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REVIEW ARTICLE

SITE SPECIFIC DRUG DELIVERY THROUGH NASAL ROUTE USING BIOADHESIVE POLYMERS

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ABSTRACT:

This review explains some aspects of mucoadhesion related to the nasal drug delivery system. On the first count, the theories of the adhesion of mucoadhesive polymers to the mucosa epithelium are described. Secondly, the characteristics and application of several widely used mucoadhesive polymers in nasal drug delivery are presented. The nasal mucosa provides a potentially good route for systemic drug delivery. One of the most important features of the nasal route is that it avoids first-pass hepatic metabolism, thereby reducing metabolism. The application of mucoadhesive polymers in nasal drug delivery systems has gained to promote dosage form residence time in the nasal cavity as well as improving intimacy of contact with absorptive membranes of the biological system. The aspiration of any drug delivery system is to endow with a therapeutic amount of drug to the proper site in the body to achieve promptly & then uphold the desired drug concentration. That is why the drug delivery system should deliver drug at a state dictated by the needs of the body over a specified period of treatment. This idealized objective points to the two aspects most important to drug delivery, namely, spatial placement relates to targeting a drug to a specific organ or tissue while temporal delivery refers to the control of rate of drug delivery to the target tissue. Over the last few decades, the relevance of mucoadhesive polymers in nasal drug delivery systems has gained significance among pharmaceutical scientists as a means of promoting dosage form residence time in the nasal cavity as well as for improving intimacy of contact with absorptive membranes of the biological system. In addition, the improved paracellular absorption subsequent the swelling of the mucoadhesive polymers on the nasal membranes provides an important way for the absorption of the macromolecules through the nasal cavity.

Keywords: Nasal route, Mucoadhesive polymers, Paracellular absorption

INTRODUCTION:

The development of sustain release dosage form can achieve the aim of releasing the drug slowly for a long period but this is not sufficient to get sustained therapeutic effect. They may be cleared from the site of absorption before emptying the drug content. Instead, the mucoadhesive dosage form will serve both the purposes of sustain release and presence of dosage form at the site of absorption. In this regard, our review is high lighting few aspects of mucoadhesive drug delivery systems.

Nasal administration offers an interesting alternative for achieving systemic drug effects to the parenteral route, which can be inconvenient or oral administration, which can result in unacceptably low bioavailabilities. The nasal epithelium is a highly permeable monolayer, the sub mucosa is richly vascularized, and hepatic first-pass metabolism is avoided after nasal administration. Other attractive features include the rather large surface area of the nasal cavity and the relatively high blood flow, which promotes rapid absorption.[1] In the early 1980s, the concept of mucosal adhesives, or mucoadhesives, was introduced into the controlled drug delivery area. Mucoadhesives are synthetic or natural polymers that interact with the mucus layer covering the mucosal epithelial surface and main molecules constituting a major part of mucus. The concept of mucoadhesives has alerted many investigators to the possibility that these polymers can be used to overcome physiological barriers in long-term drug delivery. Extensive research efforts throughout the world have resulted in significant advances in understanding the various aspects of mucoadhesion. The research on mucoadhesives, however, is still in its early stage, and further advances need to be made for the successful translation of the concept into practical application in controlled drug delivery.[2]

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Nasal administration offers an interesting alternative for achieving systemic drug effects to the parenteral route, which can be inconvenient or oral administration, which can result in unacceptably low plasma drug levels. Conventionally the nasal cavity is used for the treatment of local diseases, such as rhinitis and nasal congestion. However, in the past few decades, nasal drug delivery has been paid much more attention as a promising drug administration route for the systemic therapy. This is due to the anatomy and physiology of the nasal passage, such as, the large surface area, highly vascularized epithelium, porous endothelial membrane, and the avoidance of first-pass metabolism.[3,4]

Despite the high permeability of nasal membrane, generally, only small molecular weight drugs (<1000 Da) show adequate absorption in the nasal cavity, most hydrophilic and macromolecular drugs such as insulin show low bioavailability or even no abrosrption.[5, 6] The main reason for this is that they are lowly permeable and susceptible to the proteases in the nasal mucosal membrane, so these drugs can be rapidly cleared from the cavity, by ciliary movement or enzymatic degradation before they reach the bloodstream, and cannot cross the mucosal barriers. Penetration enhancers such as surfactants bile salts, fusidate derivatives and phospholipids [7, 8, 9, 10, 11] have been used to improve the drug absorption through nasal mucosa, but toxicity tests have proved that they were of limited clinical use because of their irreversible damage to nasal mucosa accompanied with their absorption-enhancing effects. [12, 13]

Benefits and Precincts of nasal drug delivery:

Benefits:[14]

- Avoids degradation of drug in gastrointestinal tract resulting from acidic or enzymatic degradation
- Avoids degradation of drug resulting from hepatic first-pass metabolism
- Results in rapid absorption and onset of action
- Results in higher bioavailability thus needing lower doses of drug
- Easily accessible, non-invasive route
- Self-medication is possible through this route
- Direct transport into systemic circulation and CNS is possible
- Offers lower risk of overdose
- Does not have any complex formulation requirement
- Unlike the skin, nasal mucosa is not constructed from the keratinized stratum corneum. The subepithelial layer of the nasal mucosa with numerous microvilli is highly vascularized, with large and fenestrated capillaries facilitating rapid absorption.
- The rate and extent of absorption as well as plasma concentration *vs* time profiles are comparable with I.V. administration.

