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UTILIZING MUCOADHESIVE POLYMERS FOR NASAL DRUG DELIVERY SYSTEM

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ABSTRACT: Nasal drug delivery has been recognized as a promising route for delivery of therapeutic compounds including biopharmaceuticals. It has been demonstrated that absorption of drugs can enhanced by using absorption enhancers or increasing the drug residence time in the nasal cavity. Mucoadhesive polymers can serve both functions. The residence time in the nasal cavity is considerably increased for microspheres compared to solutions. However, this is not the only factor to increase the absorption of large hydrophilic drugs. Microspheres also exert a direct effect on the mucosa, resulting in the opening of tight junctions between the epithelial cells. This review focuses on the background of nasal mucoadhesive drug delivery with special references to the biological and pharmaceutical considerations for nasal mucoadhesive drug administration.

INTRODUCTION: Nasal drug delivery for systemic effects has been practiced since long times. In modern pharmaceutics, the nose had been considered predominate route for local drug delivery. Recent advancement in pharmaceutical biotechnology resulting in possibilities for largescale productions of biopharmaceuticals especially proteins and peptides. The inability to administer these drugs by routes other than parenteral injection motivated scientists to explore other possibilities such as nasal and pulmonary administration. The initial enthusiasm was soon challenged with disappointing in vivo results showing poor bioavailabilitiese specially for large molecules. On the other hand, very good results were obtained with small molecules, which led to the successful development of a number of products currently on the market [1], and list of products that is steadily increasing.

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The short residence time of the formulation within the nasal cavity coupled to the low permeability is the main cause of failure in delivery of these drugs. The evaluation of mucoadhesive polymers showed promising results, some of which would even demonstrate additional permeation-enhancing capabilities [2, 3]. Another advantage of nasal administration is that 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[4].

Furthermore, selfmedication is easy and convenient. Recent challenges stimulated the development of new generations of polymers based on pH or thermal responsiveness [5, 6] or modified existing polymers having improved bioadhesive or permeation-enhancing properties [7-9]. The potential of nasal drug delivery including the ability to target drugs across the blood–brain barrier (BBB), are very high and hence, the toxicity of this drug delivery needs to be evaluated.

This review paper discuss the background of nasal mucoadhesive drug delivery with special references to the biological and pharmaceutical considerations for nasal mucoadhesive drug administration and the mucoadhesive polymers.

Advantages of Nasal Route: Systemic nasal absorption of drug is a alternative to parenteral drug delivery system, as it various advantages, which include [10]:

- The nasal mucosa consists of subepithelial layer of the nasal mucosa with numerous microvilli is highly vascularized, with large and fenestrated capillaries facilitating rapid absorption.
- Drug enters directly in systemic circulation through transnasal route e.g., Thiomeerosal, Amastatin, Puromycin, Nifedipine, etc.
- The plasma concentration vs time profiles as well as rate and extent of absorption are comparable with I.V. administration.
- Aviod first pass elimination, destruction in gastrointestinal tract and gut wall metabolism.
- Nasal drug delivery systems are available for userfriendly noninvasive painless application.

Limitation of Nasal Drug Delivery System: There is risk of irreversible damage of the cilia on the nasal mucosa and local side effects, both from the drug substances and from the constituents added to the dosage forms [10].

- Certain compounds when used as absorption enhancers may disrupt and even dissolve the nasal membrane in high concentration.
- The conditions like nasal atrophic rhinitis and severe vasomotor rhinitis can reduce the capacity of nasal absorption, e.g., Caerulein.
- Potential loss of the dosage form into the other parts of the respiratory tract like lungs.
- Untoward immunogenic effects might arise with the route.
- It can result in low bioavailability results from enzymatic degradation and metabolism at mucosal site and low residence time.

Nasal Cavity: The nasal cavity serves important protective functions in which, it filters, warms, and humidifies the inhaled air before it reaches the lower airways. Any inhaled microorganisms or particels are trapped by the hairs in the nasal vestibule or by the mucus layer covering the respiratory area of the nasal cavity. The mucociliary clearance mechanism, layer will gradually carry such particulates to the back of the throat, down the esophagus, and further into the gastrointestinal tract. Furthermore, the nasal layer mucosa has a metabolic capacity that will help convert endogenous materials into compounds that lies beneath are more easily eliminated [11].

