Pharmacophore
(An International Research Journal)
Available online at http://www.pharmacophorejournal.com

Review Article

FORMULATION AND BIOLOGICAL FACTORS INFLUENCING THE ABSORPTION OF DRUGS THROUGH NASAL EPITHELIUM AND CURRENT NASAL FORMULATIONS - AN OVERVIEW

Atul S. Pratapwar*, Vijay A. Agrawal and Aditya P. Chiddarwar

Department of Industrial Pharmacy,
S.N. Institute of Pharmacy,
Pusad., Yawatmal-445204, India

ABSTRACT

The present overview deals with the formulation and biological factors that affects absorption of drug through nasal epithelium and currently available different types of formulations and the current trends in nasal drug delivery. More recently, nasal drug delivery has generated widespread interest among the scientific community as an alternative route for the administration of drugs and biomolecules that are susceptible to enzymatic or acidic degradation. Various physiochemical characteristic of drug affect nasal absorption of the drug. Nasal route may also be preferred when rapid onset of action is required and when small molecular weight polar drugs, peptides and proteins are not easily administered via other routes than by injection. Formulation properties of drugs, formulation excipients and biological factors affect nasal drug permeation. This paper focus on potential advances and hurdles for delivering bioactive agent through nasal route and formulations like suspensions, powders, emulsions and ointments, microspheres, liposome's and proliposomes, viscous solution, gel and in-situ gel.

Keywords: Nasal drug delivery, Microspheres, Gel and in-situ gel, Drugs, Biomolecules, Formulation.

INTRODUCTION

For systemic therapy, drugs are traditionally administered by oral and parenteral routes. The most desirable and convenient method of drug administration is the oral route and most favored dosage forms include tablets, capsules and solutions because of their ease of manufacture and administration. However in many instances, oral administration is unsuitable when the drug undergoes significant degradation in the gastrointestinal tract or is metabolized to a high degree via the first pass effect in the liver.[1] Researchers resorted to the parenteral route as an easy solution to the problem. Absorption through the intravenous route and other parenteral routes like intramuscular and subcutaneous provides satisfactory delivery of most drugs. But parenteral route is undesirable or impractical if a drug is intended for the treatment of chronic diseases. Therefore an alternative route of administration would be preferred. For the past few decades, the transdermal route has been explored for a number of drugs, but its use is limited due to low permeability of the skin to many drugs.[2] There has been significant interest in drug delivery via nonparenteral routes in recent years. Nonparenteral routes for drug

delivery include nasal, buccal, pulmonary and transdermal routes. All these application routes are suitable for self-administration in an ambulatory setting. The nasal application is the only route of administration from this list of nonparenteral delivery systems which gives rapid onset of action; high absorption of small molecular weight hydrophobic drugs, relatively high bioavailability, avoidance of first pass effect and ease in administration by patients favors this route of application.[3] Traditionally, the nasal route has been used for delivery of drugs for local treatment of diseases such as nasal congestion, allergy and infections. More recently, nasal drug delivery has generated widespread interest among the scientific community as an alternative route for the administration of drugs and biomolecules that are susceptible to enzymatic or acidic degradation and first pass hepatic metabolism or incompletely absorbed in the gastrointestinal tract or gives undesirably slow effects when administered orally. Nasal route may also be preferred when rapid onset of action is required and when small molecular weight polar drugs, peptides and proteins are not easily administered via other routes than by injection.[4] Heightened interest in this route of administration is due in part to the relatively large surface area of 180 cm^2 because of the presence of large number of microvilli, a porous endothelial membrane and highly vascularised tissue providing an attractive site for rapid and efficient systemic absorption.

FACTORS INFLUENCING THE ABSORPTION OF DRUGS THROUGH NASAL EPITHELIUM

Physicochemical Properties of Drugs

Various physiochemical characteristic of drug affect nasal absorption of the drug.

