Evaluation And Characterization Of Bioadhesive Drug Delivery Systems

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DOI: 10.47750/pnr.2023.14.02.006

Abstract

Due to their capacity for localized medication administration and sustained release, bio adhesive systems are gaining more and more attention. As a result of the non-specific targeting, side effects are reduced. This review gives a general overview of the knowledge of bioadhesive drug delivery systems and the most current developments in their composition.

Keywords- Bioadhesive, Mucoadhesion, Nanoparticles, Drug Delivery Systems.

INTRODUCTION

Adhesion may be defined simply as a process of "fixing" of two surfaces to one another. Bioadhesion may be defined as the binding of a natural or synthetic polymer to a biological substrate. When the substrate is Mucus layer, the term is known as Mucoadhesion. The rationale behind using mucoadhesive system is the prolonged retention time in the Gastro-intestinal tract resulting in maximum absorption and hence enhanced bioavailability.

(i) General Concepts of Mucoadhesion-Mucus is a viscous and heterogeneous biological product that covers many epithelial surfaces. Cells secreting mucus are located at various locations in the body like Gastrointestinal, Ocular, Nasal, Buccal, Reproductive and Respiratory tracts. Mucus functions as a lubricant to reduce shear stress and acting as barrier against harmful substances. Goblets cell containing Mucus are located in the epithelium. Mucus is located in large granules in the goblet cells. Mucus granules are located in the apical side of the goblet cell giving a balloon shaped appearance of these cells. It is released by the process of Exocytosis or Exfoliation of the Whole cell. Secretion of Mucus varies with the age, sex, body location, and health condition but the average mucus turnover is nearly 6 hr. Apart from this mucus includes secretory IgA, lysozyme, Lactoferrin, lipids, polysaccharides, and various other ionic species. Goblet cells undergo two types of granules exocytosis: Basal secretion, which is featured by a low level, continuous and unregulated secretion, and stimulated secretion, which is a regulated exocytosis of granules in response to extracellular stimuli. The stimulated Pathway dramatically increases the mucus secretion. (Serra, Doménech, and Peppas, 2009) Mucus is mainly composed of water (>95) and mucins, which are glycoproteins of very high molecular weight (2-14 x 1012 g/mol). Along with these, proteins, lipids and mucopolysaccharides are found in small proportions (<1%). Mucin

glycoproteins form a highly entangled network of macromolecules that associate with one another co-valent bonds. This is responsible for its rheological properties. Moreover, pendant sialic acid having a pKa of 2.6 and sulphate groups located on the glycoprotein molecules are responsible for mucin behaving as an anionic polyelectrolyte at neutral pH. Mucin glycoproteins may be described as consisting of a basic unit made up of a single-chain polypeptide backbone containing two distinct regions-a large glycosylated central protein core that is attached to many carbohydrate side chains, mostly by O-glycosidic linkages. And One or two terminal peptide where there is less glycosylation and hence termed as "Naked Proteins region". The negative charge of mucus is shielded by calcium ions, which causes the tight packing of such molecules. At the time of release into luminal space, out flux of calcium exposes these negative charges leading to electrostatic repulsion and an approximate 400-fold increase in size of the molecule. These elongated mucin chains entangle and form non-covalent interactions such as hydrogen, electrostatic, and hydrophobic bonds leading to the development of a viscoelastic gel. Overlapping and interpenetration of these mucin chains in presence of water leads to a structured network, which functions as a mucus. The final rheological behavior of mucus is due to flow resistance exerted by individual chain segments, physical chain entanglement and non-covalent intermolecular interactions (Andrews, Laverty, and Jones, 2009).

MECHANISM OF BIOADHESION

(i)Types of Interaction

(a)Physical or Mechanical bonds- Physical bonds involve the entanglement of mucin glycoprotiens with the polymer chains, and the interpenetration of the mucin chains in the polymer matrix. Factors affecting these are Chain flexibility and Diffusion Coefficients (Serra, Doménech, and Peppas, 2009).

