Original Article

Review The Article On The Nasal Drug Delivery System

Gleans Vivek[1]*, Mr. Nirav Rathi[2], Dr. Pragnesh Patani[3]

[1]*Khyati College of Pharmacy, Gujarat Technological University, Ahmedabad, Gujarat, India. Email: vivekgelani47@gmail.com
[2]Department of Quality Assurance, Khyati College of Pharmacy, Gujarat Technological University, Ahmedabad, Gujarat, India.
[3]Department of Pharmacology, Khyati College of Pharmacy, Gujarat Technological University, Ahmedabad, Gujarat, India.

***Correspondence Author Name**: Gelani Vivek

*Khyati College of Pharmacy, Gujarat Technological University, Ahmedabad, Gujarat, India. Email: vivekgelani47@gmail.com
Doi: 10.47750/pnr.2022.13. S05.371

Abstract

Drugs have been inhaled for a long time to have a local effect on the mucosa (e.g. Antihistamines, decongestant, vasoconstrictors and antibiotics). Many medications have been proven to achieve a higher systemic bioavailability when administered orally as opposed to nasally in more recent years. It has been demonstrated that several of them replicate the plasma profile as i.v. administration. More recently, systemic delivery of vaccines, hormones, peptides, and other medications has drawn attention to the intranasal route. The pharmacy offers a wide variety of nasal sprays, both over-the-counter and on prescription. Decongestants, glucocorticoids, antihistamines, mast cell stabilisers, saline, and antibiotics are some of them. In this article, nasal sprays are briefly reviewed.

Keyword: Nasal; Factors; MOA; Formulation types; Advancement ; Limitation; Nasal Cycle;

INTRODUCTION:

The Ayurvedic school of Indian medicine has long recognised therapy delivered intravenously as a valid method of care. Numerous medications have recently been proven to exhibit greater systemic bioavailability when administered orally as opposed to nasally. Numerous protein and peptide drugs are now widely available for the treatment of numerous ailments because to advancements in biotechnology. Because they are significantly digested by first pass action in the liver or significantly destroyed in the gastrointestinal system, many medications are not suited for oral administration. For long-term therapy, even the parenteral route is inconvenient. Intranasal drug delivery has therefore been proven to be quite promising for the administration of these treatments after many alternative routes have been tested.[1] It seems sense that the nose provides simple access to a sizable mucosal surface that is ideal for the delivery of drugs and vaccines. It has generally been difficult to solve issues relating to nasal anatomy, physiology, and aerodynamics that have the potential to significantly limit this capability. The most recent FDA guidance for nasal devices provides comprehensive guidelines for in vitro testing of the physical properties of mechanical liquid spray pumps and pressurised metered-dose inhalers (pMDIs) for nasal use, including in vitro reproducibility and accuracy of plume characteristics and dose uniformity.[2] However the primary function of the nose is olfaction, it heats and humidifies inspired air and also filters airborne particulates.[3] Consequently, the nose functions as a protective system against foreign material.[4] There are three distinct functional zones in the nasal cavity, namely: vestibular, olfactory, and respiratory areas. The vestibular area serves as a baffle system; it functions as a filter of air bone particles.[5] the nasal route of drug delivery can be used for both local and systemic drug deliviery.[6]

NASAL PHYSIOLOGICAL FACTORS:

A. *Blood flow*:-

Nasal mucosa is an ideal location for medication absorption since it has a big surface area and is well-supplied with blood. The systemic nasal absorption of medications is substantially influenced by blood flow rate; when it rises, more drugs pass through the membrane and enter the circulatory system. Given that the majority of medication absorption occurs through diffusion, maintaining the gradient of concentration from the site of absorption to the blood is actually crucial. It is therefore widely established that vasodilatation and vasoconstriction can affect blood flow, which in turn affects how quickly and thoroughly a medicine will be absorbed. Numerous research were conducted to assess its influence. For example, [10] showed that phenylephrine, a vasoconstrictor agent, inhibited the absorption of acetylsalicylic acid in nasal cavity.[7]

