A REVIEW ON FACTORS AFFECTING THE DESIGN OF NASAL DRUG DELIVERY SYSTEM

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ABSTRACT

Transmucosal nasal delivery is a promising drug delivery option where common drug administrations (e.g., intravenous, intramuscular, or oral) are inapplicable. Recently, it has been shown that many drugs have better bioavailability by nasal route than by oral route. This has been attributed to rich vasculature and a highly permeable structure of the nasal mucosa coupled with avoidance of hepatic first-pass elimination, gut wall metabolism and/or destruction in the gastrointestinal tract. The physiology of the nose presents obstacles, but offers a promising route for non-invasive systemic delivery of numerous therapies and debatably drug delivery route to the brain. To overcoming problems in nasal drug delivery requires deep understanding of the various factors affecting nasal delivery. Thus present review focuses on various aspects of nasal drug delivery with special emphasis to factors affecting nasal drug administration.

KEYWORDS: Transmucosal nasal delivery, hepatic first-pass metabolism, non-invasive, systemic delivery

INTRODUCTION

Oral drug delivery is the most desirable route for drug administration whenever systemic effects are intended [1, 2]. But low oral bioavailability of some compounds has prompted the search of more effective routes for their systemic delivery [3]. Transmucosal routes of drug delivery (i.e., the mucosal linings of the nasal, rectal, vagina, ocular and oral cavity) offer distinct advantages over peroral administration for systemic drug delivery. These advantages includes possible bypass of the first pass effect, avoidance of pre-systemic elimination of gastro intestinal tract and depending on the particular drug. The nasal cavity as a site for systemic drug delivery has been investigated by many research groups. However, the potential irritation and irreversible damage to the ciliary action application of nasal dosage forms, as well as the large intra and inter subject variability in mucus secretion in the nasal mucosa could significantly effect drug absorption from this site.

Currently, many nasal drug products on the market are indicated for the treatment of local disease such as allergic rhinitis, pain and for centrally acting drugs where the direct pathway from the nose to brain might offer a quicker and further specific therapeutic effect. Many low-molecular-weight, non-polar drugs (<300Da) in solution form are able to infiltrate the nasal epithelium with effortlessness. The effectiveness of a particular delivery system is also affected by its formulation as a liquid[4], powder[4], gel[5], microsphere[6], liposome[7] or nanoparticle[8]. Intranasal drug delivery is now recognized to be a useful and reliable alternative to oral and parenteral routes. In general, among the primary targets for intranasal administration are pharmacologically active compounds with poor stability in gastrointestinal fluids, poor

intestinal absorption and/or extensive hepatic first-pass elimination, such as peptides, proteins and polar drugs [9]. The nasal delivery seems to be a favorable way to circumvent the obstacles for blood-brain barrier (BBB) allowing the direct drug delivery in the biophase of central nervous system (CNS)-active compounds. It has also been considered to the administration of vaccines [10-13]. In addition, intranasal absorption avoids the gastrointestinal and hepatic pre-systemic metabolism, enhancing drug bioavailability in comparison with that obtained after gastrointestinal absorption [14, 15]. Hence, it appears to be an appropriate route for the treatment of not only acute or chronic nasal diseases, but also for a range of acute or chronic conditions requiring considerable systemic drug exposure [9].

The present review outlines anatomical and physiological features of nasal cavity, the major factors affecting nasal drug delivery. Additionally, this review focuses on the strategies used to enhance the nasal drug absorption and research carried out on nasal drug delivery.

NASAL ANATOMY AND PHYSIOLOGY OF NOSE

The human nasal cavity has a total volume of about 16 to 19 ml, and a total surface area of about 180 cm^2, and is divided into two nasal cavities via the septum. The volume of each cavity is approximately 7.5 ml, having a surface area around 75 cm^2.

The vestibular region: It is located at the opening of nasal passages and is responsible for filtering out the air borne particles. It is considered to be the least important of the three regions with regard to drug absorption.

The respiratory region: The respiratory region is the largest having the highest degree of vascularity and is mainly responsible for systemic drug absorption.

The olfactory region: It is of about 10 cm^2 in surface area, and it plays a vital role in transportation of drugs to the brain and the CSF. Human olfactory region comprises of thick connective tissue lamina propria, upon which rests the olfactory epithelium. Lamina propria has axons, bowans bundle and blood vessels whereas epithelium consists of three different cells i.e. basal cells, supporting cells and olfactory receptor cells. Neurons are interspersed between supporting cells. The olfactory receptor cells are bipolar neurons with a single dendritic and extending from the cell body to the free apical surface where it ends in an olfactory knob carrying non-motile cilia, which extend above the epithelium.

The epithelium of the nasal passage is covered by a mucus layer, which entraps particles. The mucus layer is cleared from the nasal cavity by cilia, and is renewed every 10 to 15 minutes [17]. The pH of the mucosal secretions ranges from 5.5 to 6.5 in adults and 5.0 to 6.7 in children. The mucus moves through the nose at an approximate rate of 5 to 6 mm/min resulting in particle clearance within the nose every 15 to 20 minutes. Numerous enzymes for instance, cytochrome P450 enzymes, carboxylesterases and glutathione S-transferases are found in nasal cavity [18-20].

REASON FOR DEVELOPMENT OF NASAL DELIVERY

Nasal drug delivery is a useful delivery method for drugs that are active in low doses and show no or minimal oral bioavailability. The nasal route circumvents hepatic first pass elimination associated with the oral delivery: it is easily accessible and suitable for self-medication. Currently, tow classes of nasally delivered therapeutics are on the market. The first one comprises low molecular weight and hydrophobic drugs for the treatment of the nasal mucosa and sinus, including decongestants, topical steroids, antibiotics and other (OTC) products. The second class encompasses a few drugs, which have sufficient nasal absorption for displaying systemic effects. Important candidates are the compounds, generally administered by injection and hardly absorbed after oral administration, due to their instability in gastrointestinal tract, poor absorption properties, and their rapid and extensive biotransformation [21-23].

MECHANISM OF DRUG ABSORPTION THROUGH NASAL MUCOSA

The first step in the absorption of drug from the nasal cavity is passage through the mucus [22]. Small, unchanged particles easily pass through this layer. However, large or charged particles may find it more

difficult to cross. Mucin, the principle protein in the mucus, has the potential to bind to solutes, hindering diffusion. Additionally, structural changes in the mucus layer are possible as a result of environmental changes (i.e. pH, temperature, etc.)[24]. Subsequent to a drug's passage through the mucus, there are several mechanisms for absorption through the mucosa [25]. These include transcellular or simple diffusion across the membrane, paracellular transport *via* movement between cell and transcytosis by vesicle carriers[24]. Obstacles to drug absorption are potential metabolism before reaching the systemic circulation and limited residence time in the cavity. Several mechanisms have been proposed but the following two mechanisms have been considered predominantly.