(b)Chemical Interaction- Chemical interactions include Van der Waals Dispersive Interactions or Hydrogen Bonds. Van der waals Forces are further classified into Debye Forces due to permanent dipole-induced interactions, Keesom forces due to permanent dipole-permanent dipole interactions and London forces due to induced dipole-induced dipole interactions. Hydrogen bond also plays a key role in adhesion. Groups which form Hydrogen bonds are Hydroxyl, Carboxyl, Sulfate, amino groups, and others (Mikos and Peppas, 1990). Covalent bonds are formed by the chemical reaction of the polymer and the substrate. This type of bond leads to permanent adhesion. Therefore, only mucus turnover and the epithelial desquamation would result in the separation and loss of the polymer from the tissue (Serra, Doménech, and Peppas, 2009).

(ii) Steps in Mucoadhesion

In spite of the extensive research in this field, the mechanisms of mucoadhesion are not completely clear. However, it is agreed upon that mucoadhesion takes place in two steps.

(a)The Contact Stage- In this step the intimate contact occurs between the mucoadhesive and mucous membrane. Initially mucoadhesive and the mucous membrane come together to form an intimate contact. The gastrointestinal tract is an inaccessible mucosal surface, which means that the adhesive material cannot be placed directly onto the target mucosal surface, or delivered to the surface by organ design. Generally speaking, adhesion and possible blockage of the gastrointestinal tract can prove to be detrimental. For larger particles, peristalsis and other gastrointestinal movement may help to force the dosage form into contact with the mucosa. However, evidence of successful adhesion of larger dosage forms has yet been less often reported in the literature, other than the potentially dangerous case of esophageal adhesion. For smaller particles in suspension, adsorption onto the gastrointestinal mucosa would be an essential prerequisite for the adhesion process. The physicochemical processes taking place here can be described by DLVO Theory. A particle approaching a surface will experience both repulsive and attractive forces. Repulsive forces arise from osmotic pressure effects as a result of the interpenetration of the electrical double layers, steric effects and also electrostatic interactions when the surface and particle carry the same charge. Attractive forces result from van der Waals' interactions, surface energy effects and electrostatic interactions if the surface and particles carry opposite charges. The relative magnitude of these opposing forces will alter depending on the nature of the particle, the aqueous environment, and the distance between the particle and surface. For example, the smaller the particle, the surface-area-to-volume ratio is greater giving greater the attractive forces. Particles can be weakly held at a secondary minimum (circa 10 nm separation), a region where the attractive forces are balanced by the repulsive forces, which allows the particles to be easily dislodged. For stronger adsorption to occur, particles have to overcome a repulsive barrier (the potential energy barrier) to get into the Primary Minimum. The situation becomes more complicated when it is borne in mind that the surface of adhesion is a mucus gel rather than a solid, and the particles in-vivo may become hydrated and/or coated with biomolecules, significantly varying their physicochemical properties. However, if the forces causing the displacement are small, then the mucoadhesive forces can counter act these forces. Further consideration of the Mucus structure and

Liquid layers suggest of an unstirred layer at the top functioning as a solid component, which strengthens the above discussed hypothesis.

(b)The Consolidation Stages- In this step, various physicochemical interactions occur to consolidate and strengthen the adhesive joint, resulting in a prolonged adhesion. It is proposed that in order to achieve strong or prolonged adhesion, a second 'consolidation' stage is required. For achieving strong adhesion, a change in the physical properties of the mucus layer will be required otherwise it will fail to hold on to the bioadhesive polymer on application of dislodging stress. There are two theories explaining this process. First theory based on the intermolecular interaction proposes that the mucoadhesive molecules interpenetrate and bond by secondary interactions with mucus glycoprotein. The second theory is the dehydration theory, which proposes that when a material capable of rapid gelation in an aqueous environment is brought into contact with a second gel water movement occurs between gels until equilibrium is reached.

The latter theory explains why mucoadhesion occurs in a matter of seconds, while the former requires the polymers to interpenetrate several micrometer distances within a short time. The rheological studies suggest that interpenetration of mucus and mucoadhesive polymer leads to formation of a surface gel layer, which will substantially inhibit any further interpenetration (Dodou, Breedveld, and Wieringa, 2005).

