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Review Article

Mucoadhesive Polymers: Drug Carriers for Improved Nasal Drug Delivery

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ABSTRACT

Drug actions can be improved by developing new drug delivery systems; one such formulation being a mucoadhesive system. These systems remain in close contact with the absorption tissue, the mucous membrane, releasing the drug at the action site leading to increased bioavailability for both local and systemic effects. Over the last few decades, the application of mucoadhesive polymers in nasal drug delivery systems has gained interest 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 enhanced paracellular absorption following the swelling of the mucoadhesive polymers on the nasal membranes provides an important way for the absorption of the macromolecules through the nasal cavity. This review describes 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 mucoadhesive polymers have enormous potential for the delivery of therapeutic macromolecules, genes, and vaccines through the nasal cavity with enhanced bioavailability.

INTRODUCTION

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 [1]. 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 [2]. Evaluation of potential advantages and limitations [3, 4] of nasal drug delivery is outlined in Table 1. Because of its ready accessibility, nasal drug administration has been considered as an alternative route for systemic use of drugs restricted to intravenous administration [5].

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This is particularly important for the delivery of peptides and proteins that currently are mainly administered through intravenous route because of their susceptibility to the gastrointestinal proteases [6]. Nasal drug delivery can also provide a route of entry to the brain that circumvents the blood–brain barrier because the olfactory receptor cells are in direct contact with the central nervous system [7, 8]. Recently, the nasal mucosa is considered as an attractive site for the delivery of vaccines, not only because it has a relatively large absorptive surface and low proteolytic activity, but also because, the nasal vaccines are patient compliant and reduce the production costs compared with the parenteral products. Extensive studies report that, when administered intranasally, vaccines can induce both local and systemic immune response [9, 10].

Despite the high permeability of nasal membrane, generally, only small molecular weight drugs (<1000 Da) show adequate absorption in the nasal cavity [11]; most hydrophilic and macromolecular drugs such as insulin show low bioavailability or even no absorption at all[12].

Table 1: Potential advantages and limitations of nasal drug delivery

Advantages	Limitations
• 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	• 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 • Irritation of nasal mucosa by drugs • Limited understanding of mechanisms and less developed models at this stage

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 [13]. Penetration enhancers such as surfactants [14], bile salts [15,16], fusidate derivatives [17], and phospholipids [18] 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 [19].

Some mucoadhesive polymers, such as cellulose, polyacrylate, starch, and chitosan, have proven to be effective on improving intranasal absorption of hydrophilic macromolecules. These polymers achieve this by increasing the drug residence time in the nasal cavity or enhancing intranasal absorption; some of them can serve both the functions. Most of these polymers are generally recognized as safe (GRAS) pharmaceutical excipients and not absorbed, so they would not be expected to display systemic toxicity.

Even though a number of challenges are still to be overcome, the encouraging results stimulate pharmaceutical researchers to exercise further efforts in order to develop new nasal formulations to replace the conventional parenteral products. In this article, the use of mucoadhesive polymers for the intranasal delivery of drugs is reviewed. Their ability of enhancing the intranasal absorption of macromolecular hydrophilic drugs will be focused on.

Mucoadhesive polymers

Mucoadhesive polymers [20] 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 mucin-epithelial surface can be conveniently divided into three broad classes:

1. Polymers that become sticky when placed in water and owe their mucoadhesion to stickiness.
2. Polymers that adhere through nonspecific, non-covalent interactions that are primarily electrostatic in nature (although hydrogen and hydrophobic bonding may be significant).
3. Polymers that bind to specific receptor site on tile self-surface.

All three polymer types can be used for drug delivery

Characteristics of an ideal mucoadhesive polymer [21]

1. The polymer and its degradation products should be nontoxic and should be nonabsorbable from the gastrointestinal tract.
2. It should be non-irritant 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 incorporation to the daily dose of 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.