Precincts: [14]

- Nasal atrophic rhinitis and severe vasomotor rhinitis can reduce the capacity of nasal absorption, e.g., Caerulein.
- There could be mechanical loss of the dosage form into the other parts of the respiratory tract like lungs.
- Volume that can be delivered into nasal cavity is restricted to 25–200 µl
- High molecular weight compounds cannot be delivered through this route (mass cut off ~1 kDa)
- Adversely affected by pathological conditions.
- Large interspecies variability is observed in this route.
- Normal defence mechanisms like mucociliary clearance and ciliary beating affects the permeability of drug.
- Enzymatic barrier to permeability of drugs.

Mucoadhesion/Bioadhesion: [15, 16]

Good defined mucoadhesion as the state in which two materials, at least one biological in nature,

are held together for an extended period of time by interfacial forces **.**It is also defined as the ability of a material (synthetic or biological) to adhere to a biological tissue for an extended period of time. In case of mucoadhesion, the biological tissue is the mucous membrane. For mucoadhesion to occur, a succession of phenomena is required. The first stage involves an intimate contact between a mucoadhesive polymer and a membrane, either from good wetting of the mucoadhesive surface or from the swelling of the mucoadhesive. In the second stage, after contact is established, penetration of the mucoadhesive into the crevice of the tissue surface or interpenetration of the chains of the mucoadhesive with those of the mucus takes place. Low chemical bonds can then settle. Mucoadhesive polymers Mucoadhesive polymers are water soluble and water insoluble polymers, which are swellable networks, jointed by cross-linking agents. These polymers possess optimal polarity to make sure that they permit sufficient wetting by the mucus and optimal fluidity that permits the mutual adsorption and interpenetration of polymer and mucus to take place. Mucoadhesive polymers that adhere to the musin epithelial surface can be conveniently divided into three broad classes:

- Polymers that become sticky when placed in water and owe their mucoadhesion to stickiness.
- Polymers that adhere through nonspecific, non covalent interactions that is primarily electrostatic in nature (although hydrogen and hydrophobic bonding may be significant).
- Polymers that bind to specific receptor site on tile self surface. All three polymer types can be used for drug delivery.

Uniqueness of mucoadhesive polymer:

The polymer and its degradation products should be nontoxic and should be non absorbable from the gastrointestinal tract.

2. It should be nonirritant to the mucous membrane.

3. It should preferably form a strong non-covalent bond with the mucin-epithelial cell surfaces.

4. It should adhere quickly to most tissue and should possess some site-specificity.

5. It should allow daily incorporation to the drug and offer no hindrance to its release.

6. The polymer must not decompose on storage or during the shelf life of the dosage form.

7. The cost of polymer should not be high so that the prepared dosage form remains competitive.

Mucoadhesion Theories:

Mucoadhesion is a complex process and numerous theories have been proposed to explain the mechanisms involved. These theories include:

- Wetting theory
- Diffusion theory
- Fracture theory
- Adsorption theory
- Electronic theory

Mechanism of mucoadhesion:

The process of mucoadhesion following nasal administration relates to the interaction between the mucoadhesive polymer and the mucus secreted by the sub-mucosal glands. The sequential events that occur during the mucoadhesion include the proper wetting and swelling of the polymer, and intimate contact between the polymer and the nasal mucosa. Then, the swollen mucoadhesive polymer penetrates into the tissue crevices followed by the interpenetration between the polymer chains and the protein chains of the mucus (Figure1).

To obtain sufficient absorption of drugs, firstly, the formulation should spread well on the nasal mucosa. Therefore, the spreadability is very important for the liquid mucoadhesive formulation, so does the flowability and wettablility for the solid mucoadhesive formulation.

Hydration of the polymer (swelling) plays a very important role in mucoadhesion, through which

the polymer chains are liberated and interact with the biological tissue. During hydration, there is a dissociation of hydrogen bonds of the polymer chains. When the polymer– water interaction becomes greater than the polymer– polymer interaction, adequate free polymer chains will be available for interaction between the polymer and the biological tissue. The Vander Waals, hydrogen, hydrophobic, and electrostatic forces between the polymer and the biological tissue (including the mucus), which form secondary chemical bonds, result in the adhesion of polymer to the mucosa. There is a critical degree of hydration required for optimum mucoadhesion. The incomplete hydration because of the lack of the water leads to incomplete liberation of the polymer chains.[17, 18, 19, 20, 21, 22,]

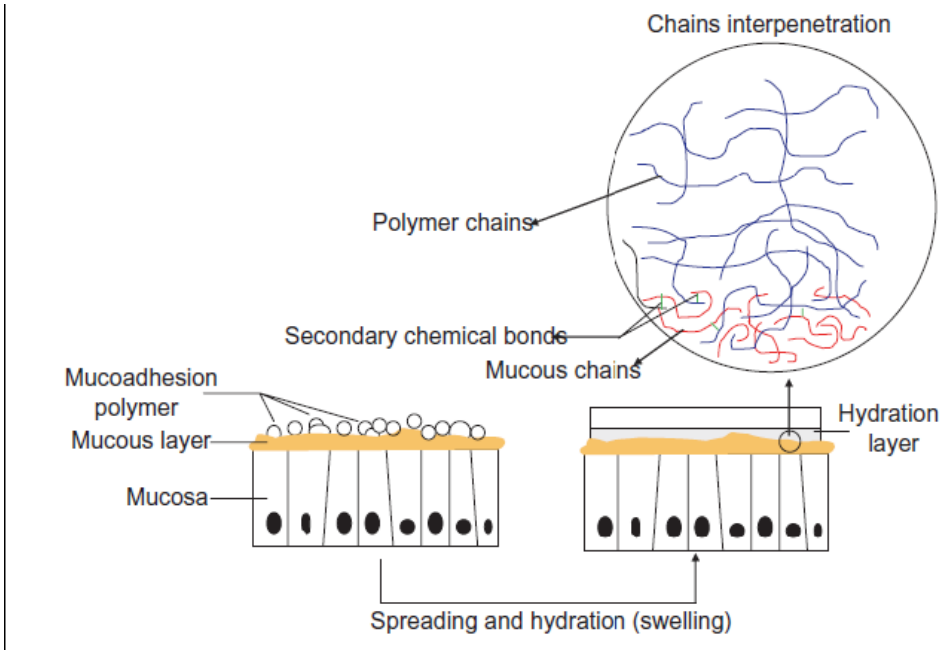

Figure 1: Schematic representation of the process of mucoadhesion on the nasal mucosa surface

