International Standard Serial Number (ISSN): 2249-6807

International Journal of Institutional Pharmacy and Life Sciences 6(3): May-June 2016

INTERNATIONAL JOURNAL OF INSTITUTIONAL PHARMACY AND LIFE SCIENCES

Pharmaceutical Sciences

Review Article……!!!

Received: 26-04-2016; Revised: 10-05-2016; Accepted: 11-05-2016

A REVIEW ON NASAL DRUG DELIVERY SYSTEM FOR BRAIN TARGETING

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Keywords:

Olfactory Pathway, Blood Brain Barrier

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ABSTRACT

The Nasal administration of drug is the best option for local and systemic delivery of many therapeutic agents. Nasal route of administration is acceptable for those drugs which are unstable on oral administration because they are significantly degraded in G.I.T or metabolized by first pass effect in liver. The delivery of drugs to the brain has been fraught with low bioavailability of drugs in the brain. This is due to blood brain barrier and blood cerebrospinal fluid barrier which block therapeutics from going access to central nervous system. The olfactory pathway is beneficial for the delivery of drugs via nasal route. Nasal route is an alternative route parentral therapy and also useful for long term therapy. Nasal mucosa is highly vascularised and most permeable giving rapid absorption and onset of action. The nasal administration of drugs, including numerous compounds, peptides and protein drugs. Drugs are cleared rapidly from nasal cavity resulting in rapid systemic drug absorption. Therefore, approaches are discussed here for increasing the residence time of drug in nasal cavity resulting in improved nasal drug absorption. In this article, the importance of Nasal drug delivery system with respect to Bioadhesive properties and various aspects like factor affecting Nasal absorption, strategies to improve bioavailability are discussed.

INTRODUCTION

Earlier the Nasal route has been used for the delivery of drugs in the treatment of local diseases. Nasal therapy has been recognized form of treatment in the Ayurvedic system of Indian medicines [1]. The early 1980s saw the introduction of nasal route as a promising systemic delivery alternative to other conventional drug delivery routes [2]. The delivery of drugs to the brain has been fraught with issues of low bioavailability. The Central Nervous System which is made up of brain and the spinal cord do not have adequate access to the blood compartment due to a Blood Brain Barrier and others barriers. The lipophillic substances with molecular weight less than 600 Daltons are well known to permeate the BBB, which implies that the more lipophillic the molecules of drug the better is the permeability of the drug. The low metabolic environment of nose has potential to overcome the limitation of oral route and duplicate the benefit of intravenous administration. Nasal route has also been considered for the administration of vaccines. The interest in intranasal route for therapeutic purposes arises from the anatomical, physiological and histological characteristics of the nasal cavity, which provides rapid systemic drug absorption and quick onset of action. The main purpose for this type of study is to design a prolonged release dosage form to be used for targeted and controlled release of drug delivery.

ADVANTAGES OF NASAL DRUG DELIVERY SYSTEMS [3, 4,5]

- Absorption of drug is rapid via highly vascularised mucosa.
- Availability of large nasal mucosal surface area for dose absorption.
- Improved bioavailability.
- Side effects are reduced due to low dose.
- Offers lower risk of overdose.
- A self administration is possible.
- Does not have any complex formulation requirement.
- Patient convenience and compliance is improved.
- Onset of action is rapid.
- Non invasive and easy for administration.
- Bypass the BBB.
- Degradation of drug observed in GIT is reduced.
- Nasal bioavailability of small drug molecules is good.

VARIOUS TYPES OF FORMULATIONS FOR NASAL DELIVERY SYSTEM

1. **Liquid dosage form**

- Nasal drops

  Nasal drops are one of the most simple and convenient delivery systems among all formulations. The main disadvantage of this system is the lack of dose precision.

- 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 anywhere from 25 -200 μL.[6]
- Nasal emulsions, Micro emulsions

  Intranasal emulsions have not been studied as extensively as other liquid nasal delivery systems. Nasal emulsions offer the advantages for local application mainly due to the viscosity.