Robinson and his group[22], using the fluorescence technique, concluded that:

- Cationic and anionic polymers bind more effectively than neutral polymers.
- Polyanions are better than polycations in terms of binding/potential toxicity, and further, that water-insoluble polymers give greater flexibility in dosage form design compared with rapidly or slowly dissolving water-soluble polymers.
- Anionic polymers with sulfate groups bind more effectively than those with carboxylic groups.
- Degree of binding is proportional to the charge density on the polymer.
- Highly binding polymers include carboxymethyl cellulose, gelatin, hyaluronic acid, carbopol, and polycarbophil.

Molecular characteristics

Investigations into polymers with various molecular characteristics conducted by many authors[23]have led to a number of conclusions regarding the molecular characteristics required for mucoadhesion.

The properties exhibited by a good mucoadhesive may be summarized as follows[24]:

1. Strong hydrogen bonding groups (-OH, -COOH).
2. Strong anionic charges.
3. Sufficient flexibility to penetrate the mucus network or tissue crevices.
4. Surface tension characteristics suitable for wetting mucus/mucosal tissue surface.
5. High molecular weight.

Although an anionic nature is preferable for a good mucoadhesive, a range of nonionic molecules (e.g., cellulose derivatives) and some cationics (e.g., Chitosan) can be successfully used.

Mucoadhesion/bioadhesion

In 1986, Longer et al. defined the term 'bioadhesion' as 'the attachment of a synthetic or biological macromolecule to mucus and/or an epithelial surface for an extended period of time'[25]. Similarly, Gu et al. described the term 'mucoadhesion' as 'the binding of polymers to mucin/epithelial surface' [26]. In nasal drug delivery, mucoadhesion means the adherence of a polymeric material to nasal epithelial surface (bioadhesion) or nasal mucus (mucoadhesion).

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[27]. 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 [28] and the protein chains of the mucus (Figure 1).

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[29, 30].

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[31]. 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[32, 33]. 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.

