A REVIEW ON APPLICATION OF NATURAL BIOADHESIVE POLYSACCHARIDES FOR INTRANASAL DRUG DELIVERY

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ABSTRACT

There are several routes of drug administration like oral, trans-dermal, parenteral, rectal, ocular, intro-vaginal, nasal etc. Amongst them nasal drug delivery shows great impact. Extensive efforts have done to target a drug in a particular region of body for long period of time not only for local targeting of drugs but also for control release of drug from delivery system. Many nasal formulations have reported till now with improved bioavailability. However, the major limitation with nasal route administration is the poor contact of the formulations with the nasal mucosa due to mucoceliary clearance. Many attempts have been done in the recent past to increase the residence time of drug formulations in the nasal cavity, resulting in improved nasal drug absorption by using mucoadhesive polymers. A variety of polymers has been used for the development of nasal formulation. Uses of natural polymers for development of drug delivery systems are the foremost priority of the researchers from recent past.The pharmaceutical researchers are moving towards the development of drug delivery system by using natural polymers. These efforts are done to maximize their bio-availability and patient protection by minimizing toxic effect which is highly associated with synthetic polymers. This review focuses on the various natural mucoadhesive polymers that have been used and showed a potential for muscoadhesion in to nasal cavity.

KEY WORDS:

Nasal drug delivery system, Natural polysaccharide, Mucociliary clearance, Mucilage, Mucoadhesion, Nasal cavity

INTRODUCTION:

Nasal drug delivery system has shown great attraction in the past years to optimized therapeutic effect of drug, due to high permeability of nasal epithelial membrane so that rapid absorption of drug is possible, as compared to other non-invasive routes.[1,2] Nasal drug delivery system provides excess of easy application of drug, with the possibility of self administration by removing the chance of unwanted painful condition associated with injection form of drug delivery. Furthermore, lipophilic and low molecular weight drugs can

easily penetrate through nasal mucosa with less degradation. Fast absorption can be achieved due to large absorption surface area and high vascularisation. Nasal route can be used as an alternative to parentral in case of emergency therapy.[3,4] Nasal drug delivery system is a potential route for direct delivery of drug to the central nervous system through olfactory region by bypassing hepatic first pass metabolism.[5,6] Side by side nasal drug delivery system has some limitations like large dose cannot be administered by this route conveniently due to administrative problems. Administration of solid formulation is quite difficult by nasal route.[5] Fast clearance of the administered formulation occurs from the nasal cavity as the result of mucociliary clearance causes poor absorption of drug.[7]

These difficulties of nasal route can be minimized by utilization of various kinds of mucoadhesive polymers in the formulation. These polymers can effectively increase the retention time with improved permeation enhancing effect. In some research these polymers also possess the controlled release of drug. A variety of polymers have been discovered which includes, synthetic as HPMC, HEC, Chitosan, Carbopol and natural as gelatin, albumin, starch. Utility of synthetic polymers are associated with large numbers of risk such as high cost, toxicity, environmental pollution during synthesis, non renewable sources, side effects and poor patient compliance.[8] These limitations of synthetic polymers may be avoided by utilization of natural polymers as they are biodegradable, chemically inert, less expensive, nontoxic, and widely available.[1,8] Natural products are now accepted worldwide due to their biodegradability, which leads low chance of risk during uses.

This review mainly focuses on the various natural mucoadhesive polymers that have been be used as a carrier for drug delivery through the nasal cavity for the improvement of bioavailability by minimizing the high risks which are associated with synthetic polymers.

ANATOMY OF NOSE:

Nose is divided into two nasal cavities via the septum. The volume of each cavity is about 7.5 ml and has a surface area around 75 cm^2. pH of the mucosal secretions ranges from 5.0 to 6.7 in children and 5.5 to 6.5 in adults. [7,9,10] There are four distinct functional regions in nose called vestibular, atrium, respiratory and naso-pharynx. The nasal vestibule opens to the face by the nostril. The atrium is a region among the vestibule and the respiratory region. The nasal turbinate shows the major part of the nasal cavity, having walls which divide it into 3 sections: the superior, middle and inferior turbinate. These folds provide very high surface area within small volume. [8] Naso-pharynx is a lateral part of nasal cavity and uppermost part of pharynx.

