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Review Article

Polymers in mucoadhesive buccal drug delivery system – A review

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ABSTRACT

Mucoadhesion is defined as the ability of material adheres to biological tissue for an extended period of time. Over the last few decades' pharmaceutical scientists throughout the world are trying to explore transdermal and transmucosal routes as an alternative to injections. Among the various transmucosal sites available, mucosa of the buccal cavity was found to be the most convenient and easily accessible site for the delivery of therapeutic agents for both local and systemic delivery as retentive dosage forms. Buccal delivery of the desired drug using mucoadhesive polymers has been the subject of interest since the early 1980s. Advantages associated with buccal drug delivery have rendered this route of administration useful for a variety of drugs. The mucoadhesive interaction is explained in relation to the structural characteristics of mucosal tissues and the theories & properties of the polymers. The success and degree of mucoadhesion bonding is influenced by various polymer-based properties. Evolution of such mucoadhesive formulations has transgressed from first-generation charged hydrophilic polymer networks to more specific second-generation systems based on lectin, Thiol and various other adhesive functional groups. This paper aims to review the mucoadhesive polymeric platforms, properties & characteristics to provide basics to the young scientists, which will be useful to circumvent the difficulties associated with the formulation design.

Keywords: Mucoadhesive; buccal; polymers; drug delivery system.

1. INTRODUCTION

The sites of drug administration in the oral cavity include the floor of the mouth (sublingual), the inside of the cheeks (buccal) and the gums (gingival). In general, the delivery of a drug requires some type of dosage form, present in the oral cavity, to release a drug, which then diffuses through the mucosa into the local blood circulation and is then taken further to the systemic blood circulation. Buccal drug delivery has several advantages over peroral delivery. Administration of compounds via the mucosa of the oral cavity avoids pre-systemic metabolism in the gastrointestinal (GI) tract and hepatic firstpass elimination. In addition, the buccal mucosa is a well-vascularized tissue and is easily accessible for both application and removal of a delivery device. It's having facility to include permeation enhancer/enzyme inhibitor or pH-modifier in the formulation and versatility in designing as multidirectional or unidirectional release systems for local or systemic actions etc, (Alur et al., 2001).

The disadvantages associated with this route of drug delivery are the low permeability of the buccal membrane (Rojanasakul et al., 1992), specifically when compared to the sublingual membrane (Gandhi et al., 1994), and a smaller surface area. The total surface area of the membranes of the oral cavity available for drug absorption is 170 cm^2 (Collins et al., 1987), of which ~50 cm^2 represents non-keratinized tissues, including the buccal membrane (Lee et al., 2000). The continuous secretion of saliva (0.5–2 l/day) leads to subsequent dilution of the drug (Gandhi et al., 1994). Swallowing of saliva can also potentially lead to the loss of dissolved or suspended drug and, ultimately, the involuntary removal of the dosage form. These problems are associated with buccal drug delivery. Moreover, the hazard of choking by involuntarily swallowing the delivery system is a concern, in addition to the inconvenience of such a dosage form when the patient is eating or drinking.

Adhesion as a process, simply defined as the ''fixing" of two surfaces to one another (Kinloch 1980). There are many different terminological subsets of adhesion depending upon the environment in which the process occurs. When adhesion occurs in a biological setting it is often termed ''bioadhesion", furthermore if this adhesion occurs on mucosal membranes it is termed ''mucoadhesion". Bioadhesion can be defined as the binding of a natural or synthetic polymer to a biological substrate. When this substrate is a mucous layer, the term mucoadhesion is often used (Henriksen et al., 1996). Mucoadhesion has been widely promoted as a way of achieving site-specific drug delivery through the

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incorporation of mucoadhesive hydrophilic polymers within pharmaceutical formulations along with the active pharmaceutical ingredient (API). The rationale being that the formulation will be 'held' on a biological surface for localised drug delivery. The API will be released close to the site of action with a consequent enhancement of bioavailability (Woodley 2001). Whilst mucoadhesive drug delivery systems provide a means of enhancing retention at defined sites, if systemic uptake occurs the use of mucoadhesive polymers will not prevent a wider distribution of the API.

1.1 Structure and function of oral mucosal membrane

Buccal region is that part of the mouth bounded anteriorly and laterally by the lips and the cheeks, posteriorly and medially by the teeth and/or gums, and above and below by the reflections of the mucosa from the lips and cheeks to the gums. Numerous racemose, mucous, or serous glands are present in the submucous tissue of the cheeks (Wikipedia.org). The buccal glands are placed between the mucous membrane and buccinator muscle: they are similar in structure to the labial glands, but smaller. About five, of a larger size than the rest, are placed between the masseter and buccinators muscles around the distal extremity of the parotid duct; their ducts open in the mouth opposite the last molar tooth. They are called molar glands (Gray's Anatomy). Maxillary artery supplies blood to buccal mucosa and blood flow is faster and richer (2.4ml/min/cm^2) than that in the sublingual, gingival and palatal regions, thus facilitates passive diffusion of drug molecules across the mucosa. The thickness of the buccal mucosa is measured to be 500–800 µm and is rough textured, hence suitable for retentive delivery systems (Rathbone rt al., 1996). The turnover time for the buccal epithelium has been estimated at 5–6 days (Sanders 1990).

Mucous membranes (the mucosa) have moist surfaces lining the walls of the organs of the gastrointestinal tract and respiratory passages, the inner part of the eyes, as well as the nasal and oral cavities and the genital organs (Birudaraj et al., 2005). Thus, the mucosa represent a tissue with an enormous area - the small intestine alone, with its numerous fingers- like projections of the intestinal wall and epithelial cell plasma membrane microvilli, has a surface area of 300 m^2, which is more than 100 times greater than the area of the skin (Ham et al., 2006). The rich arterial blood supply to the oral mucosa is derived from the external carotid artery. The buccal artery, some terminal branches of the facial artery, the posterior alveolar artery, and the infraorbital artery are the major sources of blood supply to the lining of the cheek in the buccal cavity (Stablein et al., 1984).

The structure of the mucous membrane of the mouth is shown in Fig. 1. The mucous gelatinous layer (*1*) covers the epithelium (*2*), beneath which lies the connective-tissue lamina propria (*3*), which has an abundant supply of blood and lymph vessels; beneath this is a thin layer of smooth muscle tissue (*4*). The thickness of the mucus layer varies in different mucosal tissue surfaces from 50 to 500 µm in the stomach and to less than 1 µm in the oral cavity (Valenta 2005, & kharenko et al., 2009).

The epithelium may consist of a single layer (stomach, small and large intestine, bronchi) or multiple layers (esophagus, vagina). The upper layer contains goblet cells, which secrete mucus components directly onto the epithelial surface. Specialized glands producing components of the mucous layer may also be located beneath the epithelium (Salamat et al., 2005). The moist surface of the tissue results from the mucus – a viscous, gelatinous secretion whose composition includes glycoproteins, lipids, inorganic salts, and up to 95% water (Salamat et al., 2005). Mucus may be secreted either constantly or intermittently. The volume of secretion changes under the influence of external and internal factors (kharenko et al., 2009).