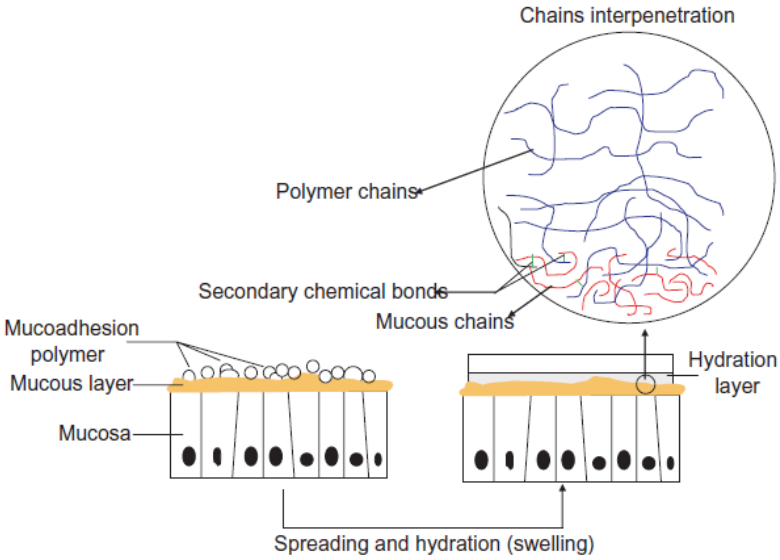
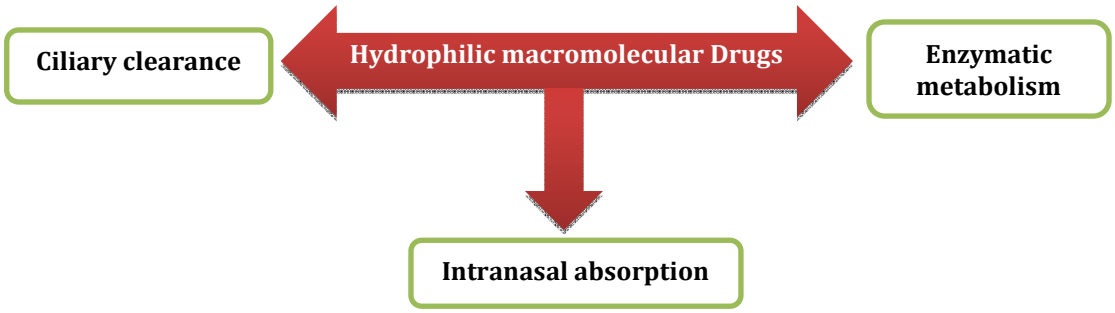
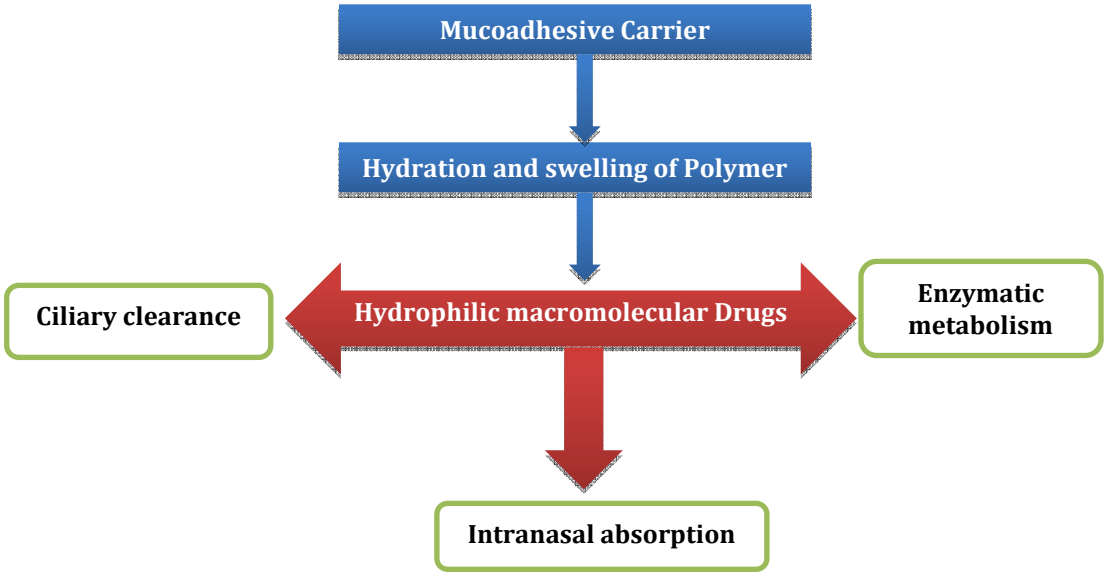


Figure 1: Schematic representation of the process of mucoadhesion on the nasal mucosa surface



(A) Ordinary Intranasal delivery: A small fraction of drugs can be absorbed because of the low permeability of the hydrophilic macromolecular drugs; most of the drug will be cleared by the ciliary movement or be metabolized by the enzymes existing in the nasal cavity.



(B) Mucoadhesive intranasal drug delivery: the mucoadhesive carrier enhances the intranasal absorption by increasing the retention time of the drugs and promoting the paracellular absorption in the nasal cavity, whereas, the ciliary clearance is reduced. The mucoadhesive carrier can also protect the drugs from the enzymatic metabolism to a large extent.

Figure 2: Schematic representation of the comparison of ordinary intranasal formulation with mucoadhesive intranasal formulation.

On the other hand, an excessive amount of water will weaken the mucoadhesive bonds by over diluting the polymer solution[34].

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 [35]. Furthermore, the existence of the mucoadhesive carrier also reduces the contact between the drugs and the enzymes existing in the mucosa. These both can enhance the intranasal absorption of hydrophilic drugs. The comparison of ordinary intranasal formulation (A) with mucoadhesive intranasal formulation (B) is displayed in Figure 2. 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. 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 structure [36]. This function of the mucoadhesive polymer is very important for the enhancement of the intranasal absorption of macromolecules weighing above 1000 Da[37].

