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An Overview on Intranasal Drug Delivery System: Recent Technique and Its Contribution in Therapeutic Management

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ABSTRACT

Nasal drug administration has been used as an important another route for the systemic availability of drugs. Intranasal route has large surface area, high total blood flow, avoidance of first-pass metabolism, porous endothelial membrane, and ready accessibility. For nasal route administration various drugs including peptide and protein drugs, for systemic medication has been widely used in recent few years. This review article highlights the importance, strategies and advantages of the nasal drug delivery systems. Various methods are discussed here for increasing the residence time of drug formulations in the nasal cavity, for improving nasal drug absorption. In this review article we discuss the effects of bioadhesive drug delivery systems on nasal drug administration. Drug delivery systems (such as nanoemulsion, microspheres, liposome and gels) have good bioadhesive characteristics which swell easily when in contact with the nasal mucosa. These types of drug delivery systems protect the drug from enzymatic degradation in nasal secretions and also control the rate of drug clearance from the nasal cavity.

Keywords: Protein, Peptides, Intranasal drug delivery, Permeation enhancer, Bioavailability

1. INTRODUCTION

The primary function of the nose by the olfaction, it heats and humidifies inspired air and also filters airborne particulates.⁹ Therefore, the nose functions as a protective system against foreign material.⁸ The nose has a large surface area available for the drug absorption.³ Low concentration of dose, more rapid absorption of drug results in faster onset of pharmacological action.^{1,2} The sub epithelial layer of nose is highly vascularized the venous blood from the nose passes directly into the systemic circulation and therefore avoids the loss of drug by the first pass metabolism in the liver. Nasal route also prevent the enzymatic or acidic degradation of drug.^{4,5} conventionally, nasal route was selected for the delivery of drugs or the treatment of local diseases such as nasal congestion, nasal allergy and nasal infections. But recently, nasal drug delivery has been exploited for the systemic delivery of low molecular weight polar drugs, peptides and proteins which are not easily administered by any other routes except injection or when there is a need for rapid action. Nasal therapy and nasal route has received attention since ancient times in the ayurvedic system of Indian medicine and remains potential route till date.⁶ Ailments of central nervous system such as schizophrenia, meningitis Alzheimer's disease, migraine and Parkinson's disease require the delivery of therapeutic amount of drug directly to the brain. And this is only possible when the drug is administered through the nasal route bypassing the blood brain barrier and first pass metabolism. This vast interest in intranasal route for therapeutic purpose is due to anatomical, physiological and histological characteristics of the nasal cavity which provides rapid systemic drug absorption and onset of action.⁷

1.1 Advantages of intranasal drug delivery ^{10, 11, 12}

- Intranasal design allows direct drug delivery to the brain.
- It is a painless strategy.
- It does not need use of sterile technique, intravenous catheters or any invasive equipment.
- This strategy is readily and immediately available.
- It also bypasses the first pass effect, thus enhance the bioavailability of those drugs which are susceptible to intestinal and first pass metabolism. In this way it allows drug to be cost effective.
- Nasal mucosa is close to brain so the brain drug level can exceed plasma drug level.
- Intranasal route is helpful to obtain rapid therapeutic brain concentration.
- Nasal mucosa has more surface area and has rich blood supply as a result shows rapid absorption.
- There is less metabolic activity in nose thus has capability to circumvent the limitation of oral route.
- Intranasal drug delivery system shows excellent bioavailability for low molecular weight drugs.

1.2 Limitations of intranasal drug delivery ¹¹

- Administration volume in a nasal cavity is moderate to 25–1000 µl.
- High molecular weight compounds cannot be administrated by this route (mass cut off ~1 kDa).
- The major problem associated with intranasal drug delivery is the mucociliary clearance, which reduces the residence time of administered drugs.
- Nasal congestion due to different factors such as cold and allergies interferes with the delivery of drugs.
- Once the drug is administered through this route, removal or withdrawal is impossible.
- There is a chance of nasal irritation with many therapeutic agents.

- Regular use of intranasal route for the drug delivery may result in the mucosal damage.
- Volume that can be administered to nasal cavity is restricted to 25-200 µl.
- Limited understanding of mechanism and less developed models at this stage.
- May cause systemic toxicity due to the presence of absorption enhancers
- Smaller absorption surface compared to GIT.