Glycoproteins (mucins) are the most important components of mucus and are responsible for its gelatinous structure, cohesion, and antiadhesive properties (Peppas et al., 1996). Despite the various body sites at which mucus is secreted, glycoproteins usually have similar structure (Fig. 2) and are highly glycosylated protein molecules with molecular weights reaching 5 $\times 10^5$. In space, glycoproteins form a branched three-dimensional network with large numbers of loops (Fig. 2*b)*. The polypeptide chain consists of 800 – 4500 amino acid residues and is characterized by two types of area – strongly glycosylated areas (Fig. 2*a*, shown by thick lines in Fig. 2*b*) and areas lacking carbohydrate side chains (shown by thin lines in Fig. 2*b*). Glycosylation increases the resistance of the molecules to proteolytic hydrolysis (Ugwoke et al., 2005). The terminal domains of the glycoprotein (C- and N-) are areas containing more than 10% cysteine. These parts of the domains are responsible for the formation of large mucin oligomers due to the formation of disulfide bonds (Ponchel et al., 1998). The greater part of the protein carcass consists of a repeating sequence of serine, threonine, and proline residues. Oligosaccharide sequences are attached to 63% of the protein core, at every third residue within the glycosylated areas, with the result that there are more than 200 carbohydrate chains per glycoprotein molecule (Ludwig 2005). Each carbohydrate side chain contains from two to 20 sugar residues. Thus, the carbohydrate areas can account for more than 80% of the molecular weight of the molecule (Ugwoke et al., 2005). As the polysaccharide side chains usually terminate with either fucose or sialic acid (N-acetylneuraminic acid, pK_a = 2.6), the glycoproteins are negatively charged at physiological pH values (Ludwig 2005). Human mucins are divided into "anchored" mucins, i.e., those bound to the membrane, and secreted mucins. Secreted mucins can also be subdivided into gel-forming or soluble on the basis

of their ability to form associates. Membrane-bound mucins contain short tails pointing towards the cytoplasm, which are hydrophobic and anchored in the depth of the membrane domain, holding the molecule in the apical surface of the cell, and an extracellular domain generally containing a repeating glycosylated sequence. The length of the glycosylated region has been shown to reach 200 – 500 µm from the cell surface, depending on the number of repeat sequences present (kharenko et al., 2009).

The main functions of the mucus are to protect and lubricate the supporting epithelial layer. In the gastrointestinal tract, the mucus facilitates the movement of food boluses along the digestive canal and protects the epithelium from harmful influences due to intrinsic peristaltic movements and proteolytic enzymes. The components of the mucus secreted onto the surface of the eye by goblet cells adhere tightly to the glycocalyx of corneal-conjunctival epithelial cells, protecting the epithelium from damage and facilitating the movement of the eyelids (Ludwig 2005).

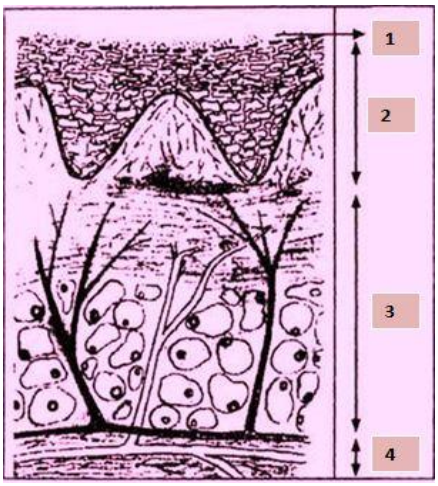

Figure 1: Structure of the mucosa of the oral cavity: 1) mucus layer; 2) epithelium; 3) connective tissue (lamina propria); 4) smooth muscle layer (kharenko et al., 2009)

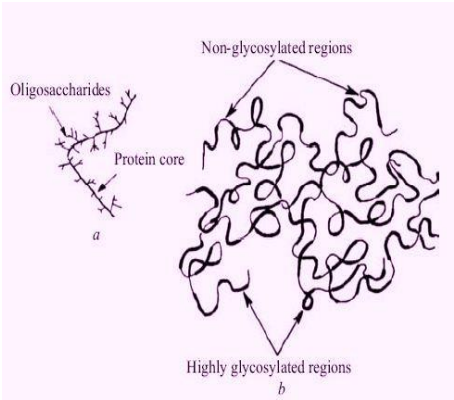

Figure 2: Structure of glycoprotein (diagram); a) structure of branched section; b) formation of network structure (kharenko et al., 2009).

2. Permeation Enhancers

Membrane permeation is the limiting factor for many drugs in the development of buccal adhesive delivery devices. The epithelium that lines the buccal mucosa is a very effective barrier to the absorption of drugs. Substances that facilitate the permeation through buccal mucosa are referred as permeation enhancers (Chattarajee et al., 1995). As most of the penetration enhancers were originally designed for purposes other than absorption enhancement, a systemic search for safe and effective penetration enhancers must be a priority in drug delivery. The goal of designing penetration enhancers, with improved efficacy and reduced toxicity profile is possible by understanding the relationship between enhancer structure and the effect induced in the membrane and of course, the mechanism of action. However, the selection of enhancer and its efficacy depends on the physicochemical properties of the drug, site of administration, nature of the vehicle and other excipients. In some cases usage of enhancers in combination has shown synergistic effect than the individual enhancers. The efficacy of enhancer in one site is not same in the other site because of differences in cellular morphology, membrane thickness, enzymatic activity, lipid composition and potential protein interactions are structural and functional properties. Penetration enhancement to the buccal membrane is drug specific (Shojaei 1998). Effective penetration enhancers for transdermal or intestinal drug delivery may not have similar effects on buccal drug delivery because of structural differences; however, enhancers used to improve drug permeation in other absorptive mucosae improve drug penetration through buccal mucosa. These permeation enhancers should be safe and non toxic, pharmacologically and chemically inert, non-irritant, and non-allergenic (Aungst 1994). However, examination of penetration route for transbuccal delivery is important because it is fundamental to select the proper penetration enhancer to improve the drug permeability. The different permeation enhancers available are listed in Table.1. (Lee 1991).

Table 1: List of permeation enhancers

Permeation Enhancers	
Chelators	EDTA, Citricacid , Sodium salicylate, Methoxy salicylates.
Surfactants	Sodium lauryl sulphate, Polyoxyethylene, Polyoxyethylene-9-laurylether, Polyoxythylene-20-cetylether, Benzalkonium chloride, 23-lauryl ether, Cetylpyridinium chloride, Cetyltrimethyl ammonium bromide.
Bile salts	Sodium glycocholate,

	Sodium deoxycholate, Sodium taurocholate, Sodium glycodeoxycholate, Sodium taurodeoxycholate.
Fatty acids	Oleic acid, Capric acid, Lauric acid, Lauric acid/ propylene glycol, Methyloleate, Lysophosphatidylcholine, Phosphatidylcholine.
Non-surfactants	Unsaturated cyclic ureas.
Inclusion complexes	Cyclodextrins
Others	Aprotinin, Azone, Cyclodextrin, Dextran sulfate, Menthol, Polysorbate 80, Sulfoxides and various alkyl glycosides.
Thiolated polymers	Chitosan-4-thiobutylamide, Chitosan- 4-thiobutylamide/gsh, Chitosan-cysteine, Poly (acrylic acid)-homocysteine, Polycarbophil-cysteine, Polycarbophil-cysteine/gsh, Chitosan-4-thioethylamide/gsh, Chitosan- 4-thioglycholic acid.

2.1. Mechanisms of action

Mechanisms by which penetration enhancers are thought to improve mucosal absorption are as follows (Ganem et al., 1996).