Molecular weight and size

Extent of the absorption of the drug depends on molecular weight particularly for hydrophilic compounds. Nasal route is suitable for efficient delivery of drugs up to 1000 Daltons. Absorption reduces the significantly if the molecular weight is greater than 1000 Daltons except with the use of penetration enhancers. It has been reported that a good linear correlation exists between the log percentage drug absorbed nasally and the log molecular weight of water-soluble compounds suggestion the participation of aqueous channels in the nasal absorption of water-soluble molecules.[5] It has been reported that particle size greater than 10 μm are deposited in the nasal cavity. Particles that are 2 to 10 μm can be retained in the lungs and particles of less than 1μm are exhaled.[6]

Solubility and dissolution

Drug solubility is a major factor determining absorption of drug through biological membranes. It limits a formulator's ability to formulate a product if the drug is not sufficiently soluble in the desired vehicles. As nasal secretions are more watery in nature, a drug should have appropriate aqueous solubility for increased dissolution. Particles deposited in the nostrils need to be dissolved prior to absorption. If the drug remains as particles in nostrils, or if they are cleared away from the nasal cavity, one may not observe absorption of the drug.[5]

Partition coefficient and pKa

Jiang *et al.* conducted a study to find out the quantitative relationship between the physicochemical properties of drugs and their nasal absorption, using diltiazem hydrochloride and paracetamol as model drug. The result showed that a quantitative relationship exist between the partition coefficient and nasal absorption constant. As per the pH partition theory, unionized species are absorbed better compared with ionized species and it holds true in the case of nasal absorption. The extent of absorption is pH dependent, being higher at a pH lower than the pKa and decreases beyond the pKa. In general, the authors found that nasal absorption increases with the lipophilicity of permeant. Various studies indicate that the drug concentration in the cerebrospinal fluid (CSF) rise with an increase in lipophilicity or partition coefficient of the drugs.[5]

Chemical form

The chemical form in which a drug is presented at the nasal mucosa can be important in determining its absorption. For example, conversion of drug into salt or ester form can alter its absorption. Huang *et al.* studied the structural modification of drug on absorption. It was observed that in situ nasal absorption of carboxylic acid ester of L-tyrosine was significantly greater than that of L-tyrosine. This phenomenon is associated with the increase in lipophilicity following esterification, which increase the rate and extent of absorption.[5]

Physical state: *particle size and morphology*

Particle size and morphology of drug particles constitute important properties for particular nasal drug products. Particle size and morphology are related to the rate of drug dissolution and should be controlled to obtain suitable drug dissolution properties in the nostrils. Too fine particles, below five microns may be inhaled into the lungs and should be avoided for the nasal products. Generally, particles in the 5-10 micron range are deposited in the nostrils.[5]

Formulation Properties of Drugs

Drug concentration, dose and dose volume

Drug concentration, dose and dose volume of administration are three interrelated parameters that impact the performance of nasal delivery system. Nasal absorption of L-tyrosine was shown to increase with drug concentration in nasal perfusion experiments. However, in another study, aminopyrine was found to absorb at a constant rate as a function of concentration.[7] Several studies have reported the effect of drug dose on nasal absorption, e.g. calcitonin, GnRH agonist, desmopresin, secretin. In general, higher nasal absorption or therapeutic effect was observed with increasing dose. It is important to note how the dose is varied. If the drug is increasing by increasing formulation volume, there may be a limit as to what extent nasal absorption can be increased. The nostril can retain only a limited volume, beyond which a formulation wile drain out of the nasal cavity. The ideal dose volume range is 0.05-0.15 ml with an upper limit of 0.20 ml.[8]

Physical form of formulation

Nasal drug absorption depends on the physical form of the formulation. A powder form was found to be more effective than liquid formulations in delivering insulin in rabbits. Resta *et al.* who compared the powder reported a similar finding and solution dosage forms of sodium cromoglycate in humans suffering with allergic rhinitis. Their data show that both powder and solution forms were effective for treatment and suggested that the powder form was somewhat better than solution because powder is readily washed out with the nasal secretions.[5] Generally a more viscous formulation will provide less efficient systemic nasal drug delivery. Harris et al studied the nasal delivery of desmopressin and reported that although the addition of viscous agent to nasal formulations may produce a somewhat more sustained effect. It would seem logical that more viscous formulations e.g. gel should be more appropriate for those drugs which cause unpleasant taste in the mouth via a nasal drip of solution or spray formulations.[9]