Biological and pharmaceutical considerations for nasal mucoadhesive drug delivery:

Nasal Anatomy and Physiology: The nostrils are a pair of nasal cavities divided by a nasal septum; their total volume is approximately 15 cc , with a total surface area of 150 cm . These nasal cavities are covered by a mucosa with a thickness of 2 to 4 mm, whose function in human beings is 20% olfactory and 80% respiratory. The nasal epithelium has a relatively high permeability, and only two cell layers separate the nasal lumen from the dense blood vessel network in the lamina propria cavity which is lined with three types of epithelia: Squamous, respiratory, and olfactory **Fig. 1** [12, 13]. The mucosa in the anterior part of the nose is squamous and without cilia. Within the anterior nostrils, a transitional epithelium is found that precedes the respiratory epithelium. The olfactory epithelium is present in the posterior part of the nasal cavity. The epithelium contains ciliary cells that produce a unidirectional flow of mucus toward the pharynx [14]. A drug deposited posteriorly in the nose is cleared more rapidly from the nasal cavity than a drug deposited anteriorly, because clearance is slower at the anterior part of the nose than in the more ciliated posterior [15].

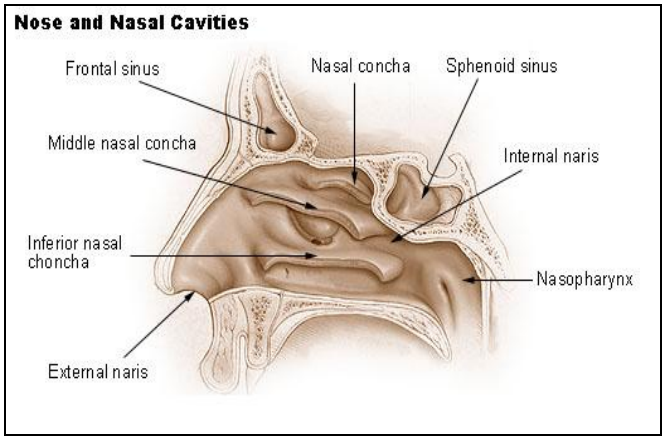

FIG. 1: LATERAL WALL OF THE NASAL CAVITY

Nasal Mucosal: The nasal lining has pseudostratified ciliated columnar same as the rest of the respiratory tract epithelium. There are up to 200 cilia per cell whose tips lie in the superficial gel layer **Fig. 2**. At the anterior end of the inferior and middle turbinate, which is the area which has most contact with inspired air, there can be metaplasia with cuboidal cells which have no cilia.

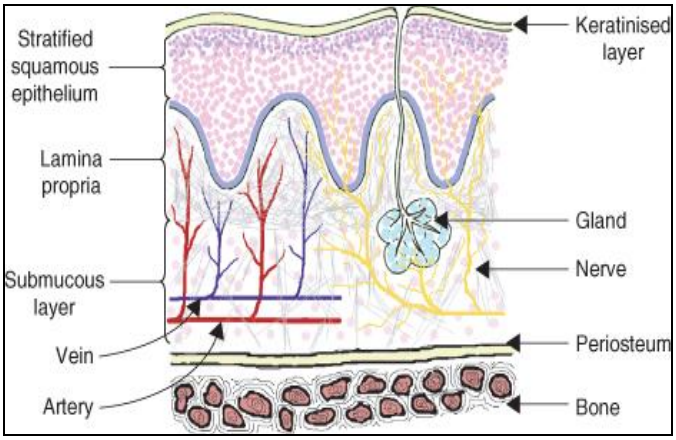

FIG. 2: STRUCTURE OF NASAL MUCOSA

Mucoadhesion/bioadhesion: The term 'bioadhesion' is described as 'the attachment of a synthetic or biological macromolecule to mucus and/or an epithelial surface for an extended period time' by Longer et al. [16]. Similarly, the term is described as 'mucoadhesion' as 'the binding of polymers to mucin/epithelial surface' by Gu et al. [17]. In nasal drug delivery, mucoadhesion means the adherence of a polymeric material to nasal mucus (mucoadhesion) or nasal epithelial membrane (bioadhesion).