- *Changing mucus rheology:* Mucus forms viscoelastic layer of varying thickness that affects drug absorption. Further, saliva covering the mucus layers also hinders the absorption. Some permeation enhancers' act by reducing the viscosity of the mucus and saliva overcomes this barrier.
- *Increasing the fluidity of lipid bilayer membrane*: The most accepted mechanism of drug absorption through buccal mucosa is intracellular route. Some enhancers disturb the intracellular lipid packing by interaction with either lipid packing by interaction with either lipid or protein components.
- *Acting on the components at tight junctions*: Some enhancers act on desmosomes, a major component at the tight junctions there by increases drug absorption.
- *By overcoming the enzymatic barrier*: These act by inhibiting the various peptidases and proteases present within buccal mucosa, thereby overcoming the enzymatic barrier. In addition, changes in membrane fluidity also alter the enzymatic activity indirectly.
- *Increasing the thermodynamic activity of drugs*: Some enhancers increase the solubility of drug there by alters the partition coefficient. This leads to increased thermodynamic activity resulting better absorption.

Surfactants such as anionic, cationic, nonionic and bile salts increases permeability of drugs by perturbation of intercellular lipids whereas chelators act by interfering with the calcium ions, fatty acids by increasing fluidity of phospholipids and positively charged polymers by ionic interaction with negative charge on the mucosal surface. Chitosan exhibits several favorable properties such as biodegradability, biocompatibility and antifungal/antimicrobial properties in addition to its potential bioadhesion and absorption enhancer (Schipper et al., 2004).

3. Buccal Mucoadhesive Polymers

Polymer is a generic term used to describe a very long molecule consisting of structural units and repeating units connected by covalent chemical bonds. The term is derived from the Greek words: polys meaning many, and meros meaning parts. Many Studies showed that addition of various polymers to Drug Delivery System, such as gums, increased the duration of attachment of the Medicinal Formulations to the mucous surface and increased the efficacy of antibiotic treatment (Salamat et al., 2005). The development of the mucoadhesion theory and improvements in practical methods were accompanied by investigation of many polymers used in pharmaceuticals and new materials and their mixtures for the presence of mucoadhesive properties.The classification of mucoadhesive polymers and examples are presented in Table-2. Bioadhesive formulations use polymers as the adhesive component. These formulations are often water soluble and when in a dry form attract water from the biological surface and this water transfer leads to a strong interaction. These polymers also form viscous liquids when hydrated with water that increases their retention time over mucosal surfaces and may lead to adhesive interactions. Bioadhesive polymers should possess certain physicochemical features including hydrophilicity, numerous hydrogen bond-forming groups,flexibility for interpenetration with mucus and epithelial tissue, and visco-elastic properties (Batchelor 2004).

3.1. Ideal Characteristics of a Buccal Adhesive Polymer

- Polymer and its degradation products should be non-toxic, non-irritant and free from leachable impurities.
- Should have good spreadability, wetting, swelling and solubility and biodegradability properties.
- pH should be biocompatible and should possess good viscoelastic properties.
- Should adhere quickly to buccal mucosa and should possess sufficient mechanical strength.
- Should possess peel, tensile and shear strengths at the bioadhesive range.

Table 2: Classification of mucoadhesive polymers (Salamat et al., 2005)

Property used for classification	Examples	
	Natural and modified natural polymers	**Synthetic**
Source	Agarose, Chitosan, Gelatin, Hyaluronic acid, Carrageenan, Pectin, Sodium alginate. **Cellulose derivatives** CMC, thiolated CMC, Na CMC, hydroxyethylcellulose, HPC, HPMC, methylcellulose, Methylhydroxyethylcellulose.	**Polymers based on poly(meth)acrylic acid.** Carbopol, Polycarbophil, Polyacrylic acid, Polyacrylates, Copolymer of acrylic acid and PEG, Copolymer of methylvinyl ether and Methacrylic acid, Poly-2-hydroxyethylmethacrylate, Copolymer of acrylic acid and Ethylhexylacrylate, Polymethacrylate, Polyalkylcyanoacrylates:- Polyisobutylcyanoacrylate, Polyisohexylcyanoacrylate. **Others** Poly-N-2-hydroxypropylmethacrylamide, Polyhydroxyethylene, PVA, PVP, Thiolated polymers
	Water-soluble	**Water-insoluble**
Solubility in water	**Cellulose derivatives** CMC, Thiolated CMC, Na CMC, Hydroxyethylcellulose, HPC, HPMC, Methylcellulose, Methylhydroxyethylcellulose. **Others** Poly-N-2-hydroxypropylmethacrylamide, Polyhydroxyethylene, PVA, PVP, Thiolated polymers. Ethylcellulose, polycarbophil	**Polymers based on poly(meth)acrylic acid** Carbopol, Polycarbophil, Polyacrylic acid, Polyacrylates, Copolymer of acrylic acid and PEG, Copolymer of methylvinyl ether and Methacrylic acid, Poly-2-hydroxyethylmethacrylate, Copolymer of acrylic acid and Ethylhexylacrylate, Polymethacrylate, Polyalkylcyanoacrylates:- Polyisobutylcyanoacrylate, Polyisohexylcyanoacrylate.
	Cationic and Anionic	**Uncharged**
Charge	Aminodextran, dimethylaminoethyldextran, chitosan, quaternized chitosan Chitosan-EDTA, PAC, carbopol, polycarbophil, pectin, sodium alginate, Na CMC, CMC	Hydroxyethylated starch, HPC, PEG, PVA, PVP
Possible mechanism of formation of Bioadhesive bonds	Covalent Hydrogen bonds Electrostatic interactions	Cyanoacrylate Acrylates, carbopol, polycarbophil, PVA Chitosan
Notes. CMC = carboxymethylcellulose; HPMC = hydroxypropylmethylcellulose; PEG = polyethylene glycol; PVA = polyvinyl alcohol; PVP = polyvinylpyrrolidone; HEC = hydroxyethylcellulose; HPC = hydroxypropylcellulose; PAA = polyacrylic acid; EDTA = ethylenediami netetraacetate.		

- Polymer must be easily available and its cost should not be high.
- Should show bioadhesive properties in both dry and liquid state.
- Should demonstrate local enzyme inhibition and penetration enhancement properties.
- Should demonstrate acceptable shelf life.
- Should have optimum molecular weight.
- Should possess adhesively active groups.

- Should have required spatial conformation.
- Should be sufficiently cross-linked but not to the degree of suppression of bond forming groups.
- Should not aid in development of secondary infections such as dental caries.

3.2. Mucoadhesion Theories of Polymer Attachment

Mucoadhesion is a complex process and numerous theories have been presented to explain the mechanisms involved. These theories include mechanical-interlocking, electros-tatic, diffusion–interpenetration, adsorption and fracture processes. Whilst undoubtedly the most widely accepted theories are founded surface energy thermodynamics and interpenet-rateion /diffusion (Madsen et al., 1998).These numerous theories should be considered as supplementary processes involved in the different stages of the mucus/substrate interaction, rather than individual and alternative theories (Gavin et al., 2009).

3.2.1 The Wettability Theory

The wettability theory is mainly applicable to liquid or low viscosity mucoadhesive systems and is essentially a measure of the ‘‘spreadability” of the API delivery system across the biological substrate (Fig. 3). This theory postulates that the adhesive component penetrates surface irregularities, hardens and anchors itself to the surface. The adhesive performance of such elastoviscous liquids may be defined using wettability and spreadability; critical parameters that can be determined from solid surface contact angle measurements. 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 substrate (Gavin et al., 2009).Therefore the contact angle(θ), which may be easily determined experimentally, is related to interfacial tension (γ), of both components using

$$\gamma_{SG} = \gamma_{SL} + \gamma_{LG} \cos\theta \quad (1)$$

$$S = \gamma_{SG} - (\gamma_{SL} - \gamma_{LG}), \quad (2)$$

Where γ_{LG} is liquid–gas surface tension, γ_{SL} is solid–liquid surface tension and γ_{SG} is solid–gas surface tension.