MUCOADHESION THEORIES OF POLYMER ATTACHMENT

Numerous theories have been present to explain this complex process of Mucoadhesion. These numerous theories should be considered as complementary processes during the entire mucoadhesion process. Therefore, they should be considered together while explaining mucoadhesion (Andrews, Laverty, and Jones, 2009).

(i)Wettability Theory- This theory holds good for liquid or low viscosity mucoadhesive systems. It essentially measures the "spreadability" of the Bioadhesive polymer on the mucus. It proposes that the adhesive component penetrates the surface irregularities, hardens and anchors itself to the surface. Essential characteristics for the bioadhesive materials include zero or nearly zero contact angle, relatively low viscosity and an intimate contact that excludes air entrapment. Therefore, the interfacial energies are responsible for the contact of the two surfaces and for the adhesive strength. Contact angle (θ), can be easily determined experimentally and can be correlated to the Interfacial tension using.Where h is angle of contact, γ LG is liquid–gas surface tension, γ SL is solid–liquid surface tension, γ SG is solid–gas surface tension. (Andrews, Laverty, and Jones, 2009). It can be concluded from the above equation that the mucoadhesive polymer systems that exhibit similarity in structure and functional groups with the mucin layer will show increased miscibility resulting in a greater spread across the mucosal surface. Lower water content in the polymer will facilitate the hydration of the polymer leading to more intimate contact, while hydrophilic polymer containing a lot of water will have a lower contact angle and will therefore discourage intimate contact (Andrews, Laverty, and Jones, 2009).

(ii)The Electronic Theory- Electronic Theory describes adhesion as a phenomenon in which there occurs electron transfer between the mucus and the mucoadhesive system as a result of the differences in their electronic structures. This electron transfer leads to a formation of double layer of electric charges at the mucus and the mucoadhesive interface. The result of this is the formation of attractive forces within this double layer. There is a controversy over the acceptance of this theory due to the fact that it explains the electrostatic forces, which are much weaker as the causes of bond adhesion (Andrews, Laverty, and Jones, 2009).

(iii)The Fracture Theory- This theory states that the adhesive bond between the systems is force required to segregate both the surfaces from each other. In this case the force of separation of the polymer from the mucus is related to the strength of the bioadhesive bond. It is found that the work fracture is greater when the polymer network strands are longer or the case in which the degree of cross-linking within the system is reduced.

(iv)The Adsorption Theory- According to this theory adhesion is an outcome of different surface interactions (primary and secondary bonding) between the bioadhesive polymer and mucus substrate. Primary bonds, also stronger, such as ionic, covalent and metallic bonding leads to adhesion and is called chemisorptions. These forces are somewhat undesirable due to their permanency. Apart from these, there are secondary forces, also weaker, which constitute the van der waals forces, hydrophobic interactions and hydrogen bonding. These interactions are weak in nature requiring less energy to break. But as the mucoadhesion requires being a transient event, it is desirable to have these forces (Andrews, Laverty, and Jones, 2009).

(v)The Diffusion-Interlocking Theory- This theory postulates that mucoadhesive polymer chains diffuse into the glycoprotein chain network of the mucus layer in a time-dependent manner. In the process of interpenetration, the molecules of the polymer and the glycoprotein network of the mucus come into intimate contact with each other. This leads to an establishment of a concentration gradient leading to the inter-diffusion of the both polymer inside each other. The penetration rates of this two-way diffusion process are dependent upon the diffusion coefficient of both the interacting polymers. Basic properties that affect this process are molecular weight, cross-linking density, chain

mobility/flexibility, and temperature and expansion capability of both networks. Typical values of the polymer diffusion coefficient through the glycoprotein network of the mucus may be in the range of 10-10 to 10-16 cm2/sec. Long chain polymer diffuses, interpenetrate and entangle to a greater extent. The critical chain length of at least 100,000 Da is necessary to achieve interpenetration and molecular entanglement. Excessive chain cross-linking may decrease the polymer mobility and in turn the interfacial penetration. Apart from this the miscibility also plays a crucial role. Therefore, it can be postulated that solubility parameter of polymer and glycoprotein network plays a key role in predicting the interpenetration. It is found, using the AFT-FTIR that the time at which maximum interpenetration occurs is (Andrews, Laverty, and Jones, 2009).

