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Nasal drug delivery: factors affecting and strategies to improve drug absorption

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ABSTRACT

Over the recent decades, the interest in nasal delivery as a feasible alternative to oral or parenteral administration for some drugs is increased, because of the high permeability of the nasal epithelium, rapid drug absorption across this membrane and avoidance of hepatic first-pass metabolism. Therefore, it is important to understand the potential and limitations of various nasal drug delivery systems.

The aim of this review article is to outline the advantages and limitations of the nasal route and to investigate factors influencing the permeability of the nasal mucosa to various compounds such as physiological factors, physicochemical characteristics of the substance, and pharmaceutical factors that must be considered during the process of discovery and development of nasal drugs as well as in their incorporation into appropriate nasal pharmaceutical formulations.

Key Words:, Intra-nasal, bioavailability, drug delivery systems, drug administration, absorption enhancers

Introduction

The nasal administration of drugs for the symptomatic relief and prevention or treatment of topical nasal conditions has been widely used for a long period, including the treatment of congestion, rhinitis, sinusitis and related allergic or chronic conditions, and has resulted in a variety of different medications including corticoids, antihistamines, anti-cholinergic and vasoconstrictors [1].

However, in recent years, the nasal mucosa has seriously emerged as a therapeutically viable route for the systemic drug delivery, and therefore, an alternative for achieving systemic drug effects to the parenteral route, which can be inconvenient, or oral administration, which can result in unacceptably low bioavailabilities [24].

The nasal epithelium has been considered as a potential administration route to achieve faster and higher level of drug absorption, the submucosa is richly vascularized, and hepatic first-pass metabolism is avoided after nasal administration [5].

Other attractive features include the rather large surface area of the nasal cavity and the relatively high blood flow, which promotes rapid absorption [12].

Furthermore, the nasal route is suitable for self-medication.

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 [48].

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 [29].

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Accordingly, the present review outlines anatomical, physiological and histological features of nasal cavity and the major factors affecting nasal drug delivery, highlighting simultaneously the properties of drugs and formulation characteristics that determine decisively the pharmacokinetics of nasal preparations.

Advantages and limitations

Descripted on (Table A)

Mechanism of nasal absorption

When a drug is nasally administered to induce systemic effects it needs to pass through the mucus layer (composed chiefly of mucin), where it serves as a diffusion barrier against contact with exogenous substances, and then through the epithelial membrane before reaching the blood stream (Figure 1) [54]. The passage across the epithelium may occur essentially by paracellular passive diffusion (hydrophilic and small polar drugs) and transcellular passive diffusion (lipophilic drugs and compounds with a molecular weight higher than 1 kDa, such as peptides and proteins. [16, 17] (Figure 2).

Tight junctions are dynamic structures localized between the cells, which open and close accordingly to activation of signaling mechanisms. [30,78]

Finally, it is evident that the molecular weight and lipophilicity of drugs may have a great impact in the rate and extent of its nasal absorption. (Figure 1) and (Figure 2).

Factors influencing the absorption of drugs across the nasal epithelium

A multitude of factors affect nasal absorption: physiological properties of the nasal cavity, the physiochemical properties of the drugs and the type and the properties of the specific drug formulation. These factors play key role for most of the drugs in order to reach therapeutically effective blood levels after nasal administration. The factors influencing nasal drug absorption are described as follows.

Physiological Factors/ Barriers

- **Mucociliary clearance**

The nasal mucociliary clearance system (MCC)

epithelium towards the nasopharynx by ciliary beating. Its function is to protect the respiratory transports the mucus layer that covers the nasal foreign substances, pathogens and particles carried by inhaled air [65]. These particles adhere to the mucus layer and are transported to the nasopharynx and to the gastrointestinal tract. In physiological conditions, the speed of mucociliary clearance is about 5 mm/ min and its transit time in nasal cavity is reported to be 15-20 min. [48,17] Several workers have investigated ciliary beat frequency in order to evaluate the effects of drugs, formulation additives or infections in the upper airways on the mucociliary system.