Mechanism of mucoadhesion: The process of mucoadhesion, following nasal administration is the interaction between the mucoadhesive polymer and the mucus secreted by the submucosal glands [18]. The sequential events that occur during the mucoadhesion include the proper wetting and swelling of the polymer, and close contact between the polymer and the nasal mucosa. Then, the swelled mucoadhesive polymer penetrates into the tissue crevices followed by the interpenetration between the polymer chains and the protein chains of the mucus (**Fig. 2**) [19]. In order 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, which depends on the flowability and wettablility for the solid mucoadhesive formulation [20, 21]. The polymer chains are liberated and interact with the biological tissue through hydration of the polymer (swelling), it plays a very important role in mucoadhesion [22]. There is a dissociation of hydrogen bonds of the polymer chains during hydration. 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 [19]. The adhesion of polymer to the mucosa form the secondary chemical bond between the polymer and the biological tissue (including the mucus) through van der Waals, hydrogen, hydrophobic, and electrostatic forces [23, 24].

Optimum mucoadhesion is governed by the critical degree of hydration. The incomplete hydration because of the lack of the water, leads to incomplete liberation of the polymer chains. On the other hand, an excessive amount of water will weaken the mucoadhesive bonds by overdiluting the polymer solution [4]. The 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]. Furthermore, the presence of the mucoadhesive carrier also reduces the contact between the drugs and the enzymes existing in the mucosa [19]. These both can enhance the intranasal absorption of hydrophilic drugs, **Fig. 3**. Apart from these, the dehydration of the epithelial cells after hydration may also temporarily open the tight junctions between the epithelial cells and improve the paracellular absorption of macromolecular drugs [4, 25]. The opening mechanism has been demonstrated by the decrease in ZO-1 proteins and the change in the cytoskeletal protein F-actin from a filamentous to a globular structure33. The enhancement of the intranasal absorption of macromolecules weighing above 1000 Da is a function of the mucoadhesive polymer [26].

Mucoadhesion can slow down the mucociliary clearance, but with time, mucus production will lead to the excessive swelling of the mucoadhesive polymer and the reduction of the mucoadhesion bond strength, allowing a recovery of normal mucociliary movement rate and the clearance of the polymer from the mucosa [19].

Although many references indicate that the mucoadhesive polymer is effective in enhancing the intranasal absorption of macromolecular drugs, very few papers focus on the changes of gel structure and rheology of the mucus caused by the mucoadhesive polymer and to what extent the interaction between the polymer and the mucus influences the release of the drugs, including in the disease condition. Disease conditions can affect mucoadhesion because of their influence on either mucus production or ciliary movement, and then may result in undesired drug release. Thus a good understanding of the nature of mucus in these diseases is imperative in designing a good nasal drug delivery system. Mucoadhesive capabilities of polymers should be studied under such disease conditions during the product development.