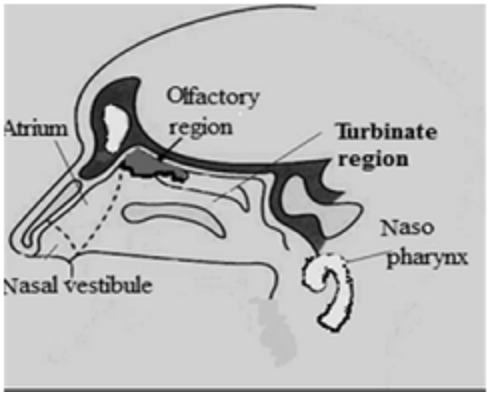

Figure 1: Diagram of various part of nasal cavity

Mechanism of nasal absorption: First mechanism involves paracellular route of transport, which is a passive process of absorption through nasal route. Hydrophilic drugs transport through this route. The drugs with molecular weight greater than 1000 daltons show poor bioavailiblity. [11]

Second mechanism involves transcellular process. Lipophilic drugs transport through this route. It is an active route of transport. [12]

Nasal characterstics: [11,13,14]

There is mainly four parts in the nasal cavity called vestibule, atrium, respiratory region and olfactory region. Each part distinguishes from one other due to their specific characteristic, function and permeability.

Table: **1-** A feature of specific parts of nasal cavity

Nasal parts	Characteristics	Function	Permeability
Vestibule	Keratinized and stratified squamous epithelial cells with nasal hairs	Support and protection	Poor
Atrium	Stratified squamous cells and pseudostratified cells	Support	Reduced
Respiratory region	Columnar ciliated cells, columnar non ciliated cells, globet	Support, muciliary clearance and Mucus secretion	Good

	cells and basal cells		
Olfactory region	Sustentacular cells, olfactory receptor 6cells, and basal cells	Suppor and olfaction Perception	Direct access to CNS

METHODS TO IMPROVE NASAL ABSORPTION: [3,15,16,17,18,19,20]

Many of researches have been studied the methods to improve the bioavailability through nasal route. These works was mainly focused on the limitations of nasal route. Followings are some approaches which have been used successfully for the improvement of nasal drug absorption.

Nasal enzymes inhibitors: The metabolism of drug in the nasal cavity can be minimized by using various kinds of enzyme inhibitors for minimization of activity of nasal enzymes. Example of enzyme inhibitor includes protease and peptidase, used as inhibitors for the formulation of peptide and protein molecule.

Structural modification: Drug structure can be modified without changing the pharmacological activity to improve the nasal absorption. Chemical modifications were mainly used to modify the drug structure.

Permeation enhancer: Various type of permeation enhancers have been investigated to improve the nasal absorption like surfactants, cyclodextrins, fatty acids, bile salts, phospholipids, etc.

Particulate drug delivery: These are used as carriers for the encapsulation of drug. These carries was found suitable for prevention of exposure of drug and improve the retention capability in to nasal cavity. These carriers may include microspheres, liposomes, nanoparticles and neosomes.

Prodrug approach: Prodrugs are the inactive chemical moiety which becomes active at the target site. This approach is mainly used to improve the physicochemical properties such as taste, odor, solubility, stability.

Bioadhesive polymer: Bioadhesive polymers are used to improve the nasal absorption of the drug. They improve the retention time of the drug inside the nasal cavity by making an adhesive force between formulation and nasal mucosa. Bioadhesion leads the minimization of mucociliary clearance of formulation.

***In situ* gel:** These formulations generally controlled the problems of administration along with conversion into gel by the influence of stimuli includes temperature, pH and ionic concentration. Thick consistency of gel, makes the formulation difficult to drain by he influence of ciliate movement.