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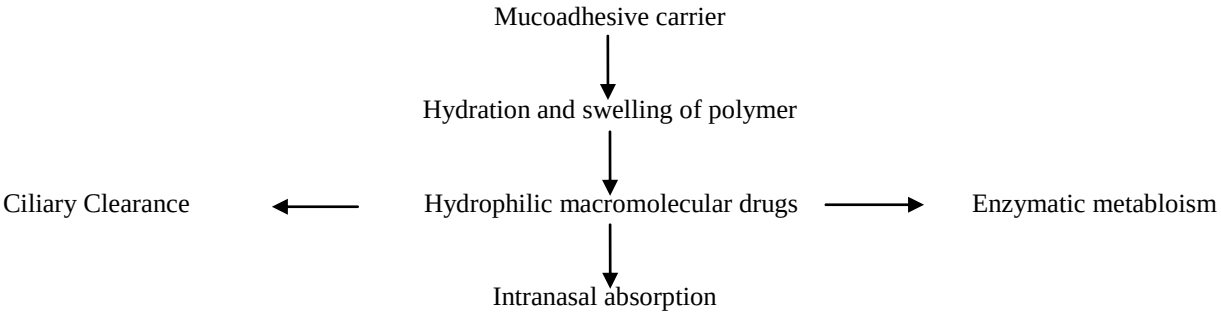

Figure 2: Schematic representation of the mucoadhesive intranasal formulation.

Nasal anatomy and physiology: [23, 24]

The nasal cavity is divided into two halves by the nasal septum and extends posteriorly to the nasopharynx, while the most anterior part of the nasal cavity, the nasal vestibule, opens to the face through the nostril (Figure 1). The atrium is an intermediate region between the vestibule and the respiratory region. The respiratory region, the nasal conchae or turbinates, which occupies the major part of the nasal cavity, possesses lateral walls dividing it into 3 sections:

- The superior
- Middle
- Inferior nasal turbinates.

The nasal vestibule has the smallest cross-sectional area in the respiratory tract (approximately 0.3 cm2 on each side) that extends from the entrance of nostril, which is guarded by vibrissae (hairs), to the anterior end of the inferior turbinate. The area from the anterior ends of the turbinate to the anterior portion of the nasopharynx constitutes the main nasal passages.The epithelial cells in the nasal vestibule are stratified, squamous and keratinized with sebaceous glands. Due to its nature, the nasal vestibule is very resistant to dehydration and can withstand noxious environmental substances and limits permeation of substances. Microvilli are found on the columnar cell, which increases the surface area available for absorption. The nasal mucosa is highly vasculature, superficial and deep layers of arterioles supply the lamina propria and between the venules and capillaries. Most of the area of the nasal cavity serves the function of cleaning the air we breathe before it reaches the lungs. It does this with the help of the respiratory mucosa, which lines the walls of the nasal cavity. Within this mucosa, small, hair-like cilia move in a wave-like motion, moving mucus to the back of the throat.

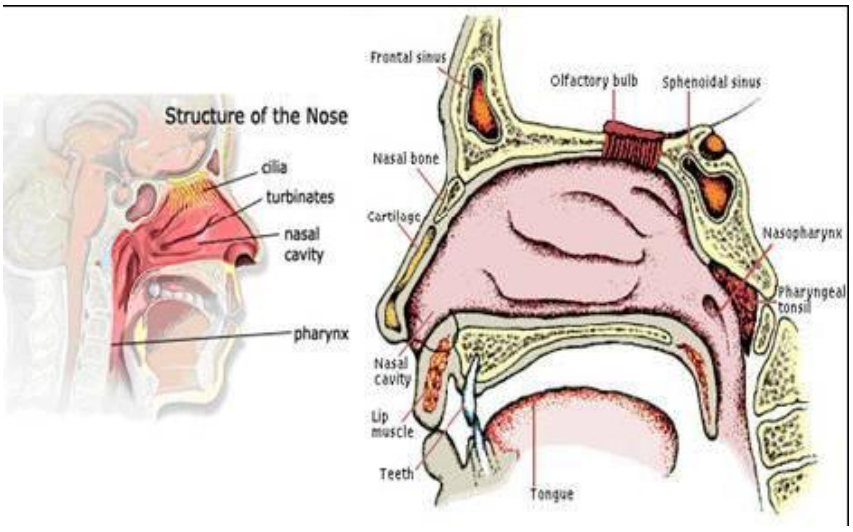

Figure: 3 Diagram of nasal route

Compatibility of Nasal route with diverse dosage forms:

The ultimate dosage form worn for nasal drug delivery is preferred after contemplation of a wide range of factors, covering patient convenience, efficiency of drug delivery and formulation reasons. Nasal sprays, squeeze bottles, and liquid droppers are some of the more common liberation methods that can be seen as nasal dosage forms. There are three chief ways of depositing inhaled particles or the nasal lining: impaction, sedimentation and diffusion. Impaction

occurs when there is a change in direction of the airflow - as happens when inspired air passes through the nasal valve – and the inertia of large or fast-moving particles carries them in their original direction. Sedimentation happens when the moving slowly and the particles settle slowly under the force of gravity. The final method of deposition diffusion occurs by Brownian motion and is thus limited to very small particles (< 0.5 mm). Nasal dosage forms will usually contain the drug in a liquid or powder formulations delivered by a pressurized or pump system.

