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A COMPREHENSIVE REVIEW ON MUCOADHESIVE POLYMER USED IN NASAL DRUG DELIVERY SYSTEM

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➤ ABSTRACT:

This review is on mucoadhesive polymers used in nasal dosage forms. Drug actions can be improved by developing new drug delivery systems; one such formulation being a mucoadhesive system. 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. 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 various new technology uses in development of nasal drug delivery dosage forms are discussed. The various dosage forms are vesicular carriers (liposome, noisome), nanostructured particles, prodrugs, *in situ* gelling system with special attention to *in vivo* studies.

➤ KEY WORDS:

In vivo, mucoadhesive polymers, nasal drug delivery system.

➤ INTRODUCTION:

Since the early 1980, the concept of mucoadhesion has gained considerable interest in pharmaceutical technology. 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. Drugs have been administrated nasally for therapeutic and recreational purpose since ancient times. Psychotropic drugs and hallucinogens were snuffed for these purposes by the Indian of South America, and this practice is currently widespread among abusers of cocaine and heroin. The interest in and importance of the systemic effects of the drugs administrated through the nasal route have expanded over 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. Furthermore, self-medication is easy and convenient.

➤ **ADVANTAGES OF NASAL ROUTE:**

Systemic nasal absorption of drug is a new attractive alternative to parenteral drug delivery system, as it offers the following advantages:

- A non-invasive route
- Transnasal delivery provides direct entry of drug into systemic circulation, e.g., Thiomeerosal, Amastatin, Puromycin, Nifedipine, etc.
- Rapid onset of action with lower dose and minimal side effects
- Hepatic first pass metabolism is avoided
- Avoid drug degradation in the gastrointestinal tract
- The rate and extent of absorption as well as plasma concentration vs. time profiles are comparable with I.V. administration.
- Avoidance of first pass elimination, gut wall metabolism, and destruction in gastrointestinal tract.
- Various nasal drug delivery systems are available for user-friendly noninvasive painless application.
- Convenient route when compared with parenteral route for long term therapy.

➤ **LIMITATIONS OF NASAL ROUTE:**

- There is risk of local side effects and irreversible damage of the cilia on the nasal mucosa, both from the drug substances and from the constituents added to the dosage forms.
- Certain compounds when used as absorption enhancers may disrupt and even dissolve the nasal membrane in high concentration.
- Nasal atrophic rhinitis and severe vasomotor rhinitis can reduce the capacity of nasal absorption, e.g., Cerulean.
- There could be mechanical loss of the dosage form into the other parts of the respiratory tract like lungs.
- Frequent use of this route may lead to mucosal damage and or irritation of nasal mucosa
- Low bioavailability results from enzymatic degradation and metabolism at mucosal site and low residence time.

➤ **THE NASAL CAVITY :**

The nasal cavity has an important protective function in that it filters, warms, and humidifies the inhaled air before it reaches the lower airways. Any inhaled particles or microorganisms are trapped by the hairs in the nasal vestibule or by the mucus layer covering the respiratory area of the nasal cavity. Due to 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.

➤ **NASAL ANATOMY AND PHYSIOLOGY:**

The nostrils are a pair of nasal cavities divided by a nasal septum . 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 [Figure 1]

Nasal Cavity

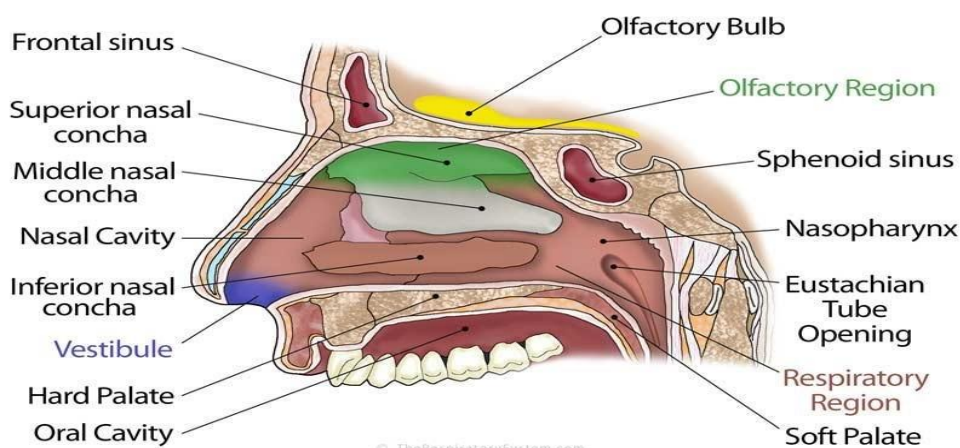


Fig.1 Anatomy and physiology of nose

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. 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.

