

AN OVERVIEW ON NASAL DRUG DELIVERY SYSTEM

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Summary

Nasal drug delivery system offers lucrative way of drug delivery of both topical and systemic therapies. The high permeability, high vasculature and low enzymatic environment of nasal cavity are well suitable for systemic delivery of drug molecules via nose. The noninvasiveness and self administrative nature of nasal delivery also attracts the formulation scientists to deliver protein and peptide compounds. Despite of all the advantages of nasal drug delivery, the bioavailability of nasally administered products, especially for protein and peptide molecules, is affected by many barriers such as physiological barriers, physicochemical barriers, and formulation barriers. This review will focus on the various bioavailability barriers in nasal drug delivery and the strategies to improve the bioavailability of nasal dosage form.

Key- Word: Nasal drug delivery system, olfactory regions, nasal gels.

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1. INTRODUCTION

The administration of drugs via nose is not a novel approach for drug delivery. In ancient days, nasal drug delivery was used for the systemic administration of psychotherapeutic compounds and other similar substances. But in modern pharmaceutics, nasal delivery is considered as a route of choice for local effect rather than systemic effect. Delivery of drugs via nose for maintenance therapy of nasal allergy, sinusitis, nasal congestion, and nasal infections is a routine practice. However, there has been a great deal of research in investigating nose as a potential route for systemic therapies for both conventional as well as protein and peptide molecules. Advent of biotechnology, molecular biology, and pharmacology provided a lot of endogenous protein and peptide molecules for therapeutic use, the delivery of such molecules is possible through nasal drug delivery. Recent interest in nasal delivery of conventional molecules reflects the desire on behalf of the pharmaceutical companies to extend the life span of drugs in

the face of generic completion by delivering them via novel route. The greater permeability of nasal mucosa with large surface area affords a rapid onset of therapeutic effect. The low metabolic environment of nose has potential to overcome the limitation of oral route and duplicate the benefit of intravenous administration. In addition to that, nasal administration minimizes the lag time associated with oral drug delivery and offers non-invasiveness, self-administration, patient comfort, and patient compliance, which are the hurdles in intravenous drug therapy. The interesting advantage of nasal drug delivery is the possibility of targeting central nervous system (CNS) by bypassing blood brain barrier (BBB).

2. ANATOMY AND PHYSIOLOGY OF NOSE:

The nasal cavities divided into two symmetrical halves by the nasal septum, a central partition of bone and cartilage; each side opens at the face via the nostrils and connects with the mouth at the naso pharynx. The nasal vestibule, the respiratory region and the olfactory region are the three main regions of the nasal cavity. The lateral walls of the nasal cavity includes a folded structure which enlarges the surface area in the nose to about 150cm². This folded structure includes three turbinates: the superior, the median and the inferior. In the main nasal airway, the passages are narrow, normally only 1-3mm wide, and this narrows structure enables the nose to carry out its main functions. During inspiration, the air comes into close contact with the nasal mucosa and particles such as dust and bacteria are trapped in the mucous. Additionally, the inhaled air is warmed and moistened as it passes over the mucosa; and the high blood supply in the nasal epithelium the nasal cavity is covered with a mucous membrane which can be divided into no olfactory and olfactory epithelium areas. The no olfactory area includes the nasal vestibule, which is lined with skin-like cells, and respiratory region, which has a typical airways epithelium.

2.1 The Respiratory region:

The nasal respiratory epithelium is generally described as a pseudo-stratified ciliated columnar epithelium. This region is considered to be the major site for drug absorption into the systemic circulation. The four main types of cells seen in the respiratory epithelium are ciliated columnar cells, non-ciliated columnar cells, goblet cells and basal cells. Although rare, neurosecretory cells may be seen but, like basal cells, these cells do not protrude into the airway lumen. The proportions of the different cell types vary in different regions of the nasal cavity. In the lower turbinate area, about 15-20% of the total numbers of cells are ciliated and 60-70% is non-ciliated epithelial cells. The numbers of ciliated cells increase towards the nasopharynx with a corresponding decrease in non-ciliated cells. The high number of nonciliated cells indicates their importance for absorption across the nasal epithelium. Both columnar cell types have numerous (about 300-400 per cell) microvilli. The large number of microvilli increases the surface area and this is one of the main reasons for the relatively high absorptive capacity of the nasal cavity. The role of the ciliated cells is to transport mucus towards the pharynx. Basal cells, which vary greatly in both number and shape, never reach the airway lumen. These cells are poorly differentiated and act as stem cells to replace other epithelial cells.

