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# Novel Mucoadhesive Polymers for Nasal Drug Delivery

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Utkarshini Anand, Tiam Feridooni and Remigius U. Agu

Additional information is available at the end of the chapter

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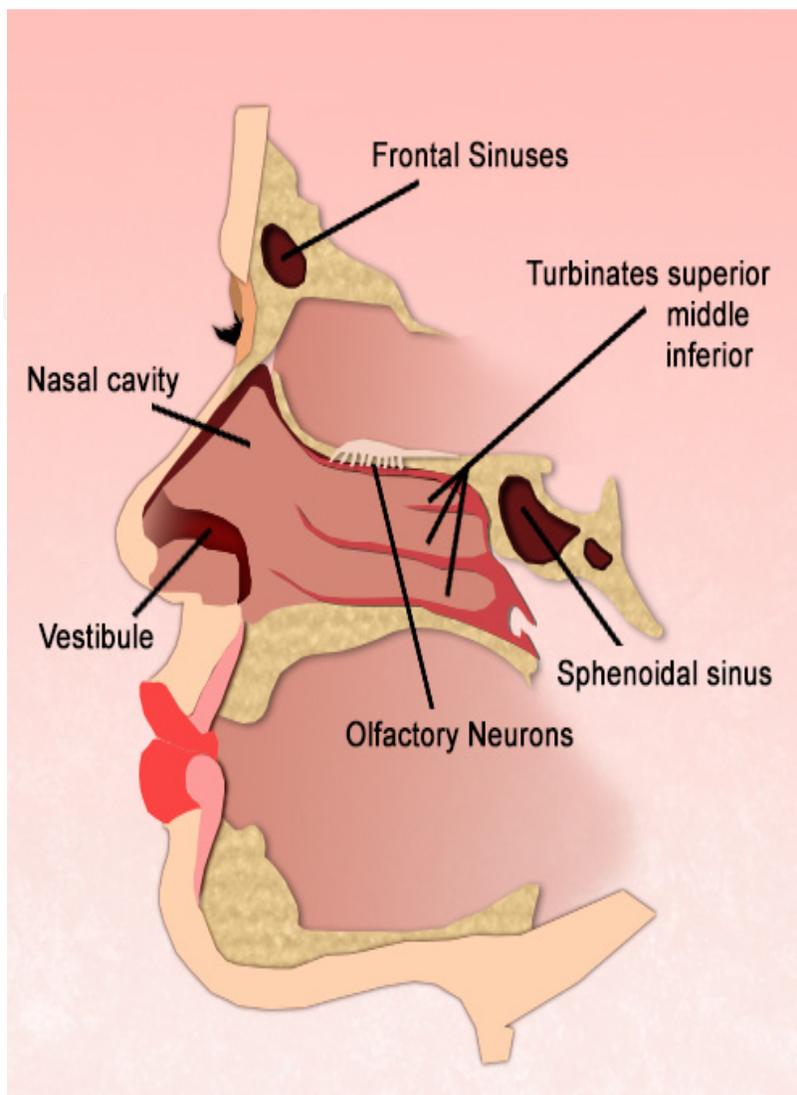
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## 1. Introduction

The use of nasal cavity as a route of administration of drugs, specifically systemically acting drugs that pose a delivery challenge, have become an area of great interest to the pharmaceutical companies in the past decade. The physiology of the nasal cavity allows for variety of drug delivery possibilities and destinations which include local, systemic, vaccine, and access to the central nervous system (CNS)[1]

Anatomically, the nasal cavity can be divided into three functional regions (**Figure 1**):

1. Vestibular region having an area of 10 to 20 sq.cm and is situated just inside the nostrils. It is covered with stratified, keratinised and squamous epithelium.
2. Respiratory region having an area of about 130 sq.cm and occupies majority of the nasal cavity and consists of three turbinates namely inferior, middle and superior.
3. Olfactory region has an area of about 10 - 20 sq.cm. It is located in the roof of the nasal cavity and on the upper part of the nasal septum. It contains the receptors for the sense of smell. Local delivery of drugs in the nasal cavity can be used to treat allergies, congestion and infection. Systemic delivery of the drugs can be used for crisis treatments during a rapid onset of symptoms, daily administration of drugs for long-term treatment of disorders or delivery of peptides or proteins that may be difficult to administer. The nasal cavity can also be used to deliver vaccines including antigens (whole cells, split cells, and surface antigens) and DNA vaccines [1]. The nasal cavity also allows access to the CNS, thus allowing drugs to circumvent the blood-brain barrier (BBB) [1]. It has been suggested that there is free communication between the nasal submucosal interstitial space and the olfactory perineuronal space, which appears to be continuous with a subarachnoid extension that surrounds the olfactory nerve [2].