The first mechanism involves an aqueous route of transport, which is also known as the paracellular route. This route is slow and passive. Insulin, mannitol and propranolol were absorbed through this mechanism. There is an inverse log-log correlation between intranasal absorption and the molecular weight of water-soluble compounds. Literature survey revealed that good bioavailability was observed for drugs with a molecular weight up to 1000 Daltons. But with the help of permeation enhancers good bioavailability can be enhanced to at least 6000 Daltons[26]. The second mechanism involves transport through a lipoidal route that is also known as the transcellular process and is responsible for the transport of lipophilic drugs that show a rate dependency on their lipophilicity. Drugs also cross cell membranes by an active transport route via carrier-mediated means or transport through the opening of tight junctions[23]. For example, Chitosan, a natural biopolymer from shellfish, opens tight junctions between epithelial cells to facilitate drug transport[27].

MERITS OF INTRANASAL DRUG DELIVERY
- ✓ Non – invasive, rapid, Self-administration thus improved convenience and compliance.
- ✓ Large nasal mucosal surface area for dose absorption
- ✓ Bypasses the BBB and targets the CNS, reducing systemic exposure and thus systemic exposure and thus systemic side effects.
- ✓ Minimal aftertaste
- ✓ Does not require nay modification of the therapeutic agent being delivered neurological and psychiatric disorders.
- ✓ Rich vasculature and highly permeable structure of the nasal mucosa greatly enhance drug absorption.
- ✓ Problem of degradation of peptide drugs in minimized up to a certain extent.
- ✓ Easy accessibility to blood capillaries[9, 14, 15, 27, 28].

DEMERITS OF INTRANASAL DRUG DELIVERY
- ✓ Concentration achievable in different regions of the brain and spinal cord varies with each agent.
- ✓ Delivery is expected to decrease with increasing molecular weight of drug.
- ✓ Some therapeutic agents may be susceptible to partial degradation in the nasal mucosa or may cause irritation to the mucosa.
- ✓ Nasal congestion due to cold or allergies may interfere with this method of delivery.
- ✓ Frequent use of this route may result in mucosal damage[29, 30].

FACTORS AFFECTING THE CHARACTERISTICS OF NASAL DRUG DELIVERY
Some of the physicochemical, formulation and physiological factors are imperative and must be considered prior to designing intranasal delivery.

Physicochemical properties of drugs
Chemical form: The chemical form of a drug is important in determining absorption.
For example, conversion of the drug into a salt or ester form can also alter its absorption**.** Huang et al 1985 studied the effect of structural modification of drug on absorption[31]. It was observed that in-situ nasal absorption of carboxylic acid esters of L-Tyrosine was significantly greater than that of L-Tyrosine.
Polymorphism: Polymorphism is known to affect the dissolution rate and solubility of drugs and thus their absorption through biological membranes.

Molecular Weight: A linear inverse correlation has been reported between the absorption of drugs and molecular weight up to 300 Da. Absorption decreases significantly if the molecular weight is greater than 1000 Da except with the use of absorption enhancers. Shape is also important. Linear molecules have lower absorption than cyclic – shaped molecules.

Particle Size: It has been reported that particle sizes greater than 10μm are deposited in the nasal cavity.

Solubility & dissolution Rate: Drug solubility and dissolution rates are important factors in determining nasal absorption from powders and suspensions. The particles deposited in the nasal cavity need to be dissolved prior to absorption. If a drug remains as particles or is cleared away, no absorption occurs.

Formulation factors

pH of the formulation: Both the pH of the nasal cavity and pKa of a particular drug need to be considered to optimize systemic absorption. Nasal irritation is minimized when products are delivered with a pH range of 4.5 to 6.5. Also, volume and concentration are important to consider. The delivery volume is limited by the size of the nasal cavity. An upper limit of 25 mg/dose and a volume of 25 to 200 μL/ nostril have been suggested.

✓ To avoid irritation of nasal mucosa;
✓ To allow the drug to be available in unionized form for absorption;
✓ To prevent growth of pathogenic bacteria in the nasal passage;
✓ To maintain functionality of excipients such as preservatives; and
✓ To sustain normal physiological ciliary movement.

Lysozyme is found in nasal secretions, which is responsible for destroying certain bacteria at acidic pH. Under alkaline conditions, lysozyme is inactivated and the nasal tissue is susceptible to microbial infection. It is therefore advisable to keep the formulation at a pH of 4.5 to 6.5 keeping in mind the physicochemical properties of the drug as drugs are absorbed in the unionized form.

Buffer Capacity: Nasal formulations are generally administered in small volumes ranging from 25 to 200μL. Hence, nasal secretions may alter the pH of the administrated dose. This can affects the concentration of unionized drug available for absorption. Therefore, an adequate formulation buffer capacity may be required to maintain the pH in-situ.

Osmolarity: Drug absorption can be affected by tonicity of formulation. Shrinkage of epithelial cells has been observed in the presence of hypertonic solutions. Hypertonic saline solutions also inhibit or cease ciliary activity. Low pH has a similar effect as that of a hypertonic solution.

Gelling / Viscosity building agents or gel-forming carriers: Pennington et al 1988 studied that increase in solution viscosity may provide a means of prolonging the therapeutic effect of nasal preparations[32]. Suzuki et al 1999 showed that a drug carrier such as hydroxypropyl cellulose was effective for improving the absorption of low molecular weight drugs but did not produce the same effect for high molecular weight peptides[33].

Solubilizers: Aqueous solubility of drug is always a limitation for nasal drug delivery in solution. Conventional solvents or co-solvents such as glycols, small quantities of alcohol, Transcutol (diethylene glycol monoethyl ether), medium chain glycerides and Labrasol can be used to enhance the solubility of drugs[34]. Other options include the use of surfactants or cyclodextrins such as HP-β-cyclodextrin that serve as a biocompatible solubilizer and stabilizer in combination with lipophilic absorption enhancers.

Preservatives: Most nasal formulations are aqueous based and need preservatives to prevent microbial growth. Parabens, benzalkonium chloride, phenyl ethyl alcohol, EDTA and benzoyl alcohol are some of the commonly used preservatives in nasal formulations. Van De Donk et al 1980 have shown that mercury containing preservatives have a fast and irreversible effect on ciliary movement and should not be used in the nasal systems[35].

Antioxidants: Usually, antioxidants do not affect drug absorption or cause nasal irritation. Commonly used antioxidants are sodium metabisulfite, sodium bisulfite, butylated hydroxyl toluene and tocopherol.

Humectants: Many allergic and chronic diseases are often connected with crusts and drying of mucous membrane. Therefore humectants can be added especially in gel-based nasal products. Humectants avoid

nasal irritation and are not likely to affect drug absorption. Common examples include glycerin, sorbitol and mannitol.

