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RESEARCH ARTICLE

MUCOADHESIVE FLIMS - AN OVER REVIEW

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ABSTRACT

Mucoadhesive flims leads direct access to the systemic circulation through the internal jugular vein bypasses drugs from the hepatic first pass metabolism leading to high bioavailability. Buccal route is an attractive route of administration for systemic drug delivery. Buccal bioadhesive films, releasing topical drugs in the oral cavity at a slow and predetermined rate, provide distinct advantages over traditional dosage forms for treatment of many diseases. This article aims to review the recent developments in the buccal adhesive drug delivery systems to provide basic principles to the young scientists, which will be useful to circumvent the difficulties associated with the formulation design.

INTRODUCTION

Oral administration is the preferred method for systemic administration of drugs, particularly because it is simple and relatively safe. However, in spite of following advantages, many molecules present only a poor oral bioavailability. There can be various reasons for this (Ponchel, 1998) including: (i) a low mucosal permeability inherent to the physicochemical properties of the drug; (ii) a drug permeability restricted to specific gastrointestinal (GI) regions; (iii) a poor dissolution rate in intestinal fluids generally related to low water solubility of the compound; and (iv) drug instability in the GI environment, resulting in drug degradation before absorption. Buccal mucosa is a potential site for drug absorption in alternative to oral drug delivery. Active molecules administered through the buccal mucosa pass directly into the systemic circulation, thereby minimizing the first hepatic pass and adverse gastro-intestinal effects (De Vries, 1991 and Del Consuelo, 2005). Other important advantages are the low enzymatic activity, suitability for drugs or excipients that mildly and reversibly damage or irritate the mucosa, painless administration, easy drug withdrawal, 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 (Sudhakar, 2006). Moreover, it is easily accessible for self-medication and suitable for dosage forms administration and removal. Various bioadhesive transmucosal dosage forms have been developed including adhesive tablets (Park, 2002) gels (Chang, 2002), ointments (Petelin, 2004), patches (Nafee, 2003) and films (Peh, 1999; Consuelo, 2007 and Yoo, 2006). However, transmucosal films are preferable over adhesive tablets in terms of flexibility and comfort as these films are thin. Over the last 30 years, the market share of transmucosal drug delivery systems has significantly increased with an estimated value of $6.7 million in 2006 (Transdermal and Trancemucosal Drug Delivery, 2007). According to a recent report published by Kalorama, worldwide revenue in this area is expected to increase approximately 3.5% a year to reach $7.9bn by 2010. This growth can be related to the ease with which transmucosal products may be designed and administered. Furthermore, the sustained growth of biotechnology drugs and the inherent need for novel drug delivery technologies that provide easier and more controlled modes of administration has resulted in a dramatic increase in the use of transmucosal systems.

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ANATOMY AND PHYSIOLOGY OF MUCUS

Mucus: structure, function and composition: Mucus is a dense viscous adherent secretion which is synthesized by specific goblet cells. These goblet cells are glandular columnar epithelium cells and line all organs that are exposed to the external environment. Mucus is found to serve many roles

within these locations for example lubrication for the passage of objects, maintenance of a hydrated epithelium layer, a barrier function with regard to pathogens and noxious substances and as a permeable gel layer allowing for the exchange of gases and nutrients to and from underlying epithelium (Bansil, 2006). From an engineering point of examination, mucus is an outstanding water-based lubricant whose properties are extensively exploited within nature. Giraffes can be seen using their sensitive mucus-laden tongues to strip the foliage from thorny acacia trees whilst slugs can crawl unharmed over a new razor blade (Davies, 1998). Mucus is self-possessed mainly of water (>95%) and mucins, which are glycoproteins of exceptionally high molecular weight (2–14 _ 106 g/mol). Also found within this ‘‘viscoelastic soup” are proteins, lipids and mucopolysaccharides, which are found in smaller extent (<1%). The mucin glycoproteins form a highly entangled network of macromolecules that associate with one another through non-covalent bonds. Such molecular association is central to the structure of mucus and is responsible for its rheological properties. Furthermore, pendant sialic acid (pKa = 2.6) and sulphate groups situated on the glycoprotein molecules result in mucin behaving as an anionic polyelectrolyte at neutral pH (Capra, 2007). Other non-mucin components of mucus include secretory IgA lysozyme, lactoferrin, lipids, polysaccharides, and numerous other ionic species. Some of these non-mucin components are believed to be responsible for the bacteriostatic action observed in mucus (Allen, 1972) Obviously, a thorough understanding of the glycoprotein mucin component is very important with regard to understanding the properties of mucus. Mucin glycoproteins may be described as consisting of a basic unit made from a single-chain polypeptide\ backbone with two separate regions (Fiebrig, 1995).

- A heavily glycosylated central protein core to which many large carbohydrate side chains are attached, predominantly via O-glycosidic linkages.
- One or two terminal peptide regions where there is little glycosylation. These regions are often referred to as ‘naked proteins regions (Willits, 2001).

Anatomy and Physiology of Oral Mucosa

The anatomical and physiological properties of oral mucosa had been comprehensively reviewed by several authors (Shojaei, 1998; Gandhi, 1994; Salamat-miller, 2005). The oral cavity encompasses the lips, cheek, tongue, hard palate, soft palate and floor of the mouth. The lining of the oral cavity is referred to as the oral mucosa, and includes the buccal, sublingual, gingival, palatal and labial mucosa. For about 60% of the oral mucosal surface area on account of buccal sublingual and the mucosal tissues at ventral surface of tongue. The top quarter to one-third of the oral mucosa is made up of closely compacted epithelial cells. The primary function of the oral epithelium is to protect the underlying tissue against potential harmful s in the oral environment and from fluid loss (Dowty, 1992). Beneath the epithelium are the basement membrane, lamina propia and submucosa. The oral mucosa also contains many sensory receptors including the taste receptors of the tongue.

