INDO AMERICAN JOURNAL OF PHARMACEUTICAL RESEARCH

NATURAL MUCOADHESIVE POLYMERS IN NASAL DRUG DELIVERY SYSTEM: A REVIEW

Arunima Kamal*, Dr. K Premaletha

Department of Pharmaceutics, College of Pharmaceutical Sciences, Government Medical College, Kannur, Kerala University of Health Sciences, Kerala, India.

ARTICLE INFO

Article history

Received 17/03/2023

Available online 31/03/2023

Keywords

Intranasal,

Mucoadhesive,

Natural Polymers.

ABSTRACT

Intranasal drug delivery is considered to be a useful and reliable alternative to the oral and parenteral route. Benefits of nasal drug delivery include large surface area, avoiding first pass effect, rapid onset of action, the potential for direct delivery to the brain, etc. There are different barriers to nasal delivery which decrease the drug bioavailability. One of the approaches to increase bioavailability is the mucoadhesive drug delivery system. The mucoadhesive system is the ideal choice of drug delivery system for systemic nasal delivery because it improves the residence time thus prolonging the duration of action as well as the extent of absorption. This article is a review of the natural mucoadhesive polymers used in nasal drug delivery systems. This includes the mechanism of mucoadhesion, advantages, and disadvantages of mucoadhesive polymers, and the different mucoadhesive polymers used.

Corresponding author

Arunima Kamal

Department of Pharmaceutics,

College of Pharmaceutical Sciences,

Government Medical College, Kannur,

Kerala University of Health Sciences, Kerala, India.

arunimakamal97@gmail.com

(+91)8547067546

*Please cite this article in press as **Arunima Kamal** et al. Natural Mucoadhesive Polymers in Nasal Drug Delivery System: A Review. Indo American Journal of Pharmaceutical Research.2023:13(03).*

INTRODUCTION

In recent years, nasal medication delivery systems have drawn a lot of attention as an easy and dependable way for systemic drug administration. Intranasal drug delivery is considered an alternate route for administering drugs, vaccines, and biomolecules including proteins, peptides, and non-peptide medicines. The nasal route is advantageous for medications that are unstable when taken orally because they undergo considerable GIT degradation or undergo first pass hepatic metabolism. Parenteral therapy is an alternative to nasal therapy, which is also helpful for long-term therapy. Nasal routes are non-invasive, frequently utilised for local treatments, and can also be used for systemic treatments.

Due to the lack of pancreatic and gastric enzymatic activity, the neutral pH of the nasal mucus, and reduced dilution by gastrointestinal contents, nasal mucosa has been investigated as a viable delivery route to obtain faster and greater levels of drug absorption [1,2].

Advantages of nasal drug delivery systems [3,4,5]

- Rapid medication absorption occurs through highly vascularized mucosa.
- A sizable surface area of the nasal mucosa is available for dosage absorption.
- Quick start of the action.
- Non-intrusive and simple to administer.
- Avoid the BBB.
- Prevents medication degradation in the GIT.
- Prevents first pass hepatic metabolism.
- Nasal bioavailability of small drug molecules is good.
- By using absorption enhancers, the bioavailability of big medication molecules can be improved.
- A substitute for parenteral administration, particularly for proteins and peptides.
- Convenient path for patients receiving long-term treatment.
- Increased biological availability.
- The modest dose reduces side effects.
- Patient comfort and compliance are increased.
- One could self-administrate.
- Direct transport can reach the brain and systemic circulation.
- Offers a lower risk of overdose.

Limitations of nasal drug delivery system [3,4,5]

- The delivery volume in the nasal cavity is capped at 25 to 200 L.
- This delivery method cannot be used to deliver high molecular weight chemicals.
- Negatively impacted by pathological circumstances.
- On this route, significant interspecies heterogeneity is seen.
- Common defensive mechanisms like ciliary beating and mucociliary clearance have an impact on the permeability of the substance.
- Nasal mucosa irritation is caused by medications like Budesonide.
- Presently underdeveloped models and little understanding of mechanisms.
- Systemic toxicity happening owing to absorption enhancers is yet not documented.
- Smaller absorption surface compared with GIT.
- Potential for nose discomfort, making it less convenient than taking it orally.

MUCOADHESION

The definition of mucoadhesion is the attachment of artificial or biological macromolecules to any mucous lining found on the surface of biological epithelial cells. Mucoadhesive polymers are used to do it primarily. The non-covalent links between the mucus gel layer and polymers, such as hydrogen bonds, ionic interactions, or physical entanglements, create mucoadhesion[6].