Drug Concentration, Dose & Dose Volume: Drug concentration, dose and volume of administration are three interrelated parameters that impact the performance of the nasal delivery performance. Nasal absorption of L-Tyrosine was shown to increase with drug concentration in nasal perfusion experiments.

Role of Absorption Enhancers: Absorption enhancers may be required when a drug exhibits poor membrane permeability, large molecular size, lack of lipophilicity and enzymatic degradation by amino peptidases. Osmolarity and pH may accelerate the enhancing effect. Absorption enhancers improve absorption through many different mechanisms, such as increasing membrane fluidity, increasing nasal blood flow, decreasing mucus viscosity, and enzyme inhibition.

Physiological factors

Effect of Deposition on Absorption: Deposition of the formulation in the anterior portion of the nose provides a longer nasal residence time. The anterior portion of the nose is an area of low permeability while posterior portion of the nose where the drug permeability is generally higher, provides shorter residence time.

Nasal blood flow: Nasal mucosal membrane is very rich in vasculature and plays a vital role in the thermal regulation and humidification of the inhaled air. The blood flow and therefore the drug absorption will depend upon the vasoconstriction and vasodilatation of the blood vessels.

Effect of Enzymatic Activity: Several enzymes that are present in the nasal mucosa might affect the stability of drugs. For example, proteins and peptides are subjected to degradation by proteases and amino-peptidase at the mucosal membrane. The level of amino-peptidase present is much lower than that in the gastrointestinal tract. Peptides may also form complexes with immunoglobulin (Igs) in the nasal cavity leading to an increase in the molecular weight and a reduction of permeability.

Effect of Mucociliary Clearance[36,37]: The absorption of drugs is influenced by the residence (contact) time between the drug and the epithelial tissue. The mucociliary clearance is inversely related to the residence time and therefore inversely proportional to the absorption of drugs administered.

Effect of Pathological Condition: Intranasal pathologies may affect the nasal mucociliary transport process and/or capacity for nasal absorption.

CHALLENGES AND OPPURTUNITIES FOR NASAL DELIVERY SYSTEMS

Existing nasal delivery devices such as spray pumps and pipettes cannot fully exploit the described potential advantages of nasal delivery. A large fraction of the dose is deposited on the anterior segment lined by skin, which is not the target for either topical drugs or systemic drugs. Drugs transported along the floor of the nose may cause bad taste and irritation and reduce patient acceptance. Finally, inadequate and variable deposition in the remote region housing the openings to the sinuses and middle ears, as well as the olfactory region, represents a real challenge for extended use of nasal administration of drugs and vaccines. This applies in particular to the new advanced and expensive drugs requiring demanding combination of reliable dosing, high patient compliance and reproducible bio-availability to ensure their efficacy and safety. Regarding actual formulation, most nasal products are currently formulated as liquids and delivered by metered spray pumps. Liquid formulations can be limited by the solubility, stability and dose volume. Powders, on the other hand, are more stable and it is easier to customize the size and surface properties. Some studies indicate reduced local irritation and more rapid absorption of powders. Bioactis Ltd. ("Bioactis"; CEO, Ryoichi Nagata, MD, PhD) has been developing nasal devices, which are medical devices that deliver drugs to the nose[38].

CURRENT APPROACHES FOR INCREASING NASAL BIOAVAILABILITY

Bioavailability of nasally administered drugs is particularly restricted by low drug solubility, rapid enzymatic degradation in nasal cavity, poor membrane penetration and rapid MCC. Thus several approaches have been suggested to overcome these limitations.

Prodrugs

Intranasal drugs are commonly administered as solutions or as powder formulations which need to undergo a dissolution process before absorption. Lipophilic drugs easily pass through biomembranes, however they are poorly water soluble. In this way, they should be administered as a prodrug with higher hydrophilic character in order to make possible the production of an aqueous nasal formulation with a suitable concentration. Once in the blood stream, the prodrug must be quickly converted to the parent drug. Kao et al. produced various prodrugs of L-Dopa and observed that their solubility enhanced significantly in comparison with the parent drug, allowing, hence, the development of adequate nasal formulations[39]. Similar results were obtained for testosterone which is also poorly water-soluble[40]. In contrast, very hydrophilic polar drugs may not have ability to cross biomembranes. Thereby, if they are administered as prodrugs with higher lipophilic character, the penetration through the membrane may increase[41]. Some researches have also used the prodrug approach for improving enzymatic stability of drugs. For example, Yang *et al* stated that L-aspartate- β-ester prodrug of acyclovir was more permeable and less labile to enzymatic hydrolysis than its parent drug[42]. In addition, the potential use of prodrugs to protect peptide drugs from nasal enzymatic degradation has been discussed and suggested as a powerful strategy to increase the bioavailability of peptides when intranasally administered [43, 44].

Co-Solvents

An alternative approach to the use of prodrugs in order to increase drug solubility is the use of co-solvents[43]. Co-solvents most used in intranasal formulations include glycerol, ethanol, propyleneglycol and polyethylene glycol and may be of the most importance since they are nontoxic, pharmaceutically acceptable and nonirritant to nasal mucosa.

Enzymatic inhibitors

Nasal mucus layer and nasal mucosa act as enzymatic barriers during nasal drug delivery, because they have a wide variety of enzymes. Various approaches have been used to avoid enzymatic degradation, including the use of proteases and peptidases inhibitors. For example, bestatine and comostate amylase are used as aminoptidases inhibitors and leupeptine and aprotinin as trypsine inhibitors probably involved in the degradation of calcitonin[44]. Furthermore, bacitracin, amastatin, boroleucin and puromycin[44-46] have been used to avoid enzymatic degradation of drugs such as leucine enkephalin[47, 48] and human growth hormone[49]. Finally, enzymatic inhibition can also be achieved using certain absorption enhancers (bile salts and fusidic acid)[42]. It is demonstrated that disodium EDTA, an absorption enhancer, reduces enzymatic degradation of beta sheet breaker peptide used for the treatment of Alzheimer's disease[50].

Permeation enhancers

Small and large hydrophilic drugs may be poorly permeable across nasal epithelium and may show an insufficient bioavailability. Their permeation can improve by administered in combination with absorption enhancers which induce reversible modifications on the structure of epithelial barrier.

REFERENCES

1. Stoner CL, Cleton A, Johnson K, Oh DM, Hallak H, Brodfuehrer J et al. Integrated oral bioavailability projection using in vitro screening data as a selection tool in drug discovery. Int J Pharm. 2004; 269:241-249.
2. Hou T, Wang J, Zhang W, Xu X. ADME evaluation in drug discovery: Prediction of oral absorption by correlation and classification. J Chem Inf Model. 2007; 47:208-218.
3. Dressman JB, Thelen K, Jantratid E. Towards quantitative prediction of oral drug absorption. Clin Pharmacokinet. 2008; 47:655-667.