Anatomy and physiology of vaginal mucosa

Anatomy and physiology of the vagina associated to drug delivery The vagina plays a major role in reproduction (Desphande, 1992; Platzer, 1978) and it is vital organ of the reproductive tract. It is a strong canal of muscle and approx. 7.5 cm long that extends from the uterus to the vestibule of the external genitalia. For sufficient elasticity the vaginal wall is crosswise fold. The vagina is positioned between rectum, bladder and urethra (Rakoff, 1944). The function and construction is significantly different to the intestinal wall. In contrast to the intestine there is no peristaltic motion but it is also not rigid. The vaginal wall consists of three layers: the epithelial layer, the muscular coat and tunica adventitia. A cell turnover of about 10–15 layers is estimated to be in the order of 7 days. The epithelium is a noncornified, stratified squamous epithelium. The thickness is dependent on age. With hormonal activity the vaginal epithelium increases in thickness and is highest in the proliferative stage and reaches the highest glycogen content during ovulation. Although the cyclic changes of the vaginal epithelium are less pronounced than of the endometrium, although differential cytology of the vaginal epithelium can be used to identify the cycle stages. Dependent on the different life stages like newborn, child, adult and menopause the epithelium thickness can be seen. The vaginal branch of the uterine artery mainly supplies blood to the vagina. The vagina has fashionable features in terms of microflora, pH and cyclic changes, and these features must be considered during the development and evaluation of vaginal delivery systems.

Physiological considerations of nasal mucosa

The nasal mucosa is wrinkled with extensive pseudo stratified columnar epithelium and includes ciliated cells and mucous-secreting goblet cells. Cilia are present at the apical surface, and mucous resides within the apices of the flask-shaped goblet cells. The epithelium rests on a lamina propria of loose connective tissue, containing mucous glands. Whilst tight junctions seal intercellular pathways, agents that disrupt these may facilitate the transport of molecules through to the underlying connective tissue. Throughout the nasal cavity, trachea, bronchi and bronchioles the pseudo stratified columnar epithelium is found (Boyaka, 2003).

Anatomy and physiology of gastrointestinalary tract and it’s mucosa (Blanchette, 2004)

Systems utilized for the delivery of therapeutic agents via the oral route must be designed conscious of the physiology of the gastrointestinal tract. The anatomy and physiology of route of administration may dictate many of the necessities for the systems. For example, the device must be able to withstand the saliva, as saliva contains digestive enzymes and other reagents for breaking down whatever is placed in the mouth. The stomach, the main digestive organ of the body, contains many digestive enzymes and very low pH. The pH of the stomach has been measured from 1.4 to 2.1. The destruction and denaturation of proteins without protection caused, by this harsh environment. The pH of the stomach changes when food is present increasing to nearly 4.0 (Dressman, 1999). Once through the harsh circumstances of the stomach a device reaches the small intestine, which is divided into 3 regions. The first region, closest to the stomach, is the duodenum, after that the jejunum and ileum. Fewer nutrients are taken into the bloodstream, the further down the small intestine they move. The duodenum, about 10 inches in length, composes the first 5% and the jejunum, the following 40% of the length of the small intestine. The whole length of the small intestine is 5

meter and residence time within the organ typically ranges from 2-4 hr. The inside layer of the small intestine are composed of the serous, muscular, areolar, and mucous layers. With respect to drug delivery only the mucus layer and areolar layer are important layers. Transport of the nutrients into the body occurs through the mucious cell layer and into the areolar layer where the nutrients are taken into the blood stream. In the mucosal layer, there are cell layers that fix out of it and into the open areas of the duodenum (Ungell, 1997).

Physiological Barriers for Transmuosal Drug Delivery System

Barriers or Oral Mucoadhesive Drug Delivery System

The environment of the oral cavity presents a number of significant challenges for systemic drug delivery. The drug desires to be released from the formulation to the delivery site (e.g. buccal or sublingual area) and pass through the mucosal layers to enter the systemic circulation. pH, fluid volume, enzyme activity and the permeability of oral mucosa like physiological aspects of oral cavity plays significant role in this process. For drug delivery systems designed for extended release in the oral cavity (e.g. mucodhesive systems). The daily entire salivary secretions volume is between 0.5 and 2.01. However, the volume of saliva constantly present in the mouth is around 1.1 ml, thus providing comparatively low fluid volume available for drug release from delivery system compared to the G.I tract. Compared to G.I fluid, saliva relatively less viscous because it containing 1% organic and inorganic materials. Saliva provides a water rich environment of the oral cavity which can be favorable for drug release from delivery system particularly those based on hydrophilic polymers. However, saliva flow decides the time span of the resealed drug at the delivery site.

This flow can let to premature swallowing of the drug before effective absorption occurs through the oral mucosa and is well accepted concept known as saliva wash out. Another major physiological barrier for oral transmucosal drug delivery is the drug permeability through the oral (e.g.buccal/sublingual) mucosa. The oral mucosal thickness varies depending on the site as dose the constitution of the epithelium. Another factor the buccal epithelium that can affect the mucoadhesion of the drug delivery system in the turnover time. the turnover time for buccal ephithelium has been estimated to be 3-8 days compared to about 30 days for the skin (Gandhi, 1994).