When MCC decreases, residence time of the drug product in nasal mucosa increase and, therefore, enhances its permeation. The opposite effect is observed when MCC increases in presence of factors that increase mucus production, decrease mucus viscosity or increase ciliary beat frequency. Polar drugs are the most affected by MCC, since they are highly soluble in mucus and their passage across the membrane is very slow. Thus, all factors that influence the efficacy and pace of MCC may modify the drug absorption profile. In addition, several pathological conditions exist in which MCC does not work properly as shown in Table 1. Furthermore, some components of drug formulations may also alter the MCC system, such as preservatives and nasal absorption enhancers. [2, 44, 67].

- **Enzymes**

Drugs nasally administered circumvent gastrointestinal and hepatic first-pass effect. However, they may be significantly metabolized in lumen of nasal cavity or during the passage across the nasal epithelial barrier due to the presence of a broad range of metabolic enzymes in nasal tissues.

Among the enzymes present are the oxidative phase I enzymes (e.g. Cytochrome P450 isoenzymes) as metabolizers of drugs such as cocaine, nicotine, alcohols, progesterone and decongestants [18,74], non-oxidative enzymes, conjugative phase II enzymes and proteolytic enzymes such as endopeptidases (serine and cysteine, which can attack internal peptide bonds) and exopeptidases (monoamino peptidases and diaminopeptidases with capability to cleave peptides at their N and C termini) [74]. The nasal enzyme population and/ or activities vary extensively among different species. However, the level of activity seems to be lower for nasal enzymes than for those in the gastrointestinal tract or liver, on the basis of the amount of tissue involved.

- **Pathological conditions of nose**

The presence of nasal pathological conditions, such as rhinitis (allergic rhinitis and common), nasal polyps and cancer and common colds may alter absorption from the nasal cavity in different ways. The majority of nasal pathologies show bleeding, excessive mucus secretion, nasal blockage and crusting. It has been reported that a rhinovirus infection in vitro causes sloughing of epithelial cells and destruction of the epithelial layer. Excessive nasal secretion may wash away a nasally administered drug before it can be absorbed.

Physicochemical characteristics of the drug

The absorption of a drug across the nasal mucosa is a function of its physicochemical properties such as molecular weight, lipophilicity, solubility, dissolution rate, charge, partition coefficient, pKa and the presence of polymorphism [7].

- **Molecular weight**

An inverse relationship between molecular weight and percent absorption has been reported by Donovan et al. [21] based on studies on polyethylene glycol of different molecular weights. [50]

Several studies demonstrated that the permeation of polar drugs with a molecular weight of less than 300 Da is not considerably influenced by their physicochemical properties [66, 15, 25].
By contrast, the rate of permeation is highly sensitive to molecular size if it is higher than 300Da [28]. An inverse relationship exists between rate of permeation and molecular weight [15,21]. For some small polar molecules, only a 10% bioavailability is suggested. The value goes down to 1% for large molecules such as proteins [55].

- **Lipophilicity**

The hydrophilic and lipophilic nature of the drug also affects the process of absorption [39]. Lipophilic drugs presenting a molecular weight lower than 1 kDa like propranolol naloxone, buprenorphine, testosterone and fentanyl are well and almost completely absorbed from the nasal cavity through transcellular mechanisms. The nasal absorption of lipophilic drugs bigger than 1 kDa is significantly reduced. [66]
By increasing lipophilicity, the permeation of the compound normally increases through nasal mucosa. [14,15]

- **Solubility**

Drug dissolution is a pre-requisite for any drug absorption, since only the molecularly disperse form of a drug at the absorption site may cross the biomembranes. Hence, before nasal absorption the drug must to be dissolved in the watery fluids of the nasal cavity.
Thus, of the utmost importance is the appropriated aqueous drug solubility to allow enough contact with the nasal mucosa and posterior absorption [79].
However, the absorption profile is influenced by drug solubility.
Thereby, drugs poorly soluble in water and/or requiring high doses may constitute a problem. This can be overtaken enhancing the drug aqueous solubility [6, 16, 38, 39, 40, 42, 70].

