep[33] given by Stoodley et.al. According to this model CSF flow from perivascular spaces into the central canal is dependent on arterial pulsations or facilitated by pulsatile arterial flow.[34]

B. Transcellular (Simple diffusion across the membrane)- Also known as transcytosis or vesicle meditated transcellular transport, it is a cellular process used to forth macro molecules (such as lipoprotein,

antibodies and albumin) from one surface of polarized cell to the other. Example- movement of lypo protein out of the circulatory system and into tissue delivery of immunoglobulins to mucosal surface.

Transcellular mechanism often involves receptor mediated uptake of a liganed into an endocytic vesicle-regulated transit of the carrier through the cytoplasm-release of cargo -via exocytosis.[35] According to crowe TP et al. In this mechanism the drugs first passes through the paracellular spaces (across the nasal epithelium) then via perineural spaces to the subarachnoid spaces of the brain then into the cerebrospinal fluid (CSF).[36]

The intracellular pathway requires hours to days to reach different brain regions, While the extracellular pathway requires few minutes.[37]




**(Figure-5)**

Flow chart illustrating extracellular mechanism for transportation of drug to CNS from nasal route.[38]

**Factors that affecting the Intranasal drug absorption**

1. Properties related to the drug.[39]

A. Lipophilicity: Directly proportional the permeation through nasal mucosa.

B. Chemical form: The salt or ester form of drug can alter its absorption.

C. Molecular weight: Molecules having molecular weight less than 1000 Dalton shows better absorption.[40]

D. pH of Formulation: It determines the extent of ionisation of drug. Ideal pH should be adjusted between 4.5 to 6.5[41] to minimise nasal irritation.

E. Solubility and Dissolution Rate: Drug should be dissolved in mucus prior to absorption, if drug remain in particle form then is will be cleared by Mucociliary Clearance mechanism.

2. Factors related to the Nose

A. Nasal pathology: Any pathology related to nasal cavity affect drug absorption ex. In acute Rhinosinusitis there is excessive nasal discharge which decreases drug availability on mucus surface.

B. Mucociliary Clearance (MCC) mechanism: It is a mechanism which washout the any type of foreign material present on nasal mucosa surface in order to protect the nasal cavity.

C. Nasal Mucus: Viscosity of nasal mucus is the main factor that influence the drug permeability.

D. Nasal Epithelium: It has tight junctions for the prevention of invading of foreign particle having molecular weight >1000 Dalton.

## CONCLUSION

Nasal route is one of the promising and versatile route for drug delivery, as it has numerous benefits in comparison to other routes. It is expected that this review article will help in understanding Intra Nasal Drug Delivery(INDD) and further development of intranasal drug to achieve specific therapeutic objectives. On comparing different morphological forms of Nasal Drug Delivery, it is clear that oil based nasal medications are absorbed radially than other form.

1. Chapman, C. D., Frey, W. H., 2nd, 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. https://doi.org/10.1007/s11095-012-0915-1.
2. Putheti, R.A.M.E.S.H.R, Patil, M.A.H.E.S.H.C, Obire, O. Nasal Drug delivery in Pharmaceutical and biotechnology: present and future. E-Journal of Science & Technology, 2009; (3).
3. Putheti, R.A.M.E.S.H.R, Patil, M.A.H.E.S.H.C, Obire, O. Nasal Drug delivery in Pharmaceutical and biotechnology: present and future. E-Journal of Science & Technology, 2009; (3).
4. Saxena, C.H.A.R.U, Arora, K.U.N.A.L, Chaurasia, L.O.V.E.L.Y. Importance of Different Novel Nasal Drug Delivery System-A Review. International Journal of Pharmaceutical and Clinical Research, 2019; 11(1): 13-19.