Solid dosage forms:

Powders:

Dry powder formulations can also avoid the utilization of preservatives and freeze storage, because they do not support microbial growth and are more stable than solution. For these reasons, the dried powder is the most commonly studied formulation for the nasal drug delivery, including small hydrophobic drugs, peptide drugs, and vaccine. Prepared dry powder nasal influenza vaccine formulation by using spray-freeze-drying method; the results indicated that the powders were amorphous and more stable with respect to liquid formulations. *In vivo* experiments demonstrated that the powders significantly increased residence time in rats and elicit enhanced serum and mucosal antibody response. Powder dosage forms of drugs for nasal administration offer several advantages over liquid formulations. In the powder form, the chemical stability of the drug is increased, a preservative in the formulation is not required, and it is possible to administer larger doses of drugs. Powder form is suitable for number of non-peptide drugs and is well suited for peptide drugs. Polymer-based powder formulations show no adhesion until their absorption of mucus occurs on the nasal mucosa surface. This allows easy application to the nasal cavity by metered dose in sufflation even if the polymer is highly mucoadhesive. In addition, liquid preparations are more easily cleared to the nasopharynx and oropharynx from where they enter the posterior part of the tongue. Therefore, administration of nasal powders may increase patient compliance, especially if the smell and taste of the delivered drug is unacceptable. After getting in contact with the nasal mucosa, polymer-based powders are believed to form a viscous gel following absorbing water from the nasal mucus. Then, the free polymer chains penetrating into the tissue crevices can hold back the ciliary movement, which will increase the retention time of the drugs in the nasal cavity.[25, 26, 27, 28]

Table 1: Summing up of some nasal drug delivery studies where solid doage from were employed [29-33]

S.No	Active pharmaceutical ingredient	Dosage form	Bioadhesive polymer	Animal species
01.	Dopamine	Powder	Hydroxy propyl cellulose	Rabbits
02.	Gentamycin	Powder	Chitosan	Rabbits
03.	Pentazocin	Powder	Chitosan	Rabbits
04.	Apomorphine	Powder	Carbopol971p	Rabbits
05.	Desmopressin	Powder	Starch	Sheeps
06.	Insulin	Powder	Starch	Sheeps
07.	Insulin	Powder	Carbopol 974p	Rabbits
08.	Morphine HCl	Powder	Strach microsphere	Sheeps
09.	Pentazocin	Powder	Chitosan microspheres	Rabbits
10.	Gentamicin	Powder	Chitosan	Rabbits
11.	Insulin	Powder	Aminated gelatin microspheres	Rabbits
12.	Insulin	Powder	Strach	Rats

Liquid dosage forms:

Solutions:

They give a better absorption of drug by directing the formulation into the anterior part of the cavity and covering a large part of the nasal mucosa. The drug solutions are nasally administered as nasal drops, sprays, and as metered dose nebulizer. The dose of the active ingredient administered depends upon the volume of drug and the concentration of drug in the formulation. The therapeutic levels of nitroglycerine, 3 ng/ml in central venous blood, 1.7 ng/ml in arterial blood, and 0.4 ng/ml in peripheral venous blood were achieved within 2 minutes following intranasal administration of 0.8 mg/ml of nitroglycerine in normal saline. The effect of formulation variables such as dose of active ingredient, pH of the solution, and its osmolarity on nasal absorption has been reported by various researchers. Liquid formulations used for nasal drug delivery are usually aqueous solutions of the drug and thus have the general benefits and drawbacks of pharmaceutical solutions. They are relatively simple to develop and manufacture compared to solid dosage forms but often have a lower microbiological and chemical stability, requiring the use of various preservatives. Squeezed bottles are often used for nasal decongestants and work by spraying a partially atomized jet of liquid into the nasal cavity.

Suspensions:

Suspensions for nasal administration are prepared by suspending the micronized drug in a liquid diluents or carrier suitable for application to the nasal mucosa. The preparation of suspension form gave a better insulin uptake and blood glucose reduction compared with that from the solution.

Table 2: Summing up of some nasal drug delivery studies where liquid dosage form were employed [34-42]

S.No	Active pharmaceutical ingredient	Dosage form	Bioadhesive polymer	Animal species
01.	Insulin	Liquid	Chitosan	Human
02.	Levonorgestrel	Liquid	Chitosan	Rats
03.	Salmon calcitonin	Liquid	Chitosan	Rats
04.	Insulin	Liquid	Chitosan/EDTA	Rats
05.	Goserelin	Liquid	Chitosan microspheres	Sheeps
06.	Metoclopramide	Liquid	Degradable starch microspheres	Human
07.	Dopamine	Liquid	HPC	Dogs
08.	Metoclopramide	Solution	Carbopol 981p	Sheeps
09.	Keterolac tromethamine	Spray	MCC	Rabbits
10.	Insulin	Spray	MCC	Rabbits
11.	Midazolam	Spray	HPMC	Humans
12.	Metaclopramide	Spray	Chitosan	Rabbits

Semi-solid dosage forms:

A gel is a soft, solid or solid-like material consisting of two or more components, one of which is a liquid, present in substantial quantity. A gel should, on a time scale of seconds, not flow under the influence of its own weight. The solid-like characteristics of gels can be defined in terms of two dynamic mechanical properties: An elastic modulus, which exhibits a pronounced plateau extending to time at least of the order of second; and a viscous modulus. The first biological uses of gels were presented by the institute for Macromolecular Chemistry in Prague in 1960 and involved the manufacturing of contact lenses, arteries, etc.