Effect of drug formulation

• Viscosity

A higher 9 viscosity of the formulation increases the contact time between drug and nasal mucosa and, thereby, the potential of drug absorption increases. However, highly viscous formulations interferes with the normal ciliary beating or mucociliary clearance and, thus, increases the permeability of drugs. This fact has been demonstrated during nasal delivery of insulin, metoprolol and acyclovir [4, 66, 76].

• pH and pKa

The nasal absorption depends on pH at the site of absorption and the pKa value of drug. In addition, the pH of formulation must be selected attending to drug stability and should be assured the greatest quantity of non-ionized drug species if it possible. However, the pH of formulation can induce nasal mucosa irritation and, hence, it should be comparable to that found on human nasal mucosa (between 5.0 and 6.5) [17,79, 77].

• Pharmaceutical form

Deposition of dosage form in different sections of nasal cavity and its retention at the site of choice depends on the pharmaceutical form of delivery systems [31].

For example, nasal drops are the simplest and the most convenient nasal pharmaceutical form, but the exact dosing control of drug to be delivered is not easily quantified and often results in overdose [73]. In addition, rapid nasal drainage can occur when using this dosage form. Solution and suspension sprays are preferred over powder sprays because the last one easily prompted the development of nasal mucosa irritation [2].

Irecent times, gel approaches have been developed for a more accurate drug delivery. They reduce postnasal drip and anterior leakage, fixing the drug formulation in nasal mucosa. This enhances the drug residence time and diminishes MCC, thereby, potentially increases the nasal absorption. During the last years, specialized systems like lipid emulsions, microspheres, liposomes and films have also been developed to improve nasal route.

• Pharmaceutical excipients

In nasal formulations, ample varieties of pharmaceutical excipients can be found according to their functions. Solubilizers, Gelling agents, buffer components, antioxidants, preservatives, humectants, viscosity enhancers, and flavoring or taste masking agents are some of the most usual excipients [73]. Although they are responsible for several nasal irritations, thus care should be taken in the selection of excipients [55].

Strategies to improve nasal absorption

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 various strategies used to improve the bioavailability of the drug in the nasal mucosa :

- To improve the nasal residence time.
- To enhance nasal absorption.
- To modify drug structure to change hysicochemical properties. [25]

Several methods have been used to facilitate the nasal absorption of drugs includes: use of prodrugs, enzymatic inhibitors, absorption enhancers, development of mucoadhesive delivery systems and new pharmaceutical forms (Table 2).

• Prodrugs

Intranasal drugs are commonly administered as solutions or as powder formulations which need to undergo a dissolution process before absorption [3]. Lipophilic drugs pass easily through membranes, but they are poorly water soluble. For this reason, they should be administered as a prodrug with hydrophilic character to make possible the production of an aqueous nasal formulation with a suitable concentration.

The prodrug must be quickly converted in the blood stream to the parent drug. Some researchers have also used the prodrug approach for improving enzymatic stability of drugs.

For example, Yang et al stated that L- aspartate- βester prodrug of acyclovir was more permeable and less labile to enzymatic hydrolysis than its parent drug. 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 administered intranasally. [38]

- **Nasal enzyme inhibitors**

Nasal mucus layer and nasal mucosa act as enzymatic barriers during nasal drug delivery, because they have a wide variety of enzymes [70]. Enzymatic degradation can be eliminated by using the enzyme inhibitors. Mainly for the formulation of proteins and peptide molecule development, enzyme inhibitors like peptidases and proteases are used. The enzyme inhibitors commonly used for the enzymatic activity are trypsin, aprotinin, borovaline, amastatin, bestatin and boroleucin inhibitors. Finally, enzymatic inhibition can also be achieved using certain absorption enhancers like salts and fusidic acid derivatives [16].

- **Absorption enhancers**

Many drugs having high water solubility have poor permeability across nasal epithelia and may present insufficient bioavailability. To enhance their permeation and bioavailability, permeation possible mechanisms such as inhibitionof enzyme activity, reductionof mucus viscosity or elsticity, decreasing mucociliary clearance, opening tight junctions and solubilizing or stabilizing the drug. The mechanism of action of absorption enhancer is increasing the rate at which drug passes through the nasal mucosa. Many enhancers act by altering the structure of epithelial cells in some way, but they should accomplish this while causing no damage or permanent change to nasal mucosa. General requirement of an ideal penetration enhancer are as follows [9, 23] :

- It should lead to an effective increase in the absorption of the drug.
- It should not cause permanent damage or alteration to the tissues.
- It should be non irritant and nontoxic.
- It should be effective in small quantity.
- The enhancing effect should occur when absorption is required.
- The effect should be temporary and reversible.
- It should be compatible with other excipients.