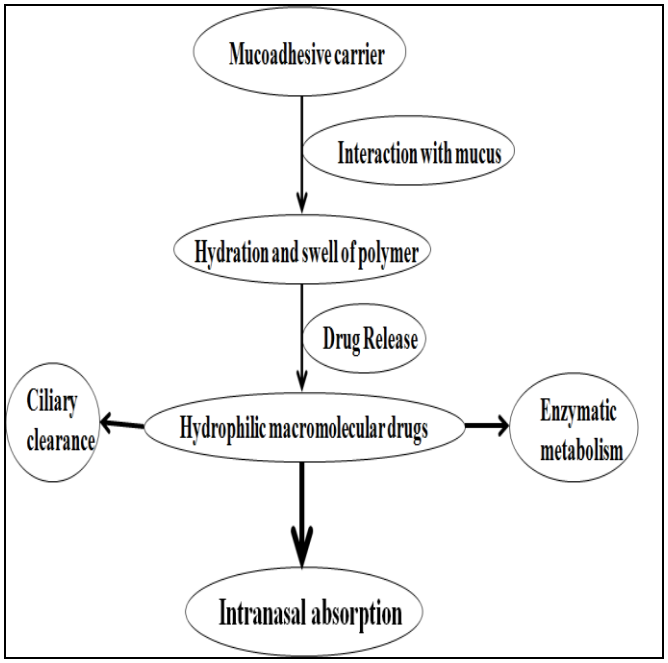

FIG. 3: SCHEMATIC REPRESENTATION OF MUCOADHESIVE INTRANASAL DRUG DELIVERY

The mucoadhesive carrier enhances the intranasal absorption by increasing the retention time of drugs and promoting the paracellular absorption in the nasal cavity whereas reducing the ciliary clearance. The mucoadhesive carrier can also protect the drugs from the enzymatic metabolism to a large extent.

Mucoadhesive polymers used in nasal drug delivery:

Polyacrylates: Polyacrylates have excellent mucoadhesive and gel-forming capability and hence, they have been investigated in many drug administration routes, such as transdermal [27, 28], ocular [29], oral [30] and nasal drug delivery systems [31]. Polyacrylates like carbomers and polycarbophil, which differ in the cross-linking condition and viscosity, are widely used in the nasal mucoadhesive drug delivery systems [32]. Polyacrylates are capable of attaching to mucosal surfaces, and can increase the residence time of drugs at the sites of drug absorption and ensure close contact between the formulation and the membrane surface.

The use of Carbopol 971P in nasal dosage forms increases their residence time in the nasal cavity has been studied. 24% of Carbopol 971P was cleared from the nasal cavity in 3 hours, whereas 70% of lactose was cleared from nasal cavity in 3 hours [15]. Sustained release of drugs can also be obtained by using polyacrylates in nasal formulation, which result in a more stable blood concentration–time curve. Another research by Ugwoke et al. showed that the T_{max} of 52.21 minutes for the Carbopol 971P-containing formulation of apomorphine, which represented a fivefold improvement compared with that of the lactose-containing formulation, whereas the C_{max} of the Carbopol 971P-containing formulation was 330.2 ng/mL, lower than that of the lactose containing formulation, which was 450.7 ng/mL [32].

Besides the mucoadhesion capability, polyacrylates may also temporarily open the tight junctions between the epithelial cells during the swelling progress in the nasal cavity and improve the paracellular absorption of drugs [33]. Based on these, polyacrylates can increase the intranasal bioavailability of both small hydrophobic drugs as well as hydrophilic macromolecular drugs.

Using the polycarbophil and Carbopol 971P in the nasal apomorphine formulation, a relative drug bioavailability of 105.0% and 99.8% compared with subcutaneous injection could be obtained, respectively [34]. An absolute bioavailability of 14.4% in rabbits was obtained for intranasal insulin formulation containing Carbopol 974P [35]. The Carbopol and polycarbophil are considered as Generally recognized as safe(GRAS) by FDA, and many studies show that they are nonirritant to the skin and eye and nontoxic orally [32].

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 [35, 36].

Starch: Starch has been reported to be effective on improving the absorption of both small hydrophobic drugs and hydrophilic macromolecular drugs and is one of the most widely used mucoadhesive carrier for nasal drug delivery. Maize starch is the most preferred class for pharmaceutical purpose, among which the drum-dried waxy maize starch (DDWM), because of its better bioadhesive property, has been considered as the finest compared with starch processed through other methods [36]. Starch can be used as nasal drug carriers in the form of microspheres, powders or nanoparticles, among which the degradable starch microspheres (DSM), also known as Spherex®, is the most widely used and also the first example of mucoadhesive microparticulate nasal delivery system [37].