2.2 The olfactory region:

In human, the olfactory region is located on the roof of the nasal cavities, just below the cribriform plate of the ethmoid bone, which separates the nasal cavities from the cranial Cavity. The olfactory tissue is often yellow in colour, in contrast to the surrounding pink tissue. Humans have relatively simple noses, since the primary function is breathing, while other mammals have more complex noses better adapted for the function of olfaction.

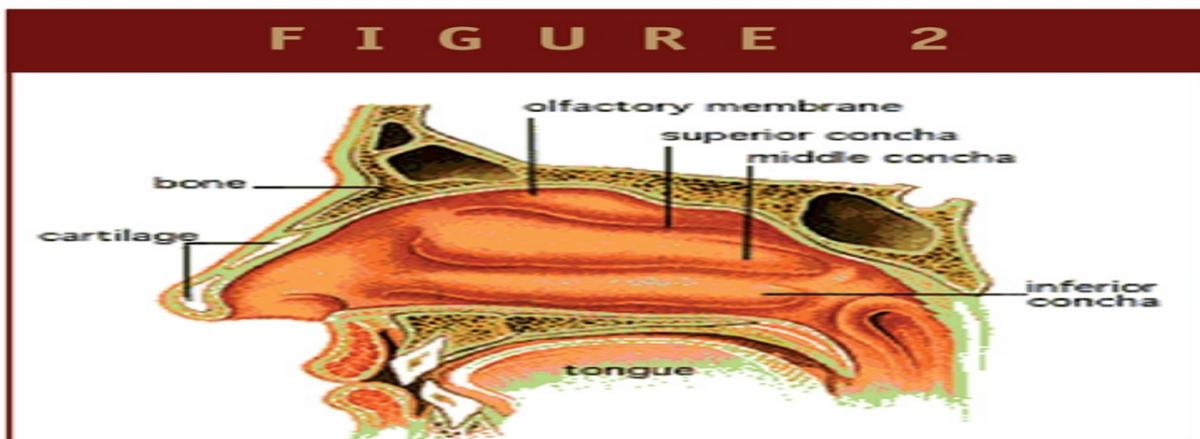


Figure 1: A Schematic diagram of olfactory epithelium

Advantages of Nasal Drug Delivery System:

- Drug degradation that is observed in the gastrointestinal tract is absent.
- Hepatic first – pass metabolism is absent.
- Rapid drug absorption and quick onset of action can be achieved.
- The bioavailability of larger drug molecules can be improved by means of absorption enhancer or other approach.
- The nasal bioavailability for smaller drug molecules is good.
- Drugs that are orally not absorbed can be delivered to the systemic circulation by nasal drug delivery.
- Studies so far carried out indicate that the nasal route is an alternate to parenteral route, especially, for protein and peptide drugs.
- Convenient for the patients, especially for those on long term therapy, when compared with parenteral medication.

Limitation:

- The histological toxicity of absorption enhancers used in nasal drug delivery system is not yet clearly established.
- Relatively inconvenient to patients when compared to oral delivery systems since there is a possibility of nasal irritation.
- Nasal cavity provides smaller absorption surface area when compared to GIT.

3. NASAL DRUG ABSORPTION:

3.1 Mechanism of Drug Absorption:

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. There is an inverse log-log correlation between intranasal absorption and the molecular weight of water-soluble compounds. Poor bioavailability was observed for drug with a molecular weight greater than 1000 Daltons. The second mechanism involves transport through a lipoidal route is also known as the transcellular process and is responsible for the transport of lipophilic drugs that show a rate dependency on their lipophilicity. Drug also cross cell membranes by an active transport route via carrier-mediated means or transport through the opening of tight junctions. For examples, chitosan, a natural biopolymer from shellfish, opens tight junctions between epithelial cells to facilitate drug transport..

3.2 Factors affecting nasal drug absorption:

Many factors affect the systemic bioavailability of nasally administered drugs. The factors can be attributed to the physiochemical properties of the drugs, the anatomical and physiological properties of the nasal passage and the type and characteristics of selected nasal drugs delivery system. These play significant role for most of the drugs in order to reach therapeutically effective blood levels after nasal administration. The factors influencing nasal drug absorption are as follows.

A) Physiochemical properties of drug.

