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NASAL DRUG DELIVERY SYSTEMS: AN OVERVIEW

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Anatomy and physiology of nose, current formulation for nasal drug delivery, nasal drug absorption enhancer, nasal drop, spray, suspension, emulsion, gel, powder

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ABSTRACT

Since ancient times, drugs have been administered via the nasal route for therapeutic and recreational purposes. The interest in, and importance, of the systemic effects of drugs administered through the nasal route, have expanded over recent decades. Intra-nasal administration of drugs offers an interesting alternative for achieving systemic therapeutic effects of drugs that are comparable to the parenteral route, which can be inconvenient at times or oral administration, which can result in unacceptably low drug bioavailability. So, it is important to understand the potential and limitations of various nasal drug delivery systems. Therefore, the aim of this review article is to discuss the various pharmaceutical dosage forms that have the potential to be utilised for local or systemic drug administration. It is intuitively expected that this review will help to understand and further to develop suitable intranasal formulations to achieve specific therapeutic objectives.

INTRODUCTION:

Nasal drug delivery, which is in the focus of this review article, has received a significant attention in recent years as a convenient and reliable route, not only for local but also for the systemic administration of drugs. The nasal cavity offers a number of distinctive advantages for systemic delivery such as

1. A large surface area for drug absorption.
2. Convenience and good patient compliance.
3. Rapid attainment of therapeutic drug levels in the blood.
4. High drug permeability, especially for lipophilic and low molecular weight drugs.
5. Avoidance of harsh environmental and gastrointestinal conditions.
6. Bypassing of hepatic first-pass metabolism

The nasal cavity is an easily accessible route which is generally well tolerated. The abundance of blood vessels in the nasal mucosa contributes to drug absorption, which is almost equal to intravenous injections in some instances. The nasal route of drug delivery can be used for both local and systemic drug delivery. For instance, localized nasal drug delivery is usually used to treat conditions related to the nasal cavity, such as congestion, rhinitis, sinusitis and related allergic conditions.

. A wide range of pharmaceutical dosage forms including solutions, gels, suspensions, emulsions, liposomes and microparticles can be used to achieve systemic drug actions. These dosage forms are mostly designed to exploit the advantage of a rapid onset of action when administered via nasal route. For example, morphine and ketamine can be delivered intra-nasally to achieve rapid analgesic effects. Moreover, vaccines can also be administered using the nose as a potential route, such as those for influenza

Anatomy and physiology of nose:

The nose is the primary entrance to the respiratory tract, allowing air to enter into the body for respiration . The nasal cavity is 120-140 mm deep, runs from the nasal vestibule to the nasopharynx and is divided into two by a cartilaginous wall called nasal septum. The nose has a surface area of around 160 cm^2 and a total volume of ~16-19 ml . The nose serves as the mean of bringing warm humidified air into the lungs. It is the primary organ for filtering out particles in the inspired air, and

it also serves to provide a first-line immunologic defence as it brings the inspired air into contact with the mucous-coated membrane. The nose has three main regions: vestibular, turbinate and olfactory regions).

The vestibular region is the anterior part of the nose and it is the narrowest part of the nasal cavity. The vibrissae cover most of this area which renders it capable of filtering out particles with an aerodynamic particle size larger than 10 μm that may be inhaled with air. In the vestibular region, the surface lining changes from skin, at the first part of the passage, to a stratified squamous epithelium

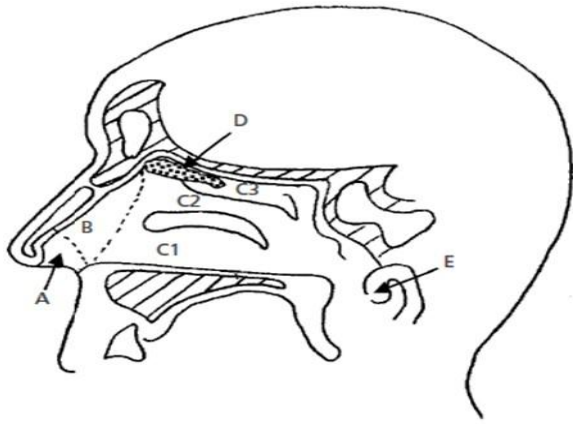

Fig. 1: Sagittal section of the nasal cavity showing the nasal vestibule (A), atrium (B), respiratory area: inferior turbinate (C1), middle turbinate (C2) and the superior turbinate (C3), the olfactory region (D) and nasopharynx (E). Reproduced with permission from

