



MUCOADHESION: A NEW POLYMERIC CONTROLLED DRUG DELIVERY

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ABSTRACT

Since last three decades delivery of the desired drug as mucoadhesive drug delivery systems has been subject of interest. Mucoadhesion involving a polymeric drug delivery system is a complex phenomenon that includes theory of diffusion, wetting, adsorption, fracture and interpenetration of polymer chains amongst various other processes. Various polymer-based properties such as the degree of cross-linking, chain length, hydration, pH and various functional groupings can influence the mucoadhesion bonding with polymer. With the right dosage form design, local environment of the mucosa can be controlled and manipulated in order to optimize the rate of drug dissolution and permeation. In research various set up of in vitro and in vivo mucoadhesion testing carried out to select correct adhesive drug delivery technique. Mucoadhesive drug delivery system has wide application such as buccal, ophthalmic, nasal and vaginal drug delivery.

Keywords: Mucoadhesion, Polymers, Dosage form, Evaluation, Application.

1. INTRODUCTION

1.1. What is bioadhesion and mucoadhesion?

Adhesion as a process is defined as the attachment of two surfaces to one another¹. Adhesion occurs biologically it is often termed "bioadhesion", and if this adhesion occurs on mucosal membranes it is called "mucoadhesion". Further Bioadhesion is the binding of a natural or synthetic polymer to a biological substrate and if this substrate is a mucous membrane, the term mucoadhesion². Mucoadhesion system is used to achieve site-specific drug delivery by adding the mucoadhesive hydrophilic polymers within pharmaceutical formulations along with the active ingredient. The formulation will be attached on a biological surface for localised drug delivery. The active ingredient will be released at the site of action with a consequent enhancement of bioavailability³.

1.2. Structure, function, composition of mucus membrane

Goblet cells synthesized mucus which is a viscous adherent secretion. Mucus play important role within these locations such as hydration of epithelium layer, lubrication for objects, barrier to pathogens and toxic substances and as a permeable gel layer allowing for exchange of gases and nutrients from epithelium⁴. Mucus is composed mainly of water, sialic acid and sulphate groups located on the glycoprotein molecules result in mucin behaving as an anionic polyelectrolyte at neutral pH⁵. Understanding of the glycoprotein mucin component is very important with the properties of mucus. Mucin glycoprotein made from a single-chain polypeptide with two regions; (1) Large carbohydrate side chains are attached to glycosylated central protein core, via O-glycosidic linkages.

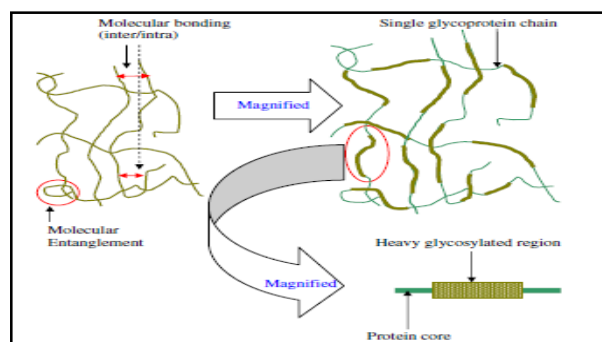


Figure 1: The composition and interaction of glycoprotein chains within mucus⁶.

(2) One or two terminal peptide regions where glycosylation occurs these regions are often called 'naked proteins regions'.

Mucin is stored in both submucosal and goblet cells, wherein the negative charges of the mucin glycoprotein are shielded by calcium ions, this allows for the compact packing of such molecules. For development of viscoelastic gel mucin chain form non-covalent interactions such as hydrogen, electrostatic and hydrophobic bonds. In the presence of water, these mucin chains begin to overlap, interpenetrate and form a structured network that mechanically functions as mucus⁷.

1.3. Theory of mucoadhesion-polymer attachment

1.3.1. Theory of wettability

For liquid or low viscosity mucoadhesive systems the wettability theory is applicable and measures the "spreadability" of the active ingredient delivery system across the biological substrate. With the help of wettability and spreadability the adhesive performance of such elastoviscous liquids may be determined. This process defines the energy required to counter the



surface tension at the interface between the two materials allowing for a good mucoadhesive spreading and coverage of the biological substrate⁸. Mucus layer and mucoadhesive polymer systems appear similar structure and functional groupings show increased miscibility; resulting in a higher degree of polymer spreadability across the mucosal surface. Lower contact angles of water: polymer systems will facilitate hydration of the polymer chains and thus promote intimate contact between polymeric delivery platform and the mucus substrate. Highly hydrophilic polymer have low contact angle than the mucosal surface, thus intimate contact due to a high interfacial surface free energy⁹.