Molecular size, Lipophilic-hydrophilic balance, enzymatic degradation in nasal cavity.

B) Nasal Effect

Membrane permeability, environmental p^H , mucociliary clearance, cold, rhinitis.

C) Delivery Effect

Formulation (Concentration, p^H , osmolarity), Delivery effects, Drugs distribution and deposition, Formulation effect on mucociliary clearance, Toxic effect on ciliary function and epithelial membranes.

3.3 Absorption Enhancement:

Factors that affect the delivery of drug across nasal mucosa such as surfactants, dose pH , osmolarity, viscosity, particle size and nasal clearance, drug structure can be used to advantage to improve absorption.

a) Drug Concentration, Dose and 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. However, in another study, aminopyrine was found to absorb as a function of concentration. In contrast, absorption of salicylic acid was found to decline with concentration. This decline is likely due to nasal mucosa damage by the permanent.

b) Formulation pH

The pH of a nasal formulation is important for the following reasons:

- 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. To avoid irritation of nasal mucosa

c) Buffer capacity

Nasal formulations are generally administered in small volumes ranging from 25 to 200 μ L with 100 μ L being the most common dose volume. Hence, nasal secretions may alter the pH of the administered dose. This can affect the concentration of unionized drug available for absorption. Therefore, an adequate formulation buffer capacity may be required to maintain the pH in *-situ*.

d) Gelling/Viscofying agents or Gel-Forming Carriers

According to a various studies, increasing solution viscosity may provide means of prolonging the therapeutic effect of nasal preparations. A drug carrier such as hydroxypropyl cellulose was effective for improving the absorption of low molecular weight but did not produce the same effect for high molecular weight peptides. Use of a combination of carriers is often recommendation from a safety (nasal irritancy) point of view.

e) Solubilisers

solubility of drug is always a limitation for nasal drug delivery in solution conventional solvents such as glycols, small quantities of alcohol, Transcutol (diethylene glycol monoethyl ether), 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 absorption enhancers. In such cases, their impact on nasal irritancy should be considered.

f) 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.

g) Antioxidants:

A small quantity of antioxidants may be required to prevent drug oxidation. Commonly used antioxidants are sodium metabisulphite, sodium bisulfite, butylated hydroxytoluene and tocopherol. Usually, antioxidants do not affect drug absorption or cause nasal irritation. Chemical/physical interaction of antioxidants and preservatives with drugs, excipients, manufacturing equipment and packaging components should be considered as part of the formulation development program.

3.4 Absorption enhancers in nasal drug delivery:

Unlike the most small drug molecules, some drugs and peptides do not cross the nasal membrane efficiently. As a result the nasal bioavailability in simple solution formulation is very low. The low nasal absorption can be attributed to poor membrane permeability due to molecular size, lack of lipophilicity or enzymatic degradation..They act by one or combination of the following mechanisms:

- Alteration of properties of mucosa layer.
- Opening tight junctions between epithelial cells.
- Reversed micelle formation between membranes.
- Increasing the membrane fluidity by,
 - a. Extraction or leaching of membrane components.
 - b. Creating disorders in the phospholipids domain in the membrane.

Various types of penetration enhancers have been evaluated for organic drugs including surfactants, bile salts, chelators, fatty acid salts, phospholipids, glycyrrhetic acid derivatives, Most peptides and proteins show insufficient nasal bioavailability. Number of approaches has been described to improve their systemic bioavailability. Insulin is poorly absorbed from nasal mucosa. Many compounds of different chemical structure have been investigated to promote transnasal insulin absorption. The STDHF enhanced the effects of absorption enhancers on intranasal insulin delivery in rats, rabbits and sheep.

3.5 Safety and Efficacy of Absorption Enhancers:

While it is important to establish the efficacy of absorption enhancers, it is equally imperative to prove their safety by measuring their effect on the mucociliary transport rate, nasal morphology and ciliary beat frequency.

(a) Mucociliary transport rate:

It is measured using a frog palate model to test potential toxicity of absorption enhancers L- α -lysophosphatidylcholine, sodium deoxycholate and taurocholate, laurth-s and sodium taurodihydrofusidate irreversibly halted the mucus transport rate.

(b) Nasal Morphology:

This was studied by differing the contact times with the nasal epithelium using scanning electron microscope to detect gross structural and cellular changes, ciliary identity as well as prevalence or extra-cellular debris.