Mucoadhesive polymer systems that exhibit similar structure and functional groupings to the mucus layer will show increased miscibility; this in turn will result in a greater degree of polymer spreadability across the mucosal surface. Lower water: polymer contact angles of such systems will facilitate hydration of the polymer chains and thus promote intimate contact between polymeric delivery platform and the mucus substrate. In the case of an extremely hydrophilic polymer however, the water contact angle will be much lower than that of the mucosal surface, thus discouraging such an intimate contact due to a high interfacial surface free energy (Shojaei et al., 1997).

3.2.2. The Electronic Theory

This theory describes adhesion occurring by means of electron transfer between the mucus and the mucoadhesive system arising through differences in their electronic structures. The electron transfer between the mucus and the mucoadhesive results in the formation of double layer of electrical charges at the mucus and mucoadhesive interface. The net result of such a process is the formation of attractive forces within this double layer (Dodou et al., 2005). Controversy has surrounded this theory arising from the statement that electrostatic forces are an important cause of bond adhesion, rather than merely a result of high joint strength.

3.2.3 The Fracture Theory

According to this theory, the adhesive bond between systems is related to the force required to separate both surfaces from one another. This ‘‘fracture theory” relates the force for polymer detachment from the mucus to the strength of their adhesive bond. The work fracture has been found to be greater when the polymer network strands are longer or if the degree of cross-linking within such as system is reduced (Ahagon et al., 1975). This theory allows the determination of fracture strength (σ) following the separation of two surfaces via its relationship to Young’s modulus of elasticity (E), the fracture energy (ε) and the critical crack length (L) through the following equation (Gavin et al., 2009):

$$\sigma = \left(\frac{E \times \varepsilon}{L}\right)^{1/2}$$

3.2.4 The Adsorption theory

In this instance, adhesion is defined as being the result of various surface interactions (primary and secondary bonding) between the adhesive polymer and mucus substrate. Primary bonds due to chemisorption result in adhesion due to ionic, covalent and metallic bonding, which is generally undesirable due to their permanency (Kinloch 1980). Secondary bonds arise mainly due to van der Waals forces, hydrophobic interactions and hydrogen bonding. Whilst these interactions require less energy to ‘break’, they are the most prominent form of surface interaction in mucoadhesion processes as they have the advantage of being semi permanent bonds (Jiménez et al., 1993).

3.2.5 The Diffusion-Interlocking Theory

This theory proposes the time-dependent diffusion of mucoadhesive polymer chains into the glycoprotein chain network of the mucus layer. This is a two-way diffusion process with penetration rate being dependent upon the diffusion coefficients of both interacting polymers (Fig. 4). Although there are many factors involved in such processes, the fundamental properties that significantly influence this inter-movement are molecular weight, cross-linking density, chain mobili-

ty/flexibility and expansion capacity of both networks (Lee et al., 2000). Furthermore, temperature also has been noted as important environmental factor for this process (vet al., 1995). Whilst it is acknowledged that longer polymer chains may diffuse, interpenetrate and ultimately entangle to a greater extent with surface mucus, it should be recognised that a critical chain length of at least 100,000 Da is necessary to obtain interpenetration and molecular entanglement. Additionally excessive chain cross-linking will act to decrease the polymer mobility and thus interfacial penetration (Ludwig 2005). Another significant contributory factor in determining interpenetration is the miscibility of both systems with one another. It is reasonable to postulate then that maximum diffusion and bioadhesive strength may be achieved when the solubility parameter (δ) of the bioadhesive polymer and the mucus glycoprotein is similar (Vasir et al., 2003). The time at which maximum adhesion occurs between two substrates during interpenetration has been supported by experimental evidence in recent studies using AFT-FTIR and rheological techniques (Madsen et al., 1998), and may be determined using the depth of interpenetration (*l*), and the diffusion coefficient (D_b) (Mikos et al., 1986),

$$t = \frac{l^2}{D_b}$$

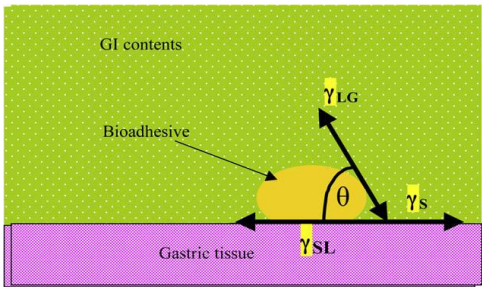

Figure 3: The interfacial forces involved in polymer spreading, where θ is angle of contact, γLG is liquid–gas surface tension, γSL is solid–liquid surface tension, γSG is solid–gas surface tension (Gavin et al., 2009)

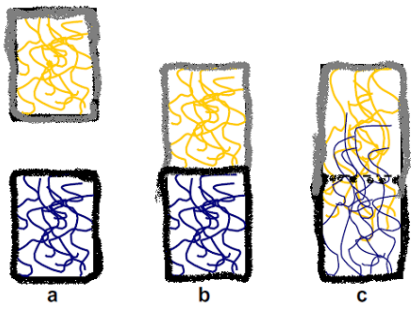

Figure 4: The diffusion theory of adhesion. (a) Top (polymer) layer and bottom (mucus) layer before contact; (b) top layer and bottom layer immediately after contact; (c) top layer and bottom layer after contact for a period of time (Gavin et al., 2009)

4. Mucoadhesive Polymeric Platforms

The polymeric attributes that are pertinent to high levels of retention at applied and targeted sites via mucoadhesive bonds include hydrophilicity, negative charge potential and the presence of hydrogen bond forming groups. Additionally, the surface free energy of the polymer should be adequate so that 'wetting' with the mucosal surface can be achieved. The polymer should also possess sufficient flexibility to penetrate the mucus network, be biocompatible, non-toxic and economically favourable. The polymers that are commonly employed in the manufacture of mucoadhesive drug delivery platforms that adhere to mucin–epithelial surfaces may be conveniently divided into three broad categories (Gavin et al., 2009).

(1) Polymers that become sticky when placed in aqueous media and owe their bioadhesion to stickiness.

(2) Polymers that adhere through non-specific, non-covalent interactions those are primarily electrostatic in nature (although hydrogen and hydrophobic bonding may be significant).

(3) Polymers that bind to specific receptor sites on the cell surface.

4.1 First-generation mucoadhesive polymers

First-generation mucoadhesive polymers may be divided into three main subsets, namely:

(1) Anionic polymers,

(2) Cationic polymers,

(3) Non-ionic polymers.

Of these, anionic and cationic polymers have been shown to exhibit the greatest mucoadhesive strength (A. Ludwig 2005).

4.1.1 Anionic Polymers

Anionic polymers are the most widely employed mucoadhesive polymers within pharmaceutical formulation due to their high mucoadhesive functionality and low toxicity. Such polymers are characterised by the presence of carboxyl and sulphate functional groups that give rise to a net overall negative charge at pH values exceeding the pKa of the polymer. Typical examples include poly (- acrylic acid) (PAA) and its weakly cross-linked derivatives and sodium carboxymethylcellulose (NaCMC). PAA and NaCMC possess excellent mucoa-dhesive characteristics due to the formation of strong hydrogen bonding interactions with mucin (Fefelova et al., 2007).