These microspheres are prepared by an emulsion polymerization technique, in which the starch is cross-linked with epichlorohydrine which, can incorporate molecules weighing less than 30 kDa [37]. Because of its mucoadhesion, the DSM can enhance the drug absorption by prolonging the residence time of drugs in the nasal cavity [38]. Illum et al. has 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 [39]. Bjork and its coworkers 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 [40].

It was suggested that the biological enhancers such as lysophosphatidylcholine (LPC) increases the extent of drug absorption even further when combined with DSM [41-43]. DSM has an added advantage of protecting the proteins wrapped in it against degradation by proteases in the mucosa. Several studies showed that the release of drugs from DSM was rapid and, this suggested that the utility of DSM in nasal drug delivery could further be exploited in the treatment of crisis diseases [44]. It was reported that DSM were well tolerated both in experimental animals and in humans; when the DSM were administered two times per day for 8 weeks in dosages of 20 mg on healthy volunteers showed that only a small hyperplasia in the septum wall was observed [40, 45, 46].

Chitosan: Chitosan [2-amino-2-deoxy-(1→4)-β-d-glucopyranan] is a linear cationic polysaccharide that is obtained by a process of deacetylation from chitin, an abundant structural polysaccharide in shells of crustacea such as shrimps, lobsters, and crabs [47]. Because of the -NH2 groups resultant 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, acetic acid and lactic acid. Toxicity tests have revealed that the LD50 of chitosan in mice exceeds 16 g/kg [48]. Because of its low cost, biodegradability, and biocompatibility, chitosan has been increasingly applied as pharmaceutical excipients in oral, ocular, nasal, parenteral, and transdermal drug delivery [49]. Chitosan and its derivatives have been shown excellent mucoadhesive properties and hence, active in enhancing the intranasal drug absorption.

It was also confirmed that coating micro- and nanoparticulates with chitosan could improve drug adsorption to mucosal surfaces 80. Besides their hydration in the nasal cavity, the interaction of the positively charged amino group with the negatively charged sites on the mucosa surface also contributes to their mucoadhesion [47]. Soane et al. reported that chitosan microspheres and solutions resulted in three- and eightfold longer clearance half-lives compared with sodium pertechnetate solution in sheep nasal cavity [14].

In addition, many studies have proved that chitosan and its derivatives could momentarily open the tight junctions between the cells and lead to the paracellular transport of drugs [50, 51]. Chemical and biological properties of chitosan, such as mucoadhesion and ability in enhancing nasal absorption, are determined by the types of derivatives, molecular weight (MW) and degree of deacetylation.

At neutral pH, most chitosan molecules will lose their charge and precipitate from solution due to solubility of chitosan is in acidic environment in which the amino groups at the C-2 position are protonated. Recent studies have shown that only protonated, soluble chitosan can trigger the opening of tight junctions and thereby facilitate the paracellular transport of hydrophilic mannitol [52]. To improve the poor water solubility of chitosan, some derivatives were synthesized, such as polyethylene glycol (PEG)-chitosan [53] and trimethyl chitosan [54, 55]. The trimethyl chitosan was soluble and effective in enhancing intranasal absorption even at neutral pH [54]. It was reported that thiolated chitosan [56], N-trimethyl chitosan hydrochloride [57, 58], and 5-methylpyrrolidinone chitosan [59], are more mucoadhesive than unmodified chitosans and show a higher bioavailability *in vivo* compared with the unmodified chitosans. The permeation-enhancing effect of chitosan increased with increasing MW up to 100 kDa [60].

Study by Tengamnuay et al. suggested that chitosans should differ in their MW by at least twofold in order to have a clearly differentiating effect on the nasal absorption enhancement of a kyotorphin analogue [61]. On the contrary, 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 MW by fourfold[62]. The same result was obtained in another study by Aspden et al [63]. Chitosan is also used in delivery of DNA because of the positive charge of chitosan in a weak acidic environment, it can also be applied to deliver the negatively charged DNA through nasal mucosa and protect them from nuclease degradation [64].