B. *Mucocilliary clearance*:-

MMC, also known as mucociliary apparatus or mucociliar clearance (MCC), is the bronchi's self-clearing system. Nasal mucus layer protects the lungs from foreign objects, infections, and particles transported by inhaled air, which is why it is crucial to the respiratory tract's defence. These substances stick to the mucus layer and are then collectively carried to the nasopharynx and, ultimately, the gastrointestinal system. This removal is known as MCC, and it has a big impact on

how well drugs are absorbed by the nose. The MCC system has been compared to a "conveyor belt," with cilia acting as the conveyor belt's driving force and mucus serving as the sticky fluid that gathers and excretes foreign particles. The bronchi's self-clearing system is known as MMC, also known as mucociliary apparatus or mucociliar clearance (MCC). Nasal mucus layer is essential to the defence of the respiratory system because it shields the lungs from foreign objects, illnesses, and particles carried by inhaled air. These compounds adhere to the mucus layer and are subsequently transported in bulk to the nasopharynx and, eventually, the digestive system. Drug absorption through the nose is significantly impacted by this removal, or MCC. The MCC system has been compared to a "conveyor belt," where mucus is the sticky fluid that collects and excretes foreign particles and cilia are the conveyor belt's driving force. In comparison to a medicine deposited anteriorly, a drug deposited posteriorly in the nose clears the nasal cavity more quickly. This is due to MCC being slower in the front of the nose than in the back, which has more cilia. On the other hand, the dose form has a significant impact on the location of drug deposition in the nose. Nasal spray formulations deposit medications more anteriorly than nasal drops, which causes a slower clearance for spray-administered medications. Due to their high mucus solubility and delayed membrane transit, polar medicines are those that are most affected by MCC.[8]

ADVANTAGES OF NASAL DRUG DELIVERY SYSTEM: [9]

1. Easy accessibility and needle free drug application without the necessity of trained personnel facilitates self medication, thus improving patient compliances compared to parenteral routes.
2. Good penetration of, especially lipophilic, low molecular weight drugs through the nasal mucosa. For instance the absolute nasal bioavailability of fentanyl is about 80%.
3. Rapid absorption and fast onset of action due to relatively large absorption surface and high vascularization. Thus the Tmax of fentanyl after nasal administration was less than or equal to 7 minute comparable to intravenous [i.v]. Nasal administration of suitable drug would therefore be effective in emergency therapy as an alternative to parenteral administration routes.
4. Avoidance of the harsh environmental conditions in the gastrointestinal tract (chemical and enzymatic degradation of drugs).
5. Avoidance of hepatic first pass metabolism and thus potential for dose reduction compared to oral delivery.
6. Potential for direct delivery of drug to the central nervous system via the olfactory region, thus by-passing the blood brain barrier.
7. Direct delivery of vaccine to lymphatic tissue and induction f a secretory immune response at distant mucosal site.

LIMITATION: [10]

1. The histological toxicity of absorption enhancers used in nasal drug delivery system is not yet clearly established.
2. Relatively inconvenient to patients when compared to oral delivery systems since there is a possibility of nasal irritation.
3. Nasal cavity provides smaller absorption surface area when compared to GIT.
4. There is a risk of local side effects and irreversible damage of the cilia on the nasal mucosa, both from the substance and from constituents added to the dosage form.
5. The common cold or any pathological conditions involving mucociliary dysfunction, can greatly affect the rate of nasal Clearance and subsequently the therapeutic efficacy of the drug administered nasally.
6. There could be a mechanical loss of the dosage form into the other parts of the respiratory tract like lungs because of the improper technique of administration

ADVANCEMENT IN THE NASAL DOSAGE FORMS: [11]