Mechanism of mucoadhesion

Typically, the mucoadhesion mechanism consists of two steps: The contact stage and the consolidation stage. The initial contact of mucoadhesive polymer with the mucous membrane, along with the subsequent swelling and spreading of the formulation, marks the beginning of its deep engagement with the mucous layer. The presence of moisture during the consolidation stage activates the mucoadhesive materials. Moisture causes the system to become plastic, which frees the mucoadhesive molecules and enables them to form weak hydrogen and van der Waals bonds.

The interaction between the mucoadhesive polymer and the mucus released by the sub-mucosal glands is what causes mucoadhesion to occur after nasal delivery. The proper wetting, swelling, and close contact between the polymer and the nasal mucosa are among the sequential actions that take place during mucoadhesion. Following the interpenetration of the polymer chains and mucus protein chains, the swollen mucoadhesive polymer enters the tissue crevices [7,8].

Mucoadhesive polymers

In order to localise the active agents to a specific region or site, mucoadhesive delivery techniques are being investigated. In order to extend the residence period of active agents in the intended area, polymers have been crucial in the creation of such systems. Both water-soluble and water-insoluble polymers are used as mucoadhesive polymers [9].

Characteristics of an ideal mucoadhesive Polymer [9,10]

The following qualities define a good mucoadhesive polymer:

1. They should not be toxic and should not be absorbed via the digestive system.
2. It must not aggravate the mucous membrane.
3. It should ideally create a powerful non-covalent bond with the surfaces of the mucin-epithelial cell.
4. It should have some site-specificity and stick to most tissues fastly.
5. It should not obstruct the release of drugs and allow for daily absorption.
6. Neither during storage nor the shelf life of the dosage form may the polymer degrade.
7. For the created dosage form to remain competitive, the price of the polymer should be low.

Classification of mucoadhesive polymers [6,9]

The classification of various mucoadhesive polymers used in the formulation based on origin:

Synthetic polymers

Cellulose derivatives like Methylcellulose, Ethylcellulose, Hydroxy-ethyl cellulose, Hydroxyl propyl cellulose, Hydroxy propyl methylcellulose, and Sodium carboxymethylcellulose. Poly (acrylic acid) polymers like Carbomers, polycarbophil, Poly (hydroxyethyl methyl acrylate), Poly (vinyl alcohol), etc.

Natural polymers

Sodium alginate, Guar gum., Xanthan gum, Lectin, Gelatin, Pectin, Chitosan, etc.

Advantages of Natural polymers [11]

a) All natural polymers should be biodegradable
b) They are biocompatible as well as non-toxic.
c) They must be economic.
d) Safe and devoid of side effects.
e) Easy availability.

Disadvantages of Natural polymers [11,12]

a) Microbial contamination.
b) Batch to batch variation.
c) The uncontrolled rate of hydration.
d) Slow process.
e) Heavy metal contamination.

Natural mucoadhesive polymers

Starch

One of the most popular mucoadhesive carriers for nasal medication administration is starch. It has been shown to be efficient in increasing the absorption of both small hydrophobic medicines and hydrophilic macromolecular pharmaceuticals. The drum-dried waxy maize starch has been regarded as the best among those processed using other methods due to its superior bioadhesive characteristic. Maize starch is the most popular class for pharmaceutical purposes. Due to its significant swelling and quick enzymatic breakdown, which causes the release of many medications to occur too quickly, native starch may not be ideal for controlled release drug delivery systems. Due to this, variants of starch that are more resistant to enzymatic degradation, crosslinking, and the creation of co-polymers are now being used. [7,11].

Xanthan gum

The fermentation of the gram-negative bacterium Xanthomonas campestris results in the production of xanthan gum, an extracellular polysaccharide with a high molecular weight. The trisaccharide side chain of **β**-D-mannose- **β**-D-glucuronic acid-**α** –D-mannose is coupled with alternate glucose residues of the main chain in the fundamental structure of this naturally occurring cellulose derivative. The distribution of the potential pyruvate function in the terminal D-mannose residue depends on the bacterial strain and the fermentation circumstances. An acetyl function can be found in the side chain of the non-terminal D-mannose unit. Due to the inclusion of glucuronic acid and pyruvic acid groups in the side chain, this polymer has an anionic structure [11,12].