Barriers for Vaginal Mucoadhesive Drug Delivery System

As discussed before the changes in hormone levels (especially estrogen) during the menstrual cycle lead to modification in the thickness of the epithelial cell layer, width of intercellular channels, pH and secretions (Owen, 1975). The alteration in enzyme activity (endopeptidases and amino peptidases) with hormonal changes more complicate the problem of achieving consistent drug delivery (Pschera, 1989 and Furuhjelm, 1980). Because of gender specificity and cyclic variations the vagina has not been extensively explored for systemic drug delivery.
A physical model of the vaginal membrane as a transport barrier has been described (Ho, 1976). Moreover, absorption of drugs targeted for local action in the vagina is not required.

Barriers for Gastrointestinal Mucoadhesive Drug Delivery System

Mucoadhesion may be affected by numerous factors, including hydrophilicity, molecular weight, cross-linking, swelling, pH, and the concentration of the active polymer (Chen, 1970; Blanchette, 2004 and Chowdary, 2003).

Hydrophilicity

Bioadhesive polymers possess numerous hydrophilic functional groups, for instance hydroxyl and carboxyl. These groups allow hydrogen bonding with the substrate, swelling in aqueous media, thereby allowing maximal exposure of potential anchor sites. In addition, swollen polymers have the maximum distance between their chains leading to increased chain flexibility and effective penetration of the substrate.

Molecular Wieght

The interpenetration of polymer molecules is favored by low-molecular-weight polymers, whereas entanglements are preferential at higher molecular weights. The optimum molecular weight for the maximum mucoadhesion depends on the type of polymer, with bioadhesive forces increasing with the molecular weight of the polymer up to 100,000. There is no further gain, Beyond this level (Chowdary, 2003).

Crosslinking

Cross-link density is inversely proportional to the degree of swelling (Bottenberg, 1990). The lower the cross-link density, the higher the flexibility and hydration rate; the larger the surface area of the polymer, the better the mucoadhesion. A lightly cross-linked polymer is favored to attain a high degree of swelling. However, if in excess of moisture is present and the degree of swelling is too great, a slippy mucilage results and this can be easily removed from the substrate (Juan, 2005). The mucoadhesion of cross-linked polymers can be improved by the inclusion in the formulation of adhesion promoters, such as free polymer chains and polymers grafted onto the preformed network (Chowdary, 2003).

Spatial Conformation

In addition to molecular weight or chain length, spatial conformation of a polymer is also significant. In spite of a high molecular weight of 19,500,000 for dextrans, they have adhesive strength similar to that of polyethylene glycol (PEG), with a molecular weight of 200,000. The helical conformation of dextran may shield a lot of adhesively active groups, primarily responsible for adhesion, unlike PEG polymers, which have a linear conformation (Chen, 1970).

pH

The adhesion of bioadhesives possessing ionizable groups can be affected by the pH at the bioadhesive to substrate interface. Several bioadhesives used in drug delivery are polyanions possessing carboxylic acid functionalities. If the local pH is above the pK of the polymer, it will be largely ionized; if the pH is below the pK of the polymer, it will be largely unionized. The approximately estimated pK^a for the poly (acrylic acid) family of polymers is between 4 and 5. The

maximum adhesive force of these polymers is observed around pH 4–5 and decreases gradually above a pH of 6. A systematic investigation of the mechanisms of mucoadhesion clearly demonstrated that the protonated carboxyl groups, rather than the ionized carboxyl groups, react with mucin molecules, presumably by the simultaneous formation of various hydrogen bonds (Sam, 1989), Concentration of Active Polymer.

Theories of Mucoadhesion

A number of theories exist to explain at least some of the experimental observations made during the bioadhesion process. Unfortunately, each theoretical model can only explain a few number of the diverse range of interactions that constitute the bioadhesive bond (Longer, 1967). However, four main theories can be distinguished.

Wetting Theory

Perhaps the oldest recognized theory of adhesion is the wetting theory. It is best applied to liquid or low-viscosity bioadhesives. It describes adhesion as an embedding process, whereby adhesive agents penetrate into surface irregularities of the substrate and ultimately harden, producing lots of adhesive anchors. It must overcome any surface tension effects present at the interface for the Free movement of the adhesive on the surface of the substrate (McBain, 1925). The wetting theory calculates the contact angle and the thermodynamic work of adhesion. The work done is related to the surface tension of both the adhesive and the substrate, as given by Dupre's equation (Pritchard, 1970).

$$\omega_A = \gamma_b + \gamma_\tau - \gamma_b \quad \text{.....(1)}$$

Where ωA is the specific thermodynamic work of adhesion and γb, γτ, and γbt represent, respectively, the surface tensions of the bioadhesive polymer, the substrate, and the interfacial tension. The adhesive work done is a sum of the surface tensions of the two adherent phases, less the interfacial tensions apparent between both phases (Wake, 1982). Figure 1shows a drop of liquid bioadhesive spreading over a soft-tissue surface.

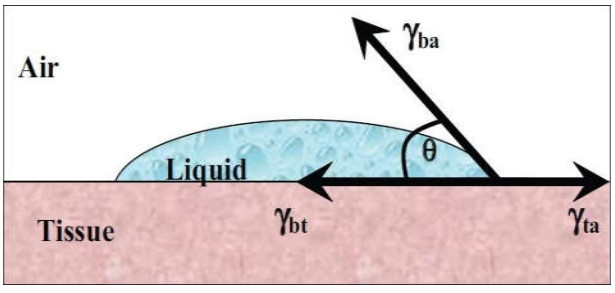

Figure 1. A liquid bioadhesive spreading over a typical soft tissue surface

Horizontal resolution of the forces gives the Young equation

$$\gamma_{ta} = \gamma_{bt} + \gamma_{ba}\cos\theta \quad \text{.....(2)}$$

where θ is the angle of contact, γ_{bt} is the surface tension between the tissue and polymer, γ_{ba} is the surface tension between polymer and air, and γ_{ta} is the surface tension between tissue and air. Equation 3 states that if the angle of contact,θ, is greater than zero, the wetting will be incomplete. If the vector γ_{ta} greatly exceeds $\gamma_{bt} + \gamma_{ba}$, that is:

$$\gamma_{ta} \geq \gamma_{bt} + \gamma_{ba} \quad \text{.....(3)}$$

Then θ will approach zero and wetting will be complete. If a bioadhesive material is to successfully adhere to a biological surface, it must first dispel barrier substances and then spontaneously spread across the underlying substrate, either tissue or mucus. The spreading coefficient, S_b, can be defined as shown in Equation 4:

$$S_b = \gamma_{ta} - \gamma_{bt} - \gamma_{ba} > 0 \quad \text{.....(4)}$$

Which states that bioadhesion is successful if S_b is positive, thereby setting the criteria for the surface tension vectors; in other words, bioadhesion is favored by large values of γ_{ta} or by small values of γ_{bt} and γ_{ba} (Wake, 1982).

Electostatic Theory of Mucoadhesion

According to this theory, transfer of electrons occurs across the adhesive interface and adhering surface. This results in the establishment of the electrical double layer at the interface and a series of attractive forces responsible for maintaining contact between the two layers (Gu, 1988). According to electrostatic theory, transfer of electrons occurs across the adhesive interface and adhering surface. This results in the establishment of the electrical double layer at the interface and s of attractive forces responsible for maintaining contact between the two layers (Deraguin, 1969).

Diffusion Theory of Mucoadhesion

Diffusion theory explains that polymeric chains from the bioadhesive interpenetrate into glycoprotein mucin chains and reach a adequate depth within the opposite matrix to allow formation of a semi permanent bond (Jimenez-Castellanos, 1993). The process can be visualized from the point of initial contact. The existence of concentration gradients will drive the polymer chains of the bioadhesive into the mucus network and the glycoprotein mucin chains into the bioadhesive matrix until an equilibrium penetration depth is achieved as shown in figure.

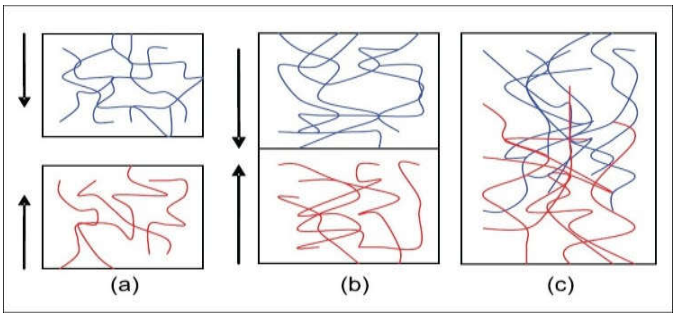

Figure 2. a) Schematic representation of the diffusion theory of bioadhesion. Blue polymer layer and red mucus layer before contact; (b) Upon contact; (c) The interface becomes diffuse after contact for a period of time

The exact depth needed for good bioadhesive bonds is unclear, but is estimated to be in the range of 0.2–0.5 μm.[48] The mean diffusional depth of the bioadhesive polymer segments, s, may be represented by Equation 5:

$$s=\sqrt{2tD} \quad \text{.....(5)}$$

Where D is the diffusion coefficient and t is the contact time. Duchene (Peppas, 1985) adapted Equation 5 to give Equation 6, which can be used to determine the time, t, to bioadhesion of a particular polymer:

$$t=\frac{l^2}{D_b} \quad \text{.....(6)}$$

in which l represents the interpenetrating depth and Db the diffusion coefficient of a bioadhesive through the substrate.
Once intimate contact is achieved, the substrate and adhesive chains move along their respective concentration gradients into the opposite phases. Depth of diffusion is dependent on the diffusion coefficient of both phases. Reinhart and Peppas (Reinhart, 1984), reported that the diffusion coefficient depended on the molecular weight of the polymer strand and that it decreased with increasing cross-linking density.

Adsorption Theory of Mucoadhesion

According to the adsorption theory, after an initial contact between two surfaces, the materials adhere because of surface forces acting between the chemical structures at the two surfaces (Ahuja, 1997). When polar molecules or groups are present, they reorientate at the interface (Wake, 1982). Chemisorption can occur when adhesion is particularly strong. The theory maintains that adherence to tissue is due to the net result of one or more secondary forces (van der Waal's forces, hydrogen bonding, and hydrophobic bonding) (Huntsberger, 1967; Kinloch, 1980 and Yang, 1998).

Fracture Theory of Adhesion

This theory describes the force required for the separation of two surfaces after adhesion. The fracture strength is equivalent adhesive strength through the following equation. This theory is useful for the study of bioadhesion by tensile apparatus.

$$\sigma = (E \times \varepsilon/L)^{1/2} \quad \text{.....(7)}$$

where σ is the fracture strength, e fracture energy, E young modulus of elasticity, and L the critical crack length (Gu, 1988).

Mucoadhesive Polymers

The polymers attributes, through mucoadhesive bonds include hydrophilicity, negative charge potential and the presence of hydrogen bond forming groups polymers are relevant to high level of retention at applied and targeted sites. Moreover, the surface free energy of the polymer should be sufficient 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 (Shojaei, 1997). 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 as defined by Park and Robinson (Park, 1984).

- When placed in aqueous media polymers that become sticky and owe their bioadhesion to stickiness.
- Polymers that adhere through non-specific, non-covalent interactions that is primarily electrostatic in nature (although hydrogen and hydrophobic bonding may be significant).
- Polymers that bind to specific receptor sites on the cell surface.