2. **Semi solid dosage form**

- Nasal gels

  Nasal gels are thickened solutions or suspensions, of high-viscosity. The advantages of a nasal gel include the reduction of post-nasal dripping due to its high viscosity, reduction of the taste impact due to reduced swallowing, reduction of anterior leakage of the formulation.[7]

3. **Solid dosage forms**

- Nasal powders

  Powder dosage forms may be developed if solution and suspension dosage forms cannot be developed, mainly due to lack of drug stability. The advantages of a nasal powder dosage form are the absence of preservative and superior stability of the drug in the formulation. 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.

- Microspheres

  Microsphere technology has been widely applied in designing formulations for nasal drug delivery. Microspheres are usually based on mucoadhesive polymers (chitosan, alginate), which present advantages for intranasal drug delivery.

- Nanoparticles

  Nanoparticles are solid colloidal particles with diameters raging from 1-1000 nm. They consist of macromolecular materials and can be therapeutically used as adjuvant in vaccines or as drug carriers, in which the active substance is dissolved, entrapped, encapsulated, adsorbed or chemically attached. Nanoparticles may offer several advantages due to their small size, but only the smallest nanoparticles penetrate the mucosal membrane by paracellular route and in a limited quantity because the tight junctions are in the order of 3.9-8.4 A.

LIMITATIONS

- Smaller absorption surface compared with G.I.T
- High molecular weight compounds cannot be delivered through this route.

IDEAL CHARACTERISTICS FOR NASAL DRUG DELIVERY

An ideal nasal drug candidate should possess the Appropriate aqueous solubility to provide the desired dose in a 25–150 ml volume of formulation administration per nostril [8].

- Appropriate nasal absorption properties.
- No nasal irritation from the drug.
- A suitable clinical rationale for nasal dosage forms e.g. rapid onset of action. Low dose generally, below 25 mg per dose.
- Suitable stability characteristics.
- No toxic nasal metabolites.

PHYSIOLOGY OF NOSE

In humans and other animal species the major functions of the nasal cavity are breathing and olfaction. However, it also affords an important protective activity once it filters, heat and humidify the inhaled air before reaching the lowest airways. Nasal cavity is lined with mucus layer and hairs which are involved in those functions like trapping inhaled particles and pathogens. Moreover, resonance of produced sounds, mucociliary clearance MCC, immunological activities and metabolism of endogenous substances are also essential functions of nasal structures. Thus, anatomically human nasal cavity fills the space between the base of the skull and the roof of the mouth. Above mouth, it is supported by the ethamoid bones and laterally by the ethamoid, maxillary and inferior conchae bones. The human nasal cavity has a

total volume of 15-20 mL and a total surface area of approximately 150cm2 [9]. It is divided by middle (or nasal) septum into two symmetrical halves, each one opening at the face through nostrils and extending posterior to the nasopharynx. Both symmetrical halves consist of four areas (nasal vestibule, atrium, respiratory region and olfactory region) that are distinguished according to their anatomic and histological characteristics. Some drugs shows adverse effects when they administered through nasal route. Ex: cocaine, Atropine, Anti histamines, Propronolol and Bile salts. During common cold or any pathological condition there is decrease in the therapeutic efficacy of many drugs due to dysfunction of mucociliary action which is necessary for nasal clearance. Several factors should be considered to optimize the nasal drug delivery of drugs and these methods are method of technique of administration, site of deposition, rate of clearance and minimization of pathological conditions. Absorption promoters have been used to achieve a better systemic bioavailability.[10]