Formulation pH

The pH of the formulation as well as that of nasal surface can affect a drug's permeation. The pH of nasal formulation is important for the following reasons, to avoid irritation of the nasal mucosa, to allow the drug to be available in unionized form for absorption, to prevent the growth of pathogenic bacteria in the nasal passage, to sustain normal physiological ciliary movement, to maintain functionality of excipients such as preservatives. Lysozymes are 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 pH of 4.5 to 6.5 keeping in mind the physicochemical properties of the

drug as drugs are absorbed in the unionized form and also to avoid nasal irritation.[5]

Formulation osmolarity

Drug absorption can be affected by tonicity of the formulation. Shrinkage of the epithelial cells has been observed in the presence of hypertonic solution. Hypertonic saline solution also inhibits or ceases ciliary activity. Low pH has similar effect as that of hypertonic solutions. Generally an isotonic formulation is preferred.[5]

Formulation excipients [5]

Solubilizers

Aqueous solubility of a drug is always a limitation for nasal drug delivery in solution. Conventional solvents or co solvents such as glycols, small quantities of alcohol, medium chain glycerides and labrasol (saturated polyglycolized C8-C10 glycerides) can be used to enhance the solubility of drugs. 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 enhancers. In such cases, their impact on nasal irritancy should be considered.

Buffer component

Nasal formulations are generally administered in small volumes ranging from 25 to 200 µl being the most common dose volume. Hence, nasal secretion may alter the pH of the administered dose. This can affect the concentration of unionized drug available for absorption. Therefore, an adequate formulation buffer component may be required to maintain the pH.

Antioxidants

Depending upon the stability profile of a given in the formulation chosen, it may be necessary to use antioxidants to prevent degradation. Commonly used antioxidants are sodium metabisulphite, sodium bisulphate, butylated hydroxytoluene and tocopherol. Usually antioxidants are used in small quantities and they may not affect drug absorption or cause any nasal irritation.

Flavor/taste

Some drugs may present problems with regard to aroma and taste. Taste becomes a problem if a substantial amount of the formulation drips into the back of throat. The choice of such agents will depend on drug being developed.

Preservative

Most nasal formulation 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 preservative in nasal formulations. Van De Donk *et al.* has shown that mercury-containing preservatives have a fast and irreversible effect on ciliary movement and should be used in nasal systems. Preservatives are based in small quantities and are not likely to affect drug absorption.

Humectants

Many allergenic and chronic diseases are often connected with crusts and drying of mucous membranes. Certain preservatives/antioxidants among the other excipients are also likely to cause nasal irritation especially when used in higher quantities. Adequate intranasal moisture is essential for preventing dehydration. Therefore, humectants can be added are not likely to affect drug absorption. Some common humectants uses include glycerin, sorbitol and mannitol.

Gelling/viscofying agents

Some formulations need to be gelled or made more viscous to increase nasal residence time. According to a study by Pennington *et al.* increasing the solution viscosity may provide a means of prolonging the therapeutic effect of nasal preparations. Suzuki et al showed that a drug carrier such as hydroxypropylcelulose was effective for improving the absorption of low molecular weight drugs but did not produce the same effect for high molecular weight peptides.

Biological Factors[5]

Nasal blood flow

The blood vessels in the nasal mucosal membrane play an important role in the thermal regulation and humidification of the inhaled air. The nasal mucosal is supplied by rich vasculature and a dense network of erectile cavernous tissue which is particularly well developed over the turbinates and septum. The highly vascular nature of the mucosal makes it a good membrane for drug absorption. The nasal vascular bed is so designed that a rapid exchange can be made for fluid and dissolved substances between blood vessels and nasal tissue. The nasal blood flow is affected by several external and physiological factors such as ambient temperature, humidity, presence of vasoactive drugs, trauma and inflammation as well as some psychological factors such as fear, anxiety and frustration.

Enzymatic activity in the nose

The nasal epithelium has a defensive enzymatic barrier against the entry of xenobiotics. Biotransformation of foreign compounds in the nasal mucosal of animals has shown extensive cytochrome P450 dependent metabolism. Many compounds are known to be metabolized by the nasal P450 dependent monooxygenase system, e.g. nasal decongestant, anaesthetics, alcohol, nicotine. Along with the P450 monooxygenase system, several other enzymes exit in the nasal secretions e.g. lactate dehydrogenase, oxydoreductases, hydrolases, acid phosphatase and esterases, which are responsible for metabolism of certain drugs. This can affect drug delivery for both systemic as well as local drugs.