**Figure 1.** Nasal Anatomy and Physiology

The pharmaceutical companies are increasingly marketing drugs as nasal formulations, drugs such as sumatriptan, estradiol, busserelin, and calcitonin, all which have shown to have faster onset of action, improved bioavailability, and a better delivery method [3].

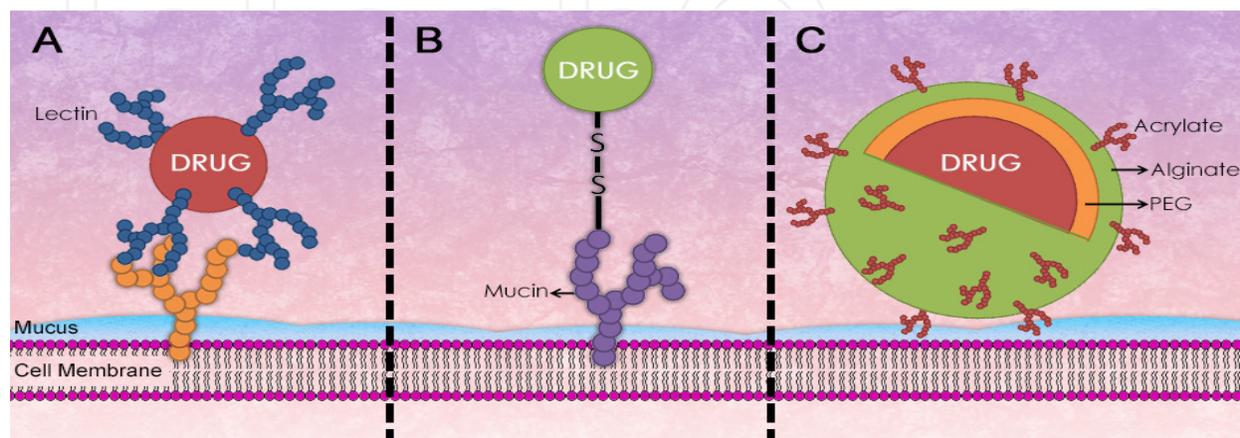
There are a number of advantages in using nasal cavity for administration of drugs. Some of the advantages are: avoidance of the gastrointestinal tract along with hepatic first pass metabolism, increased absorption and bioavailability of small and larger drug molecules<sup>4</sup>. Furthermore, drugs that have low oral bioavailability have been shown to be successfully delivered systemically using the nasal route; studies have suggested that the nasal route is a great alternative to parenteral route for delivery of protein and peptide drugs [4]. Also due to direct delivery of drugs to the systemic circulation, the onset of pharmacological action is rapid [5].

Administration of lower drug doses through the nasal route, may lead to lower side effects. The convenient delivery of drugs via the nasal route, especially in long-term therapies has proven to increase patient compliance compared to parenteral and injection methods [4].

Lipophilic drugs generally have no trouble being absorbed through the nasal cavity. In fact, the bioavailability of lipophilic drugs been shown to be very close to those of intravenous injection (100% bioavailability), for instance, fentanyl has been shown to have an 80% bioavailability for nasal administration [1].

Even though the nasal cavity has a large surface area along with extensive blood supply, it has been shown that the permeability of the nasal mucosa is low for polar molecules. The limiting-factor for nasal absorption of polar drugs such as peptides and proteins is epithelial membrane permeability. Drugs with molecular weights lower than 1000Da can generally pass the epithelial membrane via transcellular route, receptor mediated transport, vesicular transport, use of concentration gradient force [6], or travelling in the paracellular route through the tight junction between the cells. In fact tight junctions seem to have finite permeability to molecules with molecular radii less than or equal 3.6 Å and are essentially impermeable to those with molecular radii greater than or equal to 15 Å [7]. Despite the advantages of nasal drug delivery, some of the drugs may also cause inconvenience due to potential for nasal irritation. Pathological conditions such as cold and allergies may alter nasal bioavailability significantly, which can have an effect on the intended pharmacological action [8].