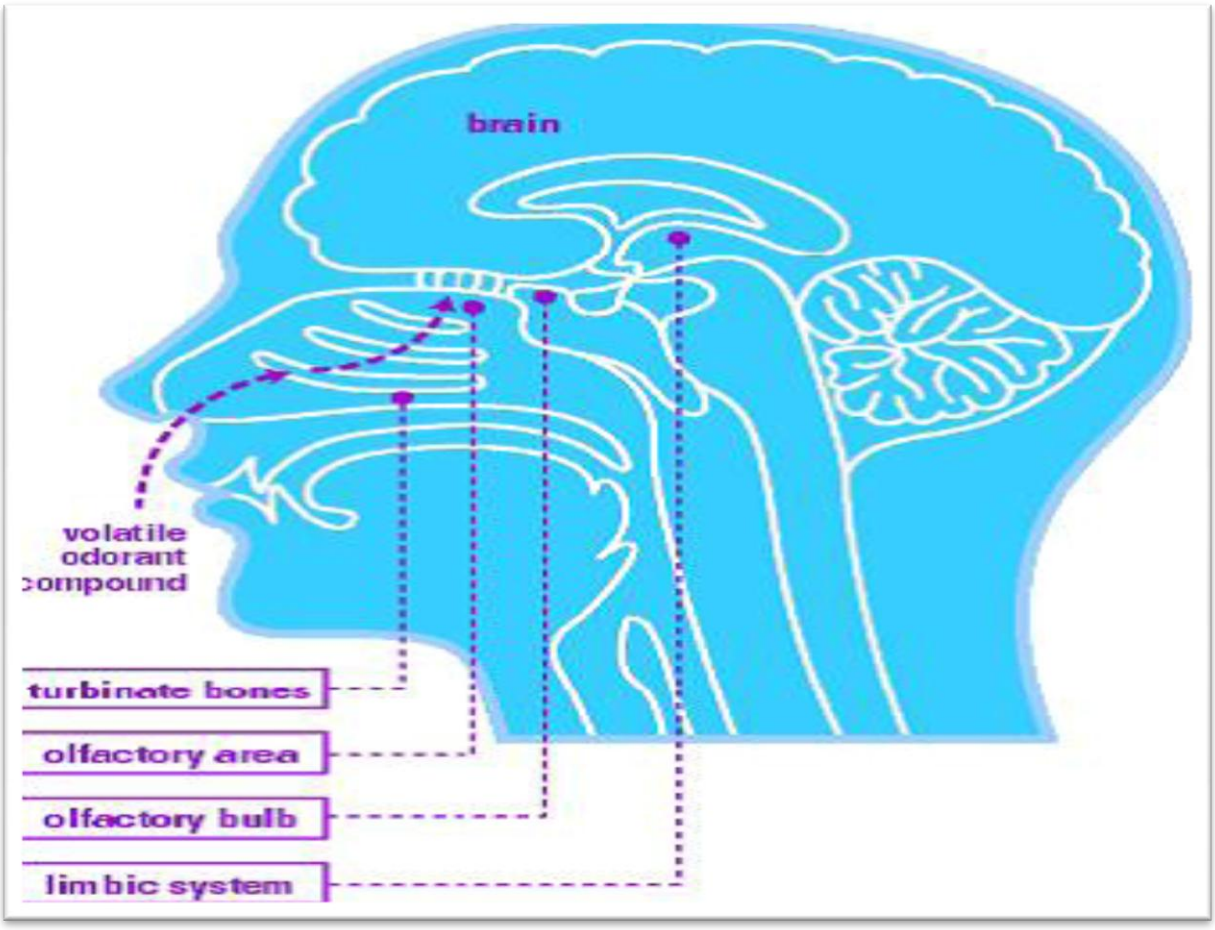

Figure 1. Nasal route

ROUTE FOR ABSORPTION OF DRUG FROM NASAL CAVITY

In the absorption of drug from the nasal cavity first step is passage through the mucus, large/charged particles may find it more difficult to cross. But small unchanged particles easily pass through this layer. Mechanisms for absorption through the nasal mucosa include paracellular transport via movement between cell and transcellular or simple diffusion across the membrane.

