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MUCOADHESION NEW AND EMERGING CONCEPT IN DRUG DELIVERY : A REVIEW

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ABSTRACT

Mucoadhesion keeps the delivery system adhering to the mucus membrane. Transmucosal drug delivery systems show various merits over conventional drug delivery systems for systemic delivery the oral route has been the preferred route of the administration for many systemically active drugs. When administered by the oral route however the hepatic first pass OR GI degradation was observed. Delivery of the drugs via the absorptive mucosa in various easily accessible body cavities like ocular, nasal, buccal, rectal and the vaginal mucosa has the advantage of bypassing the hepatic-gastrointestinal; first pass elimination associated with the oral administration Mucoadhesive are synthetic or natural polymer which interacts with the mucus layer covering the mucosal epithelial surface and mucin molecules constituting a major part of mucus. The idea of mucoadhesive stems from the need to localize drugs at a certain site in the body. Since many drugs are absorbed only from upper small intestine, localizing oral drug delivery systems in the stomach or in the duodenum would improve the extent of the drug absorption since most of the routes of the drug administration such as nasal, buccal, gastrointestinal rectal and vaginal routes are coated with mucus layer, mucoadhesives are expected to increase the residence time.

Key words: buccal mucosa, mucoadhesive polymer, factors and generation of mucoadhesion.

INTRODUCTION

The focus of pharmaceutical research is being steadily shifted from the development of new chemical entities to the development of novel drug delivery system (NDDS) of existing drug molecule to maximize their effective in terms of therapeutic

action and patent protection^{1,2}. Moreover the development of NDDS is going to be the utmost need of pharmaceutical industry especially after enforcement of Product Patent^{3,4}. The development of NDDS has been made possible by the various compatible polymers

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to modify the release pattern of drug^{5,6}. In the recent years the interest is growing to develop a drug delivery system with the use of a mucoadhesive polymer that will attach to related tissue or to the surface coating of the tissue for the targeting various absorptive mucosa such as ocular, nasal, pulmonary, buccal, vaginal etc. This system of drug delivery is called as mucoadhesive drug delivery system^{7,8}. Transmucosal delivery of therapeutic agents is a popular method because membranes are relatively permeable, allowing for the rapid uptake of a drug into the systemic circulation and avoiding the first pass metabolism^{9,10}. The efficient uptake offers several benefits over other methods of delivery and allows drugs to circumvent some of the body's natural defense mechanism¹¹⁻¹³. The market share of Transmucosal drug delivery system has been increasing, with an estimated US market share of US\$179 million in year 2000¹⁴. Transmucosal products can be designed to be administered via the oral / buccal route using mucoadhesive, quick dissolve tablets and solid lozenge formulations and via vaginal or urethral route using suppositories. All these Transmucosal delivery systems are formulated with one or more mucoadhesive polymers as an essential component for mucoadhesion and the subsequent success of the delivery system.

MECHANISM OF MUCOADHESION:

Many theories have been proposed to describe mucoadhesion, namely electronic theory, adsorption theory, wetting theory, diffusion theory and fracture theory. Mucoadhesion is believed to occur in three stages: wetting, interpenetration and mechanical interlocking between mucin and polymer. According to electronic theory, mucoadhesion occurs from the formation of an electric double layer at the mucoadhesive interface by the transfer of electrons between the mucoadhesive polymer and the mucin glycoprotein network. Adsorption theory states that mucoadhesive systems adhere to tissue through secondary molecular interactions such as van der

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Waals forces and hydrogen bonding. Intimate molecular contact is a prerequisite for the development of strong adhesive bonds, where wetting equilibrium and the dynamic behavior of the bioadhesive polymeric material with the mucus is critical. The interfacial energetic is responsible for the contact of the two surfaces and the adhesive strength. Finally, diffusion theory states that interpenetration of the chains of polymer and mucus may lead to sustained mucoadhesion and by mechanical interlocking between mucin and mucoadhesive. Hydrocolloids are believed to adhere to mucosa upon hydration, as the synthetic polymer molecules become more freely mobile and are able to orientate adhesive sites favorably with those of the substrate. As the level of hydration increases, adhesive strength was found to decrease, since mucoadhesive bonds become overextended. It is proposed that the hydrogen bond-forming capacity of the polymer is important in this effect, and may emphasize the well documented mucoadhesive properties of polymers possessing numerous carboxyl groups such as carbopol and polycarbophil. However, the greater swelling properties of the polymer-increased ionization may lead to a reduction in mechanical strength and concomitant reduction in mucoadhesive properties. Based on the mucoadhesion theories, it may be concluded that the most efficient Nonbiological adhesion such as electron transfer, wetting, diffusion, adsorption, fracture and mechanical interlocking theories explain the mechanism of mucoadhesion. The interaction between 2 molecule is composed of attraction and repulsion. For mucoadhesion the attractive interaction should be larger than nonspecific repulsion

Attractive Interaction:

1. VanderWalls Force: The vander walls force plays a role in a number of important phenomena such as adhesion, surface tension, aggregation of particles in aqueous solution, physical adsorption, and the structural maintenance of the proteins. The typical vander walls interaction energy is less than 4.184 KJ/M.