Mucoadhesion can slow down the mucociliary clearance, but with time, mucus production will lead to the inordinate 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 [27].

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 as to what extent the interaction between the polymer and the mucus influences the release of the drugs, including the diseased 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 diseased conditions during the product development.

Factors that influence mucoadhesion

The factors that influence mucoadhesiveness of a polymer include the type of functional groups present, polymer molecular mass, molecular mass between cross-links (cross-linking density), spatial orientation, contact time with mucus, polymer concentration, environmental pH and physiological variables like mucin turnover and diseased conditions. These will be further explained under the subheadings, namely polymer-related, environment-related and physiological related factors.

Polymer-related factors

The polymer molecular mass will influence its bioadhesion characteristics. There is a critical polymer molecular mass and cross-linking density below or above which there is reduced adhesive power, and this varies with the type of polymer [38–40]. Mucoadhesion requires an adequate free chain length for interpenetration to occur. Reducing the free chain length by extensive cross-linking therefore reduces mucoadhesion. An optimum polymer concentration is required at the polymer–mucus interface for bioadhesion, beyond which few polymer chains will be available for polymer–mucus interpenetration. The polymer concentration that is required for optimum bioadhesion is different between gels and solid bioadhesives. In the liquid state, an optimum concentration exists for each polymer beyond that, a reduced adhesion results because fewer polymer chains will be available for interpenetration with the mucus. On the other hand, with solid dosage forms such as buccal tablets, increased polymer concentration leads to increased mucoadhesive power [41].

Environment-related factors

Polymer hydration and swelling are required for initiation of mucoadhesion but excessive hydration with inordinate swelling of the polymer reduces its adhesive strength. The swelling/hydration rate should not be too rapid in order to prolong the adhesion time. On the other hand, inordinate swelling is eventually required to reduce polymer adhesiveness and to allow it to detach from the biological tissue. Some polymers owe their mucoadhesiveness to such forces as hydrogen bonding, Vander Waals, hydrophobic and electrostatic forces. The strength of these forces is influenced by the environmental pH. Consequently, for such polymers, environmental pH is a very important determinant of mucoadhesive strength. This has

been clearly demonstrated for polycarbophil and more recently for chitosan [42]. This has also been exploited in development of pH-sensitive mucoadhesive polymers.

Physiological-related factors

Mucociliary clearance, mucus turnover and diseased states are physiological factors which influence nasal mucoadhesion. Mucoadhesion can slow down mucociliary clearance, but with time, mucus production reduces the mucoadhesion bond strength, allowing a recovery of mucociliary clearance to normal clearance rates, thereby removing the mucoadhesive. Diseased conditions mentioned earlier can affect mucoadhesion due to their influence on either mucus production or ciliary beating. Thus a good understanding of the nature of mucus in these diseases is imperative in designing a good nasal drug delivery system. An abnormal mucus layer could present an unanticipated barrier to drug transport through the mucosa. Mucoadhesive capabilities of polymers should be studied during product development under such diseased conditions as considered relevant.

Mucoadhesive polymers used in nasal drug delivery

Cellulose derivatives

Cellulose is a class of most available polysaccharide, consisting of 8000–10,000 glucose residues linked by β-1,4glucosidic bonds. 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). Table 2 summarizes the nasal drug delivery studies where the cellulose derivatives were employed as mucoadhesive carrier.

Cellulose derivatives can markedly prolong the residence time of drugs in the nasal cavity because of their desirable mucoadhesive property [43]. Additionally, because of their high viscosity following hydration in the nasal cavity, the celluloses can sustain the release of drugs [44]. For these reasons using celluloses as absorption enhancers can lead to improved intranasal absorption and increased bioavailability. Many references show that the celluloses are effective in increasing the intranasal bioavailability of small hydrophobic and hydrophilic macromolecular drugs (Table 2). For example, Apomorphine administered nasally with CMC, can obtain a relative bioavailability of 102% compared with subcutaneous injection in rabbits. Another study reported that an absolute bioavailability up to 90.77% could be achieved for ketorolac tromethamine administered with MCC [45]. 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 [46].