Cellulose derivatives: Cellulose is a class of most available polysaccharide, containing of 8000–10,000 glucose residues linked by β-1,4 glucosidic bonds [44]. 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), methylcellulose (MC), hydroxypropyl cellulose (HPC), and carboxy methyl cellulose (CMC), and insoluble cellulose derivatives such as ethylcellulose (EC) and microcrystalline cellulose (MCC).

Cellulose derivatives has mucoadhesive property and hence, can markedly prolong the residence time of drugs in the nasal cavity [65]. Additionally, the celluloses can sustain the release of drugs because of their high viscosity following hydration in the nasal cavity [66]. Hence, using celluloses as absorption enhancer can lead to improved intranasal absorption and increased bioavailability. For example, administered nasally with CMC, apomorphine can obtain a relative bioavailability of 102% compared with subcutaneous injection in rabbits [44]. Another study reported that ketorolac tromethamine administered with MCC shows an absolute bioavailability up to 90.77% [67].

The peptide drugs leuprolide and FD-4, when dosed with MCC/HPC through nasal route, reached an absolute bioavailability of 34.9% and 35.5% in rabbits, respectively[68]. Sometimes, combination of the celluloses with other absorption enhancer would obtain better effectiveness than using the polymer alone. Ozsoy et al. reported that the intranasal absolute bioavailability of ciprofloxacin in rabbits using MC and hydroxyethyl cellulose (HEC) alone as enhancer is only 18.2% and 19.46%, respectively. When combining with the Tween 80, the bioavailability increased to 22.35% and 25.39%, respectively 45. In another study by Ikeda et al. on 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% for using HPC alone [69]. HPMC is also used in mucoadhesive buccal tablets prepared by wet granulation technique [70] using alcohol as granulating agent which has several advantages [71].

Various dosage forms given by nasal route Solution and Sprays: The drug solutions are nasally administered as nasal drops, metered dose nebulizer and nasal spray. The dose of the active ingredient administered depends upon the volume of drug and the concentration of drug in the formulation. The intranasal administration of 0.8 mg/ml of nitroglycerine in normal saline showed 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. 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 [72]. Some scienstist have studied the the absorption of drug from supersaturated solution from the nasal mucosa in vitro model. The use of precipitation inhibitors [73] will be useful for delivery of supersaturated drug solution across the membranes.

Suspensions: Suspensions for nasal administration are prepared by suspending the micronized drug in a carrier or liquid diluent 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 [74].

Powders: Powder dosage forms of drugs for nasal administration offer several advantages over liquid formulations. In the powder form, preservative in the formulation is not required, the chemical stability of the drug is increased, a and it is possible to administer larger doses of drugs. Powder form is suitable for number of on peptide drugs [75]. 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 [76]. In addition, liquid preparations are more easily cleared to the nasopharynx and oropharynx from where they enter the posterior part of the tongue [19]. Therefore, administration of nasal powders may increase patient compliance, especially if the smell and taste of the delivered drug is unacceptable. Polymerbased powders are believed to form a viscous gel after getting in contact with the nasal mucosa 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[77]. In dry powder formulations Preservatives are not needed, 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 [78] prepared dry powder nasal influenza vaccine formulation by using sprayfreezedrying 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.

Nasal Particulate Drug Delivery System: Nasal particulate systems using mucoadhesive polymers as carriers include nanoparticle and microparticle/ sphere. Particulate drug carrier systems administered through nasal mucosa may protect the drug from enzymatic degradation, increase the drug dissolution rate, enhance the uptake by the epithelium, intensify the contact of the formulation with the mucosa, and act as a controlled release system resulting in prolonged blood concentrations [79, 80]. Among the polymers widely used as nasal drug particulate carrier, the positively charged polymers such as aminated gelatin, and chitosan are most attractive because of their hydrogel nature which leads to opening of the tight junctions and their intimate contact with the negatively charged mucosa membrane [57].