Physical condition of the nasal mucosal

The condition of the nasal mucosal can have an important effect on drug absorption. In people suffering from several nasal allergies, an excessive nasal secretion can wash away the formulation before the drug has a chance of getting absorption through the mucosa or before acting locally.

Volume of administration

The optimal formulation volume for nasal administration is 25-200 µl per nostril. Large volume will drain out of the nose. The most practical volume is 100 µl per nostril. During the development process, it may be important to study the volume effect on drug absorption.

Site of deposit of formulation in the nose

Deposition of formulation in the anterior portion of the nose provides a greater nasal residence time and allows more contact time between drug and the mucosa. Depositing a formulation in the posterior part of the nose will allow a faster ciliary clearance of the formulation. The permeability of the posterior nasal passage is generally higher than the anterior passage. Slow absorbing drugs should be deposited in the anterior part of the nose and fast acting drug in the posterior part of the nose.

NASAL FORMULATIONS

The nasal formulation along with the physicochemical properties of the drug and anatomical and physiological factors of the nasal cavity affect the nasal absorption of drug molecules. Most conventional nasal cavity affects the nasal absorption of drug molecules. Most conventional nasal formulation constitutes the nasal drops, which is a simple and convenient system for nasal delivery. Although solutions are easy to use, the drug solutions are instilled in the nose is eliminated within 15 minute, because of the mucociliary clearance, thus leads to a low bioavailability especially for large hydrophilic drugs. The duration of the therapeutic effect is often short, and hence frequent dosing is necessary.

Suspensions

The nasal absorption of the human sodium insulin was found to be better from suspension when compared to the other dosage forms. This is due to increased concentration gradient for drug diffusion across nasal membrane.[5]

Powders

Many reports have appeared; describing powder dosage forms for example microspheres as co lyophilized powder using bile salts, cyclodextrins starch, cellulose and their derivatives and so on, for nasal delivery. The advantages of nasal powder dosage form are the absence of preservative and superior stability of the formulation.[10] 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.[11]

Emulsions and ointments[12]

Only a limited amount of work has been reported on the development of emulsion and ointment for nasal drug delivery. By their nature, they would seem to be more appropriate for locally acting drugs. However, their use for systemic drugs cannot be ruled out. Major disadvantages of nasal emulsion and ointments include poor acceptance by patients, developments efforts needed are high, and problems in delivering precise doses from metered dose nasal actuators. The nasal drug delivery systems, however, have not been used extensively because of some drawbacks, such as low patient's compliance. Several new preparations have been developed for nasal route not only to prolong the contact time of the vehicle on nasal mucosal surface but also to slow down the drug clearance like microspheres, liposome, proliposomes and mucoadhesive drug delivery systems.

Microspheres

Microspheres also studied to increase the residence time in nasal cavity. Several bioadhesives microsphere systems (such as degradable starch microspheres, serum albumin microspheres) have been studied for administration of the insulin, human growth hormone, oxytocin and propranolol. It had been demonstrated that a significant improvement in bioavailability could be achieved when drugs were administered as bioadhesives microsphere without absorption enhancers.[12] Illum *et al.* in their in vivo studies using formulations including bioadhesives microspheres for nasal administration in humans were reported that intranasal clearance from microspheres systems were 3 hours or longer while the half time for the clearance of control solutions or powders were approximately 15 min.[13]

Liposomes and proliposomes[14]

The use of liposomes as nasal drug delivery system has been advocated by Vyas and Goswani because of the following advantages

- The component of the liposomes are themselves considered to be bioadhesives, there is no need to add bioadhesives material.
- Multilamellar liposomes could fuse in nasal mucosa and gradual fusion of the lamellae and mucosa results in sustained and controlled released of drug.
- Liposomes due to their flexible nature do not abstract the nasal airways.