Different types of absorption/permeation enhancers are enlisted in Table 3 with their possible mechanism

Conclusion

Nasal drug delivery system is a promising alternative route of administration for the several systemically acting drugs with poor bioavailability and it has advantages in terms of improved patient acceptability and compliance compared to parenteral administration of drugs.
Nasal products will include not only drugs for acute and long-term diseases, but also novel nasal vaccines with better local or systemic protection against infections. However, it was stated that intranasal route presents several limitations that must be overcome to develop a successful nasal medicine. Physiological conditions, physicochemical properties of drugs and formulations are the most important factors determining nasal drug absorption. The use of prodrugs, enzymatic inhibitors, absorption enhancers, mucoadhesive drug delivery systems and new pharmaceutical formulations are, nowadays, among the mostly applied strategies. Each drug is one particular case and, thus, the relationship between the drug characteristics, the strategies considered and the permeation rate is essential.

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	ADVANTAGES	FACTORS
1.	Convenience and good patient compliance	- Needle free (painless) - Trained person not required
2.	High drug permeability	- In case of lipophilic drugs - In case of low molecular weight
3.	Rapid attainment of therapeutic drug levels in the blood	- A relative large surface area - High vascularization
4.	Avoidance of the harsh environment and gastrointestinal conditions	- Less chemical and enzymatic degradation
5.	low dose required	- Bypassing of hepatic first-pass metabolism
6.	Potential direct delivery of drug to central nervous system	- Via olfactory region, thus bypass the blood brain barrier

	LIMITATIONS	FACTORS
1.	Risk of local side effect and irreversible damage of cilia on nasal mucosa	- Substance and constituents added to dosage forms
2.	Disrupt and even dissolve the nasal membrane	- High concentration of absorption enhancers
3.	Reduce the capacity of nasal absorption	- Nasal atrophic rhinitis and severe vasomotor rhinitis
4.	Low bioavailability	- Enzymatic degradation and metabolism at mucosal surface

Table A : **Advantages and limitations**

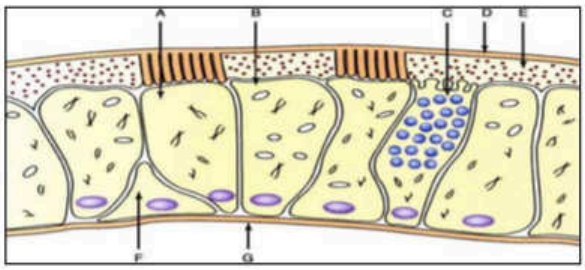

Figure 1: Cell types of the nasal epithelium with covering mucous layer showing ciliated cell ((A), non-ciliated cell(B), goblet cells(C), gel mucus layer (D), sol layer (E), basal cell (F) and basement membrane (G)

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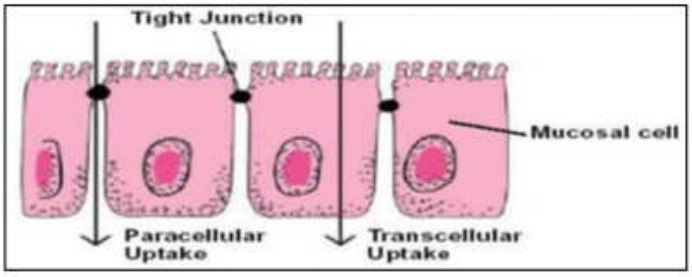

Figure 2: Mechanism of nasal absorption

Pathological conditions	Mucociliary clearance
Primary ciliary dyskinesia	- Impaired : Absence or dyskinetic beating cilia
Asthma	- Increased : Inflammatory process - Decreased : epithelial damage
Cystic fibrosis	- Impaired : Dehydratation of mucus
Viral and bacterial infections	- Compromised : loss of cilia and modification of mucus characteristics
Diabetes mellitus	- Impaired: Dehydratation and microvascular damage