MUCOADHESION: [1, 21,22,23, 24]

Mucoadhesion can be define as the state in which two materials (one should be biological in nature), held together for long period. In mucoadhesion, mucoadhesive polymer make intimate contact with biological membrane, after the establishement of contact, the mucoadhesive polymer penetrate into the tissue surface. These polymers have best polarity that permits sufficient wetting by the mucus and best fluidity that allows interpenetration of polymer inside the mucus membrane.

Characteristics of mucoadhesive polymers [22,23, 24]

1. The polymer and its degraded products should not be toxic.

2. It should form a non-covalent bond with the membrane surface.

3. It should be non-irritant to the biological membrane.

4. It should adhere quickly on the biological membrane.

5. The polymer should be stable during the shelf life.

6. It should permit incorporation to the drug and allow its release.

7. I t should be economically low.

Theories of mucoadhesion: [23, 24, 25,26]

There are following theories related to mucoadhesion:

Absorption theory: In this theory, intermolecular forces are involved. These forces are of two types first is primary force, which includes covalent bonds and secondary force, which includes hydrogen bonding, hydrophobic bonds and vander waal's forces.

Diffusion theory: This theory involves the penetration of polymer in the mucus membrane and the penetration of polymer depends on the diffusion coefficient and the contact time.

Electronic theory: This theory involves transfer of electrons among the surfaces of the nasal membrane and mucoadhesive materials, which produce electrical double layer so that attractive forces produced.

Mechanical theory: In this theory interlocked structure formed between polymer and membrane.

Wetting theory: Wetting theory is applicable for the liquid bioadhesive material. Lowers the contact angle of mucoadhesive substance with membrane then it show higher affinity towards the substrate.

Synthetic mucoadhesive polymers: [27] There are some examples of synthetic mucoadhesive polymers which have been regularly used by researchers. These polymers include methyl cellulose, Ethyl cellulose, Hydroxyl propyl methyl cellulose, Poly ethylene oxide, Poly vinyl alcohol etc.

However a large number of research has been carried out with synthetic Mucoadhesive polymers but simultaneously high risk are also associated with these polymers which includes, poor patient compliance because they produce toxicity on administration and produce more side effects similarly they are not biodegrade on the influence of body fluid and hence are non-compatible. Synthetic polymers produce environmental pollution during synthesis and have a high cost of production.

Natural mucoadhesive polysaccharide: [8, 28,29,30] The natural polymers are widely used in the Indian ayurvedha from the ancient time because of their various qualities like biocompatible and nontoxic nature. They are biodegradable in nature and can be easily metabolized hence reduced chance of biological toxicity. Availability of natural polymers can be easility ensured by natural sources which is an environmental friendly processing with low cost. They show better patient tolerance and may be obtained from renewable sources.

There are some examples of natural Mucoadhesive polysaccharide which includes Potato starch, Rice starch, Maize starch, Wheat starch, Fig fruits (*Ficus carica*) polysaccharide, Gaur gum, Tragacanthe, Xanthan gum etc.

POLYSACCHARIDE: [31,32,33]

Polysaccharides are polymeric carbohydrate and forms by the joining of repetitive units of either mono or disaccharide. These units join to one other by the help of glycoside bonds. Which on hydrolysis produces monosaccharide more than 10 units. Gums and mucilage both are polysaccharides. Gums are pathological products formed by a breakdown of cell walls while mucilage is metabolic products formed within the cell. Mucilage produces slimy mass in water while gums readily dissolve in water.

Classification of polysaccharide: [6, 34, 35]

There are following classification of polysaccharide:

1- **According to source:**

a- **Plant origin –** Starch, Cellulose.

b- **Animal origin –** Chitin

c- **Microbial origin –** Dextran, Xanthan.

2- **Storage polysaccharide:**

a- **Starches –** Potato, Rice, Maize, Wheat.