(c) Ciliary Beat Frequency:

The chicken embryo tracheal tissue and human adenoid tissue were used to measure the in vitro reduction of the ciliary beat frequency caused by various enhancers ranging from laureth-9=DC =GC=TDC (fast and irreversible ciliostasis, brought about by preservatives like BAK and Mercury compounds).

4. PHYSIOCHEMICAL PROPERTIES OF DRUGS:

4.1 Chemical form:

The form of a drug can be important in determining absorption. For example, conversion of the drug into an ester form can alter its absorption. It was observed that in situ nasal absorption of carboxylic acid esters of L-Tyrosine is significantly greater than that of L-Tyrosine.

4.2 Polymorphism:

Polymorphism is known to affect the dissolution rate, solubility of drug and thus their absorption through biological membranes. It is therefore advisable to study the polymorphic stability and purity of drugs for nasal powders and/or suspensions.

4.3 Molecular Weight:

A linear inverse correlation has been reported between the absorption of drugs and molecular weight up to 300 Daltons. Absorption decreases significantly if the molecular weight is greater than 1000 Daltons except with the use of absorption enhancers.

4.4 Particle Size:

It has been reported that particle sizes 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 1 µm are exhaled.

4.5 Solubility and 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 drugs remain as particles or are cleared away, no absorption occurs.

4.6 Delivery Systems:

The selection of delivery system depends upon the drug being used, proposed indication, patient population and last but not least, marketing preferences.

4.7 Nasal Drops:

Nasal drops are one of the most simple and convenient systems developed for nasal delivery. The main disadvantage of this system is the lack of the dose precision and therefore nasal drops may not be suitable for prescription products. It has been reported that nasal drops deposit human serum albumin in the nostrils more efficiently than nasal sprays.

4.8 Nasal sprays:

Both solution and suspension formulations can be formulated into nasal sprays. Due to the availability of metered dose pumps and actuators, a nasal spray can deliver an exact dose from 25 to 200 μm . The particles size and morphology (for suspensions) of the drug and viscosity of the formulation determine the choice of pump and actuator assembly.

4.9 Nasal Gels:

Nasal gels are high-viscosity thickened solutions or suspensions. Until the recent development of precise dosing device, there was not much interest in this system. The advantages of a nasal gel includes the reduction of post-nasal drip due to high viscosity, reduction of taste impact due to reduced swallowing, reduction of anterior leakage of the formulation, reduction of irritation by using soothing/emollient excipients and target to mucosa for better absorption.

4.10 Nasal Powder:

This dosage form may be developed if solution and suspension dosage forms cannot be developed e.g., due to lack of drug stability. The advantages to the nasal powder dosage form are the absence of preservative and superior stability of the formulation. However, the suitability of the powder formulation is dependent on the solubility, particles size, aerodynamic properties and nasal irritancy of the active drug and /or excipients. Local application of drug is another advantage of this system

5. BARRIERS TO NASAL DRUG DELIVERY:

Intranasal drug delivery is considered as a lucrative route of drug delivery system for formulation scientist because of its easy and simple formulation strategies. A large number of factors influenced therapeutic efficacy as well as toxicity of nasally administered drug product. A well designed pre-formulation program is essential for development of nasal dosage forms to overcome various barriers associated with nasal drug delivery. Clinical trials of nasal dosage forms are a costly affair; hence, if formulation fails to satisfy the regulatory criteria in bio-studies, it is not only a great financial loss but also loss of time for the pharmaceutical company.

To avoid such unfavorable situations, various factors such as safety, efficacy, bioavailability, toxicity, and stability of dosage forms need to be established during formulation development.

5.1 Physiological barriers

Nasal mucus

Airway mucus is composed of primarily water (95%), mucus glycoprotein (2%), other proteins including albumin, immunoglobulin, and lysozyme (1%), inorganic salts and lipids. Mucus glycoprotein, well known as mucin is the major component of the mucus. This compound is primarily responsible for the viscoelastic properties of mucus. The visco-elastic properties also depend on the percentage content of mucin, water, and other ions. The pH of the nasal secretion also determines the viscoelastic properties of mucus. It is important to consider the interaction between the drug and mucus.

Nasal epithelium

The nasal membrane can be classified into olfactory and nonolfactory epithelia. The olfactory epithelium is pseudostratified columnar in type, and consists of specialized olfactory cells, supporting cells, and both serous and mucous glands, whereas the nonolfactory epithelium is a highly vascular tissue covered by a ciliated pseudostratified columnar epithelium. The olfactory cells contain bipolar neurons and act as peripheral receptors and first-order ganglion cells.