4.1.2 Cationic Polymers

In the cationic polymer systems, undoubtedly chitosan is the most extensively investigated within the current scientific literature. Chitosan is a cationic polysaccharide, produced by the deacetylation of chitin, the most

Table 3: Properties and characteristics of some representative bioadhesive polymers

Bioadhesives	Properties	Characteristics
Polycarbo-phil(polyacrylicacidcrosslinked with divinylglycol)	Mw 2.2×10^5 η 2000–22,500 cps (1% aq. soln.) κ 15–35 mL/g in acidic media (pH 1–3) 100 mL/g in neutral and basic media ϕ viscous colloid in cold water Insoluble in water, but swell to varying degrees in common organic solvents, strong mineral acids, and bases.	Synthesized by lightly crosslinking of 0.5–1% w/w divinyl glycol Swellable depending on pH and ionic strength. Swelling increases as pH increases. AtpH 1–3, absorbs 15–35 ml of water per gram but absorbs 100 ml per gram at neutral and alkaline pH. Entangle the polymer with mucus on the surface of the tissue Hydrogen bonding between the nonionized carboxylic acid and mucin.
Carbopol/carbomer (carboxy polymethylene) empirical formula: (C3H4O2)x (C3H5 – Sucrose)y	Pharmaceutical grades: 934 P, 940 P, 971 P and 974 P. Mw 1×10^6 –4×10^6 η 29,400–39,400 cps at 25 °C with 0.5% neutralized aqueous solution. κ 5 g/cm^3 in bulk, 1.4 g/cm^3 tapped. pH 2.5–3.0 ϕ water, alcohol, glycerin White, fluffy, acidic, hygroscopic powder with a slight characteristic odour.	Synthesized by cross-linker of allyl sucrose or allyl pentaerythritol Excellent thickening, emulsifying, suspending, gelling agent. Common component in bioadhesive dosage forms. Gel looses viscosity on exposure to sunlight. Unaffected by temperature variations, hydrolysis, oxidation and resistant to bacterial growth. It contributes no off-taste and may mask the undesirable taste of the formulation. Incompatible with Phenols, cationic polymers, high concentrations of electrolytes and resorcinol.
Sodium carboxymethyl cellulose SCMC (cellulose carboxymethyl ether sodium salt) empirical formula: [C6H7O2(OH)3x (OCH2 – COONa)x]n	It is an anionic polymer made by swelling cellulose with NaOH and then reacting it with monochloroacetic acid. Grades H, M, and L Mw 9×10^4 –7×10^5 η 1200 cps with 1.0% soln. ρ 0.75 g/cm^3 in bulk pH 6.5–8.5 ϕ water White to faint yellow, odorless, hygroscopic powder or granular material having faint paper-like taste.	Emulsifying, gelling, binding agent Sterilization in dry and solution form, irradiation of solution loses the viscosity. Stable on storage. Incompatible with strongly acidic solutions In general, stability with monovalent salts is very good; with divalent salts good to marginal; with trivalent and heavy metal salts poor, resulting in gelation or precipitation. CMC solutions offer good tolerance of water miscible solvents, good viscosity stability over the pH 4 to pH 10 ranges, compatibility with most water soluble nonionic gums, and synergism with HEC and HPC. Most CMC solutions are thixotropic; some are strictly pseudoplastic. All solutions show a reversible decrease in viscosity at elevated temperatures. CMC solutions lack yield value. Solutions are susceptible to shear, heat, bacterial, enzyme, and UV degradation. Good bioadhesive strength. Cell immobilization via a combination of ionotropic gelation and polyelectrolyte complex formation (e.g., with chitosan) in drug delivery systems and dialysis mem-

		branes.
Hydroxypropyl cellulose partially substituted polyhydroxy propylether of cellulose HPC (cellulose 2-hydroxypropyl ether) empirical formula: $(C_{15}H_{28}O_8)_n$	Grades: Klucel EF, LF, JF, GF, MF and HF Mw 6×10^4 –1×10^6 η 4–6500 cps with 2.0% aq. soln. pH 5.0–8.0 ρ 0.5 g/cm^3 in bulk Soluble in water below 38 °C, ethanol, propylene glycol, dioxane, methanol, isopropyl alcohol, dimethyl sulphoxide, dimethyl formamide etc. Insoluble in hot water White to slightly yellowish, odorless powder.	Best pH is between 6.0 and 8.0. Solutions of HPC are susceptible to shear, heat, bacterial, enzymatic and bacterial degradation. It is inert and showed no evidence of skin irritation or sensitization. Compatible with most water-soluble gums and resins. Synergistic with CMC and sodium alginate. Not metabolized in the body. It may not tolerate high concentrations of dissolved materials and tend to be salting out. It is also incompatible with the substituted phenolic derivatives such as methyl and propyl parahydroxy benzoate. Granulating and film coating agent for tablet Thickening agent, emulsion Stabilizer, suspending agent in oral and topical solution or suspension
Hydroxypropylmethyl Cellulose HPMC (cellulose2-hydroxypropylmethyl ether) empirical formula: $C_8H_{15}O_6$ – $(C_{10}H_{18}O_6)_n$ –$C_8H_{15}O_5$	Methocel E5, E15, E50, E4M, F50, F4M, K100, K4M, K15M, K100M. Mw 8.6×10^4 η E15–15 cps, E4M–400 cps and K4M–4000 cps (2% aqueous solution.) ϕ Cold water, mixtures of methylene chloride and isopropylalcohol. Insoluble in alcohol, chloroform and ether. Odorless, tasteless, white or creamy white fibrous or granular powder.	Mixed alkyl hydroxyalkyl cellulosic ether Suspending, viscosity-increasing and film-forming agent Tablet binder and adhesive ointment ingredient E grades are generally suitable as film formers while the K grades are used as thickeners. Stable when dry. Solutions are stable at pH 3.0 to 11.0 Incompatible to extreme pH conditions and oxidizing materials.
Hydroxyethyl Cellulose non-ionic polymer made by swelling cellulose with NaOH and treating with ethylene oxide.	Available in grades ranging from 2 to 8,00,000 cps at 2%. Light tan or cream to white powder, odorless and tasteless. It may contain suitable anticaking agents. ρ 0.6 g/mL pH 6–8.5 ϕ in hot or cold water and gives a clear, colorless solution. It is soluble in hot or cold water and gives visually hazy, neutral pH solutions.	Solutions are pseudoplastic and show a reversible decrease in viscosity at elevated temperatures. HEC solutions lack yield value. Solutions show only a fair tolerance with water miscible solvents (10 to 30% of solution weight). Compatible with most water-soluble gums and resins. Synergistic with CMC and sodium alginate. Susceptible for bacterial and enzymatic degradation. Polyvalent inorganic salts will salt out HEC at lower concentrations than monovalent salts. Shows good viscosity stability over the pH 2 to pH 12 ranges. Used as suspending or viscosity builder Binder, film former.
Xanthan gum xanthan gum is an anionic polysaccharide derived from the fermentation of the plant bacteria Xanthamonas campestris	It will dissolve in hot glycerin. Solutions are typically in the 1500 to 2500 cps range at 1%; they are pseudoplastic and especially shear-thinning. In the presence of small amounts of salt, solutions shows good	Xanthan gum is more tolerant of electrolytes, acids and bases than most other organic gums. It can, nevertheless, be gelled or precipitated with certain polyvalent metal cations under specific circumstances.