4. Davis SS. Further development in nasal drug delivery. Pharmaceutical Science and Technology Today. 1999; 2: 265-266.

5. D'Souza R, Mutalik S, Venkatesh M, Vidyasagar S, Udupa N. Nasal Insulin Gel as an Alternate to Parenteral Insulin: Formulation, Preclinical, and Clinical Studies. AAPS PharmSciTech. 2005; 6: E184-E189.

6. Rathananand M, Kumar DS, Shirwaikar A, Kumar R, Prasad RS .Preparation of mucoadhesive microspheres for nasal delivery by spray drying. Indian J Pharmaceutical Sciences. 2007; 69:651-657.

7. Targeted liposomal drug delivery system.United States Patent 7169410

8. Waree Tiyaboonchai: Chitosan Nanoparticles: A Promising System for Drug Delivery. Naresuan University Journal. 2003; 11: 51-66.

9. Illum L. Nasal drug delivery: possibilities, problems and solutions. J Control Release. 2003; 87:187-198.

10. Yamaya M, Finkbeiner WE, Chun SY, Widdicombe JH. Differentiated structure and function of cultures from human tracheal epithelium. Am J Physiol. 1992; 262:L713- L724.

11. Romeo VD, Meireles J, Sileno AP, Pimplaskar HK, Behl CR. Effects of physicochemical properties and other factors on systemic nasal delivery. Adv Drug Deliv Rev. 1998; 29:89-116.

12. Illum L. Nasal drug delivery: new developments and strategies. Drug Discov Today. 2002; 7:1184-1189.

13. Graff LC, Pollock GM. Nasal drug administration: potential for targeted central nervous system delivery. J Pharm Sci. 2005; 94:1187-1195.

14. Leonard AK, Sileno AP, Brandt GC, Foerder CA, Quay SC, Costantino HR. In vitro formulation optimization of intranasal galantamine leading to enhanced bioavailability and reduced emetic response in vivo. Int J Pharm. 2007; 335:138-146.

15. Mygind N, Dahl R. Anatomy, physiology and function of the nasal cavities in health and disease. Adv Drug Deliv Rev. 1998; 29:3-12.

16. Pires A, Fortuna A, Alves G, Falcao A. Intranasal Drug Delivery: How, Why and What for? J Pharm Pharmaceut Sci (www.cspsCanada.org) 2009; 12(3): 288 – 311.

17. Chein YW and Chang S. In Transnasal Systemic Medications: Fundamental concepts and biomedical assessments, Elsevier science publishers, Amsterdam. 1985. 1-9.

18. Lewis JL, Nikula KJ, Novak R, Dahl AE. Comparative localisation of carboxylesterase in F344 rat, beagle dog and human nasal tissue. Anat Rec. 1994. 239:55-64.

19. Lewis DFV, Dickins M. Substrate SAR's in human P450s. Drug Discov Today. 2002. 7:918-925.

20. Krishna NSR, Getchell TV, Awasthi YC, Dhooper N. Age and gender related trends in the expression of glutathione S-transferases in human nasal mucosa. Ann Otol Rhin Laryng. 1995. 104:812-822.

21. Wearle LL, Crit.Rev.her.Drug carrier Sst. 1991. 8,331-394.

22. Riddle D, Washington N and Wilson CD. Drug delivery to the nasal and buccal cavities,anatomical and physiological considerations In,Duchene,D (eds.) Buccal and nasal administration as an alternative to parental administration, Editions de SanteParis. 1992. 29-39.

23. Druce HM, Ear Nose throat J. 1986. 65,201.

24. Illum L. In: Mathiowitz E, Chickering DE, Lehr CME, Bioadhesive formulations for nasal peptide delivery: Fundamentals, Novel Approaches and Development. Marcel Dekker. New York. 1999. 507-539.

25. Ingemann M. Frokjaer S. Hovgaard L. Brøndsted H. Peptide and Protein Drug Delivery Systems for Non-Parenteral Routes of Administration. In *Pharmaceutical Formulation Development of Peptides and Proteins*; Frokjaer, S, Hovgaard L, Eds; Taylor & Francis: Philadelphia, PA, USA, 2000; Chapter 10, p.189.

26. Charlton S, Jones NS, Davis SS, Illum L. Distribution and clearance of bioadhesive formulations from the olfactory region in man: Effect of polymer type and nasal delivery device. Eur J Pharm Sci. 2007. 30:295-302.

27. Arora P, Sharma S, Garg S. Permeability issues in nasal drug delivery. Drug DiscovToday. 2002. 7:967-975.

28. Aulton ME. "Pharmaceutics – The science of dosage form design" Churchill Livingston. 2002. 494.

29. Kadam SS, Mahadik KR, Pawar AP, Paradkar AR. Transnasal delivery of peptides – a review. The East. Pharm. July 1993. 47 – 49.

30. Hirai S, Yashiki T, Mima H. Effect of surfactants on nasal absorption of insulin in rats. Int. J. Pharm. 1981. 9: 165-171.

31. Huang C, Kimura R, Nassar A, Hussain A. Mechanism of nasal drug absorption of drug II: absorption of L-tyrosine and the effect of structural modification on its absorption. J Pharm Sci. 1985. 74: 298-1301.

32. Pennington AK, Ratcliffe JH, Wilson CG, Hardy JG. The influence of solution viscosity on nasal spray deposition and clearance. Int J Pharm. 1988. 43:221-224.

33. Suzuki Y, Makino. Mucosal drug delivery using cellulose derivatives as a functional polymer. J Control Release. 1999. 62:101-107.

34. Gattefosse bulletin. New lipidic systems enhancing the bioavailability of problem drugs. 1997. 1-81.

35. Van De Donk HJM, Muller Plantema IP, Zuidema J, Merkus FWHM. The effects of preservatives on the cilliary beat frequency of chicken embryo tracheas. Rhinology. 1980. 18: 119-130.

36. Merkus FW, Verhoef JC, Schipper NG, Marttin E. Nasal mucociliary clearance as a factor in nasal drug delivery. Adv Drug Deliv Rev. 1998. 29:13-38.

37. Aurora J. Development of Nasal Delivery Systems: A Review. Drug Delivery Technology. October 2002. Vol. 2 No. 7.

38. Margret chandira R, Debjit B, Chiranjib B, Jayakar B, Recent advances in nasal drug delivery systems-a review, Pharmavita.net

39. Kao HD, Traboulsi A, Itoh S, Dittert L, Hussain A. Enhancement of the systemic and CNS specific delivery of L-dopa by the nasaladministration of its water soluble prodrugs. Pharm Res. 2000. 17:978-984.

40. Hussain AA, Al-Bayatti AA, Dakkuri A, Okochi K, Hussain MA.Testosterone 17β- N,N-Dimethylglycinate Hydrochloride: A prodrug with a potential for nasal delivery of testosterone. J Pharm Sci. 2002. 91:785-789.