Traditional non-specific first-generation mucoadhesive polymers and the first-generation mucoadhesive polymers may be divided into three main subsets, namely:

- Anionic polymers,
- Cationic polymers,
- Non-ionic polymers.

Of these, anionic and cationic polymers have been shown to exhibit the greatest mucoadhesive strength [58]. Consequently, such charged polymeric systems will now be examined in more depth.

Anionic polymers

Anionic polymers are the most extensively employed mucoadhesive polymers within pharmaceutical formulation because of their high mucoadhesive functionality and low toxicity. 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, this are classified. Typical examples include poly (- acrylic acid) (PAA) and its weakly cross-linked derivatives and sodium carboxy methylcellulose (NaCMC). PAA and NaCMC possess excellent mucoadhesive characteristics due to the formation of strong hydrogen bonding interactions with mucin (Fefelova, 2007). Polycarbophil (Noveon_) and carbomer (Carbopol_), PAA derivatives have been studied widely as mucoadhesive platforms for drug delivery to the GI tract (Singla, 2000; Khutoryanskiy, 2007). Polycarbophil is insoluble in aqueous media but has a high swelling capacity under neutral pH conditions, permitting high levels of entanglement within the mucus layer. Polycarbophil is also reported to increase its mass 100 times in aqueous media at neutral pH (Khutoryanskiy, 1999). Additionally the non-ionized carboxylic acid groups bind to the mucosal surfaces through hydrogen bonding interactions (Ludwig, 2005). Poly acrylic acid polymers are available in a wide range of molecular weights, form transparent, easily modified gel networks, are non-irritant, non-toxic and are considered GRAS (Generally Recognized As Safe) status for oral use by the FDA (Ugwoke, 1999). Moreover, gel formation in such platforms is well understood, occurring as a result of electrostatic repulsion between anionic groups (Ceulemans, 2002). One clear distinction between carbomer and polycarbophil is the level of cross linking and the crosslinking agent itself. Carbomers are cross-linked with allyl sucrose or allylpentaerythritol, whereas polycarbophil polymers are cross-linked with divinyl glycol. they vary in their cross-link density that is often tailored to suit pharmaceutical and/or cosmetic performance but both compounds have the same acrylic backbone.

Cationic polymers

In the cationic polymer systems, undoubtedly chitosan is the most widely investigated within the recent scientific literature. By the deacetylation of chitin, chitosan is produced and

chitisan is cationic polysaccharide. It is most plenteous polysaccharide in the world, next to cellulose (He, 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 used as an antipathogenic (Bautista-Baños, 2006) and from an industrial standpoint investigated as a metal-recovering agent (Chassary, 2004). Chitosan has been noted for its film-forming properties and has used widely in cosmetics. Moreover, chitosan has been employed as a dye binder for textiles, a strengthening additive in paper and as a hypolipidic material in diets (Dodane, 1998). Among presently explored mucoadhesive polymers, chitosan is gaining increasing significance because of its good biocompatibility, biodegradability and due to their favourable toxicological properties (Portero, 2007).

Whereas PAAs bind to mucus through hydrogen bonds chitosan has been reported to bind through ionic interactions between primary amino functional groups and the sialic acid and sulphonic acid substructures of mucus (Rossi, 2000; Bernkop-Schnürch, 2005 and Hassan, 1990). Additionally, the hydroxyl and amino groups may interact with mucus by means of hydrogen bonding. The linearity of chitosan molecules also ensures enough chain flexibility for interpenetration (El-Kamel, 2002). While chitosan may afford improved drug delivery via a mucoadhesive mechanism, it has also been shown to improve drug absorption. Through the paracellular route through neutralization of fixed anionic sites within the tight junctions between mucosal cells (Soane, 1999; Bravo-Osuna, 2007). As earlier discussed, chitosan is derived via the deacetylation of the naturally occurring, insoluble precursor chitin. Depending on the origin, chitin will generally become soluble in an aqueous acidic media when the degree of deacetylation exceeds 50%. This increase in solubility in an aqueous media is as a result of the protonation of the –NH2 function on the C-2 position of the D-glucosamine repeat unit (Rinaudo, 2006). The chief benefit of using chitosan within pharmaceutical applications has been the ease with which numerous 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 modified to suit the requirements of particular pharmaceutical–technological challenges (Bernkop-Schnürch, 2000). Work by Onishi and Machida (Onishi, 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.

Novel second-generation mucoadhesives

The main drawback in using traditional non-specific mucoadhesive systems (first generation) is that adhesion may occur at sites excluding those intended. A scenario that is specifically 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”. Moreover as surface carbohydrate and protein composition at potential target sites vary regionally, more accurate drug delivery may be achievable.

Lectins

Lectins are naturally occurring proteins that play a vital role in biological recognition phenomena involving cells and proteins (Table 2). For example, some bacteria use lectins to attach themselves to the cells of the host organism during infection. Enrichment of mucosal delivery may be obtained through the use of suitable cytoadhesives that can bind to mucosal surfaces. The most extensively investigated of such systems in this respect are lectins. lectins can bind reversibly to specific carbohydrate residues and they belong to a group of structurally varied proteins and glycoproteins (Clark, 2000). After initial mucosal cell-binding, lectins can either remain on the cell surface or in the case of receptor-mediated adhesion possibly become internalized through a process of endocytosis (Lehr, 2000). Such systems could offer duality of function in that lectin based platforms could not only allow targeted specific attachment but additionally offer a method of controlled drug delivery of macromolecular pharmaceuticals through active cell-mediated drug uptake (Lehr, 2000). While lectins offer significant advantages in resemblance 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 so far fully reversible binding site followed by distribution of lectin-mediated drug delivery systems to the cell layer (Wirth, 2002). Even though 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. Furthermore, such antibodies may also render individuals susceptible to systemic anaphylaxis on subsequent exposure (Clark, 2000).