1. ***Nasal Drops*:** Nasal drops are one of the most simple and convenient system developed for nasal delivery. The man disadvantage of this system is the lack of the dose precision and therefore nasal drops may not be suitable for prescription products. It has been Reported that nasal Drops deposits human serum in the nostrils more efficiently than nasal spray.
2. ***Nasal Spray*:** Both solution and suspension formulations can be formulated into nasal sprays. Due to the availability of metered dose pumps and actuators, a nasal spray can deliver an exact dose. These are preferred over powder sprays because powder results in mucosal irritation.
3. ***Nasal Powders*:** This dosage form may be developed if solution and suspension dosage forms cannot be developed e.g. due to lack of drug stability. The advantages to the nasal powder dosage form are the absence of preservative and superior stability of the formulation. However, the suitability of the powder formulation is dependent on the solubility, particle size, aerodynamic properties and nasal irritancy of the active drug and/or excipients. Local application of drug is another advantage of this system.
4. ***Nasal Gel*:** The nasal gel showed growing interest due to reduction of post-nasal drip, high viscosity, reduction of taste impact due to reduced swallowing, reduction of anterior leakage of the formulation, reduction of irritation by using soothing/emollient excipients and target delivery to mucosa for better absorption.
5. ***Nasal Inserts*:** Nasal inserts are novel, bioadhesive, solid dosage forms for prolonged systemic drug delivery via the nasal route. The principle of the dosage form is to the nasal fluid from the mucosa after administration and to form a gel in the nasal cavity to avoid foreign body sensation.

THE NASAL CYCLE:

The nasal cycle is the term for the physiological cycle of congestion and decongestion seen in at least 80% of healthy persons.[12,13] The nose cycle was initially acknowledged in yoga literature centuries before a German physician first reported it in the rhinological literature in 1895.[12] Due to the fact that the overall nasal resistance is rather constant in healthy persons, they are typically unconscious of the spontaneous and irregular reciprocal 1-4-h cycling of the nasal calibre of the two separate passageways.[14] The blood content of the submucosal capacitance vessels that make up the erectile component at important places, most notably the nasal valve region, is the primary determinant of the autonomic cyclic variation in airflow resistance. Furthermore, a range of stimuli, such as physical and sexual activity, as well as emotional states, can modify and override the fundamental cyclic rhythm because the erectile tissues of the septal and lateral walls and the turbinates respond to these stimuli. [15] While sleeping, the cycle is present, but it is suppressed by pressures placed on the lateral body surface while reclining to clear the upper/contralateral nasal channel. According to certain theories, this phenomenon leads people to flip their bodies while they sleep from one side to the other.[12,16] Intubated patients experience a suppression of the cycle, although normal nasal breathing resumes the cycle's function.[17] Through direct antibacterial action and improved mucociliary clearance, the cycle may also result in the buildup of nitric oxide (NO) in the clogged tube and surrounding sinuses and help to defence against germs. [18] Measurements have revealed that the rise in NO concentration within the more crowded cavity, which nearly perfectly balances the decrease in nasal airflow, keeps the concentration of NO in the inspired air roughly constant.[19] The nasal cycle may become clinically apparent and result in bothersome blockage in some patients as a result of structural abnormalities and inflammatory mucosal edoema.[20] Because of the cycle, one nostril is typically much more crowded than the other, and the majority of airflow travels through one nostril while the other one is still fairly small, especially around the valve area. Therefore, when evaluating the effectiveness of nasal medication delivery systems, the nasal cycle must be taken into account as it greatly contributes to the dynamics and resistance in the nasal valve region.[12]

TARGETED NASAL DELIVERY:

For the majority of applications, a widespread distribution of the medication on the mucosal surfaces seems preferable for medications with a local or systemic action, as well as for vaccinations.[21] Targeted administration to the middle and superior meatuses, where the sinus apertures are and where the polyps originate, however, seems preferable in cases of chronic sinusitis and nasal polyposis.[22,23] Drugs intended for "nose-to-brain" delivery may also be an exception, where more precise distribution to the top portions of the nose that house the olfactory neurons has been thought to be crucial. Recent animal research, however, indicates that some transport may also take place along the first and second divisions of the trigeminal nerve's branches, which innervate the majority of the mucosa at and beyond the nasal valve.[24]

MECHANISM OF DRUG NASAL DELIVERY AND ABSORPTION:

The main method of drug administration and absorption through the nasal cavity is through mucus. Mucin, a protein derived from mucus, is capable of binding to solutes and interfering with the diffusion process. Numerous mechanisms, including as paracellular and transcellular pathways, are available for nasal administration and absorption through the mucosa.[25] Paracellular transport is the term used to describe the link between intranasal absorption and the molecular weight of water-soluble compounds. A drug's bioavailability is low when its molecular weight exceeds 1,000 Daltons.[26,27,28] The second mechanism, a transcellular process, transports medications with a rate reliance on their lipophilicity.[29,30] As was previously said, permeability enhancers are required to increase bioavailability.[31,32] By altering the phospholipid bilayer, permeation enhancers would cause reversible changes to the epithelial layer's structure.[33,34]