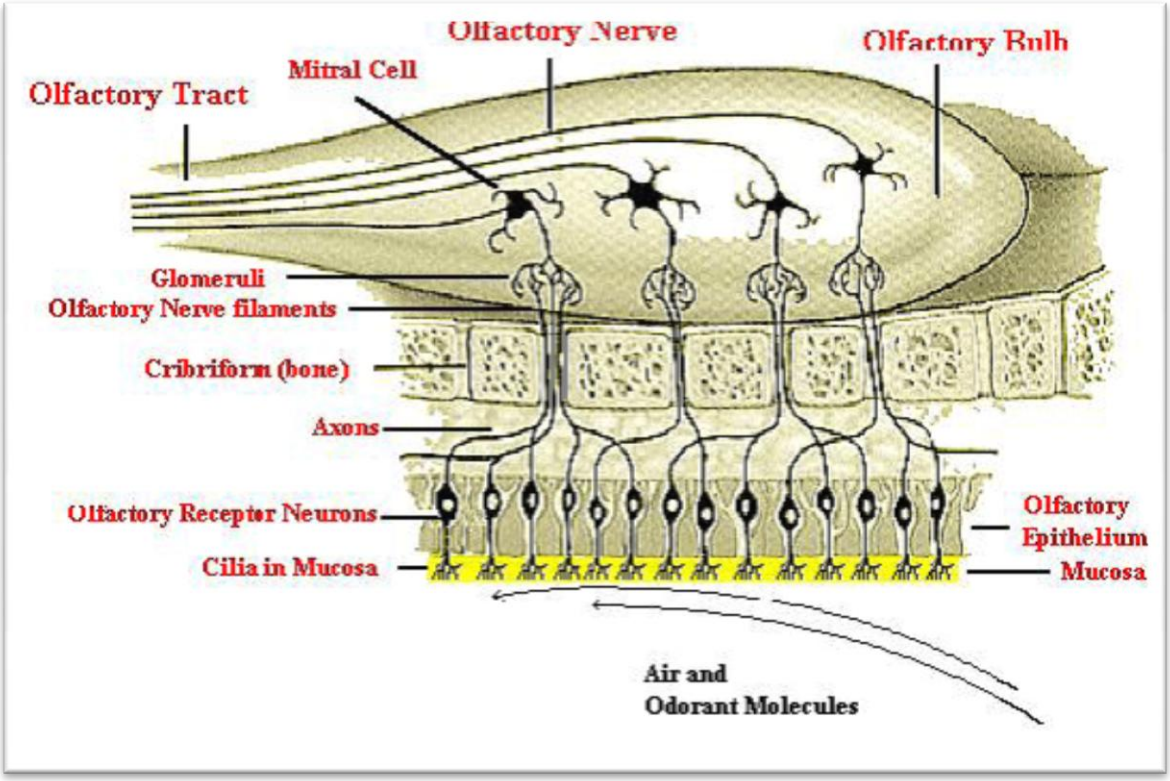

Figure 2. Structure of Nasal mucosa

1. The first mechanism includes aqueous route of transport, which is also called as the paracellular route. This is slow and passive route. Poor bioavailability was observed for drugs with a molecular weight greater than 1000 Daltons, because inverse relationship exists between molecular weight and absoption.[11]

2. Transcellular process is the second mechanism of transport through a lipoidal route and is responsible for the transport of lipophilic drugs that show a rate dependency on their lipophilicity. Drugs also cross cell membranes by an active transport route via carriermediated means or transport through the opening of tight junctions. For example, Chitosan, a natural biopolymer opens tight junctions between epithelial cells to facilitate drug transport.