- **b- Glycogen**
- **3- Structural polysaccharides** - Arabinoxylans, Cellulose, Chitin, Pectins
- **4- Homopolysaccharide**- Starch, Cellulose, Glycogen,linsulin and Chitin.
- **5- Heteropolysaccharide**- Hyaluronic acid, Chondroitin sulphate and Heparin.

Formulations for nasal cavity with natural polysaccharide: Utilization of natural polymers to develop the drug delivery systems had been the foremost priority of the researchers from recent past. The pharmaceutical researchers are now developing drug delivery system (DDS) by using natural polymers rather than synthetic one. These efforts are done to maximize their bioavailability and patient protection by minimizing toxic effect.

Nasal Gels: It is highly viscous formulation. It may be either viscous solution or suspension. The advantage of nasal gel that is reduces the postnasal drip, irritation, and show better absoption of drug. For example- Secaris nasal gel. Nasal gel may be *in-situ* gel or simple gel.

In-situ gel may be affected from either temperature or pH. [36]

Shyamoshree Basu et al., studied on mucoadhesive *in situ* nasal gels with mucilage isolated from fig fruits (*Ficus carica*, family: *Moraceae*) by using midazolam hydrochloride as a model drug. Nasal gels were prepared by using different concentrations of natural polymer (fig fruit) mucilage and synthetic mucoadhesive polymers like Carbopol and hydroxypropylmethyl cellulose and evaluation of the prepared gels were carried out. *In situ* nasal gels of fig fruit polymer show better bioavailability of drug midazolam in comparision to gels prepared by using mucoadhesive synthetic polymers.[37]

Nasal insert: Nasal inserts are small device and light in weight. Nasal inserts are flexible because they adjust in any type of nose size. Nasal inserts are not rigid in structure. So that they are convenient, easy to use, pain free and self administered formulation and patient friendly. Each nasal insert accurate in dose because it contains already determine amount of the dose. [38]

Barbara Luppi et al., developed pectin based nasal inserts to increase the bioavailability of chlorpromazine hydrochloride (antipsychotic drug). Pectin polysaccharide was obtained from citrus peel (*citrus lemonum*) and used in different ratio in the formulation. The results show improving mucoadhesion capacity. So that pectin can be used as carrier for nasal delivery of antipsychotic drug.[39]

Nasal powder: The nasal powders are formed for that drugs which are unstable in solution and suspension. Nasal powder formulation show better stability. Nasal powder formulation does not contain any preservative which is a main advantage of it. This formulation can be administered either by insuffalation or by applicators. [40]

Sachin patil et all reported that tamarind seed (*Tamarindus indica L.*) polysaccharide can be used for the formulation of nasal mucoadhesive powder and after evaluation he found that the residence time of drug inside the nasal cavity was improved. [41]

Nasal microspheres: Microsphere is one of the specialized formulations for nasal drug delivery. Mucoadhesive microspheres may help to increase residence time of drug inside the nasal mucosa and thus improve the bioavailability. The range of microspheres for intranasal drug delivery should be 10µ- 100µ. [42]

A. V. Yadav et al., prepared intranasal mucoadhesive microspheres for the delivery of antimigraine drug domperidone by using soluble starch polysaccharide in different concentration. Better bioavailability was found at 73.11% concentration of polysaccharide. [43]

Table: **2 -** Summarized table on natural polysaccharide that have been utilized in nasal formulation:

Scientists	Natural polysaccharide	Formulation	Active agent	References
S. Basu et al.	*Ficus carica* mucilage	*In-situ* nasal gel	Midazolam	37
B. Luppi et al.	Pectin	Nasal inserts	Chlorpromazine	39
E. Gavini et al.	Alginate and cyclodextrins	Microspheres	Beta-amyloid fibril	44
C. Witschi et al.	Starch, Alginate, Chitosan	Microparticles	Protein bovine serum albumin	45
A. Alhalaweh et al.	Chitosan	Dry powder	Zolmitriptan	46
J.K. Patel et al.	Chitosan	Microspheres	Glipizide	47
H. B. Nirmal et al.	Gellan gum and Xanthan gum	*In-situ* nasal gel	Mometasone furoate	48
K. Kuotsu et al.	*Dellinia indica* mucilage	Nasal gel	Oxytocin	49
S. Basu et al.	*Linum usitatissimum* L. Seed Mucilage	Nasal gel	Midazolam	50
H. Parmar et al.	Chitosan	Nasal gel	Indomethacin and Papaverine hydrochloride	51
S. A. Sajadi				52