2. *Hydrogen Bonding*: Hydrogen bonding is weaker than the covalent bond energy of about 418.4KJ/M; it is still much stronger than the Vander walls Interaction energies. The formation of multiple hydrogen between two water soluble macromolecules results in strong intermolecular interaction which may lead to precipitation from solution.

3. *Electrostatic Interaction*: Electrostatic Attractive Interaction between two oppositely charged polyelectrolytes in the water lead to formation of water insoluble complexes. The interaction so strong that precipitation occurs immediately after mixing the two polyelectrolytes. The interaction of mucin molecules with polyanions such as polyacrylic acid, poly- L- glutamic acid, Polymethacrylic acid, hyaluronic acid depends on the pH of the medium.

4. *Physical entanglements*: The formation of physical entanglements between mucus and mucoadhesive is important, since without such entanglement the mucoadhesion occurs only at the inter phase which is just two molecular layers thick the entanglements between polymer molecules are enhanced by promoting intermolecular interaction between specific functional groups on the two polymer .strong mucoadhesion depends on moderate interaction forces between mucus and mucoadhesive which allows diffusion of polymer molecules and entanglement between polymer chain .

Repulsive interaction::If two polyelectrolyte have the same charge they repel each other. Mucin molecules are negatively charged pH 7 because of the presence of the sialic acid

Buccal Mucosa as a Site for Drug Delivery:

There are three different categories of drug delivery within the oral cavity (i.e., sublingual buccal and local drug delivery). Selecting one over another is mainly based on anatomical and permeability differences that exist among the various oral mucosal sites. The sublingual mucosa is relatively permeable, giving rapid absorption and acceptable bioavailability of many drugs, and is convenient, accessible, and generally well accepted. The sublingual route is by far the most Available online on www.ijprd.com

widely studied of these routes. Sublingual dosage forms are of two different designs, those composed of rapidly disintegrating tablets, and those consisting of soft gelatin capsules filled with liquid drug. Such systems create a very high drug concentration in the sublingual region before they are systemically absorbed across the mucosa. The buccal mucosa is considerably less permeable than the sublingual area, and is generally not able to provide the rapid absorption and good bioavailability seen with sublingual administration. Local delivery to tissues of the oral cavity has a number of applications, including the treatment of toothaches, periodontal disease, bacterial and fungal infections, aphthous and dental stomatitis and in facilitating tooth movement with prostaglandins. Even though the sublingual mucosa is relatively more permeable than the buccal mucosa, it is not suitable for an oral Transmucosal delivery system. The sublingual region lacks an expanse of smooth muscle or immobile mucosa and is constantly washed by a considerable amount of saliva making it difficult for device placement. Because of the high permeability and the rich blood supply, the sublingual route is capable of producing a rapid onset of action making it appropriate for drugs with short delivery period requirements with infrequent dosing regimen. Due to two important differences between the sublingual mucosa and the buccal mucosa, the latter is a more preferred route for systemic Transmucosal drug delivery. First difference being in the permeability characteristics of the region, where the buccal mucosa is less permeable and is thus not able to give a rapid onset of absorption (i.e., more suitable for a sustained release formulation). Second being that, the buccal mucosa has an expanse of smooth muscle and relatively immobile mucosa which makes it a more desirable region for retentive systems used for oral Transmucosal drug delivery. Thus the buccal mucosa is more fitted for sustained delivery applications, delivery of less permeable molecules, and perhaps peptide drugs. Similar to any other mucosal membrane, the buccal mucosa as a site for drug delivery has limitations as well.

One of the major disadvantages associated with buccal drug delivery is the low flux, which results in low drug bioavailability. Various compounds have been investigated for their use as buccal penetration enhancers in order to increase the flux of drugs through the mucosa. Since the buccal epithelium is similar in structure to other stratified epithelia of the body, enhancers used to improve drug permeation in other absorptive mucosa have been shown to work in improving buccal drug penetration. Drugs investigated for buccal delivery using various permeation/absorption enhancers range in both molecular weight and physicochemical properties. Small molecules such as butyric acid and butanol, ionizable low molecular weight drugs such as acyclovir, propranolol, and salicylic acid, large molecular weight hydrophilic polymers such as dextrans, and a variety of peptides including octreotide, luteinizing hormone series of studies on buccal permeation of buserelin and fluoresce in isothiocyanate (FITC) labeled dextrans reported the enhancing effects of diand tri-hydroxy bile salts on buccal penetration. Their results showed that in the presence of the bile salts, the permeability of porcine buccal mucosa to FITC increased by a 100-200 fold compared to FITC alone. Mucoadhesive polymers facilitate the mucoadhesion by their specific properties. This article reviews desirable properties of mucoadhesive polymers and the latest advancement in the field.