The ciliated and non-ciliated cells are covered with non-motile microvilli, which are responsible for increasing the surface area, thus, this is the region where the drug absorption is optimal. Ciliated cells are covered with approximately 100 motile cilia which are responsible for mucus transport.

The olfactory region is an area comprising about 8% of the total surface area of the nasal epithelium and is made of a non-ciliated, pseudo stratified columnar epithelium. It is important for transporting drugs to the brain and cerebrospinal fluid (CSF). There is a mucus layer of 5 μm in thickness covering the epithelium cells which traps unwanted particles. The mucous secretion consists of mucin, water, salts,proteins such as albumin, immunoglobulin, lysozyme, and lactoferrin, and lipids . The pH of the nasal secretions ranges from 5.0 to 6.5

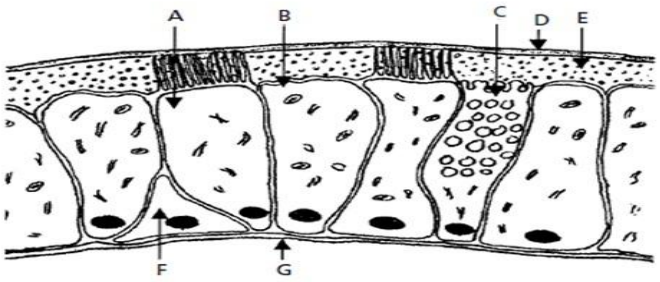

Fig. 2: Cell types of the nasal epithelium with covering mucous layer showing ciliated cell (A), non-ciliated cell (B), goblet cells (C), mucous gel-layer (D), sol layer (E), basal cells (F) and basement membrane (G). Reproduced with permission from

Biopharmaceutical Consideration:-

The easy accessibility and higher surface area makes the nose a potentially viable drug delivery organ. Pharmaceutical product development is a crucial task which is directly dependent on its therapeutic objectives. Therefore, before product development, important biopharmaceutical aspects need to be considered-firstly, whether it is intended for: I- Localised delivery

II- Systemic delivery

III- Single or repetitive administration

The feasibility of being able to achieve the therapeutic objectives will determine whether the development of a nasal delivery system is appropriate .

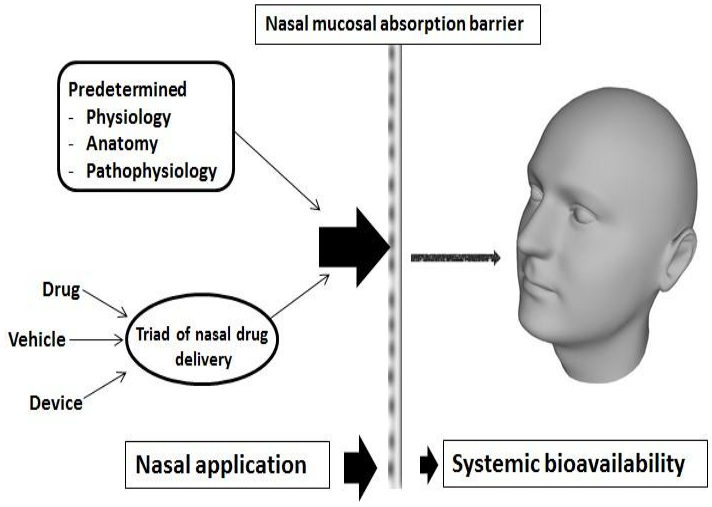

Fig. 3: Consideration of formulation elements of nasal product development

Nose as a Drug Delivery Route:

Advantages and Limitations:-

In addition to its benefits over parenteral routes in terms of convenience, the potential for delivering drugs directly into the brain along the olfactory nerves makes this route even more attractive . The brain is a delicate organ with many vital functions and it is isolated and protected from the outside environment by several specific mechanisms. The blood-brain barrier (BBB), a tight tissue junction surrounding the brain, is one of such mechanisms resulting in a greater trans-endothelial electric resistance which hinders drug transport

Table 1: Polymers used in drug delivery systems

Class of compound	Example	Possible action
Fatty acids	Dideconoylphosphatidylcholine, lysophosphatidylcholine	Membrane disruption
Surfactants	Sodium lauryl sulphate, saponin, polyoxyethylene-9-lauryl ether	Membrane disruption
Bile salts	Sodium deoxycholate, sodium glycocholate, sodium taurodihydrofusidate	Open tight junctions, enzyme inhibition, mucolytic activity
Cyclodextrines and derivatives	α-, β-, γ-cyclodextrin DMβ-, HPβ-cyclodextrin	Open tight junctions, membrane disruption
Enzyme inhibitors	Bestatin, amastatia	Enzyme inhibition
Bio-adhesive materials	Carbopol, starch microspheres, chitosan	Reduce nasal clearance, open tight junctions

2. Nasal drug absorption enhancers and mechanisms:-

In this context, over the last few years, an intra-nasal route has emerged as a promising approach for delivery of drugs to the brain. The delivery from the nose to the CNS may occur via the olfactory neuroepithelium and may involve paracellular, transcellular and/or neuronal transport with this olfactory pathway presenting the potential to bypass the BBB . The nasal route can also be a useful alternative to the oral route for drug absorption in situations where a use of the gastrointestinal route is unfeasible. Examples include: patients with nausea and vomiting; patients with swallowing difficulties children and geriatrics . The rate and extent of absorption as

well as plasma concentration vs time profiles are comparable with I.V. administration .

Physiological and anatomical factors include nasal blood flow, enzymatic degradation, mucociliary clearance and the physical condition of the nose; some conditions such as nasal atrophic rhinitis and

Table 2. Current formulations for nasal drug delivery

Indication	Active pharmaceutical ingredient	Formulation
Analgesia	Diamorphine hydrochloride Fentanyl citrate	Powder Nasal spray, solution
Acute treatment of migraine	Sumatriptan Zolmitriptan	Nasal spray, solution Nasal spray, solution
Endometriosis Ovarian stimulation	Nafarelin acetate	Nasal spray, solution
Nasal congestion (associated with sinusitis, common cold, rhinitis and other UTIs) Symptomatic relief of rhinorrhoea	Xylometazoline hydrochloride Oxymetazoline hydrochloride Azelastine Hydrochloride Ephedrine Ipatropium bromide	Nasal spray, solution, nasal drops Nasal spray, solution Nasal spray, solution Nasal drops Nasal spray, solution
Prophylaxis and treatment of perennial and seasonal allergic rhinitis	Budesonide, beclometasone dipropionate (and monohydrate (micronized), Mometasone furoate Triamcinolone acetonide Fluticasone propionate Fluticasone furoate Fluticasone with azelastine HCl Sodium cromoglicate	Nasal spray suspension Nasal spray suspension Nasal spray suspension Nasal spray suspension Nasal spray suspension Nasal spray suspension Nasal spray suspension, spray solution
Prostatic carcinoma (hormone -dependent)	Buserelin acetate	Nasal spray, solution
Nasal congestion	Levomenthol	Nasal ointment
Nasal infection	Neomycin sulfate and Chlorhexidine dihydrochoride	Nasal cream
Nicotine withdrawal symptoms	Nicotine	Nasal Spray Solution
Nocturia associated with multiple sclerosis The diagnosis and treatment of vasopressinsensitive cranial diabetes insipidus. Establishing renal concentration capacity.	Desmopressin acetate	Nasal Spray Solution
Vaccinations	Influenza vaccine	Nasal spray suspension

severe vasomotor rhinitis can reduce the capacity of nasal drug absorption and the drug can be lost by dripping out of the nose or down the back of the throat, thus reducing bioavailability Nasal mucociliary clearance can also reduce contact time and drug absorption by transporting the drug to the nasopharynx and then to the gastric intestinal tract . Mucociliary clearance can be overcome by incorporating mucoadhesive polymers into the formulation, which may increase nasal absorption . The mucus layer can also be a barrier for drug absorption either by limiting drug diffusion or by binding drugs to mucins. Some conditions such as the common cold and hay fever can also change the conditions within the nose, either by increasing or decreasing mucociliary clearance, or altering the permeability of the absorbing mucosa. These limitations must be recognised and addressed when designing formulations to target drug absorption by the nasal route.