Table 1: Pathological conditions and their impact in nasal mucociliary clearance. [47,75]

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Problem	Challenge	Solution
Poor physicochemical properties of drug and formulation	Improve physicochemical properties of drug and formulation	- Prodrugs - Cosolvents - Cyclodextrins - Pharmaceutical excipients - Novel drug formulations
Enzymatic degradation	Reduce drug affinity to nasal enzymes Inhibe nasal enzymes Protect drugs from nasal enzymes	- Prodrugs - Enzymatic inhibitors - Prodrugs - Cosolvents
Low permeability	Increase drug permeability and dissolution Modify nasal membrane Enhance drug residence time in nasal cavity	- Prodrugs - Cosolvents - Absorption enhancers - Mucoadhesive systems - Viscosifying agents

Table 2: Common problems associated to low nasal bioavailability of drugs, challenges and possible solutions. [11,43]

Classification	Example	Possible action
Fatty acids	Oleic acid, Lauric acid Phosphotidylcholine	Membrane disruption
Bile salts	Sodium deoxycholate, Sodium glycocholate, Sodium taurodeoxycholate	Mucolytic activity Distrusts membrane Open tight junctions
Surfactants	Anionic: Sodium lauryl sulphate Cationic: Cetylpyridinium Chloride Nonionic: Poloxamer, Span, Tween	Membrane disruption
Chelators	EDTA, Citric Acid Sodium citrate	Interfere with Ca Polyacrylates
	Sodium Salicylate	
Cyclodextrins and derivatives	α, β, γ Cyclodextrin Methylated β–Cyclodextrins	Inclusion of membrane Compounds, Open Tight junctions
Cationic compounds	Poly-L-arginine L-lysine	Ionic interaction with negative charge on the mucosal surface
Mucoadhesive Materials	Carbopol Starch microspheres Chitosan	Reduce nasal clearance Open tight junctions
Positive charged polymers	Chitosan Trimethyl chitosan	Ionic interaction with negative charge on the mucosal surface

Table 3: Mucosal penetration enhancers and mechanisms of action [4,16,17,19,27,48,52,54,64]

References

1. 1. A J. Hickey, Pharmaceutical Inhalation Aerosol Technology, 2nd edition, Marcel Dekker, NY, 2004
2. Afzelius B.A, The lung: Scientific Foundations, Lippincott–Raven, Philadelphia, 1997.
3. Alagusundaram M., Deepthi N., Ramkanth S., Angala-parameswari S., Mohamed Saleem T.S., Gnanapra-kash K.. Thiruvengadarajan V. S, Madhusudhana Chetty C, Dry Powder Inhalers - An Overview ,Int. J. Res. Pharm. Sci. 2010, 1;1: 34-42
4. Alsarra IA, Hamed AY, Mahrous GM, El Maghraby GM, Al-Robayan AA, Alanazi FK. Mucoadhesive polymeric hydrogels for nasal delivery of Acyclovir. Drug Dev Ind Pharm, 2009; 35:352-62.
5. Armengot,M., Basterra, J. and Macro,J., Rev.Larngol.Octol.Rhinol. 1990, 111,219- 226
6. Arora P, Sharma S, Garg S. Permeability issues in nasal drug delivery. Drug Discov Today 2002; 7, 18, 967-975.
7. Aulton M.E. " Pharmaceutics – The science of dosage form design" Churchill Livingston., 494, 2002
8. Aurora J. Development of Nasal Delivery Systems: A Review. Drug Deliv Technol 2002; 2,7, 1-8.
9. Bawarshi RN, Hussain A, Crooks PA. Nasal absorption of 17a-ethinyloestradiol in the rat. J Pharm Pharmacol 1989; 41: 214-215.
10. Bernstein J.M., Reddy M.S., Scannapieco F.A, Faden H.S., Ballow M., The microbial ecology and immunology of the adenoid: implications for otitis media, Ann. N.Y. Acad. Sci.1997,830, 19 – 31.
11. Buri P. Hydrogels destines a la muqueuse nasale. Contrô le physiologique, Pharm. Acta Helv. 1966,41, 88–101.
12. Chien Y.W., Su K.S.E., Chang S.F., Nasal Systemic Drug Delivery, Ch. 1, Marcel-Dekker, New York, 1-77, 1989
13. Chien YW, Chang SF. Intranasal drug delivery for systemic medications. Crit Rev Ther Drug Carr Syst 1987;4:67-194
14. Corbo DC. Drug absorption through mucosal membranes: effect of mucosal route and penetrant hydrophilicity. Pharm Res, 1989; 6:848-852.
15. Corbo DC, Liu JC, Chien YW. Characterization of the barrier properties of mucosal membranes. J Pharm Sci 1990; 79: 202-206
16. Costantino HR, Illum L, Brandt G, Johnson PH, Quay SC. Intranasal delivery: Physicochemical and therapeutic aspects. Int J Pharm, 2007; 337:1-24.
17. Dae-Duk Ki, Drug Absorption Studies: In situ, In vitro and In silico models, chapter 9, Springer, USA, 2007.
18. Dimova S, Brewster ME, Noppe M, Jorissen M, Augustijns P. The use of human nasal in vitro cell systems during drug discovery and development. Toxicol In Vitro, 2005; 19:107-122.
19. Dodane V, Khan MA, Merwin JR. Effect of chitosan on epithelial permeability and structure. Int J Pharm 1999; 182: 21-32.
20. Donnelly A, Kellaway IW\, Taylor G, Gibson M. Absorption enhancers as tools to determine the route ofnasal absorption of peptides.J Drug Target 1998;5:121-7