2. FACTORS INFLUENCING NASAL DRUG ABSORPTION ^{8, 13}

There are several factors affect the systemic bioavailability of drugs which are administered through the nasal route. The factors can be affecting by the physiochemical properties of the drugs, the anatomical and physiological properties of the nasal cavity and the type and characteristics of selected nasal drugs delivery system. These factors play important role for the most of drugs in order to reach therapeutically effective blood levels after nasal administration. Various factors influencing the nasal drug absorption are described as follows.

2.1 Biological Factors

2.1.1 Structural features

Nasal cavity has five different sections like nasal vestibule, atrium, respiratory area, olfactory region and the nasopharynx. These structures and the number of cells present in that region increase the permeability. Various types of absorption enhancers used with drugs for increasing the permeation of compounds. ¹⁴

2.2 Biochemical changes

Nasal mucosa has a different enzymatic barrier for the delivery of drugs because the presence of the large number of enzymes, which include oxidative and conjugative enzymes, proteases and peptidases. These nasal mucosa enzymes are responsible for the degradation of drugs in the nasal mucosa and formation of a pseudo-first-pass effect. ¹⁵ Alcohols, nicotine and cocaine is metabolized due to p-450 dependent mono-oxygenase system. A pre-systemic degradation by the protease and peptidase cause lower permeation of various peptide drugs, such as calcitonin, insulin, LHRH and desmopressin. ¹⁶

2.3 Physiological Factors

2.3.1 Blood supply and neuronal regulation

Nasal mucosa has a high permeability. High blood supply due to parasympathetic stimulation gives a high blood supply causes a congestion and sympathetic stimulation caused a low blood supply and gives a relaxation, drug permeation regulate by the rise and fall in the blood supply, respectively.¹⁷ Based on the above observations drug permeability increased due to parasympathetic stimulation.

2.3.2 Nasal secretions

Anterior serous and seromucus glands produced nasal secretions. About 1.5–2 ml mucous produced daily. The permeability of drug through the nasal mucosa is affected by the:

2.3.3 Viscosity of nasal secretion

If the mucosa sol layer is too thin inhibit the viscous surface layer and mucociliary clearance is impaired if the sol layer is too thick, is due to because contact with cilia is lost. Drug permeation is affected due to impairment of mucociliary clearance.

2.3.4 Solubility of drug in nasal secretions

For the drug permeation solubilisation is necessary factor. An appropriate physicochemical characteristic of a drugis need for dissolution in the nasal secretions.

2.3.5 pH of nasal cavity

Adults and infants pH are different (adults 5.5–6.5, infants 5.0–7.0). In lower nasal pH drug permeation is greater than pKa of drug because under such conditions molecules exist as unionized formed. pH of drug formulation should be in between 4.5 to 6.5 for better absorption and should also have good buffering capacity.¹⁸

2.3.6 Mucociliary clearance (MCC) and ciliary beating

Drug particles entrapped in the mucus layer are transported and effectively cleared from the nasal cavity. The combined action of cilia and mucus layer is called a mucociliary clearance. A non-specific physiological defense mechanism of the respiratory tract to protect the body against noxious inhaled materials.¹⁹ In human normal mucociliary transit time has been reported to be 12 to 15 min.²⁰ There are the various factors that affect

mucociliary clearance include physiological factors (age, posture, sex, sleep,²¹ exercise),¹¹ common environmental pollutants (sulphur dioxide, nitrogen dioxide, sulphuric acid, ozone, hair spray and tobacco smoke),²² diseases (immotile cilia syndrome, asthma, bronchiectasis, primary ciliary dyskinesia-Kartagener's syndrome, cystic fibrosis, acute respiratory tract infection)²² and additives and various drugs.²³

2.3.7 Pathological conditions

Hypo or hyper secretions, mucociliary dysfunctioning and irritation of the nasal mucosa occur due to diseases such as the common cold, rhinitis and nasal polyposis, and permeation of drug is affected by this.

