



A Review: Mucoadhesive Drug Delivery System

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ABSTRACT

Drug moves may be progressed with the aid of using new drug transport machine, consisting of mucoadhesive machine. This machine stays in near touch with the absorption tissue, the mucous membrane, liberating the drug on the motion web page main to development in each nearby and systemic effects. There are many routes of mucoadhesive drug transport machine, oral course is the maximum historical in addition to favored with the aid of using affected person being handy to take. However, peroral course has shortcomings consisting of hepatic first by skip metabolism and enzymatic degradation in GIT that's a dilemma to the absorption of maximum proteins and peptides agencies of drugs. The mucosa of the oral hollow space provides a powerful barrier to drug penetration, and one technique of optimizing drug transport is with the aid of using the usage of adhesive dosage bureaucracy and the mucosa has a wealthy blood deliver and it's far rather permeable. The buccal mucosa could be very appropriate for a bioadhesion machine due to a easy and rather motionless floor and accessibility. Mucoadhesion may be completed with the aid of using the use of mucoadhesive polymers. There are unique varieties of mucoadhesive polymers are available. Laminated gadgets were advanced to attain sustained drug release.

Introduction

MUCOADHESIVE DRUG DELIVERY SYSTEM Mucoadhesive drug transport structures are transport structures which make use of the assets of bioadhesion of sure polymers which emerge as adhesive on hydration and consequently may be used for focused on a drug to a specific area of the frame for prolonged intervals of time. Bioadhesion is an interfacial phenomenon wherein materials, at the least certainly considered one among that is biological, are held collectively by using interfacial forces. The Attachment might be among an synthetic fabric and organic substrate, which includes adhesion among a polymer and a organic membrane. In the case of polymer connected to the mucin layer of a mucosal tissue, the term "mucoadhesion" is used. [1] Mucoadhesive drug transport structures may be introduced through numerous routes:-

- Buccal delivery system
- Oral delivery system
- Vaginal delivery system
- Rectal delivery system
- Nasal delivery system
- Ocular delivery system

Mucoadhesive Oral Drug Delivery Systems

Oral course is the maximum desired course for the transport of any drug. Drug transport thru the membranes of the oral hollow space may be subdivided as:-

- Sublingual transport: This is systemic transport of capsules via the mucosal membranes lining the ground of the mouth.
- Buccal transport: This is drug management via the mucosal membranes lining the cheeks (buccal mucosa).
- Local transport: This is drug transport into the oral hollow space. Within the oral mucosal hollow space, the buccal area gives an appealing course of management for managed systemic drug transport. Buccal transport is the management of medication via the mucosal membrane lining the cheeks. Although the sublingual mucosa is thought to be extra permeable than the buccal mucosa, the latter is the desired course for systemic transmucosal drug transport. This is due to the fact the buccal mucosa has an expanse of easy muscle and comparatively motionless mucosa, which makes it a extra applicable area for retentive systems. Thus, the buccal mucosa is extra suitable for sustained route of drug transport. [2]

Advantages of Oral Mucoadhesive Drug Delivery Systems:

- Prolongs the house time of the dosage shape on the web website online of absorption, for this reason will increase the bioavailability.
- Excellent accessibility, fast onset of action.

- Rapid absorption due to sizable blood deliver and suitable blood waft rates.
- Drug is blanketed from degradation withinside the acidic surroundings withinside the git.
- Improved affected person compliance. [3]

Disadvantages of Mucoadhesive Drug Delivery Systems:

- Occurrence of nearby ulcerous outcomes because of extended touch of the drug owning ulcerogenic property.
- One of the principal boundaries withinside the improvement of oral mucosal shipping is the dearth of an amazing version for in vitro screening to pick out tablets appropriate for such administration.
- Patient acceptability in phrases to flavor and irritancy.
- Eating and Drinking is prohibited. [3]

Components / Structural Features of Oral Cavity

Oral hollow space is that vicinity of mouth delineated with the aid of using the lips, cheeks, difficult palate, tender palate and ground of mouth. The oral hollow space includes regions.