➤ NASAL MUCOSA:

The nasal lining has the same lining as the rest of the respiratory tract with pseudo stratified ciliated columnar epithelium. There are up to 200 cilia per cell whose tips lie in the superficial gel layer [Figure 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

ANATOMY OF NASAL MUCOSA

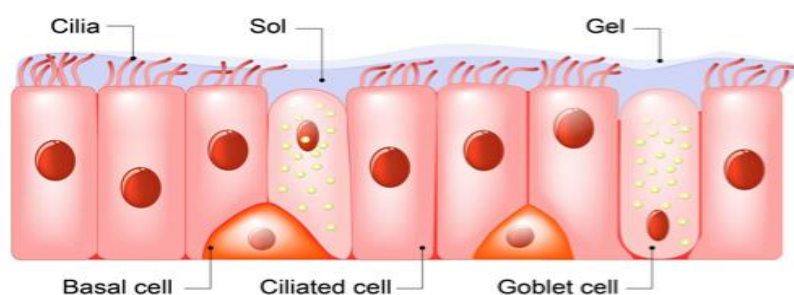


Fig.2 Structure of mucosa

➤ VARIOUS DOSAGE FORMS GIVEN BY NASAL ROUTE:

▪ Solution and sprays:

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 mg/ml in central venous blood, 1.7 mg/ml in arterial blood, and 0.4 mg/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.

▪ **Suspensions:**

Suspensions for nasal administration are prepared by suspending the micronized drug in a liquid diluent 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.

▪ **Powders:**

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 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 [Figure 2]. 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.

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

▪ **NASAL PARTICULATE DRUG DELIVERY SYSTEM:**

Nasal particulate systems using mucoadhesive polymers as carriers include micro particle/sphere and nanoparticle. Particulate drug carrier systems administered through nasal mucosa may protect the drug from enzymatic degradation, increase the drug dissolution rate, intensify the contact of the formulation with the mucosa, enhance the uptake by the epithelium, and act as a controlled release system resulting in prolonged blood concentrations. Among the polymers widely used as nasal drug particulate carrier, the positively charged polymers such as chitosan and aminated gelatin 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. *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. It has been believed that nanoparticles possess superiority over microspheres as nasal drug carrier because their larger surface area results in more intimate contact with the mucosa, which leads to higher local concentration gradient.

▪ 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, which is considerably smaller than. The first biological uses of gels (polymerized methyl methacrylate) 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 (i) covalent bond formation (chemical cross-linking) or (ii) noncovalent bond formation (physical crosslinking). 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, and 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 mechanism.

▪ 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 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:

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 noncovalent 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 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 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

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]. Similarly, Gu et al. described the term 'mucoadhesion' as 'the binding of polymers to mucin/epithelial surface'. 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. 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 wettability 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

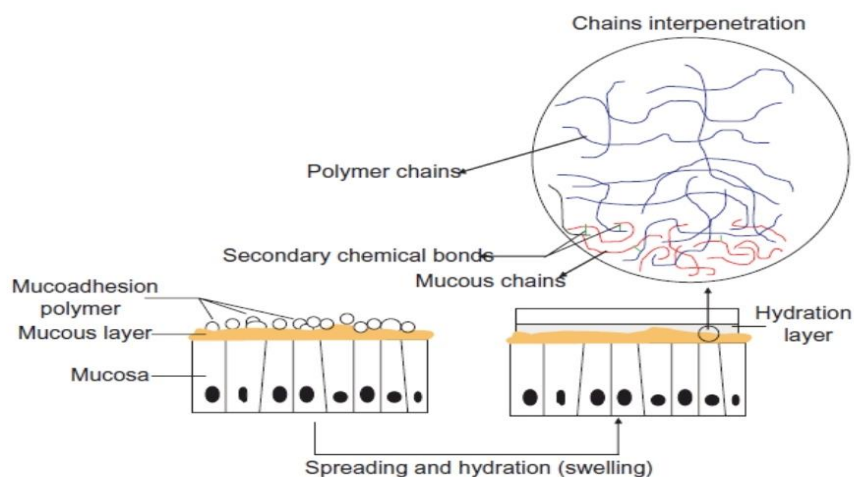
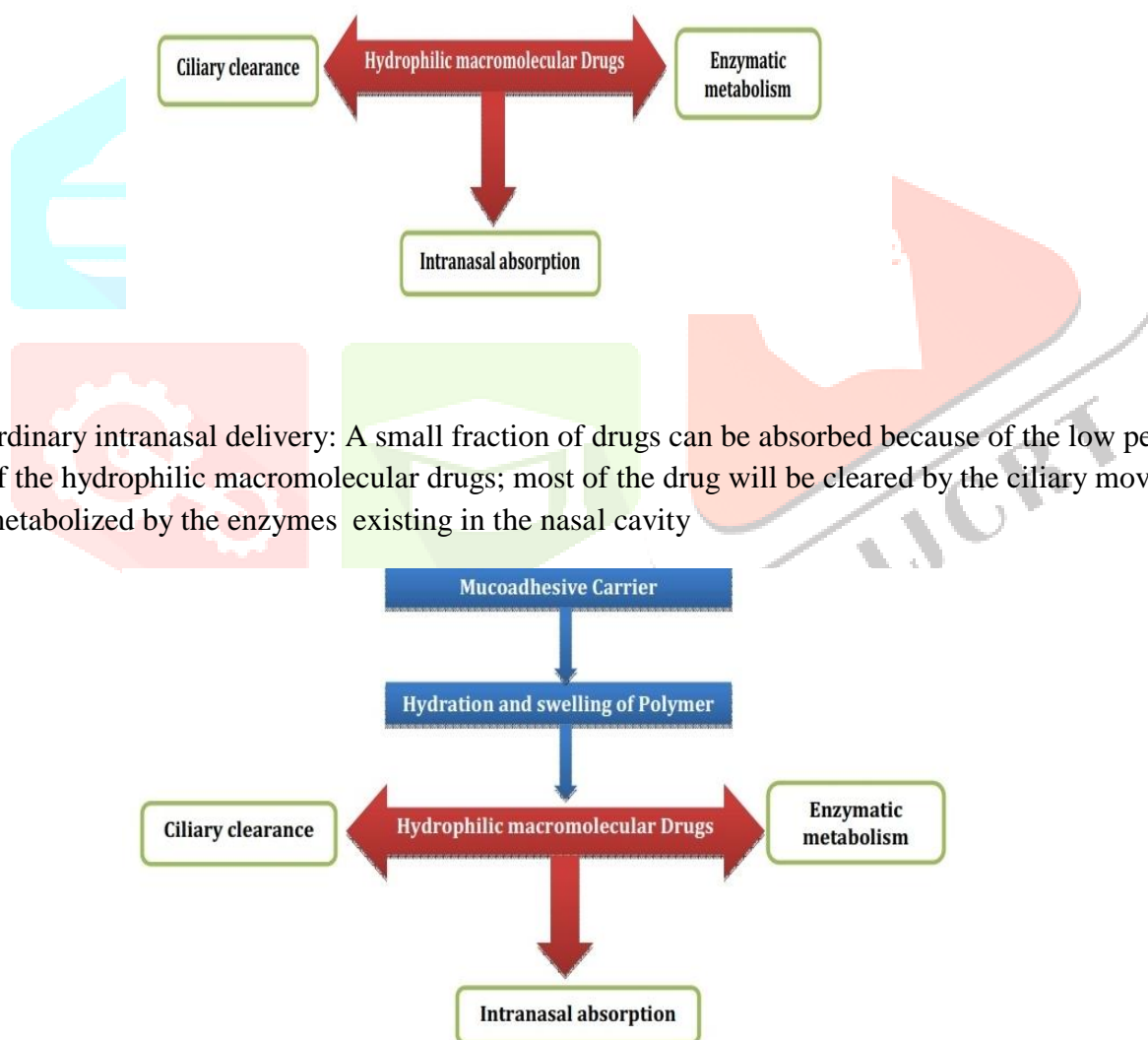