	viscosity stability at elevated temperatures. Solutions possess excellent yield value.	Solutions show very good viscosity stability over the pH 2 to 12 range and good tolerance of water-miscible solvents. It is more compatible with most nonionic and anionic gums, featuring useful synergism with galactomannans. It is more resistant to shear, heat, bacterial, enzyme, and UV degradation than most gums.
Guar gum (galactomannan polysaccharide) empirical formula: $(C_6H_{12}O_6)_n$ consists chiefly of a high molecular weight hydrocolloid polysaccharide composed of galactan and mannan units combined through glycosidic linkages	Obtained from the ground endosperms of the seeds of Cyamposis tetyragonolobus (family leguminosae). MW approx. 220,000 η 2000–22500 Cps (1% aqueous solution.) Forms viscous colloidal solution when hydrated in cold water. The optimum rate of hydration is between pH 7.5 and 9.0.	Stable in solution over a pH range of 1.0–10.5. Prolonged heating degrades viscosity. Bacteriological stability can be improved by the addition of mixture of 0.15% methyl paraben or 0.1% benzoic acid. The FDA recognizes guar gum as a substance added directly to human food and has been affirmed as generally recognized as safe. Incompatible with acetone, tannins, strong acids, and the alkalis. Borate ions, if present in the dispersing water, will prevent hydration of guar. Used as thickener for lotions and creams, as tablet binder, and as emulsion stabilizer.
Hydroxypropyl Guar non-ionic derivative of guar. Prepared by reacting guar gum with propylene oxide.	Φ in hot and cold water Gives high viscosity, pseudoplastic solutions that show reversible decrease in viscosity at elevated temperatures. Lacks yield value.	Compatible with high concentration of most salts. Shows good tolerance of water miscible solvents. Better compatibility with minerals than guar gum. Good viscosity stability in the pH range of 2 to 13. More resistance to bacterial and enzymatic degradation.
Chitosan a linear polysaccharide composed of randomly distributed β-(1-4)-linked D-glucosamine (deacetylated unit) and N-acetyl-Dglucosamine (acetylated unit).	Prepared from chitin of crabs and lobsters by Ndeacetylation with alkali. Φ dilute acids to produce a linear polyelectrolyte with a high positive charge density and forms salts with inorganic and organic acids such as glutamic acid, hydrochloric acid, lactic acid, and acetic acid. The amino group in chitosan has a pKa value of ~6.5, thus, chitosan is positively charged and soluble in acidic to neutral solution with a charge density dependent on pH and the %DA-value.	Mucoadhesive agent due to either secondary chemical bonds such as hydrogen bonds or ionic interactions between the positively charged amino groups of chitosan and the negatively charged sialic acid residues of mucus glycoproteins or mucins. Possesses cell-binding activity due to polymer cationic polyelectrolyte structure and to the negative charge of the cell surface. Biocompatible and biodegradable. Excellent gel forming and film forming ability. Widely used in controlled delivery systems such as gels, membranes, microspheres. Chitosan enhance the transport of polar drugs across epithelial surfaces. Purified qualities of chitosans are available for biomedical applications. Chitosan and its derivatives such as trimethylchitosan (where the amino group has been trimethylated) have been used in non-viral gene

		delivery. Trimethylchitosan, or quaternised chitosan, has been shown to transfect breast cancer cells. As the degree of trimethylation increases the cytotoxicity of the derivative increases. At approximately 50% trimethylation the derivative is the most efficient at gene delivery. Oligomeric derivatives (3–6kDa) are relatively non-toxic and have good gene delivery properties.
Carrageenan an anionic polysaccharide, extracted from the red seaweed Chondrus crispus.	Available in sodium, potassium, magnesium, calcium and mixed cation forms. Three structural types exist: Iota, Kappa, and Lambda, differing in solubility and rheology. The sodium form of all three types is soluble in both cold and hot water. Other cation forms of kappa and Iota are soluble only in hot water. All forms of lambda are soluble in cold water.	All solutions are pseudoplastic with some degree of yield value. Certain ca-Iota solutions are thixotropic. Lambda is non-gelling, Kappa can produce brittle gels; Iota can produce elastic gels. All solutions show a reversible decrease in viscosity at elevated temperatures. Iota and Lambda carrageenan have excellent electrolyte tolerance; kappa's being somewhat less. Electrolytes will however decrease solution viscosity. The best solution stability occurs in the pH 6 to 10. It is compatible with most nonionic and anionic water-soluble thickeners. It is strongly synergistic with locust bean gum and strongly interactive with proteins. Solutions are susceptible to shear and heat degradation. Excellent thermoreversible properties. Used also for microencapsulation.
Sodium Alginate consists chiefly of the alginic acid, a polyuronic acid composed of β-D-mannuronic acid residues. Empirical formula: ($C_6H_7O_6Na$) an anionic polysaccharide extracted principally from the giant kelp Macrocystis Pyrifera as alginic acid and neutralized to sodium salt.	Purified carbohydrate product extracted from brown seaweed by the use of dilute alkali. Occurs as a white or buff powder, which is odorless and tasteless. pH 7.2 η 20–400 Cps (1% aqueous solution.) ϕ Water, forming a viscous, colloidal solution. Insoluble in other organic solvents and acids where the pH of the resulting solution and acids where the pH of the resulting solution falls below 3.0.	Safe and nonallergenic. Incompatible with acridine derivatives, crystal violet, phenyl mercuric nitrate and acetate, calcium salts, alcohol in concentrations greater than 5%, and heavy metals. Stabilizer in emulsion, suspending agent, tablet disintegrant, tablet binder. It is also used as haemostatic agent in surgical dressings Excellent gel formation properties Biocompatible Microstructure and viscosity are dependent on the chemical composition. Used as immobilization matrices for cells and enzymes, controlled release of bioactive substances, injectable microcapsules for treating neurodegenerative and hormone deficiency diseases. Lacks yield value. Solutions show fair to good tolerance of water miscible solvents (10–30% of volatile solvents; 40– 70% of glycols) Compatible with most water-soluble thickeners and resins. Its solutions are more resistant to bacterial and enzymatic degradation than many other organic thickeners.
Poly (hydroxy butyrate), Poly (e-caprolactone)	Biodegradable Properties can be changed by chemi-	Used as a matrix for drug delivery systems, cell microencapsulation.

and copolymers	cal modification, copolymerization and blending.	
Poly (ortho esters)	Surface eroding polymers.	Application in sustained drug delivery and ophthalmology
Poly (cyano acrylates)	Biodegradable depending on the length of the alkyl chain.	Used as surgical adhesives and glues Potentially used in drug delivery.
Polyphosphazenes	Can be tailored with versatile side chain functionality	Can be made into films and hydrogels. Applications in drug delivery.
Poly (vinyl alcohol)	Biocompatible	Gels and blended membranes are used in drug delivery and cell immobilization.
Poly (ethylene oxide)	Highly biocompatible.	Its derivatives and copolymers are used in various biomedical applications.
Poly (hydroxytheyl methacrylate)	Biocompatible	Hydrogels have been used as soft contact lenses, for drug delivery, as skin coatings, and for immunoisolation membranes.
Poly (ethylene oxide-b-propylene oxide)	Surfactants with amphiphilic properties	Used in protein delivery and skin treatments.

abundant polysaccharide in the world, next to cellulose (He et al., 1998). The intriguing properties of chitosan have been known for many years with many examples of its use in agriculture, industry and medicine. Agriculturally, chitosan has been utilised as an antipathogenic (Bautista et al., 2006), Chitosan has been noted for its film-forming properties and has used extensively in cosmetics. Among presently explored mucoadhesive polymers, chitosan is gaining increasing importance due to its good biocompatibility, biodegradability and due to their favourable toxicological properties (Portero et al., 2007). Whilst chitosan may provide improved drug delivery via a mucoadhesive mechanism, it has also been shown to enhance drug absorption via the paracellular route through neutralisation of fixed anionic sites within the tight junctions between mucosal cells (Bravo-Osuna et al., 2007).