- Outer oral vestibule, that's bounded with the aid of using cheeks, lips, tooth and gingival (gums).
- Oral hollow space proper, which extends from tooth and gums returned to the fauces (passage which lead to pharynx) with the roof comprising the difficult and tender palate. The tongue initiatives from the ground of the hollow space.

Anatomy and Nature of Oral Cavity:

The oral hollow space can be divided into regions, the outer oral vestibule, bounded with the aid of using the lips and cheeks And the oral hollow space itself the borders being, and shaped with the aid of using the hardened tender palates, the ground of the mouth and tonsils .Physical Description of Oral Cavity: The mucosa that strains the oral hollow space can be divided into 3 types, categorized in step with their feature as:-

1. Masticatory mucosa: Which consists of the mucosa across the enamel and at the difficult palate and those areas have keratinized epithelium.
2. Lining mucosa: Which covers the lips, cheeks, base of the oral hollow space, decrease a part of tongue, buccal mucosa and the tender palate and those areas have non keratinized epithelium.
3. Specialized mucosa: Covering the dorsum of the tongue with especially keratinization. [1]

Overview of The Oral Mucosa Structure

The oral mucosa is made from squamous stratified (layered) epithelium, basement membrane, the lamina propria and submucosa. It additionally consists of many sensory receptors inclusive of the flavor receptors of the tongue. The epithelium of the buccal mucosa is approximately 40-50 mobileular layers thick, at the same time as that of the sublingual epithelium consists of rather fewer. Permeability The oral mucosa in wellknown is rather leaky epithelia intermediate among that of the epidermis and intestinal mucosa. It is anticipated that the permeability of the buccal mucosa is 4-4000 times extra than that of the skin. In wellknown, the permeabilities of the oral mucosae lower withinside the order of sublingual extra than buccal and buccal extra than palatal. This rank order is primarily based totally at the relative thickness and diploma of keratinization of those tissues, with the sublingual mucosa being fantastically skinny and non-keratinized, the buccal thicker and non-keratinized, and the palatal intermediate in thickness however keratinized. Environment The cells of the oral epithelia are surrounded through an intercellular floor substance, mucus, the precept additives of that are complexes made of proteins and carbohydrates. These complexes can be freed from affiliation or a few perhaps connected to sure areas at the mobileular surfaces. This matrix can also additionally simply play a function in mobileular-mobileular adhesion, in addition to appearing as a lubricant, permitting cells to transport relative to at least one another. Along the equal lines, the mucus is likewise believed to play a function in bioadhesion of mucoadhesive drug transport systems. Composition of Mucus Layer: Mucus is a translucent and viscid secretion which paperwork a thin, contentious gel, suggest thickness of this layer varies from approximately 50-450 μm in human beings secreted through the goblet cells lining the epithelia. It has the subsequent wellknown composition.

- Water -95%
- Glycoprotein and lipids – 0.5-3.00%
- Mineral salts – 1%
- Free proteins – 0.5-1.0% [1]

Functions of Mucus Layer:

1. Protective: ensuing mainly from its hydrophobicity.
2. Barrier: The function of the mucus layer as a barrier in tissue absorption of the medicine and affect the bioavailability.
3. Adhesion: Mucus has robust adhesion properties.
4. Lubrication: It is to preserve the mucus from the goblet mobileular is essential to atone for the elimination of the mucus layer because of digestion, bacterial degradation and solubilisation of mucin molecules. [1]

Role of Saliva:

Saliva consists of 99% water and is complicated fluid containing natural and inorganic material. Secretion of saliva is maximum throughout operating hours.

1. Protective fluid for all tissues of the oral cavity.
2. Continuous mineralization / demineralization of the enamel enamel.
3. Moistens the oral cavity. [4]

Theories of Mucoadhesion

There are six trendy theories of adhesion, which were tailored for the research of mucoadhesion:- **The electronic concept** shows that electron switch takes place upon touch of adhering surfaces due to variations of their digital structure. This is proposed to bring about the formation of an electrical double layer on the interface, with next adhesion because of appealing forces.