- Gelation occurs through the cross-linking of polymer chains, something that can be achieved by covalent bond formation.
- Non-covalent bond formation. Gels have been used for the delivery of drugs for both systemic and local actions. Many different methods using gels have been reported, including subcutaneous delivery for sustained release, buccal delivery, deliveries to the stomach, colon, rectum, vagina, and nasal.

Gel formulations with suitable rheological properties increase the contact time with the mucosa at the site of absorption. The increased contact time is caused by the mucoadhesive properties of the polymer in the gel and by the rheological properties of the formulation reducing the clearance by the nasal and ocular protective mechanisms.

Table 3: Summing up of some nasal drug delivery studies where semi-solid dosage form were employed[43-44]

S.No	Active pharmaceutical ingredient	Dosage form	Bioadhesive polymer	Animal species
01.	Ciprofloxacin	Gel	HPMC	Rabbits
02.	Ciprofloxacin	Gel	MC	Rabbits
03.	Ciprofloxacin	Gel	Tween 80	Rabbits
04.	Metoclopramide	Gel	Carbopol	Rabbits

Bioadhesive polymers used for the delivery through nasal route:

Chitosan:

Chitosan and its derivatives have been shown to be active in enhancing the intranasal drug absorption due to their excellent mucoadhesive properties. It was also confirmed that coating micro- and nanoparticulates with chitosan could improve drug adsorption to mucosal surfaces shows various chitosan derivatives used in nasal drug delivery system. Chitosan [2-amino-2-deoxy-(1-4)-β-dglucopyranan] is a linear cationic polysaccharide that is obtained by a process of deacetylation from chitin, an abundant structural polysaccharide in shells of crustacean such as lobsters, shrimps, and crabs. Because of the NH2 groups resulting from the deacetylation process, chitosan is insoluble at neutral and alkaline pH. However, it can form water-soluble salts with inorganic and organic acids including glutamic acid, hydrochloric acid, lactic acid, and acetic acid.[45, 46, 47]

Literature review of chitosan based delivery of drugs through for nasal route:

- Soane et al. have reported that chitosan microspheres and solutions revealed a three and eightfold longer clearance half-lives compared with sodium pertechnetate labelled solution in sheep nasal cavity, respectively.[48]
- Thanou *et al*. reported that the trimethyl chitosan was soluble and effective on enhancing intranasal absorption even at neutral pH.N-trimethyl chitosan hydrochlorides are more mucoadhesive than unmodified chitosans and show a higher

bioavailability *in vivo* compared with the unmodified chitosans. To improve the poor water solubility of chitosan, some derivatives were synthesized, such as trimethyl chitosan.[49, 50, 51]

- Mei *et al*. reported that the permeation-enhancing effect of chitosan increased with increasing molecular weight up to Mw 100.[52]
- Tengamnuay *et al*. suggested that chitosans should differ in their molecular weight by at least two-fold in order to have a clearly differentiating effect on the nasal absorption enhancement of a kyotorphin analogue.[53]
- Zaki *et al*. found that there is no significant difference between the constants of intranasal absorption for metoclopramide HCl administered with chitosan high weight (600 kDa) and low weight (150 kDa) even though they differ in molecular weight by four-fold.[54]

Starch:

The starch is one of the most widely used mucoadhesive carrier for nasal drug delivery, which has been reported to be effective on improving the absorption of both small hydrophobic drugs and hydrophilic macromolecular drugs. Maize starch is the most preferred class for pharmaceutical purpose, among which the drum-dried waxy maize starch, due to its better bioadhesive property, has been considered as the best one compared with starch processed through other methods.[55]

Starch can be used as nasal drug carrier in the form of powders, microspheres, or nanoparticles, among which the degradable starch microspheres (DSM), also known as SpherexR.

Literature review of strach based delivery of drugs through for nasal route[56, 57, 58, 59]:

- Bjork and Edman suggested that water uptake by DSM and subsequent swelling might cause dehydration of the epithelial cells leading to the widening of tight junctions and as a consequence facilitate the paracellular transport of large hydrophilic molecules such as insulin. It was suggested that the extent of drug absorption was improved even further when DSM were combined with the biological enhancers such as lysophosphatidylcholine (LPC). DSM can also protect the proteins wrapped in it against degradation by proteases in the mucosa.
- Illum et al. have observed that the half-life of clearance for DSM was prolonged to 240 minutes compared with 15 minutes for the liquid and powder control formulations.

Cellulose derivatives:

Cellulose derivatives can markedly prolong the residence time of drugs in the nasal cavity due to their desirable mucoadhesive property. Additionally, due to their high viscosity following hydration in the nasal cavity, the celluloses can sustain the release of drugs. For these reasons, using celluloses as absorption enhancer can lead to improved intranasal absorption and increased bioavailability. Many references show that the celluloses are effective on increasing the intranasal bioavailability of small hydrophobic as well as hydrophilic macromolecular drugs.[60, 61]

There are many pharmaceutical grade derivatives of cellulose widely used in different administration routes. Several cellulose derivatives have proved to be effective in enhancing the intranasal absorption of drugs, including soluble cellulose derivatives such as hydroxypropyl methylcellulose (HPMC), hydroxypropyl cellulose (HPC), methylcellulose (MC) and carboxymethyl cellulose (CMC), and insoluble cellulose derivatives such as ethylcellulose (EC) and microcrystalline cellulose (MCC).

Literature review of cellulose derivative based delivery of drugs through for nasal route[62]:

Ikeda et al. involving the intranasal delivery of dopamine, the combination of the HPC and azone led to an absolute bioavailability of almost 100% whereas it was only 25% with HPC alone.