1.3.2. Theory of electron

Electron transfer between the mucoadhesive system and the mucus due to differences in their electronic structures will result in adhesion. Such transfer of electron results in the formation of a double layer of electrical charges at the mucus and mucoadhesive interface. The result of such a process is the formation of attractive forces within this double layer¹⁰.

1.3.3. Theory of fracture

The adhesive bond between mucus and mucoadhesive system is related to the force required to separate both surfaces from one another that is the force required for polymer detachment from the strength of their adhesive bond. The work fracture greater when degree of cross-linking within system is reduced or polymer network strands are longer. This theory determines the fracture strength following the separation of two surfaces via its relationship to Young's modulus of elasticity¹¹.

1.3.4. Theory of adsorption

It defined the result of various surface interactions between the adhesive polymer and mucus substrate. Primary bonds result in adhesion due to ionic, covalent and metallic bonding and secondary bonds arise due to vander Waals forces, hydrophobic interactions and hydrogen bonding. These interactions require less energy to break, is the important form of surface interaction in mucoadhesion processes¹².

1.3.5. Theory of diffusion

The diffusion coefficients of both interacting polymers define the diffusion process with penetration rate. Various properties which influence this intermovement are expansion capacity of polymer network, molecular weight, cross-linking density, chain mobility¹². Temperature also has been noted as important environmental factor for this process¹³. Longer polymer chains can diffuse, interpenetrate and ultimately entangle to a greater extent with surface mucus and critical chain length of at least 100,000 Da is necessary to obtain interpenetration and molecular entanglement. Highly chain cross-linking will act to decrease the polymer mobility and thus interfacial penetration¹⁴. Another significant contributory factor in determining

interpenetration is the miscibility of both systems with one another¹⁵.

1.4. Properties of polymer affecting mucoadhesion

1.4.1. Functional group

The secondary non-covalent bonding between biological substrates and bioadhesive polymers through interpenetration results in attachment and bonding. Secondary bonding arises due to hydrogen bond formation, it is well accepted that mucoadhesive polymers possessing hydrophilic functional groups such as, carboxy, hydroxyl, amide and sulphate groups. Mucoadhesive polymers are generally hydrophilic networks that contain numerous polar functional groups. Such functionalized polymers interact with the mucus through physical entanglements and secondary chemical bonds, results in the formation of weakly cross-linked network⁵.

1.4.2. Hydration (swelling)

Capillary attraction and osmotic forces between the dry polymer and the wet mucosal surface which act to dehydrate and strengthen the mucus layer resulting adhesion¹⁶. Such attachment is called as mucoadhesion, it is important to clearly distinguish such processes from "wet-on-wet" adhesion in which swollen mucoadhesive polymers attach to mucosal surfaces¹⁷. For the relaxation and interpenetration of polymer chains hydration is necessary. Excess hydration caused slippery mucilage which decreased mucoadhesion and retention¹⁸.

1.4.3. Molecular weight, chain length and cross-linking

A large molecular weight is essential for bonding. Long polymer chains lose their ability to diffuse and interpenetrate mucosal surfaces. Critical length is necessary to produce bioadhesive interactions, additionally the size and shape of the interpenetrating polymeric chains must be considered¹⁹. The degree of cross-linking within polymer system significantly influences chain mobility and resistance to dissolution²⁰.

1.4.4. Charge and pH

For bioadhesion with polycations, charge density of macromolecules is an important when considering both toxicity and bioadhesion²¹. Macromolecular charge is affected by the pH of the physiological environment due to the dissociation of functional groups. Undoubtedly there is the greatest potential for polymer mucus hydrogen bonding with undissociated anionic pendant functional groups. In relation to carboxylated polymers, pH values below the respective pKa value would then be more favorable²².

1.4.5. Concentration of polymer

The strength of mucoadhesion can be influence by polymer concentration. Physical state of the delivery system defines the polymer concentration, with observational differences between semisolid and solid-state platforms. In semisolid state, an optimum



concentration exists for each polymer beyond which reduced adhesion occurs because a lower number of polymer chains are available for interpenetration with mucus. On other hand, solid dosage forms such as buccal tablets exhibit increased adhesive strength as the mucoadhesive polymer concentration increases⁸.