Another factor that plays an imperative role in low membrane transport of nasally administered drug therapeutics is rapid drug clearance by the mucociliary clearance mechanism. This problem is common with drugs that are not easily absorbed across the nasal membrane. It has been shown that drugs that do not readily cross the nasal membrane, whether liquid or power form are removed from the nasal cavity in 15-20 min [9]. Mucociliary clearance tends to decrease the residence time of the administered drug. This problem can be overcome using formulation strategies. Novel delivery platforms based on polymeric drug carriers along with variety of methods that can be used to improve the absorption of drugs through the nasal route will be discussed in the following paper. These delivery systems work by attaching themselves to the mucus layer and thus preventing clearance of the drug delivery system. Some of these delivery systems are still experimental, whereas others have advanced to clinical use. **Figure 2** summarizes the various mechanisms involved in mucoadhesion of the main drug carriers discussed in this chapter.



**Figure 2.** Mechanisms of mucoadhesion by lectins (A), Thiomers (B), Alginate Poly ethylene glycol acrylate (C).

## 2. Lectins

Lectins are classified as a group of structurally diverse proteins [10] that are found in plants as well as in the animal kingdom. They are also found in some microorganisms [11]. Lectins have the capability to identify and bind to specific sugar moieties. The sugar-binding moiety of most lectins is only a small part of the lectin, i.e., a major portion of lectin is not involved in the recognition and binding to the receptor [12]. Lectins also cause agglutination due to their ability to cross link sugar containing macromolecules. Primarily they identify only specific sugars like mannose, glucose, galactose, N-acetyl-glucosamine, N-acetyl galactosamine, fucose and N-acetyl neuramic acid [13]. The various lectins which have shown specific binding to the mucosa include lectins extracted from *Ulex europaeus* I, soybean, peanut and *Lens culinaris*. The use of wheat germ agglutinin has been on the rise due to its least immunogenic reactions, amongst available lectins [2]. Lectins have the ability to stay on the cell surface or become internalized via a process called endocytosis if the adhesion is receptor mediated. In this manner lectins offer twin functionality of not only allowing target specific attachment but also a means of delivering the drug through a controlled process to the cells by active cell mediated drug uptake [1]. Lectins have potential to be used in Nasal Drug Delivery, especially where internalization of the drug encapsulated nanoparticles is of particular importance such as DNA delivery [14]. In spite of lectins offering significant advantages, it is worth noting that such polymers suffer at least in part from premature inactivation by shed off mucus. This phenomenon has been reported to be advantageous, given that the mucus layer provides an initial yet fully reversible binding site followed by distribution of lectin-mediated drug delivery systems to the cell layer [15].

There are three types of lectins - classified based on their molecular structure:

1. *Merolectins*: lectins which have one carbohydrate recognising domain [1].
2. *Hololectins*: lectins which have two or more carbohydrate recognising domains [1].
3. *Chimerolectins*: lectins with additional unrelated domains [1].

Lectins are involved in various biological processes: cell-to-cell recognition and communication, particularly in the mammalian immune system (transendothelial migration), adhesion and attack of infectious agents on host cells, and clearance of glycoproteins from the blood circulation [16]. Lectins are used in conjugation with other mucoadhesive polymers as drug delivery vehicles to the brain or systemic circulation through the nasal cavity. It was observed that negligible penetration of nanoparticles takes place between cells in the nasal epithelium when administered on their own. Secondly, mucociliary clearance reduced the residence time of the particles in the nasal cavity (particles cleared within the nose every 15 to 20min, thus, resulting in incomplete absorption of the formulation. Also it was found that, unmodified nanoparticles distributed in the nasal cavity without selectivity. This resulted in poor brain targeting efficiency of the formulation. To deal with these problems, novel lectin-modified nanoparticles were constructed. The lectin used was wheat germ agglutinin (WGA), which specifically binds to N-acetyl-D-glucosamine and sialic acid moieties, both of which were abundantly observed in the nasal cavity especially in the olfactory mucosa [17].

Factors like low ciliary irritation and high permeability among other considerations favour the potential use of lectins for nasal drug delivery [18]. Studies in animals concluded that lectins have minimal acute irritancy and can be thus be used for further in vivo studies[19]. However, many lectins are toxic or immunogenic especially those obtained from *Ricinus communis*, *Phaseolus vulgaris* and *Lycopersicon esculentum* and *Canavalia ensiformis*[5]. There is a probability that lectins promote the production of antibodies which could lead to the blockage of lectin-based delivery vehicles. These antibodies may also expose patients to the risk of systemic anaphylaxis on successive exposure. But, by using truncated varieties of lectin molecules as mucoadhesives this potential risk of toxicity may be triumphed over [20].