The wetting concept is mostly carried out to liquid structures and considers floor and interfacial energies. It includes the capacity of a liquid to unfold spontaneously onto a floor as a prerequisite for the improvement of adhesion. The affinity of a liquid for a floor may be observed the usage of strategies along with touch attitude goniometry to degree the touch attitude of the liquid at the floor, with the overall rule being that the decrease the touch attitude, the extra the affinity of the liquid to the solid.

The adsorption concept describes the attachment of adhesives on the premise of hydrogen bonding and van der Waals` forces. It has been proposed that those forces are the principle individuals to the adhesive interplay. A subsection of this, the chemisorptions concept, assumes an interplay throughout the interface takes place due to sturdy covalent bonding.

The diffusion concept describes interdiffusion of polymers chains throughout an adhesive interface. This manner is pushed with the aid of using awareness gradients and is laid low with the to be had molecular chain lengths and their mobilities. The intensity of interpenetration relies upon at the diffusion coefficient and the time of touch. Sufficient intensity of penetration creates a semi-everlasting adhesive bond.

The mechanical concept assumes that adhesion arises from an interlocking of a liquid adhesive (onsetting) into irregularities on a hard floor. However, hard surfaces additionally offer an extended floor location to be had for interplay along side an superior viscoelastic and plastic dissipation of power throughout joint failure, that are notion to be greater critical withinside the adhesion procedure than a mechanical effect.

The fracture concept differs a touch from the opposite 5 in that it relates the adhesive power to the forces required for the detachment of the 2 worried surfaces after adhesion.[5]

Mechanisms of Mucoadhesion

The mechanism of mucoadhesion is commonly divided in steps,

1. Contact level
2. Consolidation level

The first level is characterised via way of means of the touch among the mucoadhesive and the mucous membrane, with spreading and swelling of the formulation, starting up its deep touch with the mucus layer. In a few cases, consisting of for ocular or vaginal formulations, the shipping machine is routinely connected over in different cases, the deposition is promoted via way of means of the aerodynamics of the organ to the membrane, the machine is administered, consisting of for the nasal route.

In the consolidation step, the mucoadhesive substances are activated via way of means of the presence of moisture. Moisture plasticizes the machine, permitting the mucoadhesive molecules to interrupt loose and to hyperlink up via way of means of vulnerable van der Waals and hydrogen bonds. Essentially, there are theories explaining the consolidation step:

1. The diffusion concept
2. The dehydration concept. [6]

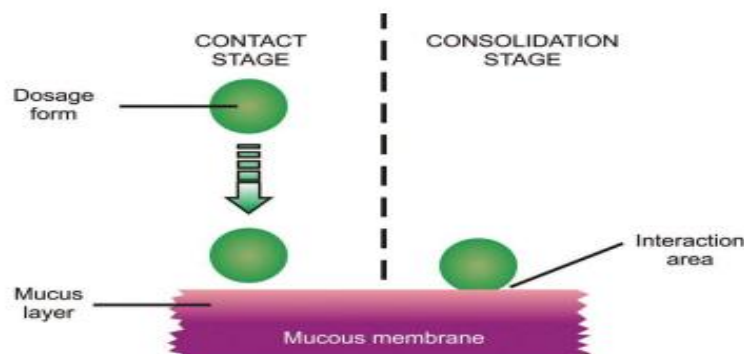


Fig. Two steps of mucoadhesion (6)

According to diffusion theory, the mucoadhesive molecules and the glycoproteins of the mucus together engage by using interpenetration of their chains and the constructing of secondary bonds. For this to take area the mucoadhesive tool has functions favouring each chemical and mechanical interactions. According to dehydration theory, substances which can be capable of with ease gely in an aqueous environment, whilst located in touch with the mucus can reason its dehydration because of the distinction of osmotic pressure.