2.3.8 Membrane permeability

Drug absorption in the nasal route is affected by the membrane permeability is the most important factor for drug absorption process. A high molecular weight drug and water soluble drugs like peptides and proteins have the low membrane permeability hence it's absorbed through an endocytic transport in fewer amounts.²⁴

3. PHYSICOCHEMICAL PROPERTIES OF DRUG

3.1 Molecular weight and size

Permeation a drug is determined by molecular size, molecular weight, hydrophilicity and lipophilicity of the compound. Physicochemical properties of the drug don't significantly changes in the permeation of drug which will mostly permeate by the aqueous phase of the membrane. Permeation of a high molecular weight compounds is highly sensitive.

3.2 Solubility

Drug solubility is a major factor for drug absorption through a biological membrane. Those drug have an appropriate aqueous solubility increased the dissolution because nasal secretions is a more watery in nature. In aqueous secretion lipophilic drugs have less solubility. Water soluble drugs are absorbed by the passive diffusion and a lipophilic drug absorbed via active transport is depending on their solubility.²⁵

3.3 Lipophilicity

Drugs have more lipophilic in the nature is more permeated through the nasal mucosa. It shows that nasal mucosa is lipophilic in nature and the lipid domain plays

an important role in the barrier function of these membranes although they have some hydrophilic characteristics. Hydrophilic nature of many drug decrease the systemic bioavailability in such cases pro-drug approach is utilized.

3.4 pKa and partition coefficient

In nasal absorption a unionized species are better absorbed compared a ionized species as per pH partition theory. There is constant relationship in between pKa and nasal absorption of these drugs. Increase the lipophilicity or the partition coefficient of the drugs is increased the concentration in biological tissues.¹³

3.5 Polymorphism

For nasal drug product Polymorphism is the important parameter in this nasal drug is administered in particulate form. Dissolution of the drugs and their absorption through biological membranes is affected by polymorphism. Polymorphism is considered as an important factor for nasal drug delivery formulation.²⁴

3.6 Physical state of drug

Particle size and physical property of drug are two main important properties for nasal drug products. These both parameters should be controlled to obtain suitable drug dissolution in the nostrils. Very fine particles below in the range of 5 microns should be avoided because it may beget inhaled in lungs. Generally, particles in the between 5–10 micron range are deposited in the nostrils.²⁴

4. PHYSICOCHEMICAL PROPERTIES OF FORMULATION

4.1 Physical form of formulation

For nasal drug absorption physical form is very important. Basically liquid formulations are less effective than powder form in delivering the insulin in rabbits. More viscous drug formulation is less effective on the systemic circulation. And more sustained effects are observed of viscous agent but its total bioavailability is not increased.

4.2 pH

The pH Nasal formulation is important an appropriate pH avoid the mucosal irritation. pH also effect the drug absorption and prevent growth of pathogenic bacteria. For

ideal formulation pH should be adjusted in between 4.5 and 6.5. The pH of the nasal surface is 7.39 and nasal secretion is 5.5–6.5 in adults and 5.0–6.7 in infants and children.

4.3 Viscosity

For increasing the time of permeation a contact time between of the drug and the nasal mucosa is increased by higher viscosity of formulation.

5. STRATEGIES TO IMPROVE NASAL ABSORPTION²⁶

There are various methods which have been successfully used for the improvement of nasal drug absorption because in nasal cavity many barriers are present which interfere the drug absorption.

5.1 Nasal enzymes inhibitors

In nasal cavity various types of enzyme inhibitors are present. Enzyme inhibitor minimizes the metabolism of protein and peptide drug formulation.

5.2 Structural modification

Drug structure modifications are used for improvement of nasal absorption without changing the pharmacological activity.

5.3 Permeation enhancer

Various types of nasal permeation enhancers are used for improving the nasal absorption likesurfactants, fatty acids, phospholipids, cyclodextrins, bile salts, etc.

5.4 Particulate drug delivery

For improving the nasal retention time various type of carriers are used is encapsulation of drug which prevent exposure of a drug to nasal environment. There are the some examples of carriers may include microspheres, liposome, noisome, nanoemulsion and nanoparticles.

5.5 Pro-drug approach

Inactive chemical moiety is called pro-drug which active at the target site. Pro-drugs are mainly used as for improved the taste, odor, solubility and stability of drugs.

5.6 Bioadhesive polymer

Bioadhesive polymer is used to improve the nasal residence time and absorption of the drug. These bioadhesive polymers improve the retention time of the drug inside in the nasal cavity and minimization of mucociliary clearance of formulation.