Table 1. Fundamental function of lectins in nature. Modified from ponchel and irache (Ponchel, 1998)

S.No.	Type	Functions
1.	Plants	Defense against phytopathogens Mediators of sybbiosis Protection against predators (animals and inserts) Storage proteins
2.	Animals	Apoptosis Binding of bacteria to epithelial cells Defence against microorganisms Endocytosis and translocation of glycoprotiens regulation of cell migration and adhesion Recognition determinants in phagocytosis
3.	Microorganisms	Attachment to host cells Recognition determinants in phagocytosis Recognition determinants in cell adhesion

Bacterial adhesions

Pathogenic bacteria readily adhere to mucosal membranes in the gastrointestinal tract, a phenomenon that has been exploited as a means by which target-specific drug delivery may be achieved. K99-fimbriae, an attachment protein derived from E. coli, have been covalently attached to Polyacrylic acid networks (Bernkop-Schnürch, 1995). The formulated polymer–fimbriae platform exhibited a significant increase in adhesion in vitro in comparison to the control (unmodified polymer).

Thiolated polymers

Thiolated polymers (thiomers) are a kind of second-generation mucoadhesive optioned from hydrophilic polymers such as polyacrylates, chitosan or deacetylated gellan gum (Leitner,, 2003). Table 2 lists typical hydrophilic polymers that have been thiolated and the subsequent effect on mucoadhesive bond strength of the thiolated polymer. The presence of thiol groups allows the formation of covalent bonds with cysteine-rich sub domains of the mucus gel layer, leading to improved residence time and bioavailability (Albrecht, 2006). In this respect \thiomers mimic the natural mechanism of secreted mucus glycoproteins that are also covalently anchored in the mucus layer by the \ formation of disulphide bonds (Bernkop-Schnürch, 2006 and Rinaudo, 2000). While first-generation mucoadhesive platforms are facilitated through non-covalent secondary interactions, the covalent bonding mechanisms involved in second- generation systems lead to interactions that are less sensitive to changes in ionic strength and/or the pH (Roldo, 2004). Furthermore the presence of disulphide bonds may significantly change the mechanism of drug release from the delivery system due to increased rigidity and cross-linking. In such platforms a diffusion-controlled drug release mechanism is more typical, whereas in first-generation polymers shows strange transport of Active Pharmaceutical Ingredient(API) into bulk solution is more common (Bernkop-Schnürch, 2004).

Table 2. Examples of thiolated polymers and the effect on measured mucoadhesion Modified from bernkop-schnurch et al. [71].

S.No	Polymer	Mucoadhesive bond strength
1.	Chitosan-iminothiolane	250-fold enhanced mucoadhesive properties
2.	Poly(acrylic acid)-cysteine	100-fold enhanced mucoadhesive properties
3.	Poly(acrylic acid)-homocysteine	Approximately 20-fold enhanced Mucoadhesive properties
4.	Chitosan-thioglycolic acid	Tenfold enhanced mucoadhesive properties
5.	Chitosan-thioethylamidine	Ninefold enhanced mucoadhesive properties
6.	Alginate-cysteine	Fourfold enhanced mucoadhesive properties
7.	Poly(methacrylic acid)-cysteine	enhanced cohesive and mucoadhesive properties
8.	Sodium Carboxymethylcellulose cysteine	enhanced cohesive and mucoadhesive properties

Common site of application for engineered mucoadhesive drug delivery

The use of mucoadhesive formulations has been extensively exploited for their targeted and controlled release delivery to many mucosal membrane-based organelles. Such formulations may deliver API for local or systemic effect, while bioavailability limiting effects such as enzymatic or hepatic degradation can be avoided or minimized.

Buccal Applications

The buccal cavity offers the following numerous advantages for drug delivery application, the majority pertinent being high accessibility and low enzymatic activity. Moreover, in the buccal drug delivery can be offering a safe and easy method of drug utilization by rapidly terminated in cases of toxicity through the removal of dosage form (Patel, 2007). Whereas first-generation mucoadhesives, that are sodium carboxymethylcellulose, hydroxypropylcellulose and polycarbophil (Cafaggi, 2005), have been extensively examined, particularly for the treatment of periodontal disease (Jones, 2000 and Jones, 1997), more recent investigations have focused on the controlled delivery of macromolecular therapeutic agents, such as peptides, proteins and polysaccharides (Junginger, 1999). Although gel and ointments are the most patient compatible; tablets, patches and films have also been examined (Peh, 1999). Drug delivery to available cutaneous sites that are the buccal cavity is often associated with high patient compliance, low levels of irritation and offers significant ease of administration. Other less reported advantages include avoidance of hepatic firstpass metabolism due to that it provide rapid onset of action (Hoogstraate, 1998). Orabase_, a first-generation mucoadhesive paste, has long been used as barrier system for mouth ulcers. More recently, formulation development has resulted in a combined corticosteroid (triamcinolone acetonide) Orabase_ product (Adcortyl in Orabase), that provides local relief of mouth ulcers through a twofold mechanism; a barrier function and an anti-inflammatory function (due to triamcinolone acetonide).