Fig.4 Schematic representation of the process of mucoadhesion on the nasal mucosa surface



(B) Mucoadhesive intranasal drug delivery: the mucoadhesive carrier enhances the intranasal absorption by increasing the retention time of the drug 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

Fig.5 Schematic representation of the comparison of ordinary intranasal formulation with mucoadhesive intranasal formulation

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. 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. This function of the mucoadhesive polymer is very important for the enhancement of the intranasal absorption of macromolecules weighing above 1000 Da. 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. 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.

➤ **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. 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

➤ **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 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.

➤ **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 ethyl cellulose (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. Additionally, because of their high viscosity following hydration in the nasal cavity, the celluloses can sustain the release of drugs. 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.

➤ **Polyacrylates:**

Polyacrylates have been investigated very frequently in many drug administration routes, such as oral, ocular, transdermal and nasal 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. Table 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. 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 T_{max} 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 C_{max} of the Carbopol 971P-containing formulation was 330.2 mg/mL, lower than that of the lactose containing formulation, which was 450.7 mg/mL.

Besides the mucoadhesion capability, polyacrylates may also temporarily open then tight junctions between the epithelial cells during the swelling progress in the nasal cavity and improve the paracellular absorption of drugs. Based on these, polyacrylates can increase

the intranasal bioavailability of both small hydrophobic drugs and hydrophilic macromolecular drugs.

➤ **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. 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 Micro particulate nasal delivery system. 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. Illume 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. 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.

➤ **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. 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. Toxicity tests have revealed that the LD₅₀ of chitosan in mice exceeds 16 g/kg. 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.

Table 1: 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 2: Summary of same 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 inisothiocyante | 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 Nano particulates with chitosan could improve drug adsorption to mucosal surfaces. 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. Saone 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 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. Table 5 summarizes the recent nasal drug delivery studies where chitosan derivatives were employed as absorption enhancers.

Table3: 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

Table4: 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 |
| Chitosan | 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. To improve the poor water solubility of chitosan, some derivatives have been synthesized, such as trimethylchitosan and polyethylene glycol (PEG)-chitosan. Thanou et al. have reported that the trimethyl chitosan was soluble and effective in enhancing intranasal absorption even at neutral pH. It was reported that 5-methylpyrrolidinone chitosan, thiolated chitosan, and N-trimethyl chitosan hydrochloride 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. 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.

➤ 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, to what extent the interaction between the polymer and the mucus influences the release of the drugs including in the disease 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. The authors believe that there will be both academic and industrial efforts to explore this new area of nasal drug delivery, and more nasal products that employ mucoadhesive polymers.

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