Tabassi et al.	Albumin	Microspheres	Propranolol HCl	
K. Bowey et al.	Chitosan and Alginate	Microparticle	Antibiotics, Anti-Inflammatory and Chemotherapeutics agents.	53
T. Loftsson et al.	Cyclodextrin	Nasal spray	Alprazolam, Midazolam and Triazolam	54
X. Xin et al.	Chitosan	Nanaparticle	Proteoglycans	55
I. A. Alsarra et al.	Chitosan	Hydrogel	Acyclovir	56
J. K. Patel et al.	Chitosan	Microspheres	Glipizide	57
A. Grenha et al.	Chitosan	Nanoparticle	Bovine insulin	58
O. Borges et al.	Chitosan and Alginate	Nanoparticle	Hepatitis B antigen.	59
S. Charlton et al.	Pectin and Chitosan	Nasal spray	Fluorescein sodium	60

Chemically modified natural polysaccharide in nasal formulations: The chemically modified natural polysaccharides are used in nasal formulation since ancient time to increase the bioavailability and to minimize the toxicity of synthetic polysaccharide. Natural polysaccharide creates some problems like poor stability, higher bacterial growth, and some time poor bioadhesion. These problems of natural polymers can be reduced by making a chemical modification thus improved charecterstics of natural polymers. For example- Chitosan is produced by the deacetylation of chitin. [61,62]

Krauland et al. studied that insulin loaded thiolated chitosan microspheres show more bioavailability in comparison to insulin loaded chitosan microspheres. [63]

Table: **3 -** Summarized table on nasal formulations containing modified natural polysaccharide:

S.no.	Scientists	Modified Natural polysaccharide	Active agent	Formulation	Reference
1	Krauland et al.	Thiolated chitosan	Insulin	Nanoparticles	63
2	R. Challa et al.	Sulfobutylether-β-Cyclo dextrin	Midazolam	nasal spray	64
3	Tarun Kumar et al.	Deacetylated chitosan	Polypeptides	Solution formulations	65

4	Oded et al.	oxidized cellulose	anti-allergy compounds	nasal spray	66
5	Rajeswari Challa et al.	dimethylated -β-Cyclo dextrin	Salbutamol	Powder inhaler	64
6	F.M.H.M. Merkus et al	Methylated b-Cyclodextrins	Peptide and Protein	Dry powder	67
7	Muggetti L. et al.	Waxy Starch	Temazepam	Nasal gel	68
8	Hitendra Mahajan et al.	Deacetylated Chitin (Chitosan)	Ondansetron-HCL	Microspheres	69
9	Yildiz Ozsoy et al.	Crosslinked starch and Dextran	Insulin	Microspheres	70

CONCLUSION:

The conventional dosage forms as tablets and capsules are using as delivery of pharmaceutical from ancient time. But these forms of delivery system have several limitations as uncontrolled release pattern at unwanted site. Nasal drug delivery system is used to minimize the limitation of conventional dosage form. Bioavailability of pharmaceutical and biopharmaceuticals can be improved with lesser side effects due to localized form of delivery formulations and it will minimize the painful condition and reduce the dependence of patient over technical staff for delivery of drug. The natural mucoadhesive polymer as a carrier for nasal drug delivery can be used to improve the health of all living things and to minimize the unwanted effect of synthetic polymers. Researchers will motivate for the establishment of some more naturally occurring polymer and the scenario of pharmaceutical development will change with fewer side effects due to biodegradability of natural occurring polymer.

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