Sometimes, combination of the celluloses with other absorption enhancer would obtain better effectiveness than using the polymer alone. Ozsoy et al. have 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 combined with Tween 80, the bioavailability increased to 22.35% and 25.39%, respectively [47]. In another study by 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 [48].

Polyacrylates

Polyacrylates have been investigated very frequently in many drug administration routes, such as oral[49], ocular [50], transdermal[51, 52]and nasal[53] drug delivery systems, because of their excellent mucoadhesive and gel-forming capability. 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 [54]. Table 3 summarizes the studies on the use of polyacrylates in nasal drug delivery system.

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. Studies by Ugwoke et al. in rabbits have reported that the use of Carbopol 971P in nasal dosage forms increased the residence time in the nasal cavity. The percentage of the formulations cleared from the nasal cavity at 3 hours was 24% for Carbopol 971P, whereas it was 70% for

lactose [55]. Sustained release of drugs can also be obtained by using polyacrylates in nasal formulation, which resulted in a more stable blood concentration–time curve. 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 971P-containing formulation was 330.2 ng/mL, lower than that of the lactose containing formulation, which was 450.7 ng/mL [54].

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 [55]. Based on these, polyacrylates can increase the intranasal bioavailability of both small hydrophobic drugs and hydrophilic macromolecular drugs. Using the Carbopol 971P and polycarbophil in the nasal apomorphine formulation, a relative drug bioavailability of 99.8% and 105.0% could be obtained compared to subcutaneous injection [56] respectively. An absolute bioavailability of 14.4% in rabbits was reported for intranasal insulin formulation containing Carbopol 974P[57].

The Carbopol and polycarbophil are considered as generally regarded as safe (GRAS) by FDA, and many studies show that they are nonirritant to the skin and eye and nontoxic orally. 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 [57, 58].

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 (see Table 4). 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 best one compared with starch processed through other methods [57].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 Spherex®, is the most widely used and also the first example of mucoadhesive Microparticulate nasal delivery system [59]. These microspheres are prepared by an emulsion polymerization technique, in which the starch is cross-linked with epichlorohydrine that can incorporate molecules weighing less than 30 kDa. Because of its mucoadhesion, the DSM can enhance the drug absorption by prolonging the residence time of drugs in the nasal cavity [60]. 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 [61]. 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 [62]. 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) [63–65]. DSM can also protect the proteins wrapped in it against degradation by proteases in the mucosa. Several studies have revealed that the release of drugs from DSM was rapid and not sustained. This suggested that the utility of DSM in nasal drug delivery could further be exploited in the treatment of crisis diseases [66]. It was reported that DSM were well tolerated both in experimental animals and in humans; a test on healthy volunteers showed that only a small hyperplasia in the septum wall was observed when the DSM were administered two times per day for 8 weeks in dosages of 20 mg [67, 68].

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 crustacean such as lobsters, shrimps, and crabs [69]. Because of the NH_2 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. Toxicity tests have revealed that the LD50 of chitosan in mice exceeds 16 g/kg [70]. Because of its low cost, biodegradability, and biocompatibility, chitosan has been extensively used as pharmaceutical excipient in oral, ocular, nasal, implant, parenteral, and transdermal drug delivery systems [71].

Table 2: Summary of some nasal drug delivery studies where cellulose derivatives were employed

Mucoadhesive polymer	Drugs	Dosage forms	Abs. BA (%)	Animal species	Reference
EC	FD-4	Powder	38.0 ± 3.8	Rats	95
MCC, pH 5.95	Ketorolac tromethamine	Spray	90.77	Rabbits	45
MCC	Insulin	Spray	1.9	Rabbits	96
MCC	Cyanocobalamine	Powder	25.0	Rabbits	97
MCC	Glucagon	Powder	-	Human	98
MCC/HPC	Leuprolide	Powder	34.9	Rabbits	46
HPC	Dopamine	Liquid	25.0	Dogs	48
HPMC/sulfobutylether-β-cyclodextrin	Midazolam	Spray	73	Humans	99
HPMC	Ciprofloxacin	Gel	40.21 ± 6.41	Rabbits	47
MC	Ciprofloxacin	Gel	18.2 ± 4.8	Rabbits	47
MC/Tween 80	Ciprofloxacin	Gel	22.3 ± 5.5	Rabbits	47