6. EXCIPIENTS USED IN NASAL FORMULATIONS ¹³

There are various types of excipients used in nasal formulations. Commonly used excipients are as follows:

6.1 Bioadhesive polymers

Some materials have a capability to interact with a biological material by the interfacial forces and being retained for prolonged period of time these types of polymer called bioadhesive polymer. If biological material is attached with mucus membrane is called a mucoadhesive. Mucoadhesion process can be explained on the basis of attractive molecular interactions forces such as Van Der Waals, hydrogen bonding, electrostatic interactions and hydrophobic interactions. The polymer bioadhesive force on material is dependent on the nature of the polymer, the surrounding medium (pH), swelling and physiological factors (mucin turnover, disease state).

6.2 Penetration enhancer

For nasal drug delivery various chemical penetration enhancers are widely used. Classification of penetration enhancer includes following; Solvents, Alkyl methyl sulphoxides, Pyrrolidones, 1-Dodecyl azacycloheptan-2-one, Surfactants.

6.3 Buffers

Nasal formulations are mostly administered in the small volumes ranging from 25 to 200 µl. Nasal secretions may change the pH of the administrated dose which can be affecting the concentration of unionized drug available for the absorption.

6.4 Preservatives

Nasal formulation mostly is aqueous based so there is more chance of microbial growth. For prevent the microbial growth various preservatives are used. Benzalkonium chloride, parabens, phenyl ethyl alcohol, EDTA and benzoyl alcohol are some of the commonly used preservatives in nasal formulations.

7. FORMULATIONS BASED ON NASAL DELIVERY SYSTEM ^{27,28}

7.1 Nasal drops

Nasal drops are one of the most easiest and convenient delivery systems among all of the formulations. The main disadvantage of liquid dosage form is the lack of dose precision.

7.2 Nasal sprays

Nasal sprays contain both solution and suspension formulations. Nasal sprays deliver the exact dose (25-200 µl) by the availability of metered dose pumps and actuators.

7.3 Semi-solid dosage forms

Various semi-solid forms, like gels, ointments and liquid systems containing polymers. These semi-solid dose formulations particularly designing for the nasal drug delivery systems. Nasal gels are present in the high viscous forms. Nasal gel formulation reduced the post-nasal dripping due to its high viscosity and reduction of anterior leakage of the formulation.

7.4 Novel drug formulations

Nasal formulations containing various drug delivery systems like, liposomes, nanoemulsions, microspheres and nanoparticles. These drug delivery systems containing, nasal absorption enhancers, enzymatic inhibitors and mucoadhesive polymers is used to improve the stability of formulation, membrane penetration and retention time in nasal cavity. ^{27, 28, 29}

7.5 Liposomes

Liposomes are phospholipids vesicles enclosed by lipid bilayers and enclosing one or more aqueous compartments where active substance and excipients is included. Liposomal drug delivery systems have various advantages. They effectively encapsulation of small and large molecules with have a wide range of pKa values and hydrophilicity. Liposome drug delivery system is enhanced the nasal absorption of peptides such as calcitonin and insulin.

7.6 Microspheres

For nasal drug delivery system microsphere formulation has been widely used. Microspheres

formulation are usually based on mucoadhesive polymers (like chitosan, alginate). Moreover, microspheres formulation may also protect the drug from enzymatic degradation and prolonging its effect and sustain release of drug.

7.7 Nanoparticles

Nanoparticles are solid colloidal particles with diameters ranging in between 1-1000 nm. Nanoparticles are also used for the targeting drug to brain via olfactory route. Nanoparticles may have the several advantages due to their small size; because only the smallest nanoparticles penetrate through the mucosal membrane and it also cross the tight junction of brain.

8. CONCLUSION

The delivery of drug molecules across the nasal mucosa opens a new method for the both local and systemic delivery of medicaments. Nasal cavity has a large surface area. Nasal drug delivery is a promising alternative route of drug administration for local, systemic and central nervous system action. It has advantages in terms of reduces systemic absorption and hence side effects and avoiding first-pass metabolism. However, the intranasal route presents several limitations which must be overcome to develop a successful nasal medication. Physiological conditions, physicochemical properties of drug and formulation are most important factors that affect nasal absorption. In future, the extensive research is necessary to make this route of delivery more efficient and popular.

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