In vivo evaluation in rabbits has proved that chitosan nanoparticles were able to improve the nasal absorption to a great extent compared with chitosan solution due to the intensified contact of the nanoparticle with the nasal mucosa as compared with chitosan solutions [81]. It has been believed that nanoparticles possess superiority over microspheres as nasal drug carrier, which leads to higher local concentration gradient because their larger surface area results in more intimate contact with the mucosa [82]. Moreover, nanoparticles cross the mucosal epithelium better than microspheres do. Microparticles smaller than 10 μm administered intranasally are believed to be taken up by the Mcells overlaying the nasalassociated lymphoid tissue (NALT) and transported to submucosal layers. However, in case of the nanoparticles, besides the Mcell associated phagocytosis, the epithelial cells are also involved in the transport of nanoparticles by internalization [83].

Gel: Gels can promote an intimate contact between formulations and the mucosa surface and prolong the residence time by reducing the ciliary clearance rate [84]. The nasal bioavailability of metoclopramide

in gel formulation prepared by using Carbopol 981P was higher than that in solution and lyophilized powder formulation based on the same polymer [31]. However, because of its high viscosity the gel is difficult to administer and an accurate drug dose cannot be measured. To overcome this problem the nasal in situ gel has been developed, i.e., thermosensitive or pH-sensitive gel [65, 85, 86]. The in situ gel is fluid-like before nasal administration, which increases accuracy of drug dosing and convenient for administration. After the formulation contact with the mucosa, the special temperature or pH value of the mucus promotes the transition from liquid to gel, which prolongs drug residence times and improves drug bioavailability. Zaki et al. prepared an in situ gel of metoclopramide hydrochloride with solution-gel transition temperature of about 25–32°C by using poloxamer 407 as thermogelling moderator [65].

Results of rat experiment showed that this in situ gel prolonged the mucociliary transport time from 10 to 52 minutes (compared with sodium chloride) and maintained nasal mucosal integrity after 14 days of application [65]. The bioavailability study in rabbits revealed that the absolute bioavailability of metoclopramide hydrochloride was significantly increased from 51.7% in case of the oral drug solution to 69.1% by nasal in situ gel [65]. Ghosh et al. designed intranasal in situ gel systems of sumatriptan with a gelation temperature below 34°C using thermoreversible polymer Pluronic F127 and mucoadhesive polymer Carbopol 934P120.

The results of *in vitro* drug permeation studies across sheep nasal mucosa indicate that the in situ gelling formulation was effective in improving the permeation coefficient, and the histopathological examination did not detect any damage during in vitro permeation studies [85]. Wu et al. prepared thermosensitive hydrogel of insulin by simply mixing N-[(2-hydroxyl-3-trimethylammonium) propyl] chitosan chloride and PEG with a small amount of a-b-glycerophosphate. The solution-gel transition temperature of this hydrogel is about 34°C121. *In vivo* experiment demonstrated that the hydrogel formulation decreased the blood glucose concentration by 40–50% for at least 4–5 hours after administration, and no apparent cytotoxicity was found after application [87].

CONCLUSION: There are a ton of exciting developments in the field of mucoadhesive nasal drug delivery system. Mucoadhesion increases the residence time of the polymer, penetration enhancement, and enzymatic inhibition; hence, mucoadhesive polymers will undoubtedly be utilized for the nasal delivery of a wide variety of therapeutic compounds. This class of polymers has enormous potential for the delivery of therapeutic macromolecules, vaccines and gene. Unfortunately, only a few studies have been conducted with new-generation mucoadhesive polymers for nasal drug delivery, and very few papers focus on to what extent the interaction between the polymer and the mucus influences the release of the drugs including in the disease condition and the changes of structure and rheology of the mucus caused by the mucoadhesive polymer.

There is a lot of ground for optimism with respect to benefits derivable from more fundamental research and application leading to better understanding of the subject and eventually more marketed products. The safety aspects of nasal products needs to be considered, although the recent developments of both in vitro and in vivo models is a big boost to speeding up clinical developments and eventually time-to-market of new products. The recent advancements in the fields of biotechnology and cytoadhesion, has led to the belief that there will be both academic and industrial efforts to explore this new area of nasal drug delivery, and it might not be too unlikely to envision more and more nasal products that employ mucoadhesive polymers.

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