41. Wang H, Hussain AA, Wedlund PJ. Nipecotic Acid: Systemic availability and brain delivery after nasal administration of nipecotic acid and n-Butyl nipecotate to rats. Pharm Res. 2005. 22:556-562.

42. Yang C, Gao H, Mitra AK. Chemical stability, enzymatic hydrolysis, and nasal uptake of amino acid ester prodrugs of acyclovir. J Pharm Sci. 2001. 90:617-624..

43. Costantino HR, Illum L, Brandt G, Johnson PH, Quay SC. Intranasal delivery: Physicochemical and therapeutic aspects. Int J Pharm. 2007. 337:1-24.

44. Morimoto K, Miyazaki M, Kakemi M. Effects of proteolytic enzyme inhibitors on nasal absorption of salmon calcitonin in rats. Int J Pharm. 1995. 113:1-8.

45. Machida M. Effects of surfactants and protease inhibitors on nasal absorption of recombinant human granulocyte colonystimulating factor (rhG-CSF) in rats. Biol Pharm Bull. 1994. 17:1375-1378.

46. Bernkop-Schnurch A. Use of inhibitory agents to overcome the enzymatic barrier to perorally administered therapeutic peptides and proteins. J Control Release. 1998. 52:1-16.

47. Hussain MA. The use of alpha-aminoboronic acid derivatives to stabilize peptide drugs during their intranasal absorption. Pharm Res. 1989. 6:186-189.

48. Hoang VD, Uchenna AR, Mark J, Renaat K, Norbert V. Characterization of human nasal primary culture systems to investigate peptide metabolism. Int J Pharm. 2002. 238:247-256.

49. O'Hagan DT. Nasal absorption enhancers for biosynthetic human growth hormone in rats. Pharm Res. 1990. 7:772-776.

50. Greimel A, Bernkop-Schnürch A, Del Curto MD, D'Antonio M. Transport characteristicsof a beta sheet breaker peptide across excised bovine nasal mucosa. Drug Dev Ind Pharm. 2007. 33:71-77.

51. Karasulu E, Yavaşoğlu A, Evrensanal Z, Uyanikgil Y, Karasulu HY. Permeation studies and histological examination of sheep nasal mucosa following administration of different nasal formulations with or without absorption enhancers. Drug Delivery. 2008. 15:219-225.

52. Sinswat P, Tengamnuay P. Enhancing effect of chitosan on nasal absorption of salmon calcitonin in rats: comparison with hydroxypropyl- and dimethyl-β-cyclodextrins. Int J Pharm. 2003. 257:15-22.

53. Zaki NM, Mortada ND, Awad GA, Abd ElHady SS. Rapid-onset intranasal delivery of metoclopramide hydrochloride Part II: Safety of various absorption enhancers and pharmacokinetic evaluation. Int J Pharm. 2006. 327:97-103.

54. Illum L. Nanoparticulate systems for nasal delivery of drugs: A real improvement over simple systems? J Pharm Sci. 2007. 96:473-483.

55. Giunchedi P, Juliano C, Gavini E, Cossu M, Sorrenti M. Formulation and in vivo evaluation of chlorhexidine buccal tablets prepared using drug loaded chitosan microspheres. Eur J Pharm Biopharm. 2002. 53:233-239.

56. Maestrelli F, Zerrouk N, Chemto C, Mura P. Influence of chitosan and its glutamate and hydrochloride salts on naproxen dissolution rate and permeation across Caco-2 cells. Int J Pharm. 2004. 271:257-267.

57. Ravi Kumar MNV, Muzzarelli RAA, Muzzarelli C, Sashiwa H, Domb AJ. Chitosan chemistry and pharmaceutical perspectives. Chem Rev. 2004. 104:6017-6084.

58. Washington N, Steele RJ, Jackson SJ, Bush D, Mason J, Gill DA, Pitt K, Rawlins DA. Determination of baseline human nasal pH and the effect of intranasally administered buffers. Int J Pharm. 2003. 198:139-146.

59. Pujara CP, Shao Z, Duncan MR, Mitra AK. Effects of formulation variables on nasal epithelial cell integrity: Biochemical evaluations. Int J Pharm. 1995. 114:197-203.

60. Sankar C, Rani M, Srivastava A K, Mishra B. Chitosan based pentazocine microspheres for intranasal systemic delivery: development and biopharmaceutical evaluation. Pharmazie. 2001. 56(3): 223-6.

61. Sankar C, Mishra B. Development and in vitro evaluation of gelatin A microspheres of Ketorolac tromethamine for intranasal administration. Acta Pharm. 2003. 53:101-110.

62. Shah V, Sharma M, Parmar V, Upadhyay U. Formulation of sildenafil citrate loaded nasal microsphers: An in vitro, ex vivo characterization. International Journal of Drug Delivery. 2010. 2:213-220.

63. Gavini E, Rassu G, Sanna V, Cossu M and Giunchedi M. Mucoadhesive microspheres for nasal administration of an antiemetic drug, metoclopramide: in-vitro/ex-vivo studies Journal of Pharmacy and Pharmacology. 2004. 57(3):287 – 294.

64. Harikarnpakdee S, Lipipun V, Sutanthavibul N, and Ritthidej GC. Spray dried mucoadhesive microspheres: preparation and transport through nasal cell monolayer AAPS PharmSciTech. 2005 november accepted.

65. Dalpiaz A, Giunchedi P, Gavini E, Colombo G, Bortolotti F. Brain targeting of an antiischemic agent by nasal administration of microparticles, 15th international symposium on microencapsulation, Parma (Italy). 2005. 18-21.

66. Dandagi PM, Mastiholimath VS, Gadad AP, Iliger SR. Mucoadhesive Microspheres of Propranolol Hydrochloride for Nasal Delivery. Indian J Pharm Sci. 2007. 69:402.

67. Mahajan H, Gattani S, Surana S. Spray Dried Mucoadhesive Microspheres of Ondansetron for Nasal Administration, International Journal of Pharmaceutical Sciences and Nanotechnology. 1(3) 267-274.

68. Mahajan HS, Gattani SG. Nasal administration of ondansetron using a novel microspheres delivery system, Pharmaceutical Development and Technology. 2009. 14(2): 226-232.

69. Yadav AV, Mote HH. Development of starch microspheres for intranasal delivery, Indian J Pharm Sci. 2008. 70-74.

70. Jain SA, Chauk DS, Mahajan HS, Tekade AR, Gattani SG. Formulation and evaluation of nasal mucoadhesive microspheres of Sumatriptan succinate, Journal of Microencapsulation. 2009. 26(8):711-721.

71. Shaji J, Poddar A, Iyer S. Brain-targeted nasal clonazepam microspheres, Indian J Pharm Sci. 2009. 7(6), 715-718.

72. Vyas TK, Babbar AK, Sharma RK, Singh S, Misra, A. Intranasal mucoadhesive microemulsions of clonazepam: Preliminary studies on brain targeting. J Pharm Sci 2005; 95: 570-580.