Table 3: Summary of some nasal drug delivery studies where polyacrylates were employed

Mucoadhesive polymer	Drugs	Dosage forms	BA (%)	Animal species	References
Carbopol 971P	Apomorphine	Powder	99.8 ±9.7 (rel vs SC)	Rabbits	56
Polycarbophil	Apomorphine	Powder	105 ± 8.6 (rel vs SC)	Rabbits	56
Carbopol 934P	Flouresce inisothiocyanate	Powder	33 (abs)	Rabbits	100
Carbopol 981P	Metoclopramide	solution	17.48 (abs)	Sheeps	53
Carbopol 981P/HPC/Poloxamer 407	Metoclopramide hydrochloride	Gel	51.0 (abs)	Rabbits	43
Carbopol 974P/DDWM	Insulin	Powder	14.4 ± 3.5 (abs)	Rabbits	57
Gelatin/Polyacrylic microspheres	Oxprenolol	Powder	-	Rats	101

Abs: absolute, BA: Bioavailability, DDWM: drum-dried waxy maize starch, DSM: degradable starch microspheres, rel: relative, SC: subcutaneous injection

Chitosan and its derivatives have been shown to be active in enhancing the intranasal drug absorption because of their excellent mucoadhesive properties. It is also confirmed that coating micro- and nanoparticulates with chitosan could improve drug adsorption to mucosal surfaces[72]. 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 [69]. Soane et al. [73] 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. In addition, many studies have proved that chitosan and its derivatives could transiently open the tight junctions between the cells and lead to the paracellular transport of drugs [74, 75]. Table 5 summarizes the recent nasal drug delivery studies where chitosan derivatives were employed as absorption enhancers.

Table 4: Summary of some nasal drug delivery studies where starch was employed

Mucoadhesive polymer	Drugs	Dosage forms	Bioavailability (%)	Animal species	References
DSM	Apomorphine	powder	96 ±7.8 (rel vs SC)	Rabbits	66
DSM	Desmopressin	powder	4.7 ± 0.5 (abs)	Sheeps	63
DSM	Insulin	powder	3.6 (rel vs SC)	Sheeps	16
DSM	melatonin	Powder	84.07 (abs)	Rabbits	102
DDSM/carbopol 974P	Insulin	powder	13.4 ± 3.2 (abs)	Rabbits	103
DSM	Metoclopramide	liquid	137 (rel vs SC)	Humans	104
SMS/HPC	G-CSF	Powder	8.4 ± 3.4 (rel vs SC)	Sheeps	89
SMS	Morphine HCl	Powder	74.8 ± 29.2 (abs)	Sheeps	105
Starch	Insulin	Powder	19.2 ± 5.3 (abs)	rabbits	106

abs, absolute; DDWM, drum-dried waxy maize starch; DSM, degradable starch microspheres; rel, relative; SC, subcutaneous injection; SMS, starch microsphere; G-CSF, granulocyte-colony stimulating factor

Table 5: Summary of some nasal drug delivery studies where chitosan derivatives and other positively charged macromolecules were employed