NASAL DRUG DIFFERENT TYPES OF FORMULATIONS:

Nasal drops and sprays-

Apply nasal drops by squeezing the bottle's cap. Nasal drops can help with localised problems, such as mucociliary dysfunction, in specific places.[35,36] Nasal delivery is the most straightforward and straightforward approach for formulations and administration, but a major drawback of the system is the possibility of contamination during use and the difficulty of providing the drug in a precise and accurate amount.[37]

Nasal sprays have three components.

1: Chamber

2: Piston

3: Actuating actuator

The accuracy of nasal spray over nasal drops in terms of measured dose expulsion[35] Nasal spray demonstrated a consistent dose of reproducible plume shape, and formulation characteristics like surface tension, viscosity, and thixotropy can influence droplet size and dose precision.[38,39,40,41] The nasal disposition sprays can be affected by the pump's design and orifice size.[37,42]

NASAL GEL:

By its characteristics, it is soft semisolid in nature and the semisolid characteristics can be two dynamic mechanical properties (i) elastic module G and (ii) viscous module G [43] The flow properties of the nasal gel depends on vicious concentration and type of polymer for good results of biopharmaceutics bio-adhesive polymers plays a high role and these results a good improvement of patient complains [44,45] A long time contact of a drug at the absorption site can increase the

bioavailability because of slowing the mucociliary movement [46] The mechanism of the mucoadhesive was explained by various theories, but the mechanism is generally based on two keys (i) contact and (ii) consolidation a long contact of polymer can diffuse with mucus[37] Various non-harmful and biologically degradable polymers are discovered for mucoadhesive system Example Polyvinyl alcohol [47] Mucoadhesive gels for nasal administration have been studied for different antibiotics such as ciprofloxacin[48], mometasone[49], carvedilol[50], and vaccines and proteins[51,52]. Some of the gels behave pseudo plasticity and their flow properties cannot be used for nasal delivery for this purpose gelation is used for overcome form that problem[53] In polymeric formulations, the drug has to be solution form but after reaching into the body it should converted into gelation to the form of gel in a body depends on temp., pH, and ions in a body.[54]

REFERENCES:

1. CheinYW, Su KSE and Chang SF. Nasal systemic drug delivery. Dekker. 1989; 1-77
2. FDA 2003. US FDA draft guidance for industry. Bioavailability and bioequivalence studies for nasal aerosols and nasal sprays. Bethesda. http://www.fda.gov/cder/guidance/index.htm. Accessed July 2012.
3. Sarkar MA. Drug metabolism in the nasal mucosa. Pharm Res 1992; 9: 1–9.
4. Brime B, Ballesteros MP, Frutos P. Preparation and in vitro characterization of gelatin microspheres containing Levodopa for Table 2 nasal administration. J Microencap 2000; 6: 777–84.
5. Mygind N, Dahl R. Anatomy, physiology and function of the nasal cavities in health and disease. Adv Drug Del Rev 1998; 29: 3–12.
6. ¸Casettaei, L& Illum. L, Chitosan in nasal delivery system for therapeutic drugs, Journal of Controlled Release. 2014; 190:189-200.
7. Huang CH, Kimura R, Nassar RB, Hussain A. Mechanism of nasal absorption of drugs. I: Physicochemical parameters influencing the rate of in situ nasal absorption of drugs in rats. J Pharm Sci. 1985; 74: 608-611
8. Merkus FW, et al. Nasal mucociliary clearance as a factor in nasal drug delivery. Adv Drug Delivery Rev. 1998; 29: 13-38
9. Kao HD, et al. Enhancement of the systemic and CNS specific delivery of L-dopa by the nasal administration of its water soluble prodrugs. Pharm Res. 2000; 17: 978-984
10. Hirai S, et al. Absorption of drugs from the nasal mucosa of rats. Int J Pharm. 1981; 7: 317-325
11. Verma S., Tyagi Yogita., Tangri P., Review article on nasal drug delivery system, ijsdr. 2021; 6(2):100-107.
12. Cole P. *Nasal respiratory function. In: The nose.* St. Louis: Mosby-Year Book Inc.; 1993. pp. 3–60.
13. Baraniuk JN. Neural regulation of mucosal function. *Pulm Pharmacol Ther.* 2008; 21(3):442–448.
14. Cole P. Stability of nasal airflow. *Clnin Otolaryngol.* 1989; 14:177–182.
15. Sahin-Yilmaz A, Naclerio RM. Anatomy and physiology of the upper airway. *Proc Am Thorac Soc.* 2011; 8:31–39.
16. Cole P, Haight JSJ. Posture and the nasal cycle. *Ann Otol Rhinol Laryngol.* 1986; 95:223–227.
17. Havas TE, Cole P, Gullane PJ, et al. The nasal cycle after laryngoectomy. *Acta Otolaryngo (Stockh).* 1987; 103:111–116.
18. Djupesland PG, Chatkin JM, Qian W, Haight JSJ. Nitric oxide in the nasal airway: a new dimension in otolaryngology. *Am J Otolaryngol.* 2001; 22:19–32.
19. Qian W, Sabo R, Ohm M, Haight JSJ, Fenton R. Nasal nitric oxide and the nasal cycle. *Laryngoscope.* 2001; 111:1603–1607.
20. Mygind N, Dahl R. Anatomy, physiology and function of the nasal cavities in health and disease. *Adv Drug Deliv Rev.* 1998; 29:3–12.
21. Vidgren MT, Kublik H. Nasal delivery systems and their effect on deposition and absorption. *Adv Drug Deliv Rev.* 1998; 29:157–177.
22. Laube B. Devices for aerosol delivery to treat sinusitis. *J Aerosol Med.* 2007; 20(Suppl):5–18.
23. Aggrawal R, Cardozo A, Homer JJ. The assessment of topical nasal drug distribution. *Clin Otolaryngol.* 2004; 29:201–205.
24. Johnson HJ, Hanson LR, Frey WH. Trigeminal pathways deliver a low molecular weight drug from the nose to the brain and orofacial structures. *Mol Pharm.* 2010;7(3):884–893.
25. Duvvuri, S., Majumdar, S., and Mitra, A. K. (2003). Drug delivery to the retina: challenges and opportunities. *Expert Opin. Biol. Ther.* 3, 45–56.
26. Huang, C. H., Kimura, R., Nassar, R. B., and Hussain, A. A. (1985). Mechanism of nasal absorption of drugs I: physicochemical parameters influencing the rate of *in situ* nasal absorption of drugs in rats. *J. Pharm. Sci*. 74, 608–611.
27. Alex, A. T., Joseph, A., Shavi, G. V., Rao, J. V., and Udupa, N. (2014). Development and evaluation of carboplatin-loaded PCL nanoparticles for intranasal delivery. *Drug Deliv*. 23, 2144–2153
28. Li, Y., Fan, X., Li, W., Yang, P., Zhang, H., Tang, D., et al. (2018). Metoclopramide nasal spray *in vitro* evaluation and *in vivo* pharmacokinetic studies in dogs. *Pharm. Dev. Technol*. 23, 275–281.
29. Kangmieler, J. J., Osswald, C. R., and Mieler, W. F. (2014). Advances in ocular drug delivery: emphasis on the posterior segment. *Expert Opin. Drug Deliv*. 11, 1647–1660.
30. Proschak, E., Heitel, P., Kalinowsky, L., and Merk, D. (2017). Opportunities and challenges for fatty acid mimetics in drug discovery. *J. Med. Chem*. 60, 5235–5266. doi: 10.1021/acs.jmedchem.6b01287
31. Wang, Z., and Chow, M. S. (2014). Overview and appraisal of the current concept and technologies for improvement of sublingual drug delivery. *Ther. Deliv*. 5, 807–816.
32. Yamamoto, Y., Danhof, M. M., and de Lange, E. C. (2017). Microdialysis: the key to physiologically based model prediction of human CNS target site concentrations. *AAPS J.* 19, 891–909.
33. Dhuria, S. V., Hanson, L. R., and Frey, W. H. II (2010). Frey II: intranasal delivery to the central nervous system: mechanisms and experimental considerations. *J. Pharm. Sci*. 99, 1654–1673.
34. Mouez, M. A., Zaki, N. M., Mansour, S., and Geneidi, A. S. (2014). Bioavailability enhancement of verapamil HCl via intranasal chitosan microspheres. *Eur. J. Pharm. Sci.* 51, 59–66.
35. Hussein NR. Bio Adhesive Micro Particles and Liposomes of Anti Parkinson Drugs for Nasal Delivery. PhD Thesis University of Central Lanceshire; 2014.
36. Mahdi MH, Conway BR, Smith AM. Development of mucoadhesive sprayable gellan gum fluid gels. Int J Pharm 2015;488:12-9
37. Washington N, Washington C, Wilson CG. Physiological Pharmaceutics Barrier to Drug Absorption. New York: Taylor and Francis; 2011.
38. Djupesland PG. Nasal drug delivery devices: Characteristics and performance in a clinical perspective-a review. Drug Deliv Transl Res 2013; 3:42-62.
39. Hansen K, Kim G, Desai KG, Patel H, Olsen KF, Curtis-Fisk J, et al. Feasibility investigation of cellulose polymers for mucoadhesive nasal drug delivery applications. Mol Pharm 2015; 12:2732-41.
40. Rassu G, Soddu E, Cossu M, Brundu A, Cerri G, Marchetti N, et al. Solid microparticles based on chitosan or methyl-β-cyclodextrin: A first formulative approach to increase the nose-to-brain transport of deferoxamine mesylate. J Control Release 2015; 201:68-77.
41. Menaka M, Pandey VP. Formulation development and evaluation of cinnarizine nasal spray. Pharm Health Sci 2014; 2:339-46.
42. Vidgren MT, Kublik H. Nasal delivery systems and their effect on deposition and absorption. Adv Drug Deliv Rev 1998; 29:157-77.
43. Chaturvedi M, Kumar M, Pathak K. A review on mucoadhesive polymer used in nasal drug delivery system. J Adv Pharm Technol Res 2011; 2:215-22.
44. Rathbone MJ, Hadgraft J, Roberts MS, editors. Modified Release Drug Delivery Technology. Boca Raton: CRC Press; 2002.
45. Nakumura K, Tanaka Y, Sakurai M. Dynamic mechanical properties of aqueous gellan solution sol-gel transition region. Carbohydr Polym 1996;30:101-8
46. Patil SB, Sawant KK. Mucoadhesive microsphere; a promising tool in drug delivery. Curr Drug Deliv 2008;5:312-8