Although semisolid systems offer ease of administration and comfort (Jones, 2000), tablets and patches typically offer greater active ingredient stability (typically solid state), enhanced residence time and hence may provide longer periods of therapeutic drug levels at diseased sites. Commonly engineered tablet and patch platforms have included matrix devices and/or multilayer systems, containing an adhesive layer and other drug functional layers (Nafee, 2003; Cafaggi, 2005; Patel, 2007). A drug impermeable layer is often included in such systems in order to encourage unidirectional drug release thus avoiding salivary gland clearance mechanisms. A common approach to avoid clearance of a tablet from the buccal cavity is to place the dosage form under the upper lip. Buccastem_ an adhesive antiemetic tablet containing prochlorperazine maleate is administered in this way. Despite the advantages of bioadhesive tablets, the oscillatory action of talking and mastication can mean that some patients may find the use of such drug delivery platforms uncomfortable. This is one of the fundamental factors for the dominance of semisolid and flexible patch-based systems in buccal drug delivery.

Ophthalmic Applications

The drug delivery to the eye may be achieved using different kinds of dosage forms including liquid drops, gels, ointments and solid ocular inserts (both degradable and nondegradable) (Saettone, 1995 and Carlfors, 1998). Further interesting delivery platform is in situ gelling polymer that undergoes a phase transition after application. Pre-application these systems are in the liquid stat and are easily administered, whereas post-application they are transformed in highly viscous rheologically structured networks (Wei, 2002). Transitional stimuli include temperature, pH, and the presence of certain ions (calcium ions) within the ocular fluid. One of the most important concerns regarding the use of mucoadhesive polymers within the eye is the non-specificity of first-generation platforms. Mucoadhesive polymers would be expected only to attach to conjunctival mucus in vivo, but

migration may result in causing deposition of semisolid within the corneal area, bringing with it a detrimental effect on visual acuity (Lee, 2000). Furthermore limited bioavailability has been experienced in vivo for carbomer and polycarbophil as a result of the high swelling capacity of such polymers in the neutral pH environment of the eye. Maintenance of a low viscosity in such systems through pH regulation in the range 4–5 is not acceptable as it may result in patient unease and mild lacrimation, both of which will have an effect on treatment success (Robinson, 1995). Further consideration should also be given to normal ocular clearance mechanisms (blinking) as well as lacrimation, both of which will improve leakage from the applied site. Unquestionably the most common dosage form for application at this site is ophthalmic solutions. Fascinatingly, such drug delivery platforms typically show poor bioavailability and therapeutic response because high tear fluid turnover results in rapid precorneal elimination of the active agent (Srividya, 2001). Consequently, high-frequency dosing is necessary and patient non-compliance is a chief concern. Conversely, drug-loaded ocular inserts may offer improved control of drug release rate and longer residence times; however, disintegration into smaller pieces can result in occasional blurring of vision (Hornof, 2003). Furthermore, the rigidity of ophthalmic inserts is often extremely uncomfortable for patients. User acceptance and compliance may consequently be limited by physical and psychological barriers surrounding such dosage forms (Saettone, 1995).

Vaginal Applications

Vaginal drug delivery offers the following numerous advantages that are; the avoidance of hepatic first-pass metabolism, a decline in the incidence and severity of gastrointestinal side effects, a decrease in hepatic side effects and avoidance of pain, tissue damage, and infection commonly observed for parentral drug delivery routes of administration (Vermani, 2000). While the vagina provides a promising site for systemic drug delivery because of its large surface area, rich blood supply and high permeability, poor retention due to the self-cleansing action of the vaginal tract is often problematic (Pavelic, 2001). However, residence times within the vagina tend to be much higher than at other absorption sites for instance the rectum or intestinal mucosa. An additional significant consideration is the change in the vaginal membrane during the menstrual cycle and post-menopausal period (Valenta, 2001). Moreover, cultural sensitivity, personal hygiene, gender specificity, local irritation and influence of sexual intercourse are significant in determining the performance and success of the applied dosage form. Additionally, considerable variability in the rate and extent of absorption of vaginally administered drugs is observed by changes in thickness of vaginal epithelium (Hussain, 2005).

Typical bioadhesive polymers that have been in vaginal formulations include polycarbophil, hydroxypropylcellulose and polyacrylic acid (Hussain, 2005). Although the major challenge for vaginal formulations is maximising coverage in vivo while minimizing leakage (Barnhart, 2001), further significant factors such as ease of use, absence of odour and lack of colour have been shown to significantly influence formulation acceptability (Hardy, 1998). There are numerous marketed formulations currently available, but undoubtedly the most complicated challenge is to prevent vaginal leakage. ACIDFORM_, a buffered mucoadhesive gel, has been shown to exhibit a greater intra-vaginal retention than other similar products (Conceptrol_, Advantage S_, Replens_, Aci-Jel_ and K-Y jelly_). Furthermore, after dilution with vaginal fluids and semen, ACIDFORM retained its viscoelasticity to a greater extent (Garg, 2001). More recently ACIDFORM_ has been shown to be present intra-vaginally 12 h after insertion (Amaral, 2006). Whilst mucoadhesive polymeric platforms provide longevity within the vagina it is extremely essential particularly when designing drug delivery systems for the prevention of sexually transmitted disease to avoid mucosal irritation and damage of the epithelium; one of the natural protective barriers to disease. Vaginal mucosal irritation will certainly increase the susceptibility to sexually transmitted pathogens during sexual intercourse (Dhondt, 2005).

Even though a large number of studies have been conducted to examine the potential of mucoadhesive polymer systems for the prevention and treatment of sexually transmitted diseases, the delivery of active agents for systemic delivery is also feasible using such platforms. In the treatment of hyperprolactinemia Oral Bromocriptine used, gives rise to a high proportion of gastrointestinal side effects. Hence alternative routes of delivery with a much lower happening of side effects would be extremely beneficial. Patients who cannot tolerate oral treatment for those more recently research has focused on the placement of commercial tablets in the vagina as a logical alternative. Many studies have demonstrated the superiority of the vaginal placement over the oral route in terms of dramatic minimisation of general and gastrointestinal side effects (Darwish, 2005).