MUCOADHESIVE POLYMERS

Mucoadhesive polymers can be water-soluble or -insoluble polymers that are swellable networks, which are joined by the cross-linking agents. These polymers have optimal polarity for adequate wetting while sufficient fluidity allowing the mutual adsorption as well as mutual penetration of the polymer and mucus.

(i) Ideal Mucoadhesive Polymer should possess following characteristics:

- Polymer should form a strong non-covalent bond with the mucin-epithelial surfaces.
- Polymer should quickly adhere to most tissues and should possess some specificity to the desired site.
- Polymer should allow for the easy incorporation of the drug as well as its release at desired time.
- Polymer should not be irritating to the mucus membrane.
- Polymer should not be immunogenic.
- Polymer and their degradation should not be absorbed from the Gastro-intestinal Tract or if absorbed, should not be toxic to the host.
- The polymer should possess cohesiveness to provide strength inside the inter layer (Andrews, Laverty, and Jones, 2009; Asane et al., 2008).

(ii)Classification of Mucoadhesive Polymers- The polymers that are commonly employed in the preparation of Mucoadhesive drug delivery systems can be classified into 3 broad categories.

- Polymers that become sticky when placed in aqueous media and hence become bioadhesive.
- Polymers that form non-specific, non-covalent interactions, which are primarily electrostatic in nature.
- Polymers that interact with specific receptor sites on the cell surface (Park and Robinson, 1984).

(iii)First-Generation Mucoadhesive Polymers- First-generation or traditional mucoadhesive polymers may be classified into three main sub-classes, namely:

- Anionic polymers e.g. Carboxymethylcellulose, Chondroitin sulfate, polyacrylic acid, Pectin, carageenan, chitosan, Alginic acid.
- Cationic Polymers e.g. Polylysine, Polybrrene.
- Non-ionic polymers e.g. Polyethylene glycol, Polyvinyl pyrrolidone, Dextran.

Out of these the anionic and cationic polymers have found to be most effective.

(a) Anionic Polymers- Anionic polymers are the polymers of choice for formulating due to their high mucoadhesivity and low toxicity. The characteristics of these polymers are the presence of carboxyl and sulphate functional groups, which impart an overall negative charge at pH more than the pKa of the polymer. Examples of polymers commonly used in this category include polyacrylic acid (PAA) and its weakly cross-linked derivatives and sodium carboxymethylcellulose (NaCMC). The term Polyacrylates encompasses the synthetic, high molecular polymers of PAA that are also called and NaCMC form strong hydrogen bond with mucin and hence show excellent mucoadhesive properties. However, NaCMC has weaker interaction with mucus than polyacrylates. PAA derivatives like Polycarbophil (Noveon®) and Carbomer (Carbopol®) are extensively studied for their mucoadhesive potentials. Although, Polycarbophil is insoluble in water but due to its high swelling capacity under neutral pH conditions, it can achieve higher levels of entanglement within the mucus layer. Polycarbophil has been found to increase its mass 100 times in aqueous media at neutral pH. Moreover, the non-ionized carboxylic acid groups bind via hydrogen bonding to the mucosal surfaces enhancing the mucoadhesive force. PAA polymers of a wide range of molecular weights are available. They form transparent, easily modified gel networks, are non-irritant, non-toxic and are put in the GRAS (Generally Regarded as Safe) list by FDA, the gel formation occurs a result of electrostatic repulsion between anionic groups. Carbomer and polycarbophil differ in the level of cross-linking and the crosslinking agent. Carbomers are cross-linked with allyl sucrose or allyl pentaerythritol, whereas polycarbophil polymers are cross-linked with divinyl glycol. These compounds possess the same acrylic backbone but differ in their cross-link density, which is modified for the acceptable pharmaceutical performance (Andrews, Laverty, and Jones, 2009).