Mucociliary clearance

Nasal mucociliary clearance is the most important physiological barrier, which reduces the nasal residential time of drugs and/or dosage forms. Bioavailability of nasal dosage form depends on the residential time of the drug in the nasal cavity. The nasal mucociliary clearance system transports the mucus layer that covers the nasal epithelium towards the nasopharynx by ciliary beating. In true sense, mucociliary clearance is one of the defense mechanism of the respiratory tract to protect the body against any noxious material that is inhaled. Ciliated mucous cells present in the nasal mucosal membrane are responsible for mucociliary clearance. Nasal clearance proceeds at an average rate of 5-6 mm/min.

Nasal pathophysiology

The influence of physiology of abnormal nose on bioavailability of nasal drug products has not been studied in sufficient details. The most frequent and common disease associated with nose is rhinitis, hence pathology of rhinitis and its influence in drug bioavailability is briefly discussed in this section. Rhinitis is classified as allergic rhinitis and common cold. Allergic rhinitis is the allergic airway disease, which affects 10% of population. Numerous allergens are constantly present in our environment, and any one of them can cause allergic rhinitis. In this condition, air borne allergic particles including pollens, molds, animal allergens are deposited on the nasal mucosa. Allergic rhinitis, is also known as hay fever, may be acute, seasonal or chronic and perennial. Allergic rhinitis is characterized by hypersecretion, itching, and sneezing. Histamine is the most important allergic mediator, causing the symptoms associated with allergic rhinitis.

Histamine, which is released on the mucosal surface, has shown more allergic reactions than injected into nasal mucosa.

Nasal metabolism

Although nasal secretions consist of enzymes, they do not have a significant effect on the extent of absorption of most of compounds except protein and peptide molecules. The low metabolic environment offers nasal drug delivery as a lucrative route for both conventional and protein molecules. Nasal bioavailability of a significant number of drugs such as progesterone, testosterone, estradiol, naloxane, propranolol, and butorphanol is almost 100%, whereas the oral bioavailability of the above mentioned drugs is almost nil except propranolol, which has oral bioavailability ranging from 20 to 30%. Presystemic metabolism is the major rate limiting step in the bioavailability of oral drug product; which is particularly true for highly lipophilic compounds. The nasal administration of these compounds resulted in complete absorption because of a) the rate of absorption was very fast, hence enzymatic exposure time is very short and b) the level of enzymes in nasal cavity is very low and can be easily saturated with drugs.

P glycoprotein efflux transport

Drug absorption may be hindered by efflux transporters such as P-glycoproteins (Pgps). Basically, Pgps are a group of glycosylated membrane proteins found in the epithelial cells of small intestine and other body tissues. Multi drug resistance (MDR) genes present in the humans, coding for Pgps has been found in the human nasal respiratory mucosa. A large variety of hydrophilic and amphiphilic compounds are detoxified through active Pgp mediated efflux transport in nasal mucosa. Topical administration of steroids in nasal cavity may increase the expression of Pgps in the respiratory epithelium and hence affect the bioavailability of nasal dosage forms. Pgps have certain role in reducing CNS permeability of nasally administered drugs in olfactory epithelium. The maximum drug uptake and high CSF drug concentration was achieved with formulation incorporated with Pgp efflux inhibitors such as rifampin. The low level of chlorpheniramine and chlorcyclizine in CSF was most likely due to the presence of efflux transport system in olfactory epithelium.

5.2 Formulation barriers

Drug concentration, dose, and dose volume

Nasal absorption was shown to increase with certain drug substances, particularly, where concentration gradient plays an important role in drug absorption. Ex vivo experiments in rats demonstrated the effect of drug concentration on nasal absorption. Nasal absorption of l-tyrosyl - L- tyrosine was found to increase with increasing concentration of the drug. However, few experiments showed different effects of drug concentration on the absorption of drugs, for example, the absorption of aminopyrine from rat nasal mucosa was constant as a function of its concentration. Interestingly, nasal absorption of salicylic acid was decreased with increasing concentration of administered drug. Low absorption of high concentration of salicylic acid was lined with its nasal epithelial toxicity and nasal membrane resistance. The effect of three different concentrations of cetirizine on clinical efficacy was studied in patients. The clinical

efficacy was improved with drug concentration up to only 0.125%. Moreover, the clinical efficacy has been declined in the higher drug concentration of 0.250%. From the above studies one cannot judge the effect of drug concentration on absorption and bioavailability. However, the absorption of drug and its concentration cannot be correlated with the mechanism of drug absorption from the nasal mucosa. If the drug undergoes passive diffusion, it should obey linear relationship between drug concentration and absorption.