References

21. Donovan M, Flynn G, Amidon G. Absorption of polyethylene glycols 600 through 2000: the molecular weight dependence of gastrointestinal and nasal absorption. Pharm Res, 1990; 7:863-868.
22. Durrani Z, McInterney TL, McLain L, et al. Intranasal immunization with a plant virus expressing a pep-tide from HIV-1 gp41 stimulates better mucosal and systemic HIV-1-specific IgA and IgG than oral immunization. J Immunol Methods 1998; 220: 93-103.
23. Edman P, Bjork E, Ryden L. Microspheres as a nasal delivery system for peptide drugs j controlled release, 1992;21:165-72
24. Finlay, Warren H. The mechanics of inhaled pharmaceutical aerosols: an introduction. Boston: Academic Press. ISBN 0-12-256971-7, 2001.
25. Fisher A, Illum L, Davis S, Schacht E. Di-iodo-L-tyrosine labelled dextrans as molecular size markers of nasal absorption in the rat. J Pharm Pharmacol, 1992; 44:550-554.
26. Franz,M.R., Oth, M.P., U.S patent,5232704,1993.
27. Gavini E, Rassu G, Sanna V, Cossu M, Giunchedi P. Mucoadhesive microspheres for nasal administration of an antiemetic drug, metoclopramide: in-vitro/ex-vivo studies. J Pharm Pharmacol, 2005; 57:287-294.
28. Gizurarson S, Bechgaard E. Intranasal administration of insulin to humans. Diabetes Res Clin Prac 1991; 12:71-84.
29. Graff LC, Pollock GM. Nasal drug administration: potential for targeted central nervous system delivery. J Pharm Sci, 2005; 94:1187-1195.
30. Graff LC, Zhao R, Pollack GM. Pharmacokinetics of substrate uptake and distribution in murine brain after nasal instillation. Pharm Res, 2005; 22:235-244.
31. Hardy J.C., Lee S.W., Wilson C.G., Intranasal drug delivery by spray and drops, J. Pharm. Pharmacol. 1985, 37, 294–297.
32. Harris A.S., Nilsson I.M,.Wagner Z.G, Alkner U., Intranasal administration of peptides: Nasal deposition, biological response and absorption of desmopressin, J. Pharm. Sci. 1986,75, 1085–1088.
33. Harris A.S., Nilsson I.M., Wagener Z.G., Alkner U., Intranasal administration of peptides: Nasal deposition, biological response and absorption of desmopressin, J. Pharm. Sci. 1986,75, 1085–1088.
34. Harris AS, Nilsson IM, Wagner ZG, Alkner U. Intranasal administration of peptides: nasal deposition, biological response, and absorption of desmopressin. J Pharm Sci 1986; 75(11):1085-1088.
35. Hirai, S., Yashiki, T., Mima, H., Effect of surfactants on nasal absorption of insulin in rats, Int. J. Pharm., 1981,9, 165-171.
36. Hofstee BH. Specificity of esterase II. Behavior of pancreatic esterase I and II toward a homologous series of N-fatty acid esters. J Biol Chem 1952; 199:365-71
37. Hughes B.L., Allen D.L., Dorato M.A., Wolff R.K., Effect of devices on nasal deposition and mucociliary clearance in rhesus monkeys, Aerosol Sci. Technol. 1993,18, 241–249.
38. 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.