(b) Cationic Polymers- Chitosan is the most widely used cationic polymers. It is produced by the deacetylation of the chitin, which is the most abundant polysaccharide after cellulose. Chitosan is used in Mucoadhesive drug delivery systems due to its good biocompatibility, biodegradability and due to its favorable toxicological properties. Ionic interactions between the primary amino functional groups and the sialic acid, and the sulphonic acid groups of the mucus are responsible for the mucoadhesive property of chitosan. Also, there may be a hydrogen bonding formation between hydroxyl and the amino groups, and mucus constituents. Owing to the linear molecular structure of chitosan, it possesses sufficient flexibility for interpenetration. Along with the mucoadhesive potential, it also enhances drug absorption via the paracellular route via the neutralization of the fixed anionic sites found within the tight junctions between the mucosal cells. However, chitosan is a weak base with a pKa value of about 5.5, which makes it insoluble at neutral and basic environments such as in the large intestine and colon. Due to this reason, it cannot be used as a penetration enhancer in this environment. In such cases, the solubility of chitosan is enhanced by trimethylating its primary amino groups. The resultant trimethylated chitosan plays an important role in colonic drug delivery (Andrews, Laverty, and Jones, 2009; Dodou, Breedveld, and Wieringa, 2005). The major advantage of chitosan is the ease with which various chemical groups can be added, particularly to the C-2 group, for the formation of novel polymer with desired functionality. Such modifications allow chitosan to be tailored as per the pharmaceutical requirements (Andrews, Laverty, and Jones, 2009).

(iv)Second-generation Mucoadhesives -Traditionally used Mucoadhesives suffer from a drawback of non-specificity i.e. their tendency to bind to most cell surface and /or mucus without any preference. To overcome these drawback polymers which show specificity towards a specific target chemical structures on the surface of cells or in mucus are used. They are termed as "Cytoadhesives" (Andrews, Laverty, and Jones, 2009; Woodley, 2001).

(a)Lectins -Lectins is chemically protein can bind reversibly to specific carbohydrate residues. This phenomenon can be used to impart mucoadhesivity. Also, post-initial mucosal cell-binding, it may be internalized by endocytosis and hence can also act as a controlled drug delivery vehicle. In spite of these advantages, many of the lectins are toxic or immunogenic, and the implications of consistent lectin exposure are largely unknown. Also, it can induce antibodies that can block subsequent mucoadhesive interactions of the lectin delivery vehicles. Furthermore, such antibodies may cause systemic anaphylaxis to individuals on subsequent exposure. (Andrews, Laverty, and Jones, 2009).

(b)Bacterial adhesion -A phenomenon of pathogenic bacteria adhering readily to mucosal membranes in the GIT has been explored for achieving target-specific drug delivery may be achieved. (Andrews, Laverty, and Jones, 2009).

(c)Thiolated Polymers -Polyacrylates, chitosan or deacetylated gellan gum belong to the second generation of mucoadhesive polymers that are thiolated. The thiol groups of these polymers forms covalent bond with the cysteine-rich sub domains of the mucus gel layer, which results in mucoadhesion of these polymers. These disulphide interactions are relatively independent to pH or ionic strength changes. However, the mechanism of drug release from the delivery system may be significantly impaired due to increased rigidity and cross-linking. Therefore, in these cases the release can be modeled by a diffusion-controlled drug release mechanism (Andrews, Laverty, and Jones, 2009).

FACTORS AFFECTING THE MUCOADHESIVE POLYMERS

(i)Intrinsic Factors -Intrinsic Factors are the structural features of the polymer, which dictates its fundamental behavior. They are Molecular weight, crosslinking, and presence of functional groups and the concentration of the mucoadhesive dispersion (Dodou, Breedveld, and Wieringa, 2005).