Effect of solution pH :-

Adults have pH 5.52-6.5; infants have pH 5.0-6.7, increased nasal absorption at decreased pH due to unionized condition of the drug. Decreased nasal absorption at increased pH due to ionization of penetrant molecule.

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

1. To avoid irritation of nasal mucosa;
2. To allow the drug to be available in unionized form for absorption;
3. To prevent growth of pathogenic bacteria in the nasal passage;
4. To maintain functionality of excipients such as preservatives; and
5. To sustain normal physiological ciliary movement.

Factors associated with the dosage form:-

Drugs to be administered to the nasal cavity are generally formulated as nasal drops, nasal sprays, aerosol spray, and the insufflators.

1. Nasal drops which deposits a film of drug solution. Nasal sprays which deposit an aerosol particles, droplets, or particle suspended in drops.
2. The extent and deposition of an aerosol from a nasal spray will depend upon:
3. Aerodynamic diameter of the particle (which is also function of droplet size, shape and density).

4. Particle charge (which depend on the drug, formulation excipients and method of aerosolization). o The velocity at which the particle is moving (which depends on respiratory patterns).
5. Deposition mechanisms in the nose include inertial impaction, sedimentation, diffusion, interception and electrostatic attraction.
6. The structure and physiology of the nasal cavity with the small cross-section for airflow and sharp curves suggests that inertial impaction is the most significant mechanism for drug deposition in the nasal cavity.
7. Nasal drops disperse a drug solution throughout the length of the nasal cavity from atrium to nasopharynx, offering a relatively large area for immediate absorption. o Nasal sprays tend to deposit at the front of the nasal cavity with little of the dose reaching the turbinate.
8. The metered dose nebulizer has recently been introduced as a nasal drug delivery device that operates by mechanical actuation and delivers a predetermine volume with precision into the nasal cavity. The dose of active ingredient administered intranasally depends upon the volume of drug solution delivered at each actuation and the concentration of drug in the formulation.

Mechanism of Drug Absorption:-

The principal step in the absorption of a drug from the nasal cavity is the passage through the mucus. Fine particles easily pass through the mucus layer; however, large particles may find some difficulties . Mucus contains mucin, a protein with the potential to bind with solutes and thus affect the diffusion process. Structural changes can occur within the mucus layer as a result of environmental or physiological changes . Subsequent to a drug's passage through the mucus, there are numerous mechanisms for absorption through the mucosa. These include transcellular or simple diffusion across the membrane, paracellular transport via movement between cell and transcytosis by vesicle carriers. Several mechanisms have been proposed, but paracellular and transcellular routes dominate .

The second mechanism involves transport through a lipoidal route that is also known as the transcellular process 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 carrier-mediated means or transport through the opening of tight junctions .

Obstacles to drug absorption are potential metabolism before reaching the systemic circulation and inadequate residence time in the nasal cavity.

Drug Absorption Enhancement:-

Many drugs having high water solubility have poor permeability across nasal epithelia and may present insufficient bioavailability. To enhance their permeation and bioavailability permeation enhancers are frequently employed. In principle, permeation enhancers induce reversible modifications on the structure of the epithelial barrier. Although the exact mechanism of drug absorption/permeation enhancement is not well known, it is widely accepted that these materials modify the permeability of epithelial cell layer by modifying the phospholipid bilayer . Different types of absorption/permeation enhancers are enlisted in with their possible mechanism of action.