References

39. Hussain A, Hamadi S, Kagoshima M, Iseki K, Dittert L. Does increasing the lipophilicity of peptides enhance their nasal absorption? J Pharm Sci 1991; 80: 1180-1181.
40. Hussain A.A., Hirai S., Bawarshi R., Nasal absorption of natural contraceptive steroids in rats-progesterone absorption, J. Pharm. Sci.1981, 70, 466–467.
41. Hussain A.A., Hirai S, Bawarshi R, Nasal absorption of propranolol in rats, J. Pharm. Sci. 1979, 68, 1196-1199.
42. Hussain AA, Foster T, Hirai S, Kashihara T, Batenhorst R, Jone M. Nasal absorption of propranolol in humans. J Pharm Sci 1980; 69:1240-1243.
43. Hussain MA, Koval CA, Shenvi AB, Aungst BJ, Recovery of rat nasal mucosa from the effects of aminopeptidase inhibitors. J Pharm Sci 1990;79:398-400
44. Houtmeyers E, Gosselink R, Gayan-Ramirez G, Decramer M. Regulation of mucociliary clearance in health and disease. Eur Respir J, 1999; 13:1177-1188.
45. Illum L. In: Mathiowitz E, Chickering DE, Lehr CM Ed, Bioadhesive formulations for nasal peptide delivery: Fundamentals, Novel Approaches and Development. Marcel Dekker. New York; 1999; 507-539.
46. Illum L., Drug delivery systems for nasal application, S.T.P. Pharma 1987; 3: 594–598.
47. Illum L. Nasal clearance in health and disease. J Aerosol Med 2006; 19: 92–9.
48. Illum L. Nasal drug delivery: possibilities, problems and solutions. J Control Release, 2003; 87:187-198.
49. Illum L., Jorgensen H., Bisgaard H., Krogsgaard O., Rossing N., Bioadhesive microspheres as a potential nasal drug delivery system, Int. J. Pharm.,1987,39, 189–199.
50. Inagaki M, Sakakura Y, Itoh H, Ukai K, Miyoshi Y. Macromolecular permeability of the tight junction of human nasal mucosa. Rhinology 1985; 23: 213-221.
51. Jogani VV, Shah PJ, Mishra P , Mishra AK, Misra AR. Intranasal mucoadhesive microemulsion of tacrine to improve brain targeting. Alzheimer Dis Assoc Disord, 2008; 22:116-124.
52. Jorissen,M., AND Bessems, A., Eur.Arch. Otorhinolaryngol, 1995.252, 451-454.
53. Jug M, Becirevic-Lacan M. Development of a Cyclodextrin-Based Nasal Delivery System for Lorazepam. Drug Dev Ind Pharm, 2008; 34:817-826.
54. Junginger HE. Mucoadhesive hydrogels. Pharmazeutische Industrie 1956; 53: 1056-1065.
55. Kadam, S.S., Mahadik, K.R., Pawar, A.P., Paradkar, A.R., Transnasal delivery of peptides – a review, The East. Pharm. July 1993, 47 – 49.
56. Kaliner M., Marom Z., Patow C., Shelhamer J, Human respiratory mucus, J. Allergy Clin. Immunol. 1984, 73, 318 – 323.
57. Katdare A., Chaubal M.V., Excipient Development for Pharmaceutical Biotechnology and Dr Delivery Systems. Taylor & Francis Group, LLC, USA, 2006.
58. Kisan R. Jadhav, Manoj N. Gambhire, Ishaque M. Shaikh, Vilarsrao J. Kadam and Sambjahi S. Pisal, Nasal Drug Delivery System-Factors Affecting and Applications, Current Drug Therapy, 2007, 2, 27-38 27