5. Dhingra, P.L, Dhingra, Shruti, Diseases of Ear, Nose and Throat & HEAD and NECK SURGERY. (6th ed.).: Elsevier, C2014.
6. Erdő F, Bors LA, Farkas D, Bajza Á, Gizurarson S. Evaluation of intranasal delivery route of drug administration for brain targeting. Brain Res Bull, 2018 Oct; 143: 155-170. doi:10.1016/j.brainresbull.2018.10.009. Epub 2018 Oct 25. PMID: 30449731.
7. Chen CR, Kachramanoglou C, Li D, Andrews P, Choi D. Anatomy and cellular constituents of the human olfactory mucosa: a review. J Neurol Surg B Skull Base, 2014 Oct; 75(5): 293-300. doi:10.1055/s-0033-1361837. Epub 2014 Jun 26. PMID: 25302141; PMCID: PMC4176544.
8. Rey NL, Wesson DW, Brundin P. The olfactory bulb as the entry site for prion-like propagation in neurodegenerative diseases [Internet]. Neurobiology of Disease. Academic Press; 2016 [cited 2021Jan28]. Available from: https: //www.sciencedirect.com/science/article/pii/S09699 96116302947.
9. Vokshoor, A.M.I.R. Olfactory System Anatomy. (ed.). UK: Chief Editor: Arlen D Meyers, MD, MBA; 2013.
10. Bloom, G, Engstrom, H. The structure of epithethial surface in the olfactory region. KAROLINSKA, 1952; 1(699).
11. Vokshoor, A.M.I.R. Olfactory System Anatomy. (ed.). UK: Chief Editor: Arlen D Meyers, MD, MBA, 2013.
12. Doty, R.I.C.H.A.R.D.L. Handbook of Olfaction and Gustation. (2 ed.). USA: Ding, Xinxin, 2015.
13. Chen CR, Kachramanoglou C, Li D, Andrews P, Choi D. Anatomy and cellular constituents of the human olfactory mucosa: a review. J Neurol Surg B Skull Base, 2014 Oct; 75(5): 293-300. doi:10.1055/s-0033-1361837. Epub 2014 Jun 26. PMID: 25302141; PMCID: PMC4176544.
14. Carter, Lindsay & Macdonald, Jessica & Roskams, Angela. (2004). Olfactory horizontal basal cells demonstrate a conserved multipotent progenitor phenotype. The Journal of neuroscience: the official journal of the Society for Neuroscience, 24: 5670-83. 10.1523/JNEUROSCI.0330-04.2004.
15. Moran DT, Rowley JC 3rd, Jafek BW. Electron microscopy of human olfactory epithelium reveals a new cell type: the microvillar cell. Brain Res, 1982 Dec 16; 253(1-2): 39-46. doi:10.1016/0006-8993(82)90671-0. PMID: 7150975.
16. Ota Y. [Study of the fifth-type cell in the olfactory epithelium]. Nihon Jibiinkoka Gakkai Kaiho, 1998 Oct; 101(10): 1234-49. Japanese. doi:10.3950/jibiinkoka.101.10_1234. PMID: 9838792.
17. Das, A.D.I.T.Y.A. Transmucosal Drug Delivery to the Brain via the Nose. INTERNATIONAL BIOPHARMACEUTICAL INDUSTRY, 2018; 1(1): 14-17.
18. Li, Y.I.N.G, Field,, P.A.U.L.I.N.E.M, Raisman, G.E.O.F.F.R.E.Y. Olfactory Ensheathing Cells and Olfactory Nerve Fibroblasts Maintain Continuous Open Channels for Regrowth of Olfactory Nerve Fibres. GLIA, 2005; (52): 245-251.
19. Misiak MM, Hipolito MS, Ressom HW, Obisesan TO, Manaye KF, Nwulia EA. Apo E4 Alleles and Impaired Olfaction as Predictors of Alzheimer's Disease. Clin Exp Psychol, 2017; 3(4): 169. doi:10.4172/2471-2701.1000169. Epub 2017 Oct 19. PMID: 29423459; PMCID: PMC5800509.
20. Misiak, Magdalena & Hipolito, MariaMananita & Ressom, Habtom & Obisesan, Thomas & Manaye, Kebreten & Nwulia, Evaristus. (2017). Apo E4 Alleles and Impaired Olfaction as Predictors of Alzheimer's Disease. Clinical and Experimental Psychology. 03. 10.4172/2471-2701.1000169.
21. Vokshoor, A.M.I.R. Olfactory System Anatomy. (ed.). UK: Chief Editor: Arlen D Meyers, MD, MBA, 2013.
22. Purves D, Augustine GJ, Fitzpatrick D, et al., editors. Neuroscience. 2nd edition. Sunderland (MA): Sinauer Associates; 2001. Central Projections of the Olfactory Bulb.
23. Singh I. The Olfactory Pathway [Internet]. BrainKart. [cited 2021Jan28]. Available from: http: //www.brainkart.com/article/The-Olfactory-Pathway_19021/
24. Crowe TP, Greenlee MHW, Kanthasamy AG, Hsu WH. Mechanism of intranasal drug delivery directly to the brain. Life Sci, 2018 Feb 15; 195: 44-52. doi:10.1016/j.lfs.2017.12.025. Epub 2017 Dec 22. PMID: 29277310.
25. Sonne, James H., "Effects Of Intranasally Administered Dnsp-11 On The Central Dopamine System Of Normal And Parkinsonian Fischer 344 Rats" (2013). Theses and Dissertations--Anatomy and Neurobiology. Paper 5. http: //uknowledge.uky.edu/neurobio_etds/5.
26. Sonne, James H., "Effects Of Intranasally Administered Dnsp-11 On The Central Dopamine System Of Normal And Parkinsonian Fischer 344 Rats" (2013). Theses and Dissertations--Anatomy and Neurobiology. Paper 5. http: //uknowledge.uky.edu/neurobio_etds/5.
27. Perl DP, Good PF. Uptake of aluminium into central nervous system along nasal olfactory pathways. *Lancet*, 1987; 1: 1028.
28. Renner DB, Frey WH II, Hanson LR. Intranasal delivery of siRNA to the olfactory bulbs of mice via the olfactory nerve pathway. *Neurosci Lett*, 2012; 513: 193-7.
29. de Lorenzo AJD. The Olfactory Neuron and the Blood-Brain Barrier. In *Ciba Foundation Symposium - Taste and Smell in Vertebrates.*Edited by Wolstenholme GEW and Knight J. John Wiley & Sons, Ltd, 1970.
30. Broadwell RD, Balin BJ. Endocytic and exocytic pathways of the neuronal secretory process and trans-synaptic transfer of wheat germ agglutinin-