73. kwatikar PS, kulkarni NP, Yadav SP and sakarkar DM, formulation and evaluation of an anti-epileptic drug loaded microemulsion for nose to brain delivery, asian J. Pharmaceutics, april-june, 2009.

74. Florence K, Agrawal HG and Misra A. Intranasal delivery of clobazam for treatment of status epileptics.

75. Shende AJ, Patil RR and Devarajan PV, Microemulsion of lomotrigone for nasal delivery, Ind.J.Pharm. Sci., 2007, 69(5), 721-22.

76. Holvoet C, Heyden YV, and Plaizier-Vercammen J. Inclusion complexation of lorazepam with different cyclodextrins suitable for parenteral use. Drug Dev. Ind. Pharm. 2005: 31:567– 575.

77. Date AA and Nagarsenker MS. Parenteral microemulsions: an overview. Int. J. Pharm. 2008; 355:19– 30.

78. Yalin M, Öner F, Öner L and Hincal AA. Preparation and properties of a stable intravenous lorazepam emulsion. J. Clin. Pharm. Ther.1997; 22:39–44.

79. Amit AK and Vandana BP. Development and Evaluation of Lorazepam Microemulsions for Parenteral Delivery. AAPS PharmSciTech, 2008: 9(3), 966-971.

80. Pakalnis A, Kring D, Paolicchi J. Parenteral satisfaction with sumatriptan nasal spray in childhood migraine. J Child Neurol. 2003; 18:772-775.

81. Villalon CM, Centurion D, Valdivia LF, de Vries P, Saxena PR. Migraine: pathophysiology, pharmacology, treatment and future trends. Curr Vasc Pharmacol. 2003; 1:71Y84.

82. Martindale PK. The Complete Drug Reference. London, UK: Pharmaceutical Press; 1999:450Y452.

83. Gladstone JP, Gawel M. Newer formulations of the triptans: advances in migraine treatment. Drugs. 2003; 63:2285Y2305.

84. Bigal ME, Bordini CA, Antoniazzi AL, Speciali JG. The triptan formulations: a critical evaluation. Arq Neuropsiquiatr. 2003; 61:313-320.

85. Shelke RR and Devrajan PV, Aqua triggered In Situ Gelling Microemulsion for Nasal Delivery; Indian J Pharm Sci 2007; Sep-Oct, 726-727.

86. Shelke R.R. and Devrajan P.V., Aqua triggered In Situ Gelling Microemulsion for Nasal Delivery; Indian J Pharm Sci 2007; Sep-Oct, pp-726-727.

87. Tushar K Vyas AK Babbar R, Sharma K and Misra A. Intranasal mucoadhesive microemulsions of zolmitriptan: Preliminary studies on brain-targeting. Journal of Drug Targeting 2005, 13, (5), 317-324.

88. Tiwari NG and Bajaj AN. formulation development of eucalyptuss oil microemulsion for intranasal delivery. Indian J Pharm Sci 2007; Sep-Oct, pp-731-733.

89. Zhang Q, Jiang X, Jiang W, Lu W, Su L and Shi Z, Preparation of nimodipine-loaded microemulsion for intranasal delivery and evaluation on the targeting efficiency to the brain International Journal of Pharmaceutics. 2004. 275, 1-2(4), 85-96.

90. Jing Y, Jian PZ, Qi NP, Yun L and Liang C. Distribution of nobiletin chitosan-based microemulsions in brain following i.v. injection in mice International Journal of Pharmaceutics. March 2008.352:1-2(20), 256-262.

91. Jogani V, Shah P, Mishra P, and Misra AN. Intranasal mucoadhesive microemulsion of tacrine to improve brain targeting. *Alzheimer Dis Assoc Disord* .2008; 22 (2), 116-124.

92. Vyas TK, Babbar AK, Sharma RK, Misra AN. Intranasal mucoadhesive microemulsion of zolmitriptan: preliminary studies on brain targeting. *J Drug Target* 2005*; 13(5):317-324.

93. Lianly IL, Nandi I, Kim KH. Development of an ethyl laurate based microemulsion for rapid onset of intranasal delivery of diazepam. Int J Pharm 2002; 237: 77-85
94. Dongxing Wang[1], Yongliang Gao[1] and Liuhong Yun[1] Study on brain targeting of raltitrexed following intranasal administration in rats' cancer Chemotherapy and Pharmacology. 2006, 57(1); 97-104.
95. Elshafeey A, Bendas E and Mohamed O. Intranasal Microemulsion of Sildenafil Citrate: in vitro evaluation and in vivo pharmacokinetic study in Rabbits,. *AAPS PharmSciTech* 2009; 10(2):361-367.
96. Botner S, Levy HV, Sintov AC. Intranasal Delivery of Insulin via Microemulsion based Formulation; *Nanotech* 2008. Abstract no 559.
97. Knoester PD, Jonker DM, Van der Hoeven RTM, Vermeij TAC, Edelbroek PM, Brekelmans GJ. Pharmacokinetics and pharmacodynamics of midazolam administered as a concentrated intranasal spray. A study in healthy volunteers, Br J Clin Pharmacol. 2002 May; 53(5): 501–507.
98. Alpar HO, Bowen JC, Brown MRW. Effectiveness of liposomes as adjuvants of orally and nasally administered tetanus toxoid. Int J Pharm 1992; 88: 335–44.
99. Maitani Y, Asano S, Takahashi S, Nakagaki M, Nagai T. Permeability of insulin entrapped in liposome through the nasal mucosa of rabbits. Chem Pharm Bull 1992; 40: 1569–72.
100. Law SL, Huang K J, Chou HY. Preparation of desmopressin-containing liposomes for intranasal delivery. J Control Rel 2001; 70: 375–82.
101. Iwanaga K, Matsumoto S, Morimoto K, Kakemi M, Yamashita S, Kimura T. Usefulness of liposomes as an intranasal dosage formulation for topical drug application. Biol Pharm Bull 2000; 23: 323–6.
102. Morimoto K, Morisaka K, Kamada A. Enhancement of nasal absorption of insulin and calcitonin using polyacrylic acid gel. J Pharm Pharmacol 1985; 37: 134–6.
103. Callens C. Pringels E. Remon JP. Influence of multiple nasal administrations of bioadhesive powders on the insulin bioavailability. *Int. J. Pharm.* 2003, *250*, 415-422.