References

59. Krishnamoorthy R, Ashim K. Mitra, Prodrugs for nasal drug delivery. Advanced Drug Delivery Reviews1998; 29: 135–146
60. Kublik H, Vidgren MT. Nasal delivery systems and their effect on deposition and absorption. Adv Drug Deliv Rev 1998; 29: 157-177.
61. Kublik H., Vidgren M.T., Nasal delivery systems and their effect on deposition and absorption, Advanced Drug Delivery Reviews.1998, 29, 157–177
62. Lee KR, Maeng HJ, Chae JB, et al. Lack of a primary physicochemical determinant in the direct transport of drugs to the brain after nasal administration in rats: potential involvement of transporters in the pathway. Drug Metab Pharmacokinet 2010; 25:430–41.
63. Lee V.H.L., Enzymatic barriers to peptide and protein absorption, CRC Crit. Rev. Ther. Drug Carrier Syst. 1988, 5, 69–97.
64. Mahalaxmi rathananand, D. S. Kumar, A. Shirwaikar, Ravi kumar, D. Sampath kumar, Preparation of Mucoadhesive Microspheres for Nasal Delivery by Spray Drying, Indian Journal of Pharmaceutical Sciences, 2007,652.
65. Martin E, Nicolaas GM, Schipper J, Coos V,Frans WH. Nasal mucociliary clearance as a factor in nasal drug delivery. Adv Drug Del Rev 1997;29:13-38
66. McMartin C, Hutchinson LE, Hyde R, Peters GE. Analysis of structural requirements for the absorption of drugs and macromolecules from the nasal cavity. J Pharm Sci 1987; 76: 535-540.
67. 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.
68. Mestecky J, Moldoveanu Z, Michalek SM, et al. Current options for vaccine delivery systems by mucosal routes. J Control Release 1997; 48: 243-257.
69. Michael I. Ugwoke, Remigius U. Agu, Norbert Verbeke, Renaat Kinget, Nasal mucoadhesive drug delivery: Background, applications, trends and future perspectives, Advanced Drug Delivery Reviews, 2005, 57, 1640 – 1665
70. Morimoto K, Miyazaki M, Kakemi M. Effects of proteolytic enzyme inhibition on nasal absorption of salmon calcitonin in rats. Int J Pharm 1995; 133: 1-8.
71. Mygind N., Vesterhauge S., Aerosol distribution in the nose, Rhinology 1978, 16, 79–88.
72. 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.
73. Sarkar MA. Drug metabolism in the nasal mucosa. Pharm Res, 1992; 9:1-9.
74. Soane RJ, Carney AS, Jones NS, et al. (2001). The effect of the nasal cycle on mucociliary clearance. Clin Otolaryngol Allied Sci 26:9–15. Suman JD. (2003). Nasal drug delivery. Expert Opin Biol Ther 3: 519–23.
75. Varshosaz J, Sadrai H, Heidari A. Nasal delivery of insulin using bioadhesive chitosan gels. Drug Deliv 2006; 13:31–8.
76. 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, 2000; 198:139-146.
77. Westin U, Piras E, Jansson B, Bergströ m U, Dahlin M, Brittebo E, Bjö rk E. Transfer of morphine along the olfactory pathway to the central nervous system after nasal administration to rodents. Eur J Pharm Sci, 2005; 24:565-573.
78. Wynsberghe D.V., Noback R.C., Carola R., Human anatomy and physiology, McGraw-Hill Companie, UK, 1994.
79. Zaki NM, Awad GA, Mortada ND, Abd ElHady SS. Rapid-onset intranasal delivery of metoclopramide hydrochloride. Part I. Influence of formulation variables on drug absorption in anesthetized rats. Int J Pharm, 2006; 327:89-96.