Polyacrylates: [63-66]

Polyacrylates, capable of attaching to mucosal surfaces, can offer the prospects of prolonging the residence time of drugs at the sites of drug absorption and ensure intimate contact between the formulation and the membrane surface. Among the pharmaceutical polyacrylates, carbomers and polycarbophil, which differ in the cross-linking condition and viscosity, are widely used in the nasal mucoadhesive drug delivery systems.

Literature review of polyacrylates based delivery of drugs through for nasal route[62]:

Callens et al. reported that the effect of Carbopol on the mucosa is negligible and reversible, no change of the epithelium barrier was observed even after a 4-week administration of Carbopol-based powder formulation in rabbits. [67, 68]

Another research by Ugwoke et al. showed that the Tmax of the Carbopol 971P-containing formulation of apomorphine was 52.21 minutes, which represented a fivefold improvement compared with that of the lactose-containing formulation, whereas the Cmax of the Carbopol 971Pcontaining formulation was 330.2 ng/mL, lower than that of the lactose containing formulation, which was 450.7 ng/mL. [69]

CONCLUSION:

Mucoadhesive polymers will undoubtedly be utilized for the nasal delivery of a wide variety of therapeutic compounds. This class of polymers has mammoth prospective for the delivery of therapeutic macromolecules, genes, and vaccines. Unluckily, only a small number of studies have been conducted with new-generation mucoadhesive polymers for nasal drug delivery, and very hardly any papers focus on the changes of structure and rheology of the mucus caused by the mucoadhesive polymer, and as to what extent the interaction between the polymer and the mucus influences the release of the drugs including the diseased condition. With recent advancements in the

fields of biotechnology and cytoadhesion, the authors believe that there will be both academic and industrial efforts to explore this new area of nasal drug delivery, and it might not be too farfetched to envisage more and more nasal products that employ mucoadhesive polymers. Current use of mucoadhesive polymers to increase contact time for a wide variety of drugs and routes of administration has shown dramatic improvement in both specific therapies and more general patient compliance. The general properties of these polymers for purpose of sustained release of chemicals are marginal in being able to accommodate a wide range of physicochemical drug properties. Hence mucoadhesive polymers can be used as means of improving drug delivery through different routes like gastrointestinal, nasal, ocular, buccal, vaginal and rectal. Many potential mucoadhesive systems are being investigated which may find their way into the market in near future.

REFERENCES:

1. Asane GS, Nirmal SA, Rasal KB, Naik AA, Mahadik MS, Madhusudan Rao YM. Polymers for mucoadhesive drug delivery system: A current status. Drug Dev Ind Pharm. 2008; 34:1246 66.
2. KR Kamath, K Park. Mucosal Adhesive Preparations. In Encyclopedia of Pharmaceutical Technology: Swarbrick J, Boylon J.C. 1st Eds. Vol-10, Marcel Dekker, New York, **1994**, 133.
3. Gavini E, Hegge AB, Rassu G, Sanna V, Testa C, Pirisino G, Karlsen J, Giunchedi P. Nasal administration of Carbamazepine using chitosan microspheres: In vitro/in vivo studies Int J Pharm. 2006;307(1): 9–15
4. Mainardes RM, Urban MC, Cinto PO, Chaud MV, Evangelista RC, Gremiao MP. Liposomes and micro / nanoparticles as colloidal carriers for nasal drug delivery. Curr Drug Deliv. 2006; 3(3): 275-85.
5. Ugwoke MI, Verbeke N, Kinget R. The biopharmaceutical aspects of nasal mucoadhesive drug delivery. J Pharm Pharmacol. 2001; 53(1):3–21.
6. Song K, Fasano A, Eddington ND. Enhanced nasal absorption of hydrophilic markers after dosing with AT1002, a tight junction modulator. Eur J Pharm Biopharm. 2008; 69(1):231–7.
7. Khafagy E, Morishita M, Isowa K, Imai J, Takayama K. Effect of cell-penetrating peptides on the nasal absorption of insulin. J Control Release. 2009; 133(2):103–8.
8. Li L, Nandi I, Kim KH. Development of an ethyl laurate based microemulsion for rapid-onset intranasal delivery of diazepam. Int J Pharm. 2002; 237(1-2):77–85.
9. Zaki NM, Awad GAS, Mortada ND, Abdelhady SS. Rapid-onset intranasal delivery of metoclopramide hydrochloride: Part I: Influence of formulation variables on drug absorption in anesthetized rats. Int J Pharm. 2006; 327(1-2):89–96.
10. Illum L, Fisher AN, Jabbal-Gill I, Davis SS. Bioadhesive starch microspheres and absorption enhancing agents act synergistically to enhance the nasal absorption of polypeptides. Int J Pharm. 2001; 222(1):109–19.
11. Romeo VD, DeMeireles JC, Gries WJ, Xia WJ, Sileno AP, Pimplaskar HK, Behl CR. Optimization of systemic nasal drug delivery with pharmaceutical excipients. Adv Drug Deliv Rev. 1998; 29: 117–33.
12. Farraj NF, Johansen BR, Davis SS, Illum L. Nasal administration of insulin using bioadhesive microspheres as a delivery system. J Control Release. 1990; 13(2-3):253–61.
13. Hascicek C, Gonul N, Erk N. Mucoadhesive microspheres containing gentamicin sulfate for nasal administration:Preparation and in vitro characterization. IL Farmaco. 2003; 58(1):11–6.
14. Harris AS. Review: Clinical opportunities provided by the nasal administration of peptides. J Drug Targeting. 1993;1:101–16.
15. Longer MA, Robinson JR. Fundamental aspects of bioadhesion. Pharm Int. 1986; 7:114–7.
16. Gu JM, Robinson JR, Leung SH. Binding of acrylic polymers to mucin/epithelial surfaces: Structure-property relationships. Crit Rev Ther Drug Carrier Syst. 1988; 5(1):21–67.
17. Jimenez-Castellanos MR, Zia H, Rhodes CT. Mucoadhesive drug delivery systems. Drug Dev Ind Pharm.1993; 19(1-2):143–94.
18. Sriamornsak P, Wattanakorn N, Nunthanid J, Puttipipatkhachorn S. Mucoadhesion of pectin as evidence by wettability and chain interpenetration. Carbohydr Polymers. 2008; 74(3):458–67.
19. Smart JD. The basics and underlying mechanisms of mucoadhesion. Adv Drug Deliv Rev.2005;57(11):1556–68.
20. Jabbari E, Wisniewski N, Peppas NA. Evidence of mucoadhesion by chain interpenetration at a poly (acrylicacid)/mucin interface using ATRFTIR spectroscopy. J Control Release.1993; 26(2):99–108.
21. Grabovac V, Guggi D, Bernkop-Schnurch A. Comparison of the mucoadhesive properties of various polymers. Adv Drug Deliv Rev.2005; 57:1713–23.
22. Accili D, Menghi G, Bonacucina G, Martino PD, Palmieri GF. Mucoadhesion dependence of pharmaceutical polymers on mucosa characteristics. Eur J Pharm Sci. 2004; 22(4):225–34.
23. Nakamura K, Maitani Y, Lowman AM, Takayama K, Peppas NA, Nagai T. Uptake and release of budesonide from mucoadhesive, pH-sensitive copolymers and their application to nasal delivery. J Control Release 1999, 61,329– 335.
24. Park JS, Oh YK, Yoon H, Kim JM, Kim CK. In situ gelling and mucoadhesive polymer vehicles for controlled intranasal delivery of plasmid DNA. J Biomed Mater Res 2002, 59,144–151.
25. Joshi M, Misra A. Dry powder inhalation of liposomal Ketotifen fumarate; formulation and characterization. Int J Pharm. 2001; 223:15–27.
26. Kublik H, Vidgren MT. Nasal delivery systems and their effect on deposition and absorption. Adv Drug Deliv Rev. 1998; 29:157–77.
27. Castellanos J, Zia H, Rhodes CT. Mucoadhesive drug delivery systems. Drug Dev Ind Pharm. 1993; 19:143–94.
28. Lee WA, Narog BA, Patapoff TW, Wang YJ. Intranasal bioavailability of insulin powder formulations: Effect of permeation enhancer-to-protein ratio. J Pharm Sci. 1991; 80:725–9.
29. Sankar C, Rani M, Srivastava AK, Mishra B., Chitosan based pentazocine microspheres for intranasal systemic delivery: Development and biopharmaceutical evaluation. Pharmazie. 2001; 56:223–6.
30. Lim ST, Forbes B, Martin GP, Brown MB., In vivo and in vitro characterization of novel microparticulates based on hyaluronan and chitosan hydroglutamate. AAPS PharmSci Tech. 2001; 2(4):20.
31. Mao S, Chen J, Wei Z, Liu H, Bi D., Intranasal administration of melatonin starch microspheres. Int J Pharm. 2004; 272:37–43.
32. Pringels E, Vervaet C, Verbeeck R, Foreman P, Remon JP., The addition of calcium ions to starch/carbopol mixtures enhances the nasal bioavailability of insulin. Eur J Pharm Biopharm. 2008; 68:201–6.
33. Illum L, Fisher AN, Jabbal-Gill I, Davis SS. Bioadhesive starch microspheres and absorption enhancing agents act synergistically to enhance the nasal absorption of polypeptides. Int J Pharm. 2001; 222(1):109–19.
34. Sinswat P, Tengamnuay P., Enhancing effect of chitosan on nasal absorption of salmon calcitonin in rats: Comparison with