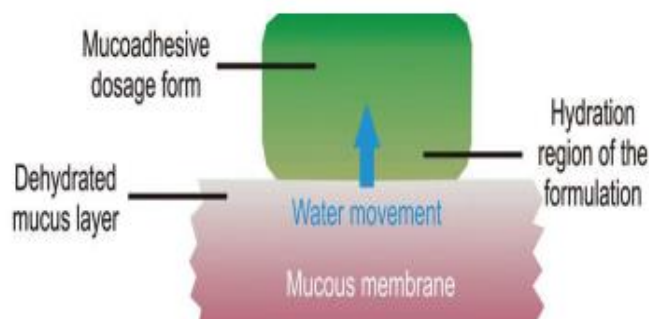


Fig. Dehydration theory of mucoadhesion

Factors Affecting Mucoadhesion :

| FACTORS | PROPERTIES | COMMENTS |
|--------------------------------|-------------------------------------|--|
| a. Polymer related factors | 1. Molecular weight | The mucoadhesive force increases with molecular weight of polymer, up to 1, 0000 and beyond this level there is no much effect. |
| | 2. Concentration of active polymers | For solid dosage forms such as tablets showed that the higher the polymer concentration the stronger the mucoadhesion. There is an optimum concentration of polymer corresponding to the best mucoadhesion. |
| | 3. Flexibility of polymer chain | Flexibility is an important factor for interpenetration and enlargement. |
| b. Environment related factors | 1.pH | pH influences the charge on the surface of both mucus and the polymers. |
| | 2.Applied strength | To place a solid mucoadhesive system, it is necessary to apply a defined strength. |
| | 3. Initial contact time | The mucoadhesive strength increases as the initial contact time increases. |
| | 4. Swelling | Swelling depends on both polymers concentration and on presence of water. |
| c. Physiological Variables | 1.Mucin turn over | a. The mucin turnover is expected to limit the residence time of the mucoadhesive on the mucus layers. b. Mucin turnover results in substantial amounts of soluble mucin molecules. |
| | 2.Diseased state | Physicochemical properties of mucus are known to change during diseased states, such as common cold, gastric ulcers, ulcerative colitis, cystic fibrosis, bacterial and fungal infections of the female reproductive tract and inflammatory conditions of the eye. |

Table 1: Commercial Mucoadhesive Drug Delivery System [7]

| DRUG | MUCOADHESIVE POLYMERS | APPLICATION SITE | NAME & FORM |
|--------------------------------|---|------------------|----------------------|
| 1) Triamcinolone acetoneide | Hydroxypropyl cellulose, cabopol 934 | Oral cavity | Attach tablet |
| 2) Nitroglycerin | Synchron (modified HPMC) | Buccal | Susadrin tablet |
| 3) Prochlorperazine Maleate | Ceronia, Xanthum Gum | Buccal | Buccastem tablet |
| 4) Beclomethasone dipropionate | Hydroxypropyl cellulose | Oral cavity | Salenat powder spray |
| | Sodium CMC, pectin, and gelatin in poly-ethylene mineral oil base | Oral cavity | Oral base gel |
| | Sodium CMC, pectin, and gelatin in polyisobutylene spread on polyethylene film | Oral cavity | Oralhesive bandage |
| 5) Beclomethasone dipropionate | Hydroxypropyl cellulose | Oral cavity | Rhinocort powder |
| 6) Aluminium hydroxide | Polyacrylic acid | Vaginal | Raplens gel |
| | Sucrose octasulfate | GIT ulcers | Sucrafate |
| 7) Fantanyl citrate | HPMC, Chitosan | Oral cavity | Fentora tablets |
| 8) Nitroglycerine | Carbopol, HPMC K15M, K4M | Oral cavity | Nitrostat tablet |
| 9) Miconazole | Na CMC, HEC | Oral cavity | Loramyc |
| 10) Testosterone | HPMC,PVA,Chitosan PC and EudragitR S-100 (Polymethacrylic acid-co-methyl methacrylate) | Oral cavity | Striant SR |
| 12) Buprenorphine | Gelatin and CP 934P CP 934P, Polyisobutylene, and Polyisoprene | Oral route | Subutex tablets |

Mucoadhesive Polymers

Mucoadhesive drug shipping structures are primarily based totally at the adhesion of a drug/ provider to the mucous membrane. To sell this adherence a appropriate provider is required.