Mucoadhesive Polymer	Dosage Formulation	Active Ingredient	Reference
Odorranalectin	Liquid	coumarin-6	Wu H et al[21]
wheat germ agglutinin conjugated PEG-PLA nanoparticles	Liquid	coumarin-6	Liu Q et al[22]
Solanum tuberosum lectin-conjugated PLGA nanoparticles	Powder	coumarin-6	Chen J et al [18]

**Table 1.** Synopsis of the studies on the use of Lectins in formulations for nasal drug delivery

### 3. Thiomers

Thiomers are mucoadhesive polymers that have side chains carrying thiols which lead to formation of covalent bonds between the cysteine groups in the mucus and the polymer by thiol/disulphide exchange reactions or simple oxidation process. These bonds are also known as disulphide bridges. These bridges sometimes improve mucoadhesion by 100 folds. They also have permeability enhancing effect and ability to control the rate at which drugs are released. This property and increased mucoadhesion leads to higher residence time of the drugs administered in combination with thiomers hence improving their bioavailability [23]. Thiomers are also used in combination with other polymers like chitosan, poly acrylic acid, etc. Due to immobilization of thiol groups, mucoadhesive properties of these polymers are increased by 140 folds and 20 folds respectively [12]. Thus, thiomers are one of the most mucoadhesive polymers known at the present [24]. Thiomers enhance the permeability of drugs with the potential advantage of not being absorbed through the nasal mucosa compared to low molecular weight permeation enhancers. Thus their permeation enhancing effects can be maintained over a longer period of time while excluding systemic toxic effects.[25] Thiomers tend to cause reversible opening of the tight junctions with glutathione as permeation mediator [26]. Thiolated polymers display in situ gelling properties due to the oxidation of thiol groups at physiological pH-values, which results in the formation of inter- and intramolecular disulfide bonds[12]. This increases the viscosity of the formulation coupled with extensive crosslinking due to formation of disulphide bonds with the nasal mucosa, which increases the residence time of the formulation tremendously [27].

Other studies on thiomers combinations with other polymers by Bernkop-Schnurch led to formation of thiolated polycarbophil which increases the uptake of Leu-enkephalin from the nasal mucosa by 82 folds, thus a promising excipient for delivery of Leu-enkephalin through the nasal mucosa<sup>[28]</sup>. In another study, thiolated polyacrylate microparticles were generated for the nasal delivery of human growth hormone (hGH). The intranasal administration of this microparticulate formulation to rats resulted in a relative bioavailability of  $8.11 \pm 2.15\%$  that represents a 3-fold improvement compared to microparticles comprising the corresponding unmodified polymer<sup>[29]</sup>.

The nasal route is an attractive alternative to parenteral delivery for a number of therapeutic peptides such as calcitonin, insulin, desmopressin, buserelin and octreotide. However, membrane permeability is low for nasally administered peptides leading to low bioavailabilities, a short local residence time at the site of absorption and a high metabolic turnover in the epithelium. The three major approaches to increase the bioavailability of intranasally administered peptide drugs are (i) the use of permeation enhancers, (ii) incorporation of enzyme inhibitors and (iii) increasing local drug residence time using mucoadhesive polymers. Thiomers are capable of combining most of these strategies. Therefore, thiomers can be used as multifunctional vehicles for systemic nasal peptide delivery<sup>[30]</sup>. Due to their high molecular mass, thiomers are not absorbed from the nasal mucosa thus systemic toxic effects can be excluded. Ciliary Beat Frequency (CBF) studies with human nasal epithelium cells show that thiomers do not cause any alteration or impact on CBF. Thiomers have also been found in various studies to not cause any irritation to mucosal cells<sup>[31]</sup>. Table 2 summarizes nasal drug delivery studies with thiomers.

Mucoadhesive Polymer	Dosage Formulation	Active Ingredient	Reference
Thiomer (polycarbophil-cysteine)	Gel	Leu-enkephalin	Bernkop-Schnürch A et al.[28]
Thiomer (polycarbophil-cysteine /glutathione gel)	Gel	Human growth Hormone	Leitner VM et al.[32]
Thiomer (polycarbophil-cysteine)	Microparticles	phosphorothioate antisense oligonucleotide	Vetter A et al <sup>[33]</sup>
Thiolated chitosan	Microparticles	insulin	Krauland AH et al <sup>[34]</sup>