Nasal Drug Delivery Systems:-

Nasal Drops and Sprays:-

Nasal drops are one of the simplest and most convenient delivery systems among all formulations. The main limitation is the lack of precision in the administered dosage and the risk of contamination during use. Nasal drops can be delivered with a pipette or by a squeezy bottle. These formulations are usually recommended for the treatment of local conditions, but challenges include microbial growth, mucociliary dysfunction and non-specific loss from the nose or down back the throat.

Nasal spray systems consist of a chamber, a piston and an operating actuator. Nasal sprays are comparatively more accurate than drops and generate precise doses (25 - 200 µl) per spray . Several studies have shown that nasal sprays can produce consistent doses of reproducible plume geometry. Formulation properties such as thixotropy, surface tension and viscosity can potentially influence droplet size and dose accuracy. Other factors such as the applied force, orifice size and design of the pump can also affect the droplet size which can impact the nasal deposition of sprays.

Nasal Gels

A gel is a soft, solid or semi-solid-like material consisting of two or more components, one of which is a liquid, present in substantial quantity. The semi-solid characteristics of gels can be

defined in terms of two dynamic mechanical properties: elastic modulus G' and viscous modulus G" . The rheological properties of gels depend on the polymer type, concentration and physical state of the gel. They can range from viscous solutions (e.g. hypromellose, methylcellulose, xanthan gum and chitosan) to very hard, brittle gels (e.g. gellan
gum, pectin and alginate).

Fig. 4: Nasal Drops and Sprays

Fig. 5: Nasal Gels

Bioadhesive polymers have shown good potential for nasal formulations and can control the rate and extent of drug release resulting in decreased frequency of drug administration and improved patient compliance. Moreover, the prolonged contact time afforded at the site of absorption can improve drug bioavailability by slowing down mucociliary movement. Gavini et al. (2011) observed improvements in the solubility of roxithromycin loaded into chitosan microspheres compared with the free drug when the intranasal drug absorption was assessed *in vivo* in rats . The mechanism of Mucoadhesion in the nasal cavity can be explained by a number of theories, but it is generally accepted that the mechanism is based on two key stages, the contact and consolidation stages. So, when formulations containing bioadhesive polymers are instilled in the nasal cavity, they can spread over the nasal epithelium. Due to the increased surface contact, the polymer chains can diffuse within the mucus. This creates sufficient contact for entanglement. Secondary chemical bonds are then formed between the polymer chains and mucin molecules . Various biocompatible and biodegradable polymers have been used to formulate mucoadhesive systems. These include poly-vinyl alcohol , chitosan , carbopol, alginate, hydroxypropyl methylcellulose, hydroxypropyl cellulose, starch and gellan gum . Nasal administration using mucoadhesive gels has been studied for different drugs: antibiotics such as roxithromycin and ciprofloxacin , insulin , scopolamine hydrochloride, mometasone furoate , carvedilol , sumatriptan succinate , vaccines and proteins . Ozsoy et al., 2000 has investigated the formulation of ciprofloxacin hydrochloride using hydroxypropyl methylcellulose (HPMC) and the results suggested that the bioavailability of ciprofloxacin gel formulation prepared with HPMC was almost identical to the oral route.

Nasal Suspensions and Emulsions:-

Suspensions are rarely used or investigated as nasal drug delivery systems. Analogous to marketed aqueous ophthalmic suspensions of the soft corticosteroid, loteprednol etabonate (e.g. Alrex®, Bausch and Lomb Pharmaceuticals), a nasal aqueous suspension of same drug containing microcrystalline sodium carboxymethylcellulose for stabilisation and retention in the nasal cavity was patented by Senju Pharmaceuticals Inc., Osaka, Japan and was intended for the local treatment of allergic rhinitis. Moreover, a nasal suspension for the delivery of insulin was investigated by Ando et al. (1998) .

Here, soybean-derived steryl glycoside and sterol mixtures (1%) were used as absorption enhancers and pharmacological bioavailabilities of 6.7% and 11.3% were achieved. However, for oral drug delivery it has been reported by several authors that emulsions were superior to suspensions in enhancing the bioavailability of poorly soluble drugs and the trend is similar with nasal formulations. Absorption enhancement has been attributed to solubilisation of the drug and the lipophilic absorption enhancers in the composition. Similarly, other low solubility compounds have been formulated in emulsions to increase the drug solubility, e.g. diazepam and testosterone .