Table 1: Nasal Bioavailability-Problems, Challenges & Solutions

Problem	Challenge	Solution
Poor physicochemical properties of drug/formulation	Improve physicochemical properties of drug and/or formulation	Prodrugs, Cosolvents Cyclodextrins Novel drug formulations
Low permeability through nasal membrane	Increase drug permeability and dissolution Modify nasal membrane Enhance drug residence time in nasal cavity	Prodrugs, Cosolvents Absorption enhancers Mucoadhesive systems
Enzymatic degradation	Reduce drug affinity to nasal enzymes Inhibit nasal enzymes Protect drugs from nasal enzymes	Prodrugs, Cosolvents, Enzymatic inhibitors

Table 2: Mucosal penetration enhancers and mechanisms of action

Classification	Examples	Mechanism
Surfactants	Anionic: Sodium lauryl sulphate Cationic: Cetylpyridinium Chloride Nonionic: Poloxamer, Span, Tween	Perturbation of intercellular lipids, Protein domain integrity, Distrusts membrane,
Bile salts	Sodium glycodeoxycholate, Sodium glycocholate, Sodium taurodeoxycholate,	Distrusts membrane, Open tight junctions, Mucolytic activity
Cyclodextrins	α, β, γ Cyclodextrin, Methylated β–Cyclodextrins	Inclusion of membrane Compounds, Open Tight junctions
Fatty acids	Oleic acid , Lauric acid, Caprylic acid, Phosphotidylcholine	Increase fluidity of phospholipid domains, Distrusts membrane

Cationic compounds	Poly-L-arginine, L-lysine	Ionic interaction with negative charge on the mucosal surface
Chelators	EDTA, Citric Acid, Sodium citrate,	Interfere with Ca Polyacrylates
+ Ve Charged polymers	Chitosan, Trimethyl chitosan	Ionic interaction with negative charge on the mucosal surface
Bioadhesive Materials	Carbopol, Starch, Chitosan	Reduce nasal clearance, Open tight junctions

Table 3: Various intranasal drug delivery systems and their purpose/application

| Drug	Delivery system	Purpose
Pentazocine[60]	Microspheres	Avoiding first pass effect
Ketorolac Trimethamine[61]	Microspheres	Avoid gastric complications
Sildenafil Citrate[62]	Microspheres	Avoid first pass metabolism
Metoclopramide HCl[63]	Microspheres	Permeation enhancement
Propranolol HCl[64]	Microspheres	Open tight junction without cell damage
N^6 Cyclopentyladenosine[65]	Microspheres	Selective brain targeting
Propranolol HCl[66]	Microspheres	Avoiding first pass effect
Ondansetron[67,68]	Microspheres	Avoiding first pass effect, improve therapeutic efficacy
Domperidone[69]	Microspheres	Selective brain targeting
Sumatriptan Succinate[70]	Microspheres	Avoid hepatic first pass metabolism and brain targeting
Clonazepam[71]	Microspheres	Brain targeting
Clonazepam[72]	Microemulsion	Brain targeting
Valproic Acid[73]	Microemulsion	Enhanced bioavailability with brain targeting
Clobazam[74]	Microemulsion	Brain targeting
Lomotrigone[75]	Microemulsion	Brain targeting
Lorazepam[76-79]	Microemulsion	Brain targeting
Sumatriptan[80-85]	Microemulsion	Enhanced the bioavailability
Zolmitriptan[86]	Microemulsion	Enhanced bioavailability
Zolmitriptan[87]	Microemulsion	Enhanced bioavailability & rapid onset of action
Eucalyptus oil[88]	Microemulsion	Enhanced bioavailability with brain targeting
Nimodipine[89]	Microemulsion	Enhanced solubility and brain targeting
Nobiletin[90]	Microemulsion	Improve bioavailability in the brain
Tacrine[91]	Microemulsion	Targeting to brain
Zolmitriptan[92]	Microemulsion	Targeting to brain
Diazepam[93]	Microemulsion	Rapid absorption
Raltitrexe[94]	Microemulsion	Targeting to brain tissue
Sildenafil Citrate[95]	Microemulsion	Improve bioavailability with shorter T_{max}
Insulin[96]	Microemulsion	Enhanced the Bioavailability
Midazolam[97]	Microemulsion	To investigate pharmacokinetics & pharmacodynamics
Tetanus toxoid[98]	Liposome	Improved immun responce
Insulin[99]	Liposome	Increased insulin permeability
Desmopressin[100]	Liposome	Enhancement of antidiuresis
Diphenhydramine[101]	Liposome	Increased drug retention in the nasal cavity
Insulin, calcitonin[102]	P-acrylic acid gel	Enhanced absorption
Insulin[103]	Powder	Improve bioavailability
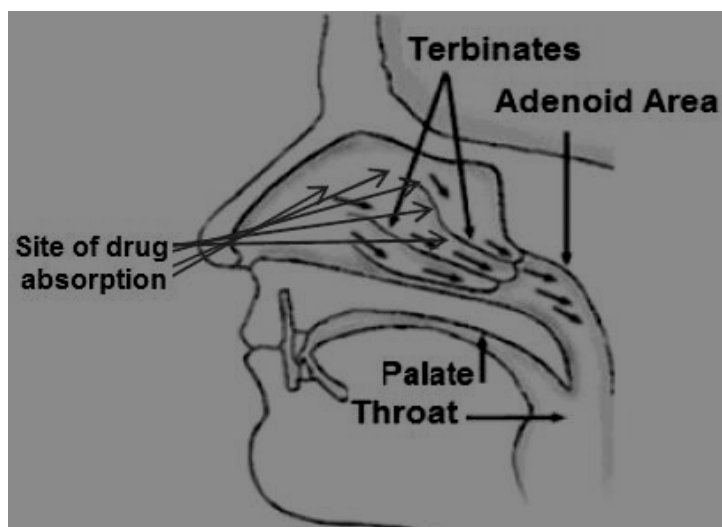
Figure 1: Showing Nasal vascular supply and various part of nasal cavity
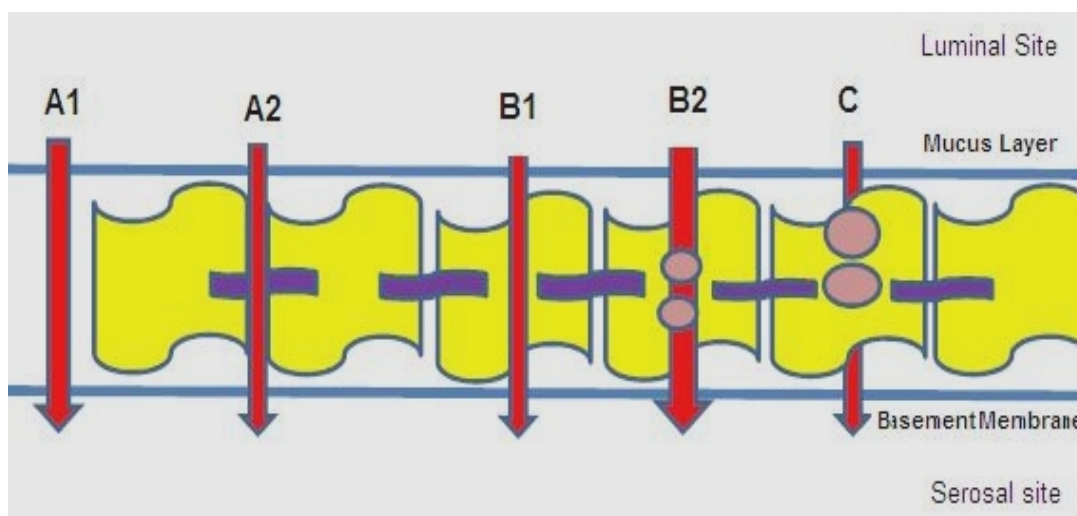