Mucoadhesive polymer	Drugs	Dosage forms	Bioavailability (%)	Animal species	References
Chitosan	Insulin	Liquid	9 – 15 (rel vs SC)	Human	71
Chitosan	Levonorgestrel	Liquid	101.7 (rel vs oral)	Rats	55
Chitosan	Salmon calcitonin	liquid	201.2 (rel vs IN plain drug)	Rats	107
Chitosan/EDTA	Insulin	liquid	8.8 ± 4.5 (rel vs SC)	Rats	108
Chitosan microspheres	Goserelin	Liquid	40 (abs)	Sheeps	109
Chitosan microspheres	Pentazocine	Powder	96.5 ± 8.4 (abs)	Rabbits	110
Chitosn	Gentamicin	Powder	31.4 ±2.7 (abs)	Rabbits	111
Chitosan /Hyaluronan	Gentamicin	Powder	42.9 ± 3.5 (abs)	rabbits	112
Aminated gelatin microspheres	Insulin	Powder	8.6 ± 2.9 (abs)	Rats	93
Chitosan	metoclopramide	Spray	87.2 ± 7.7 (abs)	Rabbits	85

Chemical and biological properties of chitosan, such as mucoadhesion and ability in enhancing nasal absorption, are determined by the types of derivatives, degree of deacetylation, and molecular weight (MW) because chitosan is only soluble in acidic environment in which the amino groups at the C-2 position are protonated. At neutral pH, most chitosan molecules will lose their charge and precipitate from solution. 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 [76]. To improve the poor water solubility of chitosan, some derivatives have been synthesized, such as trimethylchitosan [77, 78] and polyethylene glycol (PEG)-chitosan [79]. Thanou et al. have reported that the trimethyl chitosan was soluble and effective in enhancing intranasal absorption even at neutral pH [77]. It was reported that 5-methylpyrrolidinone chitosan [80], thiolated chitosan [81], and N-trimethyl chitosan hydrochloride [82] are more mucoadhesive compared to unmodified chitosans and show a higher bioavailability *in vivo* in comparison to unmodified chitosans.

Mei et al. have reported that the permeation-enhancing effect of chitosan increased with increasing MW up to 100 kDa[83]. Study by Tengamnuay et al. have revealed chitosans should differ in their MW by at least two folds in order to have a clearly differentiating effect on the nasal absorption enhancement of a kyotorphin analogue [84]. On the contrary, Zaki et al. found out 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 MW by four fold[85]. The same result was obtained in a study by Aspden et al.[86].

Because of the positive charge of chitosan in a weakly acidic environment, it can also be utilized to deliver the negatively charged DNA through nasal mucosa and protect them from nuclease degradation [87]. Compared with viral vectors, this alternative vector markedly reduced the safety risks resulting in high transfectability[88]. Recently many studies have revealed that nasal immunization with chitosan plus an inactive vaccine is a potentially effective, easily administered form of vaccination. Bordetella pertussis filamentous hemagglutinin and recombinant pertussis toxin have shown to induce very strong systemic and mucosal immune reactions against the antigens when intranasally administrated with chitosan [89, 90].

Read et al. confirmed that the standard inactivated trivalent influenza vaccine administered intranasally in combination with chitosan glutamate (0.5%, w/w) could induce both systemic and local immune responses, and the results were not statistically different from those obtained following administration of the commercial influenza vaccine by the intramuscular route [91]. Bacon et al.[92] have reported that chitosan solutions are able to enhance both the mucosal and the systemic immune responses against influenza virus vaccines. Mice that received chitosan/vaccine formulation intranasally, revealed high IgA titers in nasally revealed washings but this was not observed in mice receiving the antigen through subcutaneous injection[92].

Other cationic macromolecular materials, such as poly-L-arginine and aminated gelatin have also been investigated for their application as nasal absorption enhancers [82,93]. These polymers work in a way similar to chitosan, at least in animal models, and have been found to be effective in enhancing the absorption of fluorescein isothiocyanate (FITC)-dextran and insulin with only negligible nasal toxicity [93, 94].

CONCLUSION

With advantages such as mucoadhesion, an increase in the residence time of the polymer, penetration enhancement, and enzymatic inhibition, 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, genes, and vaccines. Unfortunately, only a few studies have been conducted with new-generation mucoadhesive polymers for nasal drug delivery, and very few 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 far fetched to envisage more and more nasal products that employ mucoadhesive polymers.

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