Mucoadhesive Polymers^{10-19:}

There are two broad classes of mucoadhesive polymers: hydrophilic polymer and hydrogels. In the large classes of hydrophilic polymers those containing carboxylic group exhibit the best mucoadhesive properties, poly vinyl pyrrolidone (PVP), Methyl cellulose (MC), Sodium carboxy methylcellulose (SCMC) Hydroxy propyl cellulose (HPC) and other cellulose derivative. Hydrogels are the class of polymeric biomaterial that exhibit the basic characteristics of an hydrogels to swell by absorbing water interacting by means of adhesion with the mucus that covers epithelia i.e.

1. Anionic group- Carbopol, Polyacrylates and their cross linked modifications
2. Cationic group- Chitosan and its derivatives
3. Neutral group- Eudragit- NE30D etc.

Important Factors of Mucoadhesion:

High molecular weight (up to 100,000), High viscosity (up to an optimum), Long chain polymers, Optimum concentration of polymeric adhesive, Flexibility of polymer chain, Spatial confirmation, Optimum cross-linked density of polymer, Charge and degree of ionization of polymer (anion >cation >unionized), Optimum medium pH, Optimum hydration of the polymer, High applied strength and duration of its application and High initial contact time, are some basic properties which a polymer must have to show a good mucoadhesive profile²⁰.

Besides the above factors, some physiological factors, like mucin turnover and disease status also affect the mucoadhesion. The mucin turnover is expected to limit the residence time of the mucoadhesive on the mucus layer. No matter, how high the mucoadhesive strength, mucoadhesive are detached from the surface due to mucin turnover. The physiochemical properties of the mucus are known to change during diseases conditions 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, thereby changing the degree of mucoadhesion. In a study, mucoadhesive forces of various polymers are used.

Next Generation Mucoadhesive Polymers:

With the disappointment in the merger of mucoadhesive systems into pharmaceuticals in the site-specific drug delivery area, there has been an increasing interest from researchers in targeting regions of the GIT using more selective compounds capable of distinguishing between the types of cells found in different areas of the GIT. Loosely termed "cytoadhesion," this concept is specifically based on certain materials that can reversibly bind to cell surfaces in the GIT²².

These next generation of mucoadhesive function with greater specificity because they are based on receptor-ligand-like interactions in which the molecules bind strongly and rapidly directly onto the mucosal cell surface rather than the mucus itself²³. One such class of compounds that has these unique requirements is called lectins. Lectins are proteins or glycoprotein's and shares the common ability to bind specifically and reversibly to carbohydrates. They exist in either soluble or cell-associated forms and possess carbohydrate-selective and recognizing parts. They are found mostly in plants, to a lesser extent in some vertebrates (referred to as endogenous lectins), and can also be produced from bacteria or invertebrates²⁴. Lectin-based drug delivery systems have applicability in targeting epithelial cells, intestinal M cells, and enterocytes. The intestinal epithelial cells possess a cell surface composed of membrane-anchored glycoconjugates. It is these surfaces that could be targeted by lectins, thus enabling an intestinal delivery concept. One lectin which has been studied to considerable extent *in vitro* binding and uptake is tomato lectin (TL), which has been shown to bind selectively to the small intestine epithelium. In one study, using the everted gut sac model, this lectin was bound to polystyrene microspheres. Uptake of (TL) into the serosal fluid was reported as eight-fold higher than the control (BSA)²⁵. Furthermore, BSA-coupled microspheres were shown to have slower uptake than TL-coupled microspheres by a factor of two. In another study, specific binding by tomato lectin-coated polystyrene microspheres (0.98 mm) to enterocytes *in vitro* was examined²⁶. Fluorescently labeled polystyrene microspheres were coated with TL, and incubated in a CaCo-2 cell line. It was observed that the lectin-coated microspheres were resistant to repeat washings compared to the control (BSA-microsphere). For optimal buccal mucoadhesion, Shojaei and Li have designed, synthesized and characterized a copolymer of PAA and PEG monoethylether monomethacrylate (PAA-co-PEG) (PEGMM)²⁷. By adding PEG to these polymers, many of the shortcomings of PAA for