MECHANISM OF ACTION THROUGH DIRECT NASAL MUCOSA TO BRAIN

The mechanism of direct nasal mucosa to brain drug delivery has not been firmly established but it has been evidenced by the work of various researchers that intranasal delivery of therapeutic agents is delivered to the brain along the olfactory and trigeminal pathway. For example administration of fluorescently labeled insulin into mice, the insulin migrated deep into the anterior area of the olfactory region moving across from the nasal mucosa epithelium to the cribriform plate to gain access to the olfactory bulb. Higher quantities of insulin were found in the olfactory nerve layer up to the glomerular layer. Various researchers have demonstrated that molecules can be transported from the nasal mucosa by widely dispersing these molecules throughout the olfactory region, carrying them across to the olfactory bulb and subsequently reaching the brain. Dhuria et al.,described the mechanism involved in the transporting drug molecules to the brain and CNS. They reported that drugs interact with the nasal mucosa comprising nasal epithelium and the drug molecules are distributed by both olfactory and trigeminal nerves where the nerve endings send chemosensory information to the brain. Drugs may be transported to the brain through perivascular spaces which is located in the lamina propria or through intracellular and extracellular pathways. On reaching the lamina propria, drugs may pass into the openings formed by ensheathing cells neighboring the olfactory nerves, and then penetrate the olfactory bulb including the CSF. From the CSF, drugs can diffuse and blend with interstitial fluid of the brain via bulk flow mechanisms. Drugs that pass through the perivascular channels may also exit through the same channels; this is an important process by which substances get eliminated from the CNS to the external environment. The mechanism may also involve the passage of the drug into the primary neurons found in the olfactory epithelium and then penetrate to the olfactory bulb via intracellular axonal transport. Axonal transport occurs when the drugs penetrate the neurons by endocytosis for onward movement to the CNS following circulation of the therapeutic into CNS. The following diagram indicates the possible transport pathway of drug into the nasal cavity.