Nasal Applications

From a histological point of examination, the nasal mucosa provides an attractive route for systemic drug delivery. The human nasal mucosa total area is about 150 cm2, which is surrounded by a complex vascular network, thus providing an excellent absorptive interface (Gu, 1988). The nasal epithelium exhibits a relatively high permeability, with only two cell layers separating the nasal lumen from the dense vasculature within the lamina propria. Such factors make the nasal cavity an attractive route for drug delivery, but they also result in nasal mucosa cells being susceptible to adverse effects of drugs and excipients delivered intranasally (Marttin, 1998). One of the crucial advantages provided by intranasal drug delivery is that the nasal cavity provides a large highly vascularised surface area through which first-pass metabolism can be avoided, as blood is drained directly from the nose into the systemic circulation (Pisal, 2004).

Successful nasal delivery has been obtained using solutions, powders, gels and microparticles. The most commonly employed intranasal APIs are solutions containing sympathomimetic vasoconstrictors for immediate relief of nasal congestion. Local delivery of these alpha adrenergic stimulators is of particular benefit to patients with high blood pressure (or those at heightened risk of cardiovascular incident), as vasoconstriction will occur to the greatest degree within the nose. In addition to local effects, the intranasal route of drug administration has also been used to achieve a distal systemic effect (Costantino, 2007). One such example is the intranasal delivery of the peptide desmopressin that exerts its action on the kidneys, mimicking the action of antidiuretic

hormone, used mainly in Diabetes insipidus. Other such formulations include Imigran_ (sumatriptan) and Miacalcic_ (Calcitonin) nasal sprays that are used in the treatment of acute migrane and post-menopausal osteoporosis, respectively. It has also been shown that transnasal administration of large number of drugs (gentamicin, nafarelin acetate and ergotamine tartarate) results in blood levels comparable to intravenous delivery (Pisal, 2004). While such delivery vehicles offer ease of administration, they suffer from a number of disadvantages, the most notable being rapid clearance from the nasal cavity thus preventing extended periods for drug release. in controlled drug delivery to pulmonary and nasal sites the polymeric components such as hydroxypropylcellulose (HPC), chitosan, carbomer, NaCMC, hyaluronic acid and polyacrylic acid have all shown promise used as mucoadhesive agents. Such polymeric delivery platforms may be used either alone or as synergistic combination systems (Nakamura, 1999; Illum, 2001; Tas, 2006 and Bertram, 2006). Poloxamers and polyethylene oxide have also found use in drug delivery to this region (Alpar, 2005). One of the most interesting areas of research within this field has been the use of intranasal drug delivery for the induction of antibody responses in serum, as well as local and distal mucosal secretions (Alpar, 2005), due to absorption through the nasal-associated lymphoid tissue (NALT).

In this respect a large body of research has been conducted using microparticulate (Krauland, 2006; Vajdy, 2001; VanderLubben, 2003 and Vila, 2005). While inhaled particulate systems impacting on the mucus layer may be cleared rapidly by ciliary motion, they may also be selectively delivered to the organised NALT structures via the overlying specialised lymphoepithelium and induce an immune response (Kuper, 2003). Significant advantages in using such an approach include ease of administration and the generation of both systemic and mucosal immunities (Woodley, 2001). In spite of the attractiveness of such a delivery pathway, there are certain problems that may arise through this type of drug delivery. Factors such as local tissue irritation, rapid mucociliary clearance, low permeability of the nasal membrane to larger macromolecules and the presence of proteolytic enzymes within intranasal cavity, may limit the full potential of API delivery in this way (Dondeti, 1996).

G.I Tract Applications

Oral route is the predominant and most preferable route for drug delivery. It also provides numerous advantages; delivery in this way allows for unassisted drug administration by the patient with the need for trained or skilled personnel being avoided. Such a situation is in contrast to what is experienced in most parenterally administered dosage forms (Streubel, 2006). Principally mucoadhesive polymers may offer increased intimacy with the lining of the GI tract and hence bioavailability (Jacobs, 2001). Moreover, ‘‘absorption windows” within the GI tract such as those making up the gastro-associated lymphatic tissue (GALT) may be targeted allowing for the absorption of larger poorly soluble therapeutic agents (Davis, 2005). In spite of a few notable exceptions, mucoadhesive drug delivery systems have to date not reached their full potential within oral drug delivery. This is simply attributed to insufficient adhesion within the GI tract to provide a prolonged residence time (Bernkop-Schnürch , 2005 and Chun, 2005).Targeted drug delivery systems in this respect have focused on mucoadhesive patches and microparticles using first-generation polymers (Säkkinen, 2006). The significant problem with large mucoadhesive solid dosage forms such as tablets is the poor adherence to mucosal surfaces due to large dosage form mass combined with the vigorous movement of the gastrointestinal tract.

Conclusion

Due to the ease of access and avoidance of the hepatic metabolism, oral transmucosal drug delivery offers a promising alternative to overcome the limitations of conventional oral drug delivery and parental administration. The buccal and sublingual routes, in particular, present favourable opportunities and many formulation approaches have been explored for such an application; although the current commercially available formulations are mostly limited to tablets and films. Oral mucoadhesive dosage forms will continue be an exciting research focus for improving drug absorption especially for the new generation of the so called „biologics“, although, the palatability and irritancy and formulation retention at the site of application need to be considered in the design of such medicines.

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