Klang et al., 2015 used a nano-suspension to target the brain through the nose. Formulation as a nanosuspension facilitated bypassing of the blood-brain barrier (BBB) for particles ranging between 1-500 nm. Moreover, recently researchers have also reported nasal administration of nano-emulsions for brain targeting .

Fig. 6: Nasal Suspensions and Emulsions

Nasal Micellar and Liposomal Formulations:-

Different types of adjuvants can affect the drug absorption (described earlier, see section 5.1) and are often required to reach therapeutic plasma levels when hydrophilic macromolecular drugs such as peptides and proteins are delivered by the nasal route . Among other surfactants used, bile salts are often used as enhancers, e.g. as micellar solutions. Tengamnuay and Mitra described the use of

micelles of sodium glycocholate and micelles thereof mixed with fatty acid (linoleic acid) as absorption enhancers for the model dipeptide (D-Arg2)-kyotorphin and for insulin in rats. The effect of mixed micelles was synergistic and superior compared to the single enhancer. Mixed micelles of sodium glycocholate and linoleic acid reduced the blood glucose level after nasal insulin administration to 47% of the glucose level after an identical nasal dosage of unenhanced insulin. Pure sodium glycocholate resulted in a reduction to 55%. Regarding the mechanism, in a difference to the membrane solubilizing effect of pure bile salts, the mixed micelles were proposed to have an effect on the nasal paracellular pathway. Hereby, the bile salts were considered to act as solubilizing agents for the fatty acids thus making them more available at the nasal mucosa . The absorption modifying effect of mixed micelles was reversible after 20-40 min and the morphological alterations of the nasal mucosa were only mild to moderate after 5 h of exposure . However, measurement of marker enzymes in rat nasal perfusate showed that the damaging effect of mixed micelles on the epithelial membrane is significantly greater compared with pure sodium glycocholate solution and phosphate buffered saline after 90 min exposure.

Liposomes have also been investigated as nasal drug delivery systems and absorption enhancing effects were found for insulin and calcitonin *in vitro* permeability studies. The enhancement effect was attributed to increased nasal retention of peptides. The best carrier effect for calcitonin was demonstrated with cationic liposomes as they were found to adhere intimately to the nasal mucosal surface, facilitating the penetration of the encapsulated drug.

Nasal Powders:-

Particulate nasal dosage forms are usually prepared by simply mixing the drug substance and the excipients, by spray-drying or freeze- drying of drug. Dry-powder formulations containing bioadhesive polymers for the nasal delivery of peptides and proteins was first investigated by Nagai et al. (1984) . Water-insoluble cellulose derivatives and Carbopol® 934P were mixed with insulin and the powder mixture was administered nasally. The powder took up water, swelled, and established a gel with a prolonged residence time in the nasal cavity. Glucose reduction was one-third of that achieved using an i.v. injection of the same insulin dose. Powder formulations for nasal drug delivery have since been widely investigated, e.g. for a somatostatin analogue using cross-linked dextran and microcrystalline cellulose , for glucagon using microcrystalline cellulose , for

leuprolide and calcitonin using microcrystalline cellulose in combination with hydroxypropyl cellulose , and for gentamicin sulfate using hydroxypropyl methylcellulose .

A bioadhesive powder containing beclomethasone dipropionate for local treatment of allergic rhinitis and hydroxypropyl cellulose as the carrier had a significantly enhanced nasal residence time compared with administration of a solution as drops . Ugwoke et al. (2000) compared the nasal retention time of apomorphine, freeze-dried with lactose, Carbopol® 971P or sodium carboxymethylcellulose. Three hours post insufflation, 58%, 12%, and 27%, respectively, of the formulation, had been cleared from the nasal cavity

Callens and Remon (2000) demonstrated nasal insulin delivery with freeze-dried powders of waxy maize starch and Carbopol® 974P, reaching an absolute bioavailability of 14.4%. Comparison of different starch / Carbopol® 974P and maltodextrin / Carbopol® 974P mixtures by oscillatory rheology showed no synergistic increase in the viscosity and elasticity when combined with mucus, which is often used as an indicator of bioadhesion .