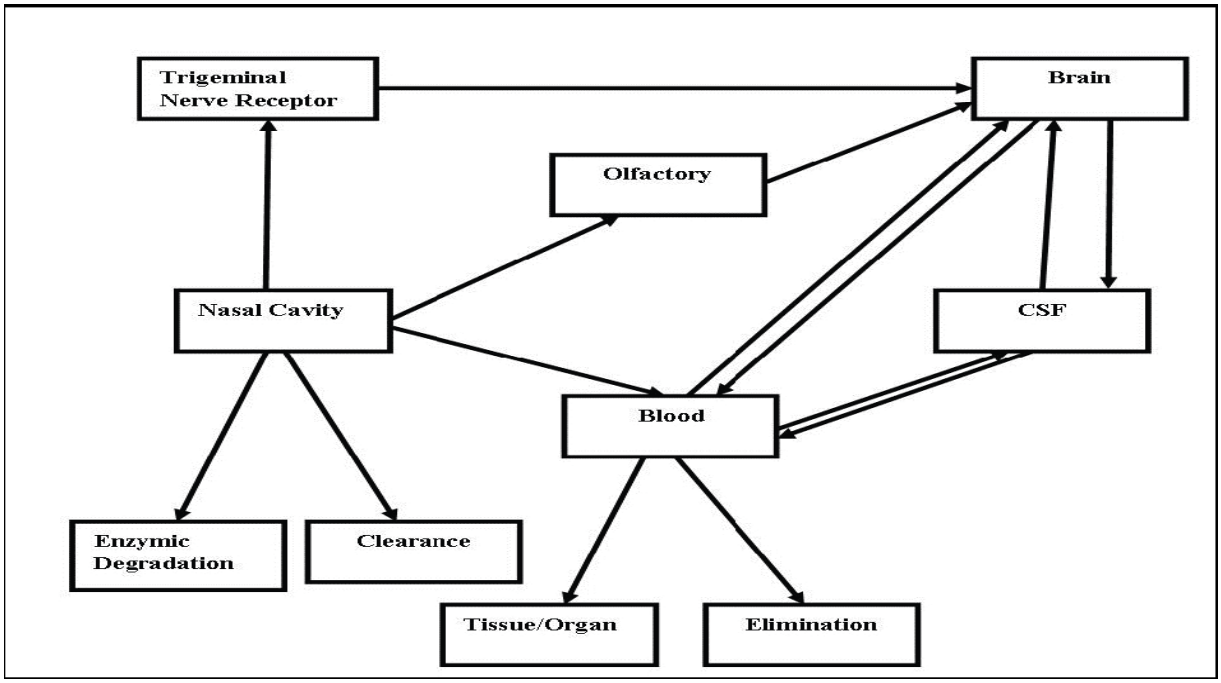

Figure 3. Transport pathways of a drug introduced into nasal cavity

FACTORS AFFECTING NASAL DRUG ABSORPTION

1. Biological Factors

- Structural features

  There are five different sections of nasal cavity: nasal vestibule, atrium, respiratory area, olfactory region and the nasopharnyx. These structures and the type of cells, density and number of cells present in that region influence the permeability. Absorption enhancers used in combination with drugs increase the permeation of compounds [12].

- Biochemical changes

  Enzymatic barrier to the of drugs is nasal mucosa because of the presence of a large number of enzymes, which include oxidative and conjugative enzymes, peptidases and proteases. These enzymes are responsible for the degradation of drugs in the nasal mucosa and result in creation of a pseudo-first-pass effect. Metabolism of nasal decongestants, alcohols, nicotine and cocaine IS due to p450 dependent monoxygenase system. Protease and peptidase were responsible for the presystemic presystemic degradation and subsequent lower permeation of various peptide drugs, such as calcitonin, insulin, LHRH and desmopressin.. To overcome these degradations various approaches have been used. These include the use of protease and peptidase inhibitors such as bacitracin, amastatin, boroleucin and puromycin.

2. Physiological Factors

- Blood supply and neuronal regulation

  Nasal mucosa is highly permeable site. High blood supply due to parasympathetic stimulation gives congestion and low blood supply due to sympathetic stimulation gives relaxation, regulate the rise and fall in the amounts of drug permeated, respectively [13]. Based on the above observations, we can conclude that the increased permeability of a compound is due to parasympathetic stimulation.

- Mucociliary clearance and ciliary beat frequency

  Whenever a substance is nasally administered, it is cleared from the nasal cavity in ~21 min by MCC because mucociliary clearance is the normal defense mechanism of the nasal cavity which clears substances adhering to nasal mucosa and cleared in GIT by draining into nasopharynx. Drug permeation is enhanced by increasing contact time between drug and mucus membrane because reduced MMC; whereas, increased MCC decreases drug permeation.

- Pathological conditions

  Mucociliary disfunctioning, hypo or hypersecretions, irritation of the nasal mucosa occurs due to diseases such as the common cold, rhinitis, atrophic rhinitis and nasal polyposis, and drug permeation is affected by this.

- Environmental conditions

  Moderate reduction in the rate of MCC occurs at the temperature of 24oC, it has been predicted that a linear increase in ciliary beat frequency occurs with increase in temperature.

- Membrane permeability

  Absorption of the drug through the nasal route is affected by membrane permeability which is most important factor. The large molecular weight drugs and water soluble drugs like peptides and proteins have low membrane permeability hence absorbed through endocytic transport in fewer amounts.[14]

3. Physicochemical properties of drugs

- Molecular weight and size

  Drug permeation is determined by molecular weight, molecular size, hydrophilicity and lipophilicity of the compound. For compounds 1 kDa, bioavailability can be directly

predicted from knowledge of MW. In general, the bioavailability of these large molecules ranges from 0.5% to 5%. Physicochemical properties of the drug don't significantly affect permeation of drug LT 300 Da, which will mostly permeate through aqueous channels of the membrane. By contrast, for compounds with MW 300 Da rate of permeation is highly sensitive.

- Solubility

  Major factor in determining absorption of drug through biological membranes is drug solubility. As nasal secretions are more watery in nature, a drug should have appropriate aqueous solubility for increased dissolution. Lipophilic drugs have less solubility in the aqueous secretions. Water soluble drugs are absorbed by passive diffusion and lipophilic drugs via active transport depending on their solubility.