(a)Molecular Weight -High molecular weight increases the cohesiveness within the polymer contributing to its rheological synergism. A large molecular weight is essential for entanglement; however, it suffers from the drawback of losing the ability to diffuse and interpenetrate mucosal surfaces. Excessively high molecular weight reduces the flexibility of the molecular and hence their diffusion. It has been shown that each polymer class has a unique optimum molecular weight for desired bioadhesive strength. Poly (acrylic) acid has an optimal MW of about 750,000, whereas polyethylene oxide has an optimum MW closer to 4,000,000 (Andrews, Laverty, and Jones, 2009; Dodou, Breedveld, and Wieringa, 2005).

(b)Crosslinking -The degree of cross-linking within a polymer system significantly affects chain mobility and resistance to dissolution. Cross-linked hydrophilic polymers swell and retain their structure when exposed to water, whereas similar high molecular weight non-crosslinked (linear) hydrophilic polymers swell and readily disperse. In mucoadhesive terms swelling is favorable as it allows greater control of drug release and increases the surface area for polymer/mucus interpenetration. Increase in cross-link density decreases mobility and therefore the effective chain length that can penetrate into the mucus layer, subsequently reducing its mucoadhesive strength. Chain flexibility is a critical parameter for interpenetration and entanglement within the mucus gel. Increased chain mobility leads to increased inter and interpenetration of the polymer within the mucus network.

(c)Functional Group -Adsorption theory suggests that mucoadhesion is as a result of the formation of bonds between the polymer and the mucus. The attachment and bonding of bioadhesive polymers to biological substrates involves interpenetration followed by formation of secondary non-covalent bonding like hydrogen bond formation between substrates. Consequently, such functionalized polymers interact with the mucus through secondary chemical bonds, which results in the formation of weakly cross-linked networks. The key mucoadhesive interactions occur on the carbohydrate residues, via electrostatic interaction or through hydrophobic bonding of fructose clusters (Andrews, Laverty, and Jones, 2009; Dodou, Breedveld, and Wieringa, 2005).

(d)Concentration -Higher concentration of mucoadhesives contains greater number of functional groups available to form molecular bonds, thus improving mucoadhesion. Every polymer has an optimum concentration for mucoadhesion. Beyond that concentration, the mucoadhesion decreases. This is because at high concentration the chains interact strongly with each other, which leads to an inflexible conformation of polymer coils that cannot participate actively in mucoadhesion (Vasir, Tambwekar, and Garg, 2003).

(ii)External Factors -External factors affecting the Polymer properties are pH, degree of Hydration, time, Temperature, Shear rate (Dodou, Breedveld, and Wieringa, 2005).

(a)Degree of Hydration -Many polymers will exhibit adhesive properties in presence of limited water. However adhesion under such condition can be assumed to be a summation of capillary attraction and osmotic forces between the dry polymer and the wet mucosal surface that act to dehydrate and strengthen the mucus layer. This is referred to as mucoadhesion which is distinct from the adhesion in which two wet surfaces undergo adhesion like the swollen mucoadhesive polymers attach to the mucosal surfaces. As per the previously discussed factors, an optimum degree of Hydration is required for the relaxation and interpenetration of polymer chains. Increase in hydration cause loss of mucoadhesion and/or retention due to the formation of slippery mucilage. In such situation a cross-linked polymers that only allows a certain degree of hydration may be beneficial for extended mucoadhesive effect (Andrews, Laverty, and Jones, 2009).

(b)pH and Charge -As the ionic polymers are used more often than the non-ionic polymers, this factor should be considered seriously. The effect of charge on anionic polymer is more profound than on the cationic polymer while considering toxicity and bioadhesion (Andrews, Laverty, and Jones, 2009).

(c)Initial Pressure at contact -Amount of mechanical pressure applied at the site of contact affects the depth of interpenetration. Application of high pressure for an adequately long period enables attractive interactions of bioadhesive polymer with mucin (Vasir, Tambwekar, and Garg, 2003).

(d)Initial Contact Time -Initial contact time determines the extent of swelling and interpenetration of the polymers. This parameter cannot be controlled for the Bioadhesive systems (Vasir, Tambwekar, and Garg, 2003).