**Table 2.** Use of thiomers in mucoadhesive nasal formulations for systemic delivery

#### 4. Alginate poly-ethylene glycol acrylate

Alginate Polyethylene glycol Acrylate is also known by the acronym Alginate-PEGAc. It has an alginate backbone with acrylated polyethylenglycol groups attached to it. This polymer meshes the properties of alginates (strength, simplicity and gelation) with characteristics specific to the acrylate functionality of PEG like mucoadhesion. PEG's have the ability to penetrate the mucus surface while the acrylate group of the polymer reacts with the sulphide group of glycoproteins present in the mucus. This results in a strong interaction

between the mucus and the polymer [35]. It is expected to be cross-linkable by two different paths: chemically via the acrylate end groups and physically through the alginate backbone [36]. Alginate is a mucoadhesive polysaccharide of 1  $\rightarrow$ 4 linked  $\alpha$ -l-glucuronic acid and  $\beta$ -d-mannuronic acid which binds to the glycoproteins in the mucus through carboxyl–hydroxyl interactions [37]. It is anionic in nature. It is known to undergo ionic sol to gel transition (gelation) upon interaction with multivalent ions such as  $\text{Ca}^{2+}$ ,  $\text{Fe}^{2+}$  [38], thus reducing its adhesion to mucosal tissues [39]. On the other hand Poly-Ethylene Glycol (PEG) is an FDA approved polymer. It is non-toxic, non-immunogenic and non-antigenic. It has high solubility in water and rapid in vivo clearance. It also has the ability to form hydrogen bonds with sugar moieties on glycosylated proteins. This causes PEG to form strong bonds with mucus leading to increased mucoadhesion [25].

Poly Acrylic Acid forms hydrogen bonds between its carboxylic acid groups and sialic acid-carboxylic acid groups present in the mucus [40]. The most recent method for synthesis of Alginate PEG-Ac is a two stage procedure. First the synthesis of alginate thiol takes place. In the second stage, a Michael type addition reaction takes place where a nucleophilic addition between PEG-Diacrylate and alginate backbone occurs conjugating the two [25].

Modification of Alginates with addition of acrylic acid is done to optimize its shortcomings such as erosion in neutral pH. Addition of acrylic acid controls the release rate of drugs and also improves its adhesive properties [29]. Also it has been found that at physiological pH of 7.4 both poly acrylic acid and sialic acid undergo ionization, thus repelling each other. This leads to rapid removal of this polymer-based drug delivery system. Addition of PEG results in H-bonding with PAA enhancing the viscosity of the resulting drug delivery vehicle. Addition of PEG to the polymer increases the viscosity of the resulting polymer complex retarding disintegration and removal of the polymer from the mucosal surface thus increasing mucoadhesion [30]. The combination of the three functional moieties of Alginate Polyethylene glycol Acrylate leads to an improved novel polymer that can be used mucoadhesive nasal drug delivery.

## 5. Poloxamer (Pluronics)

There is a great interest in Poloxamer based formulations. A number of reviews have been published describing in detail poloxamer formulations like gels, poloxamer-coated nanoparticles, o/w and w/o emulsions, and solid polymer blends [41]. Poloxamers are made up of non-ionic difunctional triblock<sup>[42]</sup> copolymers containing a centrally located hydrophobic polypropylene oxide between hydrophilic polyethylene oxides <sup>[43,44]</sup>. Aqueous solutions of poloxamers are extremely stable in the presence of acids, alkalis and metal ions. These polymers are readily soluble in aqueous, polar and non-polar organic solvents. Hence, they are widely preferred choice as excipients in formulations <sup>[45]</sup>. Poloxamers are said to contain thermoreversible property and will convert from a liquid to a gel at body temperature, thus, causing in situ gelation at the site of interest [1] preventing the drug to be removed from the nasal cavity due to mucociliary clearance. This vastly improves the bioavailability of the drug administered. The formation of the gel can be explained as follows. When the poloxamer is

cooled, the hydration layer surrounds the poloxamer molecule and hydrophobic portions are separated due to hydrogen bonding. As the temperature increases, desolvation of the hydrophilic chains occurs as the result of breakage of hydrogen bonds. This results into hydrophobic interactions amongst the polypropylene oxide domains and gel gets formed. Hydroxyl groups of the copolymer become more accessible due to hydration<sup>[46]</sup>. Thus, desolvation caused by increase in temperature and subsequently micellization results in formation of a more closely packed viscous gel <sup>[47]</sup> Various combinations of poloxamers and other mucoadhesive polymers like polycarbophil and polyethylene oxide have been found to be more advantageous since their combination tends to reduce the gelation temperature of poloxamer. This can help in making a polymer that can gel at the temperature observed in the nasal mucosa<sup>[5]</sup>. Poloxamers are also known as Pluronic. Pluronic have also been chemically combined with poly(acrylic acid)s like Dihydroxyphenylalanine (DOPA)<sup>[31]</sup> to produce systems with enhanced adhesion and retention in the nasal cavity.