Recently, intranasal administration has been investigated as a new route for systemic peptide delivery. The use of liposome as a transmucosal therapeutic system has many advantages, for example, protection of the drug from degradation by peptidase on the mucosa, maintanance of high concentration at the site of administration and facilitation of their absorption through mucosa. For the drug of very short biological half-life, the rapid absorption is unfavorable to sustain the drug level in the systemic circulation and the large mucociliary clearance of the nasal mucosa may cause poor absorption of certain drugs

Viscous solution[5]

Solutions of gentamicin sulphate were prepared and hydroxy propyl methylcellulose was used to increase the viscosity of solution and thereby increase the residence time of the preparation. The dosage form mentioned above, were delivered successfully in animals and studies were carried out to evaluate the efficiency of these formulations. The problems faced were overcome by use of absorption enhancers, increasing the contact time.

Gel and in-situ gel

Gel has been defined by Dorothy Jordan Lloyd," The colloidal condition, the gel is one which it is easier to recognize than to define". The phenomenological definition proposed in 1993 by Almdal *et al*., states that a gel is a soft, solid or solid like material, which consists of at least two components, one of which is a liquid present in abundance.[15] Gels are transparent to opaque semisolid containing a high ratio of solvent to gelling agent. When dispersed in appropriate solvent gelling agents merge or entangle to form a three-dimensional colloidal network structure. To solve the problems of conventional nasal drops, it would be desirable to develop a in situ gel which, Forms a gel at physiological condition, has suitable gel strength, not to leak out from the nasal cavity after nasal administration has a suitable bioadhesive force so as to increase the residence time.

REFERENCES

1. Illum, L (2003), "Nasal drug delivery-possibilities, problems and solutions", ***J Control Rel***, 87, 187-198.
2. Mao, S; Chen, J; Wei, Z and Liu, H (2004), "Intranasal administration of melatonin starch microspheres", ***Int J Pharm***, 272, 37-43.
3. Osth, K; Paulsson, M; Bjork, G and Edsman, K (2002), "Evaluation of drug release from gels on pig nasal mucosa in a horizontal using chamber", ***J Control Rel.***, 83, 377-388.
4. Wadell,, C; Bjork, E and Camber, O (1999), "Nasal drug deliver-evaluation of an *in vitro* model using porcine nasal mucosa", ***Eur J Pharm Sci.***,7,197-206.
5. Behl, CR; Pimplaskar, HK; Sileno, AP; Maireles J and Romeo, VD (1998), "Effect of physicochemical properties and other factors on systemic nasal drug delivery", ***Adv Drug Deliv Rev.***, 29, 89-116.
6. Arora, P; Sharma, S and Garg, S (2002), "Permeability issues in nasal drug delivery", ***Drug Deliv Tech.***, 7 (18), 967-974.
7. Sarasija, S and Shyamala, B (2005), "Nasal drug delivery: An overview", ***Ind J Pharm Sci.***,1-2, 19-24.
8. Dua, R; Zia, H and Needham, T (1997), "The influence of tonicity and viscosity on the intranasal absorption of salmon calcitonin in rabbits", ***Int J Pharm***., 147, 233-242.
9. Magithiya, JR and Murthy, RSR (2004), "Drug delivery to brain through nasal route using olfactory pathway", ***The Pharm Rev.***,13-28.
10. Callens, C (2003), "Influence of multiple nasal administration of bioadhesive powders on the insulin bioavailability", ***Int J Pharm***., 250, 415-422.
11. Nagai, T; Nishimosto, Y; Nambu, N; Suzuki, Y and Sekine, K (1984), "Powder dosage form of insulin for nasal administration", ***J Control Rel***.1, 15-20.
12. Zhang, Q; Jiangs, X; Jiang, W and Shi, Z (2004), "Preparation of nimodipine loaded microemulsion for intranasal delivery and evaluation on the targeting efficiency to the brain", ***Int J Pharm***., 275, 85-96.
13. Illum, L; Jorgensen, H; Bisgaard, N; Krogsgaard, O and Rossing, N (1984), "Bioadhesive microspheres as potential nasal drug delivery systems", ***Int J Pharm***., 39, 189-199.
14. Maitani, Y; Asano, S; Takahashi, S; Nagaki, NM and Nagai, T (1992), "Permeability of insulin entrapped in liposomes through the nasal mucosa of rabbits", ***Chem Pharm Bull***., 40 (6), 1569-1572.
15. Joel, LZ and Greory, PK *et al*. (1996), "***Pharmaceutical dosage forms: disperse system***", Vol-II, 2nd Edi., Marcel Dekker, New York, Basel, Hong Kong,172-176.