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A Review on Nasal Drug Delivery System and General Consideration

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ABSTRACT

Nasal drug delivery system offers 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 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

Keywords: Barrier, Nasal Delivery, Bioavailability

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INTRODUCTION

The 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 [2, 3]. 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[1,2]. 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 [1]. The interesting advantage of nasal drug delivery is the possibility of targeting central nervous system (CNS) by bypassing blood brain barrier (BBB) [4, 5].

Anatomy & Physiology of nose [1, 2, 3, 4]

The nasal cavity is 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 nasopharynx [1]. The nasal vestibule, the respiratory region and the olfactory region are the three main regions of the nasal cavity [2]. The lateral walls of the nasal cavity include a folded structure which enlarges the surface area in the nose to about 150cm [2.] 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 narrow's structure enables the nose to carry out its main functions [3]. During inspiration, the air comes into close contact with the nasal mucosa and particles such as dust and bacteria are trapped in the mucous [1]. 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 nonolfactory and olfactory epithelium areas. The non-olfactory area includes the nasal vestibule, which is lined with skin-like cells, and respiratory region, which has a typical airways epithelium[3,4].

The Respiratory region [3]

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 [3]. 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.

The olfactory region [3, 4]

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 [3, 4]. See Figure 1.

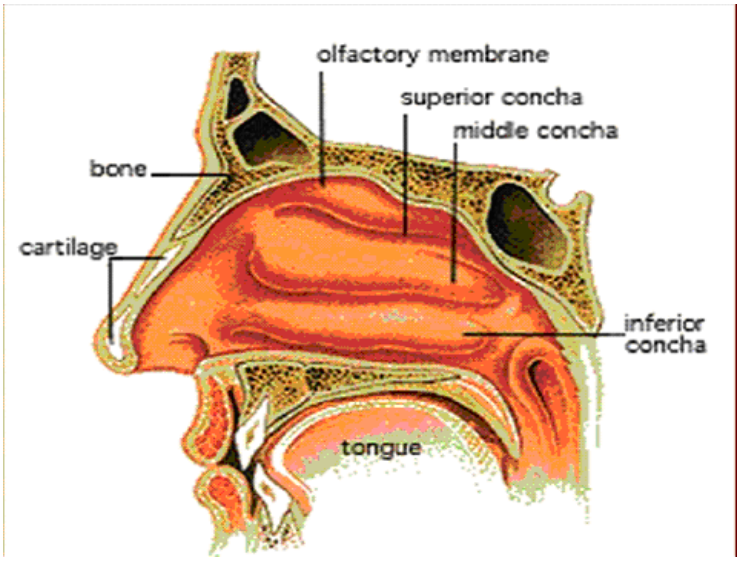

Figure 1: Anatomy and Physiology of Nose

Nasal drug absorption [4, 5, 7]

Several mechanisms have been proposed but the following two mechanism 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 [3, 4]. 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. The Drug also cross cell membranes by an active transport route via carrier-mediated means or transport through the opening of tight junctions [7]. For examples, chitosan, a natural biopolymer from shellfish, opens tight junctions between epithelial cells to facilitate drug transport [4].

Safety and efficacy of absorption enhancers [4, 5, 8]

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 [4].

Mucociliary transport rate [4, 5]

It is measured using a frog palate model to test potential toxicity of absorption enhancers L-α-lysophosphatidylcholine, sodium deoxycholate and taurocholate, laureth-s and sodium taurodihydrofusidate irreversibly halted the mucus transport rate [4, 5].

Nasal Morphology [1, 3, 4]

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 [1, 3, 4].

Ciliary Beat Frequency [3, 4]

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) [3, 4].

Delivery Systems [4, 5, 6]

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

Nasal Drops [3, 6]

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 [3, 6].

Nasal sprays [4, 7]

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, 7].

Nasal Gels [7, 8]

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 include 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 [7, 8].

Nasal Powder [3, 6, 8]

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.

Nasal permeation enhancers [6, 7, 8]

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[7]. 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[1, 5, 6]. The ideal characteristics of nasal permeation enhancers are as follows:

a. It should be pharmacologically inert.

b. It should be non-allergic, non-toxic, and non-irritating.

c. It should be highly potent.

d. It should be compatible with a wide variety of drugs and excipients.

e. It should be odorless, tasteless, and colorless.

f. It should be inexpensive and readily available in highest purity.

g. 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 [7]. 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 co workers 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 [6, 7]. Several researchers have explored the efficacy of these compounds as nasal permeation enhancer. Lyso phosphatidyl choline (LPC) is the most extensively studied phospholipid as a nasal permeation enhancer [8].

Nasal muco-adhesive drug delivery system [6, 8]

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 [3, 4]. Designing bio adhesive 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 [6]. The bio adhesion is the ability of synthetic or natural material to adhere to a biological tissue or membrane for a prolonged period of time. bio adhesive drug delivery implies attachment of drug delivery system to a specific biological tissue, which increases the local residential time of the delivery system [8]. If biological tissue is covered by mucus, the attachment of drug delivery system to the mucus is called as mucoadhesive drug delivery system [5]. 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 excipients which improve the mucoadhesion are called as mucoadhesive materials [3, 4, 8].

CONCLUSION

The intranasal route is an alternative to the intravenous route. The 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 injectable 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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