One of the most promising poloxamer is Poloxamer 407 (Pluronic F127) because of its low toxicity, high solubility, bioadhesion characteristics, and acceptability as drug delivery vehicle <sup>[48]</sup>. Some of the other investigated combination of poloxamers are polymer pluronic PF127 along with benzalkonium chloride which helped decreased the gelation onset temperature. This combination was prepared for the nasal delivery of Vitamin B12<sup>[49]</sup>. In another study, poloxamer 407 was combined with a mucoadhesive polymer or polyethylene glycol. The combination allowed the manipulation of the temperature at which the conversion of sol to gel would take place as well as decreasing and increasing the in vitro release of the drug respectively<sup>[50]</sup>. But work still needs to be done on reducing irritability which is one of the major limitations of these formulations<sup>[51]</sup>. Controlled release nasal formulations of propranolol have been made using a combination of poloxamers and other mucoadhesive polymers for such as Carbopol 934P. By controlling the release of the drug and by increasing its residence time in the nasal cavity, there was a significant increase in bioavailability of the drug<sup>[52]</sup>. Poloxamer properties are said to be affected by addition of various additives. Concentration can greatly affect the thermodynamic properties of poloxamer. Water soluble additives also affect the thermodynamic properties. The range at which gelation occurs increases with polymer concentration, whereas addition of sorbitol and PEG 15000 narrows the gel range. Significant enthalpy change occurs in gels containing sorbitol and PEG, indicative of interactions with the polymer during the phase transitions. As the concentration of the polymer increases, the aqueous gels display non-Newtonian characteristics. The hydrophobic interaction of Benzalkonium Chloride and pluronic produces a gel with higher viscosity. Addition of PEG 15000 helps achieve desired gelation characteristics for increased drug loading and use of desired formulation additives <sup>[41]</sup>. Poloxamers at low concentrations, when dispersed in liquid exist individually as monomolecular micelles. As the concentration of the pluronic in the system increases, it forms multi-molecular aggregates<sup>[53]</sup>. Different aggregate forms of poloxamers are seen depending on the molecular weight, solvent composition, and temperature<sup>[54]</sup>. Micellar behavior changes with changes in solvent composition and temperature. Various salts and additives like surfactants, polymers, cosolvents have marked effect on the micellar properties, clouding and solubilization characteristics of pluronic solutions<sup>[55]</sup>. Salts in the

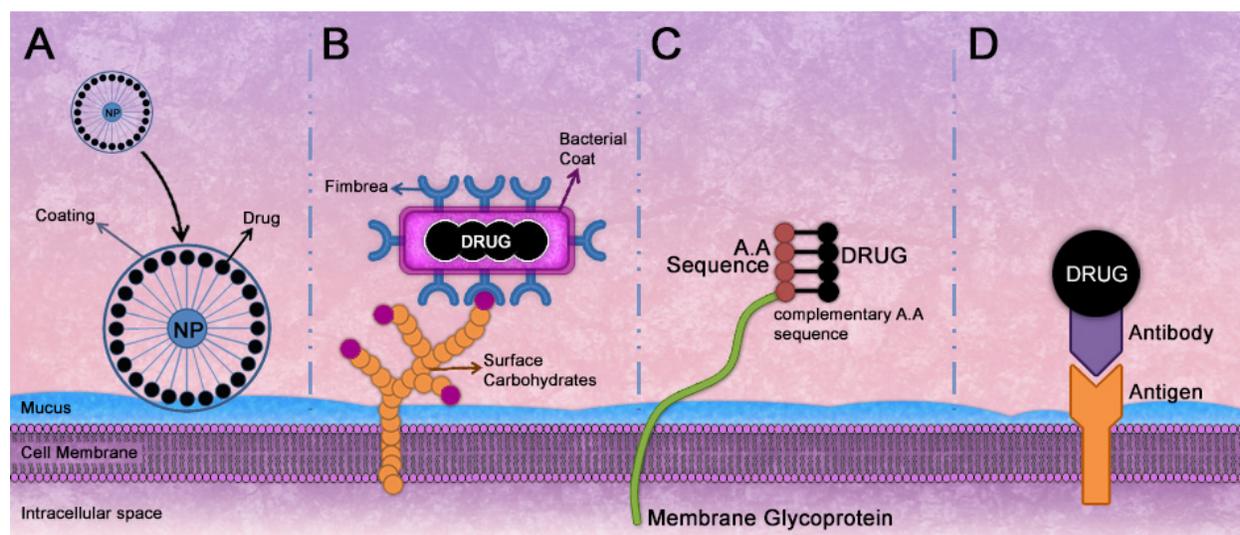
order of  $\text{Na}_3\text{PO}_4 > \text{Na}_2\text{SO}_4 > \text{NaCl}$  have been found to lower the critical micellar temperature significantly<sup>[56]</sup>. Pluronic block copolymers are amongst the most potent drug targeting systems. Recent research on pluronics has generated new findings indicating immunomodulation and cytotoxicity-promoting properties of Poloxamer 407 revealing significant pharmacological interest. Human trials are in progress based on these results<sup>[57]</sup>. Along with these new findings and favourable properties, poloxamers have generated immense interest as one of the most promising novel mucoadhesive drug delivery systems. Table 3 shows most of the published studies involving nasal drug delivery with this polymer.