Osmolarity of dosage form

The effect of formulation osmolarity on nasal absorption was studied using secretin as a model drug in rats. The results indicated profound influence of osmolarity on nasal drug absorption. The nasal drug absorption has been affected by the sodium chloride concentration in the formulation. Maximum drug absorption was observed with 0.462 M sodium chloride concentration. High concentration of sodium chloride not only leads to higher bioavailability but also toxicity to nasal epithelial cells. The maintenance of isotonicity of the formulation will reduce the nasal epithelial cell damage and hence it will reduce the toxicity of the nasal formulation.

Deposition site of dosage form

The site of deposition of nasal formulation in nasal cavity is an important factor for absorption and bioavailability of nasal dosage forms. In general, deposition of formulation in anterior portion of the nose provides a prolonged nasal residential time and better absorption. The dosage form deposited in posterior chamber of nasal cavity will be eliminated by nasal mucociliary clearance and hence show low bioavailability. The site of deposition and deposition pattern of liquid dosage form is dependent on the delivery device, mode of administration, physicochemical properties of drug molecules. Nasal drops, traditionally used in formulations suffer from short nasal residential time. The correlation between dosage form deposition and bioavailability of and/or therapeutic efficacy is not very easy to establish. Large number of factors such as position of head, viscosity, delivery device, tonicity, and volume of the dosage form affects the absorption and bioavailability of nasal drops. Powder nasal dosage forms are rarely used in clinical applications.

6. STRATEGIES TO IMPROVE BIOAVAILABILITY:

A wide number of formulation strategies are made available to improve the bioavailability of nasal dosage forms. The basic underlying mechanisms for bioavailability enhancement are as follows (i) incorporating nasal permeation enhancers to improve the absorption, (ii) usage of enzyme inhibitors to eliminate nasal metabolism, (iii) formulation of mucoadhesive dosage forms to improve the nasal residential time, and (iv) prodrug approach for optimizing favorable physicochemical properties. Any one of the approach or combination of two or more strategies is widely used to improve the bioavailability of nasal formulations. While developing novel nasal dosage form with enhanced bioavailability, range of factors such as dose, dosing frequency, duration of therapy, short term and long term toxicity of drugs and excipients, therapeutic indication, cost and type of patients to be treated should be considered to achieve both safety as well as efficacy of nasal formulations.

Enzyme inhibitors

A number of studies have described the role of enzyme inhibitors on bioavailability of nasal formulations. Particularly, enzyme inhibitors are essential components of formulation, while developing a dosage form for protein and peptide molecules. Mostly peptidase and protease inhibitors are widely used to improve the bioavailability of protein and peptide molecules. Enzymatic activity can also be reduced by addition of enzyme inhibitors such as bestatin, amastatin, boroleucin, borovaline, aprotinin, and trypsin inhibitors. The absorption enhancers such as bile salts and fusidic acid derivatives exert enzyme inhibition and hence enhance the absorption and bioavailability. The analgesic activity of leucine enkephalin and its analogue was investigated with and without enzyme inhibition.

Nasal permeation enhancers

Permeation enhancers have been employed for improving the absorption of poorly absorbed and large molecular weight compounds. Complete mechanism of drug absorption enhancement through nasal mucosa is not known. However, various mechanisms such as increase in the membrane fluidity, creating transient hydrophilic pores, decreasing the viscosity of mucous layer and opening up of tight junctions are the proposed mechanisms of permeation enhancers, which improve the bioavailability of nasal dosage forms. The ideal characteristics of nasal permeation enhancers are as follows:

- It should be pharmacologically inert.
- It should be non-allergic, non-toxic, and non-irritating.
- It should be highly potent.
- It should be compatible with a wide variety of drugs and excipients.
- It should be odorless, tasteless, and colorless.
- It should be inexpensive and readily available in highest purity.
- It should be accepted by many regulatory agencies all around the world.