Ideal Characteristics of Mucoadhesive Polymers:

A mucoadhesion promoting agent or the polymer is brought to the components which allows to sell the adhering of the lively pharmaceutical component to the oral mucosa. The agent may have such extra houses like swelling with a view to sell the disintegration while in touch with the saliva.

1. Polymer have to have a excessive molecular weight as much as 100.00 or extra. This is important to sell the adhesiveness among the polymer and mucus.
2. Long chain polymers-chain period have to be lengthy sufficient to sell the interpenetration and it ought to now no longer be too lengthy that diffusion turns into a problem.
3. High viscosity.
4. Degree of cross linking- it impacts chain mobility and resistance to dissolution. Highly pass related polymers swell in presence of water and hold their shape. Swelling favours managed launch of the drug and will increase the polymer/mucus interpenetration
5. Spatial conformation.
6. Flexibility of polymer chain- this promotes the interpenetration of the polymer in the mucus network.
7. Concentration of the polymer- an most useful awareness is needed to sell the mucoadhesive electricity. It relies upon however, at the dosage shape.
8. Charge and diploma of ionization- the impact of polymer rate on mucoadhesion changed into without a doubt proven through Bernkop-Schnurch and Frendl. Cationic chitosan HCl confirmed marked adhesiveness while in comparison to the control. The attachment of EDTA an anionic institution improved the mucoadhesive electricity significantly. DTPA/chitosan gadget exhibited decrease mucoadhesive electricity than cationic chitosan and anionic EDTA chitosan complexes due to low rate. Hence the mucoadhesive electricity may be attributed as anion>cation>non-ionic.
9. Optimum hydration- immoderate hydration results in reduced mucoadhesive electricity because of formation of a slippery mucilage.
10. Optimum pH – mucoadhesion is most useful at low pH situations however at better pH values a alternate withinside the conformation takes place right into a rod like shape making the ones extra to be had for inter diffusion and interpenetration. At very improved pH values, definitely charged polymers like chitosan shape polyelectrolyte complexes with mucus and show off sturdy mucoadhesive forces.
11. It ought to non toxic, economic, biocompatible ideally biodegradable. [8] Various mucoadhesive polymers can extensively be labeled as follow: Synthetic polymers:
 1. Cellulose derivatives (Methylcellulose, Ethyl cellulose, Hydroxyl ethyl cellulose, Hydroxyl propyl cellulose, Hydroxy propyl methylcellulose, Sodium carboxy methylcellulose).
 2. Poly (Acrylic acid) polymers (Carbomers, Polycarbophil).
 3. Poly hydroxyl ethyl methylacrylate.
 4. Poly ethylene oxide.
 5. Poly vinyl pyrrolidone.
 6. Poly vinyl alcohol.

Natural polymers: Tragacanth, Sodium alginate, Guar gum, Xanthum gum, soluble starch, Gelatin, Chitosan . Mucoadhesive polymers also can classify into following categories:

Traditional non-particular first-era mucoadhesive polymers First-era mucoadhesive polymers can be divided into 3 most important subsets, namely:

- 1) Anionic polymers,**
- 2) Cationic polymers,**
- 3) Non-ionic polymers.**

Of these, anionic and cationic polymers had been proven to show off the best mucoadhesive electricity. Consequently, such charged polymeric structures will now be tested in extra depth.