Mucoadhesive Polymer	Dosage Formulation	Active Ingredient	Reference
Poloxamer 188 or 407	Nanovesicles	olanzapine	Salama HA et al <sup>[58]</sup>
Poloxamer-Chitosan	Gel	(32)P-siRNA dendriplexes	Perez AP et al <sup>[59]</sup>
poloxamer 407/ hydroxypropyl- $\beta$ - cyclodextrin/chitosan	Gel	fexofenadine hydrochloride	Cho HJ et al <sup>[47]</sup>
chitosan-poloxamer 188	Spray	fentanyl	Fisher A et al <sup>[60]</sup>
PLGA: Pluronic F68	Nanoparticles	plasmid DNA	Csaba N et al <sup>[61]</sup>
Pluronic F127 (PF127)/ Carbopol 934P	Gel	sumatriptan	Majithiya RJ et al <sup>[62]</sup>
poloxamer 407/Polyethylene glycol	Liquid	metoclopramide hydrochloride	Zaki NM et al <sup>[63]</sup>
Poloxamer 407 /PEG 4000	Liquid	Radix Bupleuri	Chen E et al <sup>[64]</sup>
Poloxamer 407	Liquid	tetracosactide	Wüthrich P et al <sup>[65]</sup>
Pluronic F127	Microspheres	Bordetella bronchiseptica multiple antigens containing dermonecrotxin	Kang ML et al <sup>[66]</sup>
Pluronic F127 (F127)/ chitosan	Liquid	tetanus toxoid	Westerink MA et al <sup>[67]</sup>
Pluronic PF 127	Gel	Vitamin B(12)	Pisal SS et al <sup>[68]</sup>
poloxamer 188	Liquid	isosorbide dinitrate	Na L et al <sup>[69]</sup>

**Table 3.** Application of Poloxamer (pluronics) in formulations for nasal drug delivery

## 6. Future prospects

Although several novel strategies are currently used for nasal drug delivery using bio-and muco-adhesion strategies, the potential exists to improve these methods using other strategies such as nanoparticles, bacterial adhesion, altered amino acid sequence, and antibody mechanism. A graphic representation of these methods is shown in Figure 3. Each of these methods is discussed below.



**Figure 3.** Potential future novel strategies for muco-/bio-adhesive drug delivery using Mucoadhesive Nanoparticles (A), Bacterial Adhesion (B), Altered Amino Acid Sequence (C) and Antibody mechanism (D).

## 7. Mucoadhesive nanoparticles

Nanoparticles generally vary in size from 10-1000nm. Biodegradable nanoparticles have been used frequently as drug delivery vehicles due to its better encapsulation efficiency, control release and less toxic properties<sup>[70]</sup>. They offer enhanced biocompatibility, superior drug/vaccine encapsulation, and convenient release profiles for a number of drugs, vaccines and biomolecules to be used in a variety of applications in the field of medicine<sup>[71]</sup>. The average pore size of viscoelastic mucus is around  $150 \pm 50$  nm. Thus, formulations of mucoadhesive nanoparticles can lead to effective drug delivery to the target site. Commonly used materials for formulating nanoparticles are poly(lactide-co-glycolide) (PLGA) and Pluronics [55]. PEG coatings have been widely used in the development of polymeric drug carriers, including particles composed of biodegradable polyesters and polyanhydrides. PEG coatings reduce aggregation and enhance the blood circulation times of biodegradable nanoparticles designed for drug delivery<sup>[72]</sup>. Nanoparticles up to 200 nm in diameter that are coated with a dense layer of non-mucoadhesive PEG polymers, including drug carriers composed entirely of Generally Regarded As Safe (GRAS) components, readily penetrate nasal mucus. The development of polymeric particles with improved sinus mucus penetration capability should encourage the commercial development of new generations of nanoparticle-based intranasal drug delivery systems [46].