Cyclodextrins act as a solublizer and permeation enhancer for nasal drug delivery and they are well tolerated in humans. Amongst cyclodextrins, beta cyclodextrin is being considered to have a Generally Recognized As Safe (GRAS) status. All other cyclodextrins are experimental material at this time. Schipper and coworkers studied the efficacy of beta cyclodextrin as permeation enhancer for nasal drug delivery of insulin. The nasal bioavailability of protein and peptide molecules such as insulin, calcitonin, human growth hormone, and octreotide using STDHF as permeation enhancer showed increase in the bioavailability and also showed the safety of the STDHF as a permeation enhancer. Phospholipids are surface active compounds, which are found in both animal cells as well as plant cells. Several researchers have explored the efficacy of these compounds as nasal permeation enhancer. Lysophosphatidylcholine (LPC) is the most extensively studied phospholipid as a nasal permeation enhancer

Prodrug approach:

Prodrug approaches, historically, have been used to improve the pharmaceutical properties such as solubility, taste, odor, stability, etc. In recent days, designing of prodrug is used to improve the

physicochemical properties such as solubility and compound lipophilicity to overcome the pharmacokinetic demerits associated with drug molecules. However, prodrug approach has also been used to reduce the presystemic metabolism and chemical decomposition. The basic principle associated with prodrug is to cover the undesired functional group(s) with another functional group, which usually are referred as promoity. Designing prodrug for improving the nasal bioavailability is one of the lucrative approaches especially for protein and peptide molecules. The ideal prodrug for bioavailability enhancement of proteins and peptides would exhibit enhanced membrane permeability along with increased enzymatic stability. After crossing both enzymatic and membrane barrier, the prodrug should undergo enzymatic transformation to release the parent molecule.

Designing of cyclic prodrug using C and N terminal ends reduced the metabolic degradation caused by exopeptidase. A recent study involved synthesis of cyclic hexapeptide to improve the enzymatic stability and permeability through biological membranes. It showed increased permeability of cyclic prodrug than parent molecule. Derivatization is another lucrative approach for synthesis of prodrug to improve bioavailability of drug molecules especially for peptide molecules. Derivatization could be possible in C terminal amide group, N terminal amide group and phenol group in various peptide molecules. The nasal absorption enhancement of L-Tyrosine was achieved by structural modification. It was observed that carboxylic ester derivatives have enhanced absorption than their parent molecule. The enamine derivatives were prepared to improve the absorption of peptide molecules such as angiotensin II, bradykinin, carulein, carnosine, enkephalin, vasopressin, and calcitonin. These agents showed absorption enhancement with prodrug approach. The research interest and applicability of prodrug concept is not only restricted to protein and peptide molecules but also extends to conventional molecules. Nasal absorption of non absorbable hydrophilic compound, acyclovir was achieved by synthesizing a series of aliphatic ester prodrugs.

7. NASAL MUCOADHESIVE DRUG DELIVERY SYSTEM:

Although nasal enzyme inhibition and incorporation of permeation enhancers are the two popular approaches, these approaches hinder the normal physiological process and hence are prone to cause toxicity of nasal mucosa. Designing bioadhesive drug delivery system is a novel approach in nasal drug delivery, which enhances the nasal residential time of the drug molecule and hence enhances the absorption and bioavailability of nasally administered drug products. Bioadhesion is the ability of synthetic or natural material to adhere to a biological tissue or membrane for a prolonged period of time. Bioadhesive drug delivery implies attachment of drug delivery system to a specific biological tissue, which increases the local residential time of the delivery system. If biological tissue is covered by mucus, the attachment of drug delivery system to the mucus is called as mucoadhesive drug delivery system. Mucoadhesive system is the ideal choice of drug delivery system for systemic nasal drug delivery because it improves the nasal residential time. Intimate contact of drug delivery system to the nasal mucosa not only prolongs the duration of action but also increases extent of absorption. Pharmaceutical excipient which improve the mucoadhesion are called as mucoadhesive materials. The mucoadhesive synthetic and natural polymers are called as first generation mucoadhesive material. Apart from these polymers, lecithin a new second generation promising mucoadhesive material is widely used in drug delivery systems.

Conclusion

The intranasal route is an accessible alternative to the intravenous route. By using any of the mechanisms proposed, this route holds future potential for numerous drugs through the development of safe and efficacious formulations which would be useful for a simple, painless and long-term therapy. In particular, the nasal drug delivery is a promising alternative to injectables route of administration. It is very likely that in the near future more drugs will come in the market intended for systemic absorption in the form of nasal formulation.

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