Alginates

Brown seaweed is commonly used to produce alginate, an anionic polymer that is both natural and biodegradable. Its low toxicity and affordable price have led to substantial research into it in a few studies to create microparticles and beads with good bioadhesive properties. In pharmaceutical research, sodium or calcium salts of alginate are primarily used. Alginate has effective mucoadhesion properties because it contains a carboxylic acid component, which forms a hydrogen bond with the mucin glycoprotein. Alginate does not swell much at acidic pH, which causes the polymeric chain to coil up a lot. Uncoiling of polymeric chains increases the risk of entanglement with the mucous layer, leading to increased mucoadhesion. Alginate hence provides significantly less mucoadhesion in acidic ph. Alginate is typically used to create beads or microspheres by being crosslinked with a divalent cation, most frequently Ca^{++}. However, as the Ca^{++} concentration is raised, more alginate forms crosslink with Ca^{++}, which lowers the flexibility of the polymer chains. This thus weakens mucoadhesion [12,13,14].

Pectin

Pectin is a naturally occurring heterogeneous polymer that is derived from the citrus peel or apple pomace. It is biodegradable, biocompatible, nontoxic, and natural. It has linear chains of carboxyl-grouped, (1-4)-linked a-D-galacturonic acid residues interrupted by 1,2- linked l-rhamnose residues with a few hundred to about one thousand building blocks per molecule, corresponding to an average molecular weight of about 50,000 to about 1,80 000. The mucoadhesion mechanism of pectin has been described in two ways: through the establishment of a hydrogen bond with mucin and by electrostatic contact with mucin molecules [11,13,14].

Chitosan

Chitosan is the second most prevalent polysaccharide in the world after cellulose among all mucoadhesive substances. Since the early 1980s, it has been one of the polymers that have been widely examined in various scientific papers. Chitosan, a cationic mucoadhesive substance, is essentially a polysaccharide that is created by deacetylating chitin. Glucosamine and N-acetyl-glucosamine are combined to form this polymer. Chitosan is soluble in mild, diluted acids but insoluble in water. Chitosan is probably a desirable polymeric component due to its biocompatibility, biodegradability, and low toxicity. There are several processes responsible for the mucoadhesion properties of chitosan. Due to the existence of -OH and $-NH_2$ groups, the hydrogen bonding with the glycoprotein of mucin is an important process [13,14,15].

Natural mucoadhesive polymers obtained from plant sources

Artocarpus heterophyllus Lam

It is a fruit that is widely consumed throughout South East Asia and was first grown in India at the base of the Western Ghats. It is a fruit that is full of nutrients, including proteins, carbohydrates, potassium, calcium, iron, and vitamins A, B, and C. The mucoadhesive agent solution was made using Methocel K4M, Carbopol 974P, and a naturally isolated mucilage from jackfruit in various concentrations, including 1%, 2%, and 3% w/v. Shear stress was computed using a self-made tool composed of two glass slides fixed on a pulley, a wooden board with a scale, and two pans on each side. A surplus of the produced solution was sandwiched between two glass slides, and the sample was compressed to a uniform thickness over five minutes using a 1000 g weight on the glass to the pan was added weight (250 g). Shear stress was calculated as the weight needed to separate two slides. Jackfruit produced 12–15% w/w yield [16,17].

Cumin (Cuminum cyminum)

A little annual herb that is indigenous to the Mediterranean region and is cultivated for its flavourful dried fruit, which is frequently used in cooking. During the process of flowering, seed development, and maturity, cumin likes locations with low air humidity. Locally known as "Shahijeera" or "Kashmiri" cumin, bitter cumin (Cuminum nigrum L.) is primarily grown in Central Asia and India. It is a member of the Apiaceae family. Pickles, foods made with wheat and rice, garam masala, and spice mixtures all use it. Compared to the two other forms of cumin, black cumin, and regular cumin, it has a more bitter flavour. It is used as a stimulant, carminative, astringent, and beneficial for dyspepsia and diarrhoea in conventional ayurveda medicine. Our efforts have caused Cuminum cyminum to produce more than Trigonella foenum graecum and Foeniculum vulgare. Three extracts were found to have identical pH values and drying loss. Cuminum cyminum has a high starch content, indicating that it has a high binding activity. Only Cuminum cyminum was found to have a significant concentration of bitters. It has a significant preservation effect [16,18].