The major benefit of using chitosan within pharmaceutical applications has been the ease with which various chemical groups may be added, in particular to the C-2 position allowing for the formation of novel polymers with added functionality. Using such modifications, the properties of chitosan may be tailored to suit the requirements of specific pharmaceutical–technological challenges (Bernkop-Schnürch 2000). Work by Onishi and Machida (Onishi et al., 1999) has demonstrated that chitosan and its degradation products are quickly eliminated by the kidney following intraperitoneal administration to mice, thus overcoming accumulation in the body.

4.2 Novel second-generation mucoadhesive polymers

The major disadvantage in using traditional non-specific mucoadhesive systems (first generation) is that adhesion may occur at sites other than those intended. A scenario that is particularly true for platforms designed to adhere to a distal target such as those hypothesised in targeted mucoadhesion within the GI tract. Unlike first-generation non-specific platforms, certain second-generation polymer platforms are less susceptible to mucus turnover rates, with some species binding directly to mucosal surfaces; more accurately termed ‘‘cytoadhesives”. Furthermore as surface carbohydrate and protein composition at potential target sites vary regionally, more accurate drug delivery may be achievable.

4.2.1 Lectins

Lectins are naturally occurring proteins that play a fundamental role in biological recognition phenomena involving cells and proteins. For example, some bacteria use lectins to attach themselves to the cells of the host organism during infection. Enhancement of mucosal delivery may be obtained through the use of appropriate cytoadhesives that can bind to mucosal surfaces. The most widely investigated of such systems in this respect are lectins. Lectins belong to a group of structurally diverse proteins and glycoproteins that can bind reversibly to specific carbohydrate residues (Clark et al., 2000). After initial mucosal cell-binding, lectins can either remain on the cell surface or in the case of receptor-mediated adhesion possibly become internalised via a process of endocytosis. Such systems could offer duality of function in that lectinbased platforms could not only allow targeted specific attachment but additionally offer a method of controlled drug delivery of macromolecular pharmaceuticals via active cell-mediated drug uptake (Lehr 2000). Whilst lectins offer significant advantages in comparison to first-generation platforms, it is worth noting that such polymers suffer at least in part from premature inactivation by shed off mucus. This phenomenon has been reported to be advantageous, given that the mucus layer provides an initial yet fully reversible binding site followed by distribution of lectin-mediated drug delivery systems to the cell layer (Wirth et al., 2002). Although lectins offer significant advantages in relation to site targeting, many are toxic or immunogenic, and the effects of repeated lectin exposure are largely unknown. It is also feasible that lectin-induced antibodies could block subsequent adhesive interactions between mucosal epithelial cell surfaces and lectin delivery vehicles. Moreover, such antibodies may also render in-

Figure 4: Factors Affecting Mucoadhesion (NazilaSalamat-Miller et al., 2005)

Factor	Characteristics, examples
Molecular weight	
Molecular weight	**Properties Of The Mucoadhesive Polymer** Low-molecular-weight polymers penetrate the mucus layer better. High molecular weight promotes physical entangling. The optimum molecular weight is between 10^4 and 4×10^6 Dal. Polymers with higher molecular weights will not moisten quickly to expose free groups for interaction with the substrate, while polymers with low molecular weights will form loose gels or will dissolve quickly. For linear polymers, the mucoadhesion strength increases with increases in molecular weight, for example, mucoadhesive properties in a series of polyeth ylene glycols increased in the order: $2 \times 10^4 < 2 \times 10^5 < 4 \times 10^5$. At the same time, dextran with very high molecular weight, $\sim 2 \times 10^7$, shows mucoadhesion similar to that of PEG with molecular weight 2×10^5 . This may result from the molecular conformation.
Polymer chain flexibility	Required for diffusion of chains and their entanglement with mucin. For polymers with high levels of linkage, the mobilities of the individual polymer chains decrease, leading to decreases in mucoadhesion strength.
Ability to form hydrogen bonds	Presence of functional groups able to form hydrogen bonds (COOH, OH, etc.).
Concentration	Affects the availability for penetration of long polymer chains into the mucus layer; important mainly for liquid and viscous DDS.
Extent of swelling of polymer or DDS	Swelling of the polymer allows mechanical entangling because of the exposure of polymer chains and subsequent formation of hydrogen bonds and/or electrostatic interactions between the polymer and components of the mucosa.
Environmental factors	
pH	Changes in pH lead to differences in the extent of dissociation of functional groups in carbohydrate sequences or polypeptide amino acid sequences, as well as in the polymer.
Pressure applied to the system for attachment	Affects the depth of diffusion of chains. Cannot be controlled for systems used in the GIT.
Duration of initial contact	Determines the extent of swelling and diffusion of polymer chains. Cannot be controlled for systems used in the GIT.
Moistening	Moistening is required to allow the mucoadhesive polymer to spread over the surface and create a “macromolecular network” of sufficient size for the interpenetration of polymer and mucin molecules and to in crease the mobility of polymer chains. However, there is a critical level of hydration for mucoadhesive poly mers characterized by optimum swelling and bioadhesion .
Presence of metal ions	Interaction with charged groups of polymers and/or mucus can decrease the number of interaction sites and the tightness of mucoadhesive bonding .
Physiological factors	
Rate of renewal of mucosal cells	Varies extensively for different types of mucosa. Limits the persistence of bioadhesive systems on mucosal surfaces.
Concomitant diseases	Can alter the physicochemical properties of mucus or its quantity (for example, hypo-and hypersecretion of gastric juice). Increases in body temperature, ulcer disease, colitis, tissue fibrosis, allergic rhinitis, bacterial or fungal infection, and inflammation.
Tissue movement	On consumption of liquid and food, speaking, peristalsis in the GIT.

dividuals susceptible to systemic anaphylaxis on subsequent exposure (Clark et al 2000).

The recent idea of developing blectinomimeticsQ (lectin-like molecules) based on lectins, and even biotechnologically generated derivatives of such molecules, holds an interesting future for this class of bioadhesion molecules. Computer-assisted molecular modeling has demonstrated that the lectin– sugar interactions contain only a small part of lectin which recognizes the sugar, while the remaining large portion of the glycoprotein is not involved in the detection and binding to the sugar. Therefore, the opportunity of designing blectinomimeticsQ based on the bactive siteQ of natural lectin seems very attractive, especially in view of its reduced Toxicity/immunogenicity. This interaction

would presumably create the same sugar recognition pattern that mediates cellular binding, and could potentially demonstrate wide applicability in the area of target-specific bioadhesive polymers (Lehr 2000). Possible application of lectin and lectin- like molecules to control targeting, binding, and cell internalization should be explored.

4.2.2 Bacterial Adhesion

The adhesive properties of bacterial cells, as a more complicated adhesion system, have recently been investigated. The ability of bacteria to adhere to a specific target is rooted from particular cell-surface components or appendages, known as fimbriae, that facilitate adhesion to other cells or inanimate surfaces. These are extracellular, long threadlike pro-tein polymers of bacteria that play a major role in many diseases. Bacterial fimbriae adhere to the binding moiety of specific receptors. A significant correlation has been found between the presence of fimbriae on the surface of bacteria and their pathogenicity (Savage 1977). The attractiveness of this approach lies in the potential increase in the residence time of the drug on the mucus and its receptor-specific interaction, similar to those of the plant lectins.