Figure 2: (A) Paracellular route (A1) Intercellular spaces, (A2) Tight junctions, (B) Transcellular route (B1) Passive diffusion, (B2) Active transport, (C) Transcytosis
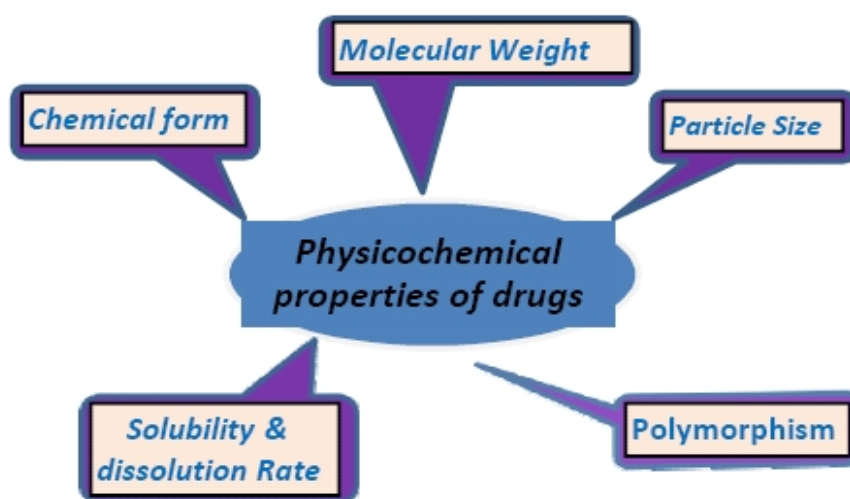

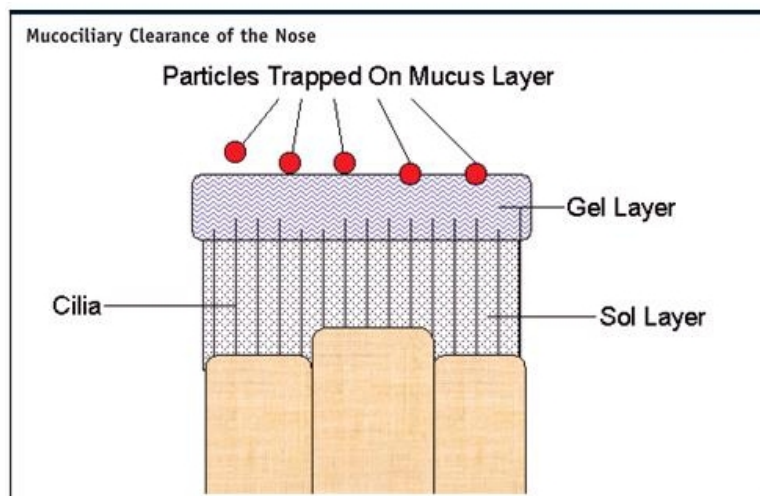**Figure 3: Drug related factors affecting nasal drug absorption**

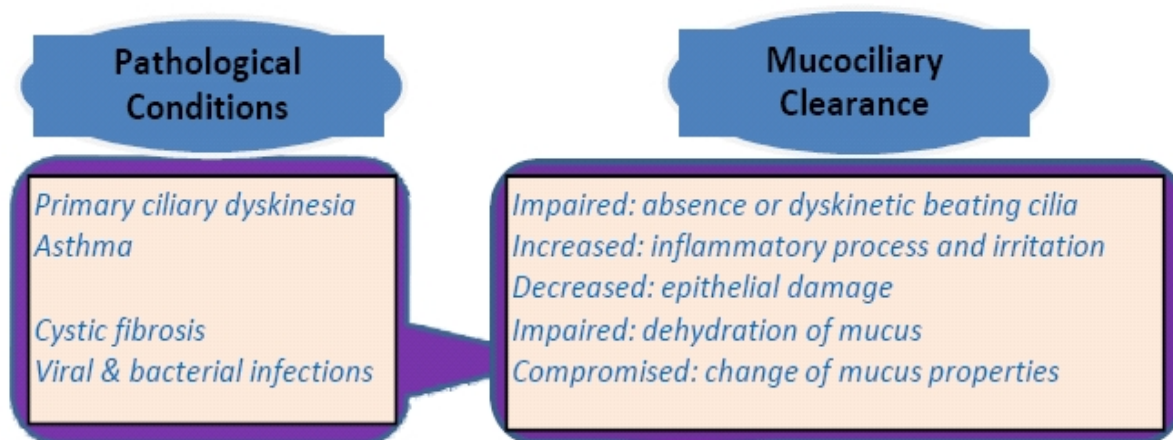**Figure 4: Effect of mucociliary clearance on nasal drug absorption**

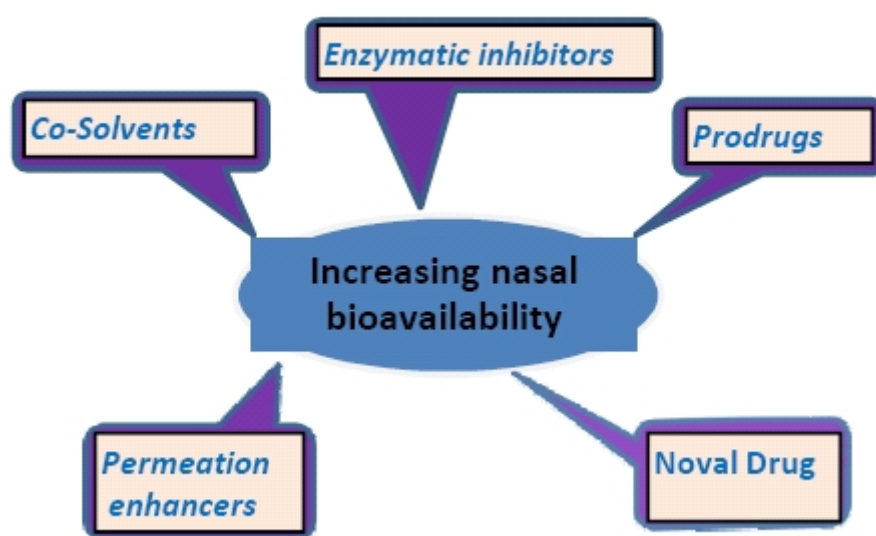**Figure 5: Effect of pathological conditions on nasal mucociliary clearance**

Figure 6: Approaches to increasing nasal drug absorption