2. CLASSIFICATION OF MUCOADHESIVE POLYMERS

| FIRST-GENERATION | | SECOND-GENERATION |
|------------------------------------|------------------------|-------------------------------------|
| Anionic polymers | Cationic polymers | Lectins ²⁶ |
| poly (-acrylic acid) ²³ | Chitosan ²⁵ | Bacterial adhesions ²⁷ |
| sodium CMC ²⁴ | | Thiolated polymers ^{28,29} |

3. DOSAGE FORM

3.1. Solid dosage forms

3.1.1. Tablets

For local or systemic drug delivery bioadhesive tablet formulations were developed. In case of buccal drug delivery tablets are placed directly onto the mucosal surface. Size is a limitation for tablets due to the requirement for the dosage form to have intimate contact with the mucosal surface. Tablets adhere to the buccal mucosa in presence of saliva. They are designed to release the drug either unidirectional targeting mucosa or multidirectional in to the saliva³⁰.

3.1.2. Microparticles

Physical properties of microparticles enable them to make intimate contact with a larger mucosal surface area. They delivered to less accessible sites including the GI tract and upper nasal cavity. The small size of microparticles compared with tablets means that they are less likely to cause local irritation at the site of adhesion and the uncomfortable sensation of a foreign object within the oral cavity is reduced³¹.

3.1.3. Wafers

Drug delivery system intended for the treatment of microbial infections associated with periodontitis. The delivery system is composite wafer with surface layers possessing adhesive properties, while the bulk layer consists of antimicrobial agents, biodegradable polymers and matrix polymers³².

3.1.4. Lozenges

Lozenges used topically within the mouth including antimicrobials, corticosteroids, local anesthetics, antibiotics and antifungals. Conventional lozenges produce a high initial release of drug in oral cavity, which rapidly declines to sub-therapeutic levels, thus multiple daily dosing is required. A slow release bioadhesive lozenge offers potential for prolonged drug release with improved patient compliance. Codd and Deasy investigated bioadhesive lozenges as a means to deliver antifungal agents to the oral cavity³³.

3.2. Semi-solid dosage forms

3.2.1. Gels

Crosslinked polyacrylic acid is a gel forming bioadhesive polymers adhere to mucosal surfaces for extended periods of time and provide controlled release release of drug at the absorption site. A limitation of gels is their inability to deliver a measured dose of drug to the site. A novel, hydrogel based, bioadhesive, intelligent response system for controlled drug release. This system combined several desirable facets into a single formulation; a poly (hydroxyethyl methacrylate) layer as barrier, poly (methacrylic acid-g-ethylene glycol) as a biosensor and poly (ethyleneoxide) to promote mucoadhesion³⁴.

3.2.2. Patches or Films

Patches or films may be used to deliver drugs directly to a mucosal membrane. They also offer advantages over creams and ointments in that they provide a measured dose of drug to the site. Buccal adhesive films are already in use commercially for example, Zilactin used for the therapy of canker sores, cold sores and lip sores³⁵.

3.3. Liquid dosage forms

In case of ocular drug delivery need to increase the viscosity and reduce the drainage rate and subsequently increase the therapeutic rate. Mucosal surface coat by viscous liquids either protectants or drug vehicles for delivery to the mucosal surface. Cellulose derivative, acrylates, chitosan, thiomers are use as a effective mucoadhesive polymer for liquid dosage form. Traditionally, pharmaceutically acceptable polymers used to enhance the viscosity of products to aid their retention in the oral cavity. Dry mouth is treated with artificial saliva solutions that are retained on mucosal surfaces to provide lubrication. These solutions contain sodium CMC as bioadhesive polymer³⁶.

4. EVALUATION

4.1. Determination of the residence time

4.1.1. *In vitro* residence time

It carried out by using modified USP disintegration apparatus as shown in (Fig.2). The disintegration medium composed of 800 ml isotonic phosphate buffer pH 6.75 maintained at 37 °C. Segment of rabbit intestinal mucosa, 3 cm long, was stick to the surface of a glass slab, vertically attached to the apparatus. The mucoadhesive tablet was hydrated from one surface using 15 ml isotonic phosphate buffer and then the hydrated surface was brought into contact with the mucosal membrane. The glass slab was vertically fixed to the apparatus and allowed to move up and down so that the tablet was completely immersed in the buffer solution at the lowest point and was out at the highest point. The time necessary for complete erosion or detachment of the tablet from the mucosal surface was recorded³⁸.