Rest phase :-

At the end of the effective stroke the cilium disengages from the mucus gel and enters the rest phase where it lies parallel to the epithelium pointing in the direction of the

mucus flow. This position is believed to discourage any reversal of mucus movement.

Recovery stroke:-

The cilium "unrolls" within the periciliary fluid ready for the next effective stroke. Undergoing the recovery stroke beneath the mucus layer prevents traditional mucus transport.

Nasal Microparticles :-

Using microparticles as another way of prolonging the residence time in the nasal cavity was introduced in 1987 . It was proposed that microspheres of albumin, starch, and DEAE-dextran (diethyl aminoethyl-dextran) absorbed water and formed a gel-like layer which was cleared slowly from the nasal cavity. Three hours after administration, 50% of the delivered amount of albumin and starch microspheres and 60% of the dextran microspheres were still present at the site of deposition. It was suggested that an increased contact time could increase the absorption efficiency of drugs. As proposed, the relative intranasal bioavailability (v.s. subcutaneous) of human growth hormone in sheep was increased from 0.1% for the solution to 2.7% for the degradable starch

microsphere formulation. The addition of absorption enhancer, lysophosphatidylcholine, further enhanced growth hormone absorption as a relative bioavailability of 14.4% was achieved . Björk and Edman (1990) showed that plasma glucose reduction after nasal insulin administration was comparable for degradable starch microspheres (cross-linked with epichlorohydrin) and insoluble starch powder (molecular weight 25 kDa) but significantly lower for soluble starch powder (molecular weight 11 kDa). It was therefore concluded that crucial parameters for the absorption promoting effect of microspheres are water absorption and aqueous insolubility. No alteration of the nasal mucosa was observable by scanning electron microscopy after 8 weeks of twice daily administration of starch microspheres, except slight hyperplasia in the septum wall . Although DEAE-dextran microspheres were retained strongly in the nasal cavity ,they were not successful in promoting nasal insulin absorption in rats . The insulin was too tightly bound to the DEAE-groups to be released by a solution with an ionic strength corresponding to physiological conditions. Dextran microparticles without ion exchange groups induced a 25% decrease in blood glucose level about 40 min after administration compared with initial levels. In a later study, dextran microspheres with a different distribution of the encapsulated insulin were compared . When insulin was situated on the microsphere surface, a 52% reduction in plasma glucose was induced 30 min after administration in rats. However, microspheres, which included the insulin in the spherical matrix, reached a maximum plasma glucose level reduction of 30% after 60 min. Possibly, the limited amount of fluid in the nasal cavity is responsible for the observed differences, as the microspheres must be completely swollen to release the entire amount of incorporated insulin .

Chitosan also has potential as an excipient in microparticulate drug delivery systems. *In vivo* studies in sheep showed a half-life of nasal clearance for chitosan microparticles of 115 min compared with 43 min for a solution of the polymer . In general, chitosan formulations, whether in the form of microparticles or powders, were shown to provide a better absorption enhancing effect than chitosan solutions . Moreover, recently solid lipid nanoparticles have also shown promising results and were shown to increase the brain targeting of rosmarinic acid following nasal delivery for potential management of Huntington's disease .

CONCLUSIONS:

Over last decade, the nasal cavity has become one the promising and potentially versatile route for delivering drugs. In particular, its unique capability of extending the drug release, by passing the hepatic first-pass metabolism and direct delivery of drugs to brain holds great promise in the field of drug delivery. A growing body of evidence relating to nasal drug delivery suggest it might the used for challenging drugs which can facilitate the pharmaceutical manufacturing and drug delivery challenges. Various pharmaceutical dosage forms and their potential to be utilised for local or systemic drug administration has been discussed in their review article. It is intuitively expected that this review will help to understand and further to develop the intra-nasal formulations to achieve specific therapeutic objectives. However, a number of technical and practical issues, which are also highlighted in this review article, remain a hurdle to be overcome in order for the full potential to be realised.

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