mucoadhesion, outlined earlier, were eliminated. Hydration studies, glass transition temperature, mucoadhesive force, surface energy analysis and effect of chain length and molecular weight on mucoadhesive force were studied. The resulting polymer has a lower glass transition temperature than PAA and exists as a rubbery polymer at room temperature. Copolymers of 12 and 16-mole% PEGMM showed higher mucoadhesion than PAA. The effects of hydration on mucoadhesion seen by the copolymers revealed that film containing lower PEGMM content, which had higher hydration levels, had lower mucoadhesive strengths. The 16-mole%PEGMM had the most favorable thermodynamic profile and the highest mucoadhesive forces. Polymers investigated in this study also showed that the molecular weight and chain length had little or no effect on the mucoadhesive force²⁸. Lele, et al, investigated novel polymers of PAA complexed with PEGylated drug conjugate²⁹. Only a carboxyl group containing drugs such as indomethacin could be loaded into the devices made from these polymers. An increase in the molecular weight of PEG in these copolymers resulted in a decrease in the release of free indomethacin, indicating that drug release can be manipulated by choosing different molecular weights of PEG. A new class of hydrophilic pressure-sensitive adhesives (PSAs) that share the properties of both hydrophobic PSAs and bioadhesive has been developed by CoriumTechnologies³⁰. These Corplex™ adhesive hydrogels have been prepared by non-covalent (hydrogen bond) cross-linking of a film-forming hydrophilic polymer (for example PVP) with a short-chain plasticizer (typically PEG) bearing complementary reactive hydroxyl groups at its chain ends. Owing to the appreciable length and flexibility of PEG chains, a relatively large space can be provided for a stoichiometric complex and a 'carcass-like' structure. The specific balance between enhanced cohesive strength and large free volume in PVP-PEG miscible blends influences their PSA behavior. Properties of these hydrophilic PSA hydrogels prepared by the carcass-like cross-linking method can be modified using a polymer

with complementary reactive groups to form 'ladder-like' cross-links with PVP. Thus, these Corplex™ PSA hydrogels have a broad range of unique adhesive/cohesive properties that enable topical and drug delivery systems to be applied to either skin or mucosa. An AB block copolymer of oligo (methyl methacrylate) and PAA has been synthesized for prolonged mucosal drug delivery of hydrophilic drugs³¹. These block copolymers form micelles in an aqueous medium, which was confirmed by fluorescence probe technique using pyrene. A model drug, doxorubicin hydrochloride, when incorporated into these micelles, results in its release being prolonged at a slower rate. Polymers with thiol groups were also investigated as a new generation of mucoadhesive polymers. A study conducted by Bernkop-Schnurch, et al. demonstrated that introduction of a sulphahydril group increased the adhesive properties of mucoadhesive polymers³². In this study, cysteine was attached covalently to polycarbophil by using carbodiimide as a mediator, forming amide bonds between the primary amino group of the amino acid and the carboxylic acid moieties of the polymer. The results showed that there was considerable improvement in the overall behavior of adhesion and adhesive properties when tested on porcine intestinal mucosa at a pH level above five. Langoth, N. et al., investigated the benefit of thiolated polymers (thiomers) for the development of buccal drug delivery systems. The matrix tablet based on this thiomers showed good stability, mucoadhesion and controlled drug release (for leuencephalin over 24 hrs)³³.

In addition, mucoadhesive microspheres were studied recently by Bogataj, et al. for application in the urinary bladder³⁴. The microspheres were prepared by a solvent evaporation method using Eudragit RL or hydroxypropylcellulose as matrix polymers. In another study, microspheres with a Eudragit RS matrix polymer and different mucoadhesive polymers, i.e. chitosan hydrogen chloride, sodium salt of carboxymethyl cellulose and polycarbophil were prepared and found to be useful as platforms for oral peptide delivery, with a high capacity of binding to bivalent captions, which

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are essential cofactors for intestinal proteolytic enzymes³⁵. Alur, H.H. et al., studied the Transmucosal sustained delivery of Chlorpheniramine maleate in rabbits using a novel natural mucoadhesive gum (from Hakea), as an excipient in buccal tablets³⁶. It was concluded that the gum not only sustained the release of drug but also provided sufficient mucoadhesion to tablets for clinical application.

CONCLUSION:

Transmucosal drug delivery systems, are gaining popularity day by day in the global pharma industry and a burning area of further research and development. To summarize, polymers with certain specific characters like high molecular weight and viscosity, long chain length, flexibility of chain length etc. are needed for the design of Transmucosal drug delivery systems.

There is no doubt that mucoadhesion has moved into a new area with these new specific targeting compounds (Tomato lectins, Corplex™ adhesive hydrogels etc.) with researchers and drug companies looking further into potential involvement of more smaller complex molecules, proteins and peptides, and DNA for future technological advancement in the ever-evolving drug delivery arena.

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