Anionic polymers are the maximum extensively hired mucoadhesive polymers inside pharmaceutical method because of their excessive mucoadhesive capability and occasional toxicity. Typical examples encompass poly (acrylic acid) (PAA) and its weakly cross-connected derivatives and sodium carboxymethylcellulose (NaCMC). PAA and NaCMC own terrific mucoadhesive traits due to the formation of robust hydrogen bonding interactions with mucin.Polycarbophil (Noveon) and Carbomers (Carbopol), PAA derivatives had been studied substantially as mucoadhesive systems for drug transport to the GI tract.

Cationic Polymers

Of the cationic polymer structures, certainly chitosan is the maximum substantially investigated inside the modern medical literature. Chitosan is a cationic polysaccharide, produced through the deacetylation of chitin, the maximum considerable polysaccharide withinside the world, subsequent to cellulose. The interesting houses of chitosan had been acknowledged for decades with many examples of its use in agriculture, enterprise and medicine. [9]

Novel second-technology mucoadhesive

The main downside in the use of conventional nonspecific mucoadhesive structures (first technology) is that adhesion may also arise at webweb sites aside from the ones intended. Unlike first-technology non-unique systems, sure second-technology polymer systems are much less at risk of mucus turnover rates, with a few species binding without delay to mucosal surfaces; greater correctly termed "Cytoadhesives".

Lectins

The maximum extensively investigated of such structures in this recognize are lectins. Lectins belong to a set of structurally various proteins and glycoproteins that can bind reversibly to unique carbohydrate residues. After preliminary mucosal mobileular-binding, lectins can both continue to be at the mobileular floor or withinside the case of receptor mediated adhesion in all likelihood come to be internalised via a procedure of endocytosis.

Thiolated polymers:

The presence of unfastened thiol organizations withinside the polymeric skeleton allows withinside the formation of disulphide bonds with that of the cysteine-wealthy sub-domain names gift in mucin that can extensively enhance the mucoadhesive houses of the polymers (e.g. poly (acrylic acid) and chitosan). Various thiolated polymers encompass chitosan–iminothiolane, poly(acrylic acid)–cysteine, poly (acrylic acid)–homocysteine, chitosan–thioglycolic acid, chitosan–thioethylamidine, alginate–cysteine, poly (methacrylic acid)–cysteine and sodium carboxymethylcellulose–cysteine.

Polyox WSR

A elegance of excessive molecular weight polyethylene molecular weight polyethylene oxide homopolymers having the subsequent houses,

- Water soluble hydrophilic nature
- Functional organization for hydrogen bonding
- Biocompatible and non poisonous
- High molecular weight

Novel polymers

- Tomato lectin confirmed that it has binding selectivity to the small gut epithelium.
- A new elegance of hydrophilic strain touchy adhesives (PSA) had been evolved with the aid of using corium technologies. Complex had been organized with the aid of using non covalent hydrogen bonding crosslinking of a movie forming hydrophilic polymer with a brief chain plasticizer having reactive OH organizations at chain ends. [8]

Recent Advances in Mucoadhesive Drug Delivery System

Mucoadhesive Polymers

Diverse training of polymers were investigated for capacity use as mucoadhesive. PAA has been taken into consideration as an awesome mucoadhesive. PAA is copolymerised with polyethylene glycol (PEG) or poly(vinyl pyrrolidone) (PVP) to enhance those properties.

Devices

Several laminated gadgets were advanced to gain sustained drug launch. It may be categorized as:-

- Monolithic (or matrix) structures wherein the drug is dissolved or dispersed withinside the polymer device – diffusion of drug from the drug/polymer matrix controls the general fee of its launch from the device.
- Reservoir (or membrane) structures wherein diffusional resistance throughout a polymeric membrane controls the general drug launch fee.[11]

Conclusion

The phenomenon of mucoadhesion may be used as a version for the managed drug shipping strategies for some of drug candidates. There isn't any doubt that the oral path is the maximum favoured and likely maximum complicated path of drug shipping. The buccal mucosa gives numerous benefits for managed drug shipping for prolonged durations of time. The mucosa is properly provided with each vascular and lymphatic drainage and first-by pass metabolism withinside the liver and pre-systemic removal withinside the gastrointestinal tract are avoided.

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