## 8. Bacterial adhesion

Non-denatured bacterial cell envelopes, also known as bacterial ghosts, are produced as a result of plasmid-encoded lysis gene *E* of bacteriophage in gram-negative bacteria<sup>[73]</sup>. Due to its hydrophobic nature, gene *E* product integrates into the inner membrane, resulting in fusion of inner and outer membrane. This leads to the formation of a trans-membrane tunnel<sup>[74]</sup>. The generated trans-membrane tunnel ranges between 40-80 nm in diameter,

through which all cytoplasmic contents are expelled<sup>[75]</sup>. It is imperative to note that the process of Protein E-specific lysis does not result in physical or chemical denaturation of bacterial surface structures. The bacterial ghosts have been suggested to be a great alternative method for inactivated non-living whole-cell vaccination <sup>[76]</sup>. Depending on the site-directed sequences included in the fusion, a variety of foreign proteins can be expressed within or on the cell envelop of bacterial ghosts <sup>[77]</sup>. The advantage of using bacterial ghosts is, bacterial ghosts can be produced in large quantities, do not require the cold-chain-storage system, and are stable for a long time. Further, the size of the foreign protein insert can be very large (>600 amino acids) thus allowing the presence of multiple epitopes simultaneously<sup>[78]</sup>.

The attachment of synthetic or natural macromolecules to mucus or epithelial surface is defined as bioadhesion. Bacteria are capable of adhering to the epithelium surface with aid of fimbriae, which are long, lectin-like proteins found on the surface of many bacterial strains<sup>[79]</sup>. There is a correlation between the pathogenicity of bacteria and the presence of fimbriae, thus, the adhesion of bacteria to epithelial surfaces can be used as an efficient method of efficient drug-delivery<sup>[80]</sup>.

Bacterial ghosts have been shown to display bio-recognitive abilities which allow their attachment to different surfaces of numerous body tissues depending on the species chosen<sup>[81]</sup>. Many of these bacterial ghosts are able to bind to surfaces due to the presence of long fimbriae which facilitate the penetration of the mucus covering epithelial tissues<sup>[65]</sup>. Thus, as a result of the properties of fimbriae a bioadhesive drug delivery system has been developed by using the ghost bacteria with a therapeutic agent coupled to *E. coli* K99 fimbriae<sup>[62]</sup>. This strategy may be applied to nasal drug delivery with the intention of reducing mucociliary clearance.

## 9. Altered amino acid sequence and antibodies

Certain amino acid sequences can be used to promote binding of drug molecules to specific cell surface glycoproteins due to the amino acids having complementary sequences present to these glycoproteins<sup>[82]</sup>. In certain disease conditions the sequence of glycoproteins is altered. This altered state can be used as a target by complementary amino acid sequences by attaching them to a drug delivery device <sup>[66]</sup>. Antibodies can be produced against selected molecules present on mucosal surfaces. Due to their high specificity, antibodies can be a rational choice as a polymeric ligand for designing site-specific mucoadhesives. This approach can be useful for targeting drugs to tumour tissues<sup>[66]</sup> or even normal cells.

## 10. Conclusion

There is no question that the nasal route has a great potential for systemic drug delivery. The physiology of the nasal cavity creates a variety of opportunities for drug companies to develop local and systemic drugs. As nose- to- brain delivery makes it possible to by-pass the blood-brain-barrier for certain drugs; administration of drugs via this route for treatment of

neurological diseases presents exciting opportunities. Despite the advantages of nasal drug delivery, the absorption and permeability of polar drugs through the nasal mucosa remains a challenge. The mucociliary clearance system compounds the problem by limiting how long the drug stays in the nasal cavity for absorption to take place. Hence several strategies have been developed to enable the drug molecules to attach onto the mucus or epithelial layer, thus preventing them from being cleared from the nasal cavity. The application of lectins, thiomers, alginate poly-ethylene glycol acrylate and poloxamers were discussed in this chapter. These polymers are not the only polymers used for nasal delivery. However, they are among the least reviewed polymers for systemic drug delivery via the nasal route. Other bioadhesive strategies including nanoparticles, bacterial adhesion, altered sequence and antibody strategies can further improve the bioavailability of polar drug molecules delivered via the nasal route. However, a lot of work remains to be done in this area.

## Author details

Utkarshini Anand, Tiam Feridooni and Remigius U. Agu  
*Biopharmaceutics and Drug Delivery Laboratory, College of Pharmacy,  
 Faculty of Health Professions, Dalhousie University, Halifax, NS, Canada*

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