horseradish peroxidase in vivo. J Comp Neurol, 1985 Dec 22; 242(4): 632-50. doi:10.1002/cne.902420410. PMID: 2418083.

31. Li, Y.I.N.G, Field,, P.A.U.L.I.N.E.M, Raisman, G.E.O.F.F.R.E.Y. Olfactory Ensheathing Cells and Olfactory Nerve Fibroblasts Maintain Continuous Open Channels for Regrowth of Olfactory Nerve Fibres. GLIA, 2005; (52): 245-251.
32. Faber, W.I.L.L.I.A.M.M. THE NASAL h!!UCOSA AND THE SUBARACHNOID SPACE. University of Wisconsin, 121-148.
33. Stoodley MA, Brown SA, Brown CJ, Jones NR. Arterial pulsation-dependent perivascular cerebrospinal fluid flow into the central canal in the sheep spinal cord. J Neurosurg, 1997 Apr; 86(4): 686-93. doi:10.3171/jns.1997.86.4.0686. PMID: 9120633.
34. Sonne, James H., "Effects Of Intranasally Administered Dnsp-11 On The Central Dopamine System Of Normal And Parkinsonian Fischer 344 Rats" (2013). Theses and Dissertations--Anatomy and Neurobiology. Paper 5. http: //uknowledge.uky.edu/neurobio_etds/5.
35. Fung KYY, Fairn GD, Lee WL. Transcellular vesicular transport in epithelial and endothelial cells: Challenges and opportunities. Traffic, 2018 Jan; 19(1): 5-18. doi:10.1111/tra.12533. Epub 2017 Nov 21. PMID: 28985008.
36. Crowe TP, Greenlee MHW, Kanthasamy AG, Hsu WH. Mechanism of intranasal drug delivery directly to the brain. Life Sci, 2018 Feb 15; 195: 44-52. doi:10.1016/j.lfs.2017.12.025. Epub 2017 Dec 22. PMID: 29277310.
37. Talegaonkar, S, Mishra, P.R. Intranasal delivery: An approach to bypass the blood brain barrier. Indian J Pharmacol, 2004; 36(3): 140-147.
38. Crowe TP, Greenlee MHW, Kanthasamy AG, Hsu WH. Mechanism of intranasal drug delivery directly to the brain [Internet]. Life Sciences. Pergamon; 2017 [cited 2021Jan28].Available from: https: //www.sciencedirect.com/science/article/abs/pii/S00 2432051730663X?via%3Dihub
39. Jadhav, Kisan & Gambhire, Manoj & Shaikh, Ishaque Mohammed & Kadam, Vilarsrao & Pisal, Sambjahi. (2007). Nasal Drug Delivery System-Factors Affecting and Applications. Current Drug Therapy, 2. 27-38. 10.2174/157488507779422374.
40. Wheatly MA, Dent J, Wheeldon EB, Smith PL. Nasal drug delivery: An *in vitro* characterization of transepithelial electrical p the presence or absence of enhancer. J Control Release, 1988; 8: 167-77
41. Saxena, C.H.A.R.U, Arora, K.U.N.A.L, Chaurasia, L.O.V.E.L.Y. Importance of Different Novel Nasal Drug Delivery System-A Review. International Journal of Pharmaceutical and Clinical Research, 2019; 11(1): 13-19.