- Lipophilicity

  The permeation of the compound normally increases through nasal mucosa with increase in lipophilicity. It appears that nasal mucosa is primarily lipophilic in nature and the lipid domain plays an important role in the barrier function of these membranes although they have some hydrophilic characteristics. Systemic bioavailability of many drugs is decreased due to excess hydrophilicity in such cases prodrug approach is beneficial.

- pKa and Partition coefficient

  As per the pH partition theory, unionized species are absorbed better compared with ionized species and the same fact is true in the case of nasal absorption. There is constant relationship between pKa and nasal absorption of these drugs. With an increase in lipophilicity or the partition coefficient of the drugs its concentration in biological tissues increases. The absorption rate of aminopyrine increased with the increase in pH and was found to fit well to the theoretical profile Major factor governing nasal absorption is partition coefficient.

- Polymorphism

  Polymorphism is the important parameter in the nasal drug product development which is administered in particulate form. Polymorphism is known to affect dissolution of drugs and their absorption through biological membranes is affected by polymorphism. This factor should be carefully considered in the dosage form development for the nasal delivery.[15]

- Chemical State

Absorption of the drug is determined by the chemical form of the drug in which it is presented to nasal mucosa. Chemically alter a drug molecule by adding a bio-cleavable lipophilic moiety is the alternative for improving absorption of the drug which is not having desired absorption properties. The prodrug approach provides many additional challenges which need to be overcome in the drug product developmental process. The toxicity of the prodrug itself needs to be fully evaluated.

- Physical state

  Particle size and morphology of drug are two main important properties for particulate nasal drug products. These both parameters should be controlled to obtain suitable drug dissolution properties in the nostrils. Too fine particles below 5 microns should be avoided because it may get inhaled in lungs. Particles in the 5–10 micron range are deposited in the nostrils.

4. Physicochemical properties of formulation

- Physical form of formulation

  Physical form of the formulation is very important in nasal drug absorption. Liquid formulations are less effective than powder form in delivering insulin in rabbits. Less efficient systemic nasal drug delivery observed with more viscous formulation. Scientist found that somewhat more sustained effects of desmopressin are observed with addition of viscous agent but total bioavailability is not enhanced. Viscous formulations may help in minimizing nasal drip.

- pH

  The extent of drug ionization IS determined by pH partition hypothesis hence it is related to formulation pH. Nasal formulation should be adjusted to appropriate pH to avoid irritation, to obtain efficient absorption and to prevent growth of pathogenic bacteria. Ideal formulation pH should be adjusted between 4.5 and 6.5. pH of the nasal surface is 7.39 and the pH of nasal secretions is 5.5–6.5 in adults and 5.0–6.7 in infants and children.

- Volume of solution applied and drug concentration

  There is no constant relationship between volume of administration and extent of absorption. Clement studied the effect of three nasal spray concentrations of cetrizine on the clinical efficacy. The results showed that 16.7%, 30.8%, 42.9%, and 26.7% of days the patients experienced appeared to improve with the drug concentration up to only 0.125%. At the higher concentration, 0.250%, the efficacy declined.

- Viscosity

  The contact time between the drug and the nasal mucosa is increased by higher viscosity of formulation thereby increasing the time for permeation.

CONCLUSION

Nasal drug delivery is a novel platform and it is a promising alternative to injectable route of administration. There is possibility in the near future that more drugs will come in the market in the form of nasal formulation intended for systemic treatment. The nasal cavity has a large surface area and a highly vascularized mucosa. Drugs absorbed by the rich network of blood vessels pass directly into the systemic circulation, thereby avoiding first-pass metabolism. Despite the potential of the nasal route, a number of factors limit the intranasal absorption of drug, especially peptide and protein drugs. The major advantages are the straightforward and needle free application mode and the permeable application site in the nasal cavity that allow a rapid onset of local and systemic drug actions.

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