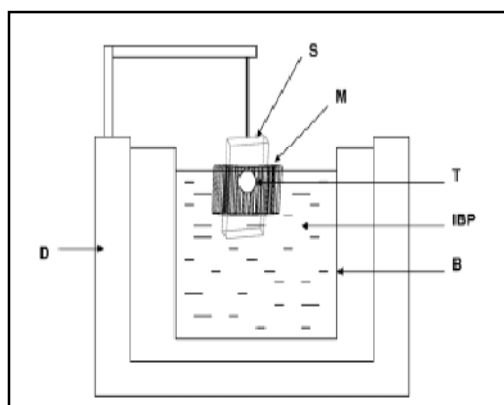


Figure 2: Schematic diagram of the apparatus used for determination of residence time³⁹.

S: glass slab; D: disintegration apparatus M: mucosal membrane; T: mucoadhesive tablet; IBP: isotonic phosphate buffer

4.1.2. *In vivo* residence time test

Four human healthy volunteers of 25–50 years old were taking for study. Plain bioadhesive tablets with optimized properties were selected for the *in vivo* evaluation. The bioadhesive tablet was placed on the buccal mucosa between the cheek and gingiva in the region of the upper canine and gently pressed onto the mucosa for about 30 s. The tablet and the inner upper lip were carefully moistened with saliva to prevent the sticking of the tablet to the lip. The volunteers were asked to monitor the ease with which the system was retained on the mucosa and note any tendency for detachment. The time necessary for complete erosion of the tablet was simultaneously monitored by carefully observing for residual polymer on the mucosa. In addition, any complaints such as discomfort, bad taste, dry mouth or increase of salivary flux, difficulty in speaking, irritation or mucosal lesions were carefully recorded. Repeated application of the bioadhesive tablets was allowed after a two days period for the same volunteer⁴⁰.

4.2.1. *In vitro* methods

An apparatus consisting of a water jacket and an internal compartment containing 50 ml of simulated saliva as dissolution medium to study the release of cetylpyridinium chloride tablet by placing in the metal die sealed at the lower end by paraffin wax to ensure the drug release from one end alone. The medium was stirred with a rotating stirrer at 250 rpm³⁷. Toyamp-Sangyo TR-553 dissolution tester used to measure the dissolution rate of disk like dosage forms by keeping in a rotating basket at 100 rpm in 900 ml of purified water. The same apparatus was used for the evaluation of oral mucosal dosage forms of insulin⁴⁰. A novel dissolution testing system that is capable of characterizing buccal dissolution. It comprises of a single, stirred, continuous flow-through filtration cell that includes a dip tube designed to remove finely divided solid particles. Filtered solution is removed continuously and used to analyze for dissolved drug⁴¹.

4.2.2. *In vivo* methods

4.2.2.1. Selection of animal species

For study of drug permeation characteristics, special attention is warranted to the selection of experimental animal species for such experiments. Animals including rats and hamsters use for permeability studies⁴². The rat has a buccal mucosa with a very thick, keratinized surface layer. The rabbit is the only laboratory rodent that has non-keratinized mucosal lining similar to human tissue. But, the sudden transition to keratinized tissue at the mucosal margins makes it hard to isolate the desired non-keratinized region⁴³. Dogs are easy to maintain and less expensive than monkeys and their buccal mucosa is non-keratinized and has a close similarity to that of the human buccal mucosa. Pigs also have non-keratinized buccal mucosa similar to that of human and their inexpensive handling and maintenance costs make them a highly suitable animal model for buccal drug delivery studies. In fact, the oral mucosa of pigs resembles that of human more closely than any other animal in terms of structure and composition⁴⁴.

4.2.2.2. Buccal absorption test

A method to measure the kinetics of drug absorption. It is carried out by swirling of a 25 ml sample of the test solution for 15 min by human volunteers followed by the expulsion of the solution. The amount of drug remaining in the expelled volume is then determined to assess the amount of drug absorbed. The drawbacks of this method are inability to localize the drug solution within a specific site of the oral cavity, accidental swallowing of a portion of the sample solution and the salivary dilution of the drug⁴⁵.

4.2.2.3. Modified buccal absorption test

Gonzalez-Younes developed this method by correcting for salivary dilution and accidental swallowing, but these modifications also suffer from the inability of site localization⁴⁶.

4.2.2.4. Perfusion system

A circulating perfusion chamber attached to the upper lip of anesthetized dogs by cyanoacrylate cement and the drug solution is circulated through the device for a predetermined period of time. Sample fractions are collected from the perfusion chamber and blood samples are drawn at regular intervals⁴⁷.