47. Pasha M, Ngn S. Derivatization of guar to sodium carboxy methyl hydroxy propyl derivative; characterization and evaluation. Pak J Pharm Sci 2008;21:40-4
48. Ugwoke MI, Agu RU, Verbeke N, Kinget R. Nasal mucoadhesive drug delivery; background application trends and future perspectives. Adv Drug Deliv Rev 2005; 57:1640-65.
49. Zitt M, Kosoglou T, Hubbell J. Mometasone furoate nasal spray: A review of safety and systemic effects. Drug Saf 2007; 30:317-26.
50. Saindane NS, Pagar KP, Vavia PR. Nanosuspension based in situ gelling nasal spray of carvedilol: Development, in vitro and in vivo characterization. AAPS PharmSciTech 2013; 14:189-99.
51. Vila A, Sánchez A, Tobío M, Calvo P, Alonso MJ. Design of biodegradable particles for protein delivery. J Control Release 2002; 78:15-24.
52. Davis SS. Nasal vaccines. Adv Drug Deliv Rev 2001;51:21-42
53. Madan M, Lewis MB, Udupa S, Baig N. In situ forming polymeric drug delivery system. Indian J P S 2009:71; 242-51.
54. Sworn G, Sanderson GR, Gibson W. Gellan gum fluid gel. Food Hydrocoll 1995; 9:265-71.