(e)Mucus Turnover -One of the critical parameters affecting the in vivo performance of the Bioadhesive system is the variable mucus turnover. In this the most critical aspect is the time required for the replenishment of the mucus layer. This phenomenon is a part of the body's immune system, which removes the pathogen, which may have attached to the mucus layer to prevent damage. Therefore, the replenishment time dictates the maximum duration to which the bioadhesive system can be in contact with the mucus gel layer. Mucus turnover in intestines is very high allowing an adherence time of maximum two hours (Andrews, Laverty, and Jones, 2009).

(f)Ionic strength -Presence of Local ions affects the interaction between the bioadhesive polymer and the mucus. Therefore ionic strength is also affects the performance of the Bioadhesive systems. Generally, the presence of the ions decreases mucoadhesion due to blocking of the functional sites available for the adhesion processes and importantly the gel network expansion. Some exceptions include polymer systems such as gellan that are dependent upon the presence of divalent cations for in situ gelation (Andrews, Laverty, and Jones, 2009).

(g)Mucus Gel Viscosity -Mucus viscosity varies throughout the GIT and in different diseased states. Low mucus viscosity leads to a weak detachable bioadhesive bond, while an extremely thick mucus layer also weakens and slows the bioadhesion process due to decreased degree of interpenetration caused by the increase in path-length as a result of the accumulation of the white blood cell DNA, dead cells and inflammatory mediators (Andrews, Laverty, and Jones, 2009).

(h)Removal Mechanisms -A bioadhesive polymer detaches from the weakest component of the joint. For a weaker adhesive, this would be the mucoadhesive-mucus interface, for stronger adhesives, it would be the mucus layer initially, but afterwards it may be the hydrating mucus layer. It was found that on applying constant tensile stress to compacts of mucoadhesive polymers, joint failure is observed due to the cohesive failure of the swelling polymer for all except the weakest adhesives. Therefore, the strength and durability of the adhesive joint depend on the cohesive nature of the weakest region. The mucoadhesive polymer forms slippery mucilage in an overhydrated condition that gets easily removed from the mucus layer. Therefore, the rate and extent of hydration by introducing cross-linking and hydrophobic

polymers have been tried. In all cases the Bioadhesive Dosage form will eventually detach due to the mucus turnover (Smart, 2005).

SPECIAL CASE OF MICROSPHERES AND NANOPARTICLES AS BIOADHESIVES

Oral administration of polymeric particle suspensions (nanoparticles or micron-range microspheres made from non-swellable polymers) leads to mucoadhesion of a significant fraction of the particles. Clearly, parts of the particles are captured by the mucus gel layer while the remaining particles undergo unmodified transit. Phenomenon of mucoadhesion of microspheres and nanoparticles can be described as follows: Administration of the suspension of particles, which comes immediately in contact with the portion of oral mucosa. From this the moment, the suspension acts as a reservoir of particles and very rapidly, an adsorption process takes that leads to the adsorption of some amount of the available particles. Adsorption occurs in the mucus layer and is an irreversible process. The particles present in the lumen travel through the intestine, sweeping progressively the whole mucosa. Simultaneously, the absorption of these particles takes place resulting in a progressive covering of the intestinal mucosal. Eventually, the particles begin to detach from the mucosa in the proximal region to the distil region. Non-adherent particles from the lumen pool and detached particles from the mucoadherent pool are finally removed with feces. This hypothetical mechanism does not take into consideration many physiological variables such as stomach emptying, intestinal transit, effect of the dilution of the particle suspensions in the GI tract fluids, mixing with ingested foods. It can be concluded that the microspheres and nanoparticles increase the bioavailability by protecting the drug from denaturation in the gastrointestinal lumen or increasing the local concentration of drug on the mucus membrane (Ponchel and Irache, 1998).

ADVANCES IN THE BIOADHESIVE DRUG DELIVERY SYSTEM

Delivery of drug through buccal route has gained considerable impetus. Recently, buccal route has been explored to deliver biologics by formulating a mucoadhesive buccal film. The buccal epithelium has been shown to be a promising route for biologics administration based on current clinical trials and there are possibilities that the first buccal film based biologic product can progress through registration and subsequent commercialization (Montenegro-Nicolini and Morales, 2017).