Some bacteria not only adhere to the epithelial cells, but also invade host cells using a mechanism resembling phagocytosis (Haltner et al., 1997). Bioinvasive drug delivery systems have been developed based on this bacterial mechanism, where bacteria could be used as a vehicle to introduce drug compounds into host cells by means of multiple h1 chain integrin cell receptors, which are a member of the cell adhesion molecule (CAM) family. This idea has led to a patent by Isberg et al. (Isberg 1994). Controlled endo- and transcytosis of microorganisms into cells by means of bacterial adhesion is another exploitable property of bacterial adhesion. The mechanism involves signal transmission associated with such binding, which then triggers the transport of the microorganism. Such characteristics can be employed for controlled cellular binding, internalization, and delivery of a variety of compounds. However, the potential of bacterial adhesion and invasion in buccal drug delivery is yet to be realized. In light of current biotechnological advances, such as cloning and expression of bacterial adhesion factors, the goal of targeted buccal drug delivery by this system does not appear all that distant.

4.2.3 Multifunctional Polymers

It has been shown that some mucoadhesive polymers can act as an enzyme inhibitor. The particular importance of this finding lies in delivering therapeutic compounds that are specifically prone to extensive enzymatic degradation, such as protein and polypeptide drugs. Investigations have demonstrated that polymers, such as poly (acrylic acid), operate through a competitive mechanism with proteolytic enzymes. This stems from their strong affinity to divalent cations (Ca2+, Zn2+). These cations are essential cofactors for the metalloproteinases, such as trypsin. Circular dichroism studies suggest that Ca2+ depletion, mediated by the presence of some mucoadhesive polymers, causes the secondary structure of trypsin to change, and initiates a further autodegradation of the enzyme (Lueßen et al.,1994). The increased intestinal permeability of various drugs in the presence of numerous mucoadhesive polymers has also been attributed to their ability to open up the tight junctions by absorbing the water from the epithelial cells. The result of water absorption by a dry and swellable polymer is dehydration of the cells and their subsequent shrinking. This potentially results in an expansion of the spaces between the cells (increased radius of the paracellular pathway) (Lueßen et al., 1995).

The use of multifunctional matrices, such as polyacrylates, cellulose derivatives, and chitosan, that display mucoadhesive properties, permeation-enhancing effects, enzyme inhibiting properties, and/or a high buffer capacity has proven successful strategies in oral drug delivery. The inhibition of the major proteolytic enzymes by these polymers is remarkable and represents yet another possible approach for the delivery of therapeutic compounds, particularly protein and peptide drugs, through the buccal mucosa. Since lectins are found in many species in the plant kingdom (e.g. tomato, wheat germ, mistletoe), they are not likely to be toxic. The fact that the source plants can be consumed raw, e.g. tomato fruit, would seem to suggest the safety of lectins. As mentioned previously, tomato lectin has been shown to bind to the surface of several cell monolayers, as well as rat intestinal epithelium without causing any harmful effects to the membranes.

4.2.4 Thiolated Polymers

These are the special class of multifunctional polymers also called thiomers. These are hydrophilic macromolecules exhibiting free thiol groups on the polymeric backbone. Due to these functional groups various features of well established polymeric excipients such as poly (acrylic acid) and chitosan were strongly improved (Haas et al., 2002). Thiolated polymers designated thiomers are capable of forming disulphide bonds with cysteine-rich subdomains of mucus glycoproteins covering mucosal membranes (Bernkop-Schnu et al., 2001). Consequently, the bridging structure most commonly used in biological systems is utilized to bind drug delivery systems on the mucosalmembranes. By immobilization of thiol groups the mucoadhesive properties of poly (acrylicacid) and chitosan, was improved to 100-fold to 250- fold (Hornof et al., 2003).

Thiomers are capable of forming intra- and interchain disulphide bondswithin the polymeric network leading to strongly improved cohesive properties and stability of drug delivery systems such as matrix tablets. Due to the formation of strong covalent bonds with mucus

glycoproteins, thiomers show the strongest mucoadhesive properties of all so far tested polymeric excipients via thioldisulphide exchange reaction and an oxidation process. Zinc dependent proteases such as aminopeptidases and carboxypeptidases are inhibited by thiomers. The underlying mechanism is based on the capability of thiomers to bind zinc ions and this property is highly beneficial for oral administration of protein and peptide drugs. They also exhibit permeation enhancing effects for the paracellular uptake of drugs based on a glutathione-mediated opening process of the tight junctions (Saviae et al., 2003).

Some of the properties and characteristics of buccal adhesive polymers are listed in Table -3 (YajamnSudhakar et al., 2006).

5. Factors Affecting Mucoadhesion

Mucoadhesion is a property for whose appearance both the bioadhesive polymer and the medium in which it is placed are important. The characteristics of the mucoadhesive and the mucosa, as well as other factors which can influence the strength and duration of the mucoadhesive interaction are summarized in Table 4.

6. Advantages of Mucoadhesive Buccal Drug Delivery System

Drugs administered via oral mucosa offers several advantages

- Ease of administration.
- Termination of theraphy is easy.
- Permits localization of drug to the oral cavity for a prolonged period of time.
- Can be administered to unconscious patients.
- Offers an excellent route, for the systemic delivery of drugs with high first pass metabolism, thereby offering a greater bioavailability.
- A significant reduction in dose can be achieved there by reducing dose related side effects.
- Drugs which are unstable in the acidic environment are destroyed by enzymatic or alkaline environment of intestine can be administered by this route.
- Drugs which show poor bioavailability via the oral route can be administered conveniently.
- It offers a passive system of drug absorption and does not require any activation.
- The presence of saliva ensures relatively large amount of water for drug dissolution unlike in case of rectal and transdermal routes.
- Systemic absorption is rapid.
- This route provides an alternative for the administration of various hormones, narcotic analgesic, steroids, enzymes, cardiovascular agents etc.
- The buccal mucosa is highly perfused with blood vessels and offers a greater permeability than the skin.

7. Limitations of Buccal Drug Administration

Drug administration via the buccal mucosa has certain limitations

- Drugs, which irritate the oral mucosa, have a bitter or unpleasant taste, odour, cannot be administered by this route.
- Drugs, which are unstable at buccal pH cannot be administered by this route.
- Only drugs with small dose requirements can be administered.
- Drugs may swallow with saliva and loses the advantages of buccal route.
- Only those drugs, which are absorbed by passive diffusion, can be administered by this route.
- Eating and drinking may become restricted.
- Swallowing of the formulation by the patient may be possible.
- Over hydration may lead to the formation of slippery surface and structural integrity of the formulation may get disrupted by the swelling and hydration of the bioadhesive polymers.

8. CONCLUSION

Buccal adhesive systems offer innumerable advantages in terms of accessibility, administration and withdrawal, retentivity, low enzymatic activity, economy and high patient compliance. Researchers are now looking beyond traditional polymer networks to find other innovative drug transport systems. At the current global scenario, scientists are finding ways to develop buccal adhesive systems through various approaches to improve the bioavailability of orally less/inefficient drugs by manipulating the formulation strategies The authors believe that the potential of the secondgeneration bioadhesive polymers is enormous, since they have revolutionized the concept of mucoadhesion through new findings arising from basic research on these new compounds. Novel buccal adhesive delivery system, where the drug delivery is directed towards buccal mucosa by protecting the local environment is also gaining interest. Currently solid dosage forms, liquids and gels applied to oral cavity are commercially successful. The future direction of buccal adhesive drug delivery lies in vaccine formulations and delivery of small proteins/peptides. Microparticulate bioadhesive 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. Exciting challenges remain to influence the bioavailability of drugs across the buccal mucosa.

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