Dellinia indica

Oxytocin nasal gel made with fruit extracts from Dellinia indica was examined. The fruit of Dellinia indica L. was used to create a new nasal gel formulation that has a natural mucoadhesive. The hydroxy propyl methyl cellulose (HPMC) and carbopol 934, which are typically employed for a similar purpose, were shown to have lower mucoadhesive strength and viscosity than this natural mucoadhesive substance. Compared to the synthetic polymers, the in-vitro drug release properties employing a Franz-diffusion cell and an excised bovine nasal membrane were also determined to be superior [16,19].

Ficus carica

It was shown that the mucilage isolated from F. carica fruits has superior mucoadhesive characteristics to the synthetic polymers HPMC and Carbopol 934, which are frequently used to make nasal gels. In comparison to gels made from synthetic polymers, in situ nasal gels made from FCM showed higher rheological, mechanical, and mucoadhesive characteristics. The structural integrity of the nasal mucosa was not adversely affected by this natural mucilage, according to a histopathological examination. Additionally, an in vivo investigation shows that the bioavailability of midazolam from FCM gels was significantly higher than that from HPMC and Carbopol 934 gels. The present findings of the study demonstrate that nasal gel made from 0.5% w/v F. carica mucilage and 0.5% sodium taurocholate as an enhancer produced repeatable outcomes. This kind of midazolam nasal in situ gel, which is made from naturally occurring mucilage taken from F. carica fruits, will surely offer a more affordable dosage form of the drug and hence open new possibilities in this area [16,20].

Trigonella foenum-graecum

Worked on fenugreek seeds to create a new diazepam delivery method. When compared to other synthetic polymers, the mucoadhesive agent made from fenugreek seeds demonstrates higher mucoadhesive characteristics, higher adherence, and higher molecular weight and viscosity. This could be because there are more carboxyl and hydroxyl groups present than in other polymers, which leads to more favourable macromolecule conformation and accessibility of its hydrogen-binding group. It is non-allergic, easily biodegradable, and edible. Diazepam is frequently given parenterally and creates dangerous side effects with minimal patient compliance. This nasal medication delivery method could take the place of the common diazepam injection [16,21].

Sterculia foetida Linn

A new in-sit mucoadhesive nasal gel formulation has been developed using a natural mucoadhesive polymer obtained from the bark of *Sterculia foetida Linn*. SFG is obtained from dried gummy exudates of stem bark of *Sterculia foetida* of the family Sterculiaceae. They are used in concentrations ranging from 0.14 to 0.22. The mucoadhesive strength and viscosity of this natural mucoadhesive polymer were found to be higher in comparison to the synthetic polymers, namely HPMC and Carbopol 934.Nasal residence time is increased by improved bioadhesion from sterculia foetida gum because the gel in the nose has a higher viscosity, which may be useful to keep the medication from draining out and it also has a permeation-improving effect, increasing the bioavailability of the drug. The bioadhesive power, gel strength, and prolonged release effect on the medication increase as sterculia foetida gum content rises. It is also beneficial for the treatment or management of migraine for a long period of time by sustaining the drug release [22].

CONCLUSION

Nasal drug delivery is the most promising method with a lot of advantages. Mucociliary clearance and rapid drainage are the limitations of the nasal route. This can be minimised using mucoadhesive polymers. The pharmaceutical scientist has achieved great success in developing systems using natural polymers. They are biocompatible and have no side effects. The use of natural polymers can make a more acceptable and excellent system.

CONFLICT OF INTEREST

The author has no conflict of interest.

ACKNOWLEDGEMENT

The authors are thankful to College of Pharmaceutical Sciences, Government Medical College, Kannur, for the support and encouragement.

ABBREVIATIONS

GIT - gastrointestinal tract,
BBB - blood-brain barrier,
HPMC - hydroxypropyl methylcellulose,
FCM - Ficus carica mucilage,
SFG - sterculia foetida gum