Carbon nanotubes (CNTs) have shown variety of biomedical applications. CNTs are straw like structures made by fusing the ends of the graphene sheet. They can be functionalized on the surface due to the sp2 hybridization of the carbon atoms. CNTs of different diameter and length can be created. The surface chemistry and aspect ratio (the ratio between length and diameter of CNTs) can influence the viability of cells. The functionalization of the surface can enhance the solubility and biocompatibility of CNTs (Rieger et al., 2015). Rieger et al synthesized CNTs-CNT-1 and Cnt-2 with 11 nm and 18 nm, respectively. CNT-1 and CNT-3 were shortened to yield CNT-2 and CNT-2 with shorter length. All the CNTs produce showed adherence to the urothelium of mouse bladders with a mean covering area of 5–10%. Viability and cytotoxicity assays revealed that the shortened CNT-2 and CNT-4 induced stronger inhibitory effects on bladder carcinoma cells compared than CNT-1 and CNT-3. Overall, CNT-1 and CNT-3 showed the most promising properties for further optimization of a multifunctional drug transporter (Rieger et al., 2015). Xu et al showed the mucoadhesive property of a novel polymer by covalently bonding catechol functional groups to the backbone of chitosan (CS) followed by cross-linking with non-toxic cross-linker genipin. While the gelation time and the mechanical properties of novel catechol-functionalized CS hydrogels are similar to those of CS only hydrogels, Catechol groups aided in significantly enhanced mucoadhesion in vitro compared to CS hydrogels (6 h vs 1.5 h) (Xu et al., 2015). The development of new xyloglucan-block-poly (ϵ-caprolactone) (XGO-b-PCL) nanoparticles coated with chitosan have been shown to possess enhanced mucoadhesive properties. Coating of chitosan increases the particle size as well as imparts positive charge, due to its positive surface, to the nanoparticles. The mucoadhesive property of chitosan can be attributed to its exceptional ability to interact with mucin through electrostatic forces (Mazzarino et al., 2014). SLNs are colloidal drug delivery systems composed of physiological and biodegradable lipids that can encapsulate hydrophilic and lipophilic drug (Jain et al., 2016). Coating of chitosan was found to significantly improve the mucoadhesive property of SLN. Along with mucoadhesion, chitosan coating improves stability, cellular uptake while sustaining drug release (Luo et al., 2015). Curcumin-loaded NLCs were coated with polyethylene glycol 400 (PEG400), polyvinyl alcohol (PVA), and chitosan (CS). It was observed that PEG-NLCs and PVA-NLCs adhere 2-fold more strongly to freshly removed porcine intestinal mucosa, compared to CS-NLCs and uncoated-NLCs. Also, coating the NLCs with these polymers decreased the aggregation of NLCs in simulated gastric fluid, which in turn shows the stability of coated NLCs (Chanburee and Tiyaboonchai, 2017). Ethosome is an elastic lipid vesicle, which has recently emerged as a new delivery system that could effectively deliver drugs (Jain et al., 2016). These ethosomes could be incorporated in a gel using a thermo reversible polymer like poloxamer 407 and a mucoadhesive polymer like carbopol 934 for intranasal delivery (Shelke et

al., 2016). In order to optimize the composition of a bioadhesive drug delivery system, well designed Design of Experiments (DOE) should be carried out. With the advent of Quality-by-Design (QbD) approach in formulation development, well-designed DoE has become imperative to minimize regulatory hurdles for commercialization. Recently, several researchers have utilized DoE approach for drug delivery like iontophoretic drug delivery, lipid based delivery (Vora, Lin, and Madan, 2013; Shah, Madan, and Lin, 2014; Patel et al., 2015). Jain et al successfully demonstrated the QbD approach in formulation, evaluation and statistical optimization of diclofenac-loaded ethosomes via transdermal route (Jain et al., 2015).

CONCLUSION

With the recent developments, bioadhesive drug delivery system looks a promising approach to achieve a targeted and sustained release of drug while maintaining patient compliance. However, it needs to address the regulatory hurdles in order to be widely accepted as a major drug delivery system.

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