5. APPLICATIONS OF MUCOADHESIVE DRUG DELIVERY

5.1. Buccal drug delivery

The buccal cavity have high accessibility and low enzymatic activity. Buccal drug delivery terminated in case of toxicity through the removal of dosage form, offering a safe and easy method of drug utilization. First-generation mucoadhesives, such as sodium carboxy methylcellulose, hydroxypropylcellulose examined for the treatment of periodontal disease and the controlled



delivery of macromolecular therapeutic agents, such as peptides, proteins and polysaccharides⁴⁸. Gel and ointments are the most patient convenient; tablets, patches and films have also been examined. Drug delivery to accessible cutaneous sites such as the buccal cavity is often associated with high patient compliance, low levels of irritation and offers significant ease of administration. Other less reported advantages include rapid onset of action due to a highly vascularised buccal mucosa and avoidance of hepatic first pass metabolism⁴⁹.

5.2. Ophthalmic drug delivery

Various types of dosage forms like liquid drops, gels, ointments and solid ocular inserts can deliver the therapeutic agents to the eye⁵⁰. Pre-application these systems are in the liquid state and are easily administered, whereas post-application they are transformed in highly viscous networks. Mucoadhesive polymers would be expected only to attach to conjunctival mucus *in vivo*, but migration may result in causing deposition of semisolid within the corneal area, bringing with it a detrimental effect on visual acuity⁵¹.

5.3. Vaginal drug delivery

Vagina provides a promising site for systemic drug delivery because of its large surface area, rich blood supply and high permeability, poor retention due to the self-cleansing action of the vaginal tract is often problematic. Another important consideration is the change in the vaginal membrane during the menstrual cycle and post-menopausal period⁵². Furthermore, cultural sensitivity, personal hygiene, gender specificity, local irritation and influence of sexual intercourse are significant in determining the performance and success of the applied dosage form. Additionally, considerable variability in the rate and extent of absorption of vaginally administered drugs is observed by changes in thickness of vaginal epithelium. Typical bioadhesive polymers that have been in vaginal formulations include polycarbophil, hydroxypropylcellulose and polyacrylic acid⁵³.

5.4. Nasal drug delivery

The nasal epitheliums have relatively high permeability, two cell layers separating the nasal lumen from the dense vasculature within the lamina propria. Nasal delivery has been obtained using solutions, powders, gels and microparticles. The most commonly employed intranasal APIs are solutions containing sympathomimetic vasoconstrictors for immediate relief of nasal congestion. In addition to local effects, intranasal route of drug administration has also been used to achieve a distal systemic effect⁵⁴. Polymeric components such as hydroxyl propylcellulose, chitosan, carbomer, NaCMC, hyaluronic acid and polyacrylic acid have all shown promise as mucoadhesive agents for use in controlled drug delivery to pulmonary and nasal sites. Such polymeric delivery platforms may be used either alone or as synergistic combination systems⁵⁵. One of the most interesting, the use of intranasal drug delivery for the induction of

antibody responses in serum, as well as local and distal mucosal secretions, due to absorption through the nasal-associated lymphoid tissue⁵⁶.

5.5. GI tract drug delivery

Mucoadhesive polymers may offer increased intimacy with the lining of the GI tract and hence bioavailability. Furthermore, "absorption windows" within the GI tract such as those making up the gastro-associated lymphatic tissue may be targeted allowing for the absorption of larger poorly soluble therapeutic agents⁵⁷. Targeted drug delivery systems in this respect have focused on mucoadhesive patches and microparticles using first-generation polymers. The significant problem with large mucoadhesive solid dosage forms such as tablets is the poor adherence to mucosal surfaces due to large dosage form mass combined with the vigorous movement of the gastrointestinal tract. Although first-generation polymers have had limited success, second-generation vehicles are now receiving increased attention. A thiolated chitosan tablet has recently been reported for the oral delivery of insulin. Further advances in this field have included the attachment of second-generation mucoadhesives to the surface of microspheres⁵⁸.

6. CONCLUSION

Mucoadhesive systems offer advantages in terms of accessibility, administration and withdrawal, retentivity, low enzymatic activity, economy and high patient compliance. At the current global scenario, scientists are finding ways to develop mucoadhesive systems through various approaches to improve the bioavailability of drug. The second generation mucoadhesive polymer is enormous, since they have revolutionized the concept of mucoadhesion through new findings arising from basic research on these new compounds. Novel mucadhesive delivery system, where the drug delivery is directed towards mucus by protecting the local environment is also gaining interest. The future direction of mucoadhesive drug delivery lies in vaccine formulations and delivery of small proteins and peptides. Microparticulate mucodhesive systems are particularly interesting as they offer protection to therapeutic entities as well as the enhanced absorption that result from increased contact time provided by the bioadhesive component.

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