REFERENCE

1. Ghori MU, Mahdi MH, Smith AM, Conway BR. Nasal drug delivery systems: an overview. Am J Pharmacol Sci. 2015;3(5).
2. Appasaheb PS, Manohar SD, Bhanudas SR, Anjaneri N. A review on intranasal drug delivery system. J Adv Pharm Educ Res. Oct-Dec 2013;Oct:3(4).
3. Alagusundaram M, Chengaiah B, Gnanaprakash K, Ramkanth S, Chetty CM, Dhachinamoorthi D. Nasal drug delivery system-an overview. Int J Res Pharm Sci. 2010;1(4):454-65.
4. Sharma PK, Garg G, Salim M. Review on nasal drug delivery system with recent advancemnt. Int J Pharm Pharm Sci. 2011;3:6-11.
5. Moinuddin S, Razvi SH, Uddin MS, Fazil M, Shahidulla SM, Akmal MM. Nasal drug delivery system: a innovative approach. Perception. 2019;15:16.
6. Samanta R, Bhaumik A, Nayak AK. The assessment of mucoadhesivity of natural polymer derived form plant sources. J Drug Deliv Ther. 2020 Apr 15;10(2-s):27-9. doi: 10.22270/jddt.v10i2-s.3952.
7. Chaturvedi M, Kumar M, Pathak K. A review on mucoadhesive polymer used in nasal drug delivery system. J Adv Pharm Technol Res. 2011 Oct;2(4):215-22. doi: 10.4103/2231-4040.90876, PMID 22247888.
8. Khurana SH, Madhav NS, Tangri PR. Mucoadhesive drug delivery: mechanism and methods of evaluation. Int J Pharm Biol Sci. 2011;2(1):458-67.
9. Kavitha K, Kumar MR, Singh SJ. Novel mucoadhesive polymers-a review. J Appl Pharm Sci. 2011 Oct 30(Issue):37-42.
10. Shaikh R, Raj Singh TR, Garland MJ, Woolfson AD, Donnelly RF. Mucoadhesive drug delivery systems. J Pharm Bioallied Sci. 2011 Jan;3(1):89-100. doi: 10.4103/0975-7406.76478, PMID 21430958.
11. Khan et al. Novel natural mucoadhesive polymers. World journal of pharmaceutical sciences.2015oct4(12). Vol. 347.
12. Chavhan SA, Shinde SK, Sapkal SB, Shrikhande VN. Herbal excipients in novel drug delivery systems. IRJDPL. 2017 May 15;6(3):2597-605. doi: 10.21276/IJRDPL.2278-0238.2017.6(3).2597-2605.
13. Chatterjee B, Amalina N, Sengupta P, Mandal UK. Mucoadhesive polymers and their mode of action: A recent update. J Appl Pharm Sci. 2017 May 30;7(5):195-203.
14. Sinha VR, Kumria R. Polysaccharides in colon-specific drug delivery. Int J Pharm. 2001 Aug 14;224(1-2):19-38. doi: 10.1016/s0378-5173(01)00720-7, PMID 11472812.
15. Kumar H, Mishra G, Sharma AK, Gothwal A, Kesharwani P, Gupta U. Intranasal drug delivery: A non-invasive approach for the better delivery of neurotherapeutics. Pharm Nanotechnol. 2017 Sep 1;5(3):203-14. doi: 10.2174/2211738505666170515113936, PMID 28521670.
16. Kumar D, Priya B. S.K. guptaa review: mucoadhesive agent in nasal drug delivery system. The Glob J Pharm Res. Mar 31, 2013;2(1):1424-33.
17. Vidya S, Vandana P, Archana P. Isolation and characterization of jackfruit mucilage and its comparative evaluation as a mucoadhesive and controlled release component in buccal tablets deetu journal of pharmaceutical science. Vol. 2(2); 2012. p. 61-9.
18. Niraimathi KL et al. Standardization studies on herbal binders and preservatives. J Pharm Res. 2012;5(4):2091-3.
19. Ketousetuo. K, Bandyopadhyay. A.K., Development of Oxytocin Nasal Gel using Mucoadhesive Agent obtained from the Fruits of Dellinia indica. L Sci Asia. 2007;33:57-60.
20. Basu S, Bandyopadhyay AK. Development and Characterization of mucoadhesive in situ Nasal Gel of midazolam Prepared with Ficus carica Mucilage. AAPS PharmSciTech. 2010 Sep;11(3):1223-31. doi: 10.1208/s12249-010-9477-x, PMID 20683687.
21. Datta Rimi BAK. Development of a new nasal drug delivery system of diazepam with natural mucoadhesive agent from Trigonella foenum-Graecum L. J Sci Ind Res. 2005;64:973-7.
22. Mahakalkar NG, Upadhye KP. Zolmitriptan nasal insitu gel using Sterculia foetidalinn gum as natural mucoadhesive polymer. Int J Pharm Sci. 2013;22:206-13.

54878478451**210307**