hydroxypropyl-beta and dimethyl-betacyclodextrins. Int J Pharm, 2003; 257:15–22.
35. Yu S, Zhao Y, Wu F, Zhang X, Lu W, Zhang H, Zhang Q. Nasal insulin delivery in the chitosan solution: In vitro and in vivo studies. Int J Pharm. 2004; 281:11–23.
36. Lim ST, Forbes B, Berry DJ, Martin GP, Brown MB., In vivo evaluation of novel hyaluronan/chitosan microparticulate delivery systems for the nasal delivery of gentamicin in rabbits. Int J Pharm. 2002; 231:73–82.
37. Vivien N, Buri P, Balant L, Lacroix S., Nasal absorption of metoclopramide administered to man. Eur J Pharm Biopharm. 1994; 40:228–31.
38. Shahiwala A, Misra A. Nasal delivery of levonorgestrel for contraception: An experimental study in rats. Fertil Steril. 2004;81:893–8.
39. Paul W, Sharma CP. Chitosan, a drug carrier for the 21st century: A review. STP Pharm Sci. 2000; 10(1):5–22.
40. Zaki NM, Mortada ND, Awad GAS, Abd Elhady SS. Rapid-onset intranasal delivery of metoclopramide hydrochloride Part II: Safety of various absorption enhancers and pharmacokinetic evaluation. Int J Pharm. 2006; 327:97–103.
41. Dondeti P, Zia H, Needham TE., In vivo evaluation of spray formulations of human insulin for nasal delivery. Int J Pharm. 1995; 122: 91–105.
42. Loftsson T, Gudmundsdottir H, Sigurjonsdottir JF, Sigurdsson HH, Sigfusson SD, Masson M, Stefansson E. Cyclodextrin solubilization of benzodiazepines: Formulation of midazolam nasal spray. Int J Pharm. 2001;212:29–40.
43. Zaki NM, Awada GA, Mortadaa ND, Abd Elhadyb SS. Enhanced bioavailability of metoclopramide HCl by intranasal administration of a mucoadhesive in situ gel with modulated rheological and mucociliary transport properties. Eur J Pharm Sci. 2007; 32(4-5):296-307.
44. Ozsoy Y, Tuncel T, Can A, Akev N, Birteksoz S, Gerceker A. In vivo studies on nasal preparations of ciprofloxacin hydrochloride. Pharmazie. 2000; 55(8):607–9.
45. Issa MM, Koping-Hoggard M, Artursson P. Chitosan and the mucosal delivery of biotechnology drugs. Drug Discov Today. 2005; 2(1):1–6.
46. Paul W, Sharma CP. Chitosan, a drug carrier for the 21st century: A review. STP Pharm Sci. 2000; 10(1):5–22.
47. Illum L. Nasal drug delivery: New developments and strategies. Drug Discov Today. 2002; 7:1184–9.
48. Soane RJ, Hinchcliffe M, Davis SS, Illum L. Clearance characteristics of chitosan based formulations in the sheep nasal cavity. Int J Pharm. 2001; 217(1-2):183–91.
49. Kotze AF, Luesen HL, De Boer AG, Verhoef JC, Junginger HE. Chitosan for enhanced intestinal permeability: Prospects for derivatives soluble in neutral and basic environments. Eur J Pharm Sci.1999;7:145–51.
50. Thanou M, Verhoef JC, Verheijden JH, Junginger HE. Intestinal absorption of octeriotide: N-trimethyl chitosan chloride (TMC) ameliorates the permeability and absorption properties of the somatostatin analogue *in vitro* and *in vivo*. J Pharm Sci. 2000; 89:951–7.
51. Lai WF, Lin MC. Nucleic acid delivery with chitosan and its derivatives. J Control Release. 2009;134:158–68.
52. Mei D, Mao S, Sun W, Wang Y, Kissel T. Effect of chitosan structure properties and molecular weight on the intranasal absorption of tetramethylpyrazine phosphate in rats. Eur J Pharm Biopharm.2008;70:874–81.
53. Tengamnuay P, Sahamethapat A, Sailasuta A, Mitra AK. Chitosans as nasal absorption enhancers of peptides: Comparison between free amine chitosans and soluble salts. Int J Pharm. 2000; 197:53–67.
54. Quadir M, Zia H, Needham TE. Toxicological implications of nasal formulations. Drug Del. 1999;6:227–42.
55. Callens C, Pringels E, Remon JP. Influence of multiple nasal administrations of bioadhesive powders on the insulin bioavailability. Int J Pharm. 2003; 250:415–22.
56. Bjork E, Bjurstrom S, Edman P. Morphologic examination of rabbit nasal mucosa after nasal administration of degradable starch microspheres. Int J Pharm.1991; 75:73–79.
57. Holmberg K, Bjork E, Bake B, Edman P. Influence of degradable starch microspheres on human nasal mucosa. Rhinology. 1994; 32(2):74–7.
58. Bjork E, Edman P. Characterization of degradable starch microspheres as a nasal delivery system for drugs. Int J Pharm. 1990; 62(2-3):187–92.
59. Illum L, Jorgensen H, Bisgaard H, Krogsgaard O, Rossing N. Bioadhesive microspheres as a potential nasal drug delivery system. Int J Pharm. 1987; 39(3):189–99.
60. Zaki NM, Awada GA, Mortadaa ND, Abd ElHadyb SS. Enhanced bioavailability of metoclopramide HCl by intranasal administration of mucoadhesive *in situ* gel with modulated rheological and mucociliary transport properties. Eur J Pharm Sci. 2007; 32:296–307.
61. Wang X, Chi N, Tang X. Preparation of estradiol chitosan nanoparticles for improving nasal absorption and brain targeting. Eur J Pharm Biopharm. 2008;70:735–40.
62. Ikeda K, Murata K, Kobayashi M, Noda K. Enhancement of bioavailability of dopamine via nasal route in beagle dogs. Chem Pharm Bull. 1992; 40(8):2155–8.
63. Bommareddy GS, Paker-Leggs S, Saripella KK, Neau SH. Extruded and spheronized beads containing Carbopol 974P to deliver non electrolytes and salts of weakly basic drugs. Int J Pharm. 2006; 321(1-2):62–71.
64. Qi H, Chen W, Huang C, Li L, Chen C, Li W, Wu C. Development of a poloxamer analogs/carbopol-based in situ gelling and mucoadhesive ophthalmic delivery system for puerarin. Int J Pharm. 2007; 337(1-2):178–87.
65. Funke AP, Gunther C, Muller RH, Lipp R. In-vitro release and transdermal fluxes of a highly lipophilic drug and of enhancers from matrix TDS. J Control Release 2002; 82(1):63–70.
66. Liu W, Hu M, Liu W, Xue C, Xu H, Yang X. Investigation of the carbopol gel of solid lipid nanoparticles for the transdermal iontophoretic delivery of triamcinolone acetonide acetate. Int J Pharm. 2008; 364(1):135–41.
67. Callens C, Remon JP. Evaluation of starch maltodextrin-Carbopol 974P mixtures for the nasal delivery of insulin in rabbits. J Control Release. 2000; 66(2-3):215–20.
68. Callens C, Adriaens E, Dierckens K, Remon JP. Toxicological evaluation of a bioadhesive nasal powder containing a starch and Carbopol 974 P on rabbit nasal mucosa and slug mucosa. J Control Release. 2001; 76(1-2):81–91
69. Ugwoke MI, Sam E, Van Den Mooter G, Verbeke N, Kinget R. Nasal mucoadhesive delivery systems of the anti-Parkinsonian drug, apomorphine: Influence of drugloading on in vitro and in vivo release in rabbits. Int J Pharm. 1999; 181:125–38.

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