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Review Article

# MUCOADHESIVE DRUG DELIVERY SYSTEMS: AN OVERVIEW

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**Abstract**: Drug actions can be improved by developing new drug delivery systems, such as the mucoadhesive system. The process of mucoadhesion involving a polymeric drug delivery platform is a complex one that, adsorption and interpenetration of polymer chains amongst various other processes. The success and degree of mucoadhesion bonding is influenced by various polymer-based properties such as the degree of cross-linking, chain length and the presence of various functional groupings. These systems remain in close contact with the absorption tissue, the mucous membrane, releasing the drug at the action site leading to a bioavailability increase and both local and systemic effects. Mucoadhesion is currently explained by six theories: electronic, adsorption, wettability, diffusion, fracture and mechanical. So this paper is an overview of chemistry of mucoadhesion, theories involved in it and various polymers used in mucoadhesion.
Key**words:** Mucoadheion, polymers, mucoadhesion theories

## 1. Introduction

The effect of a drug can now be reinforced as a result of the development of new release systems. Controlled release consists of techniques that make the active chemical agents available for a target, providing an adequate release rate and duration to produce the desired effect. The main controlled drug delivery systems currently available include matrices, pellets, floating systems, liposome, microemulsions, liquid crystals, solid dispersions, nano suspensions, transdermal systems, cyclodextrin inclusion complexes, osmotic pumps and bioadhesive systems.[1]

Adhesion as a process is simply defined as the ‘‘fixing” of two surfaces to one another. 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. Mucoadhesion has been widely promoted as a way of achieving site-specific drug delivery through the 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. While 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. Undoubtedly as a means of localising APIs to sites throughout the body, there are several advantages in using bio/mucoadhesive drug delivery systems: (1) As a result of adhesion and intimate contact, the formulation stays longer at the delivery site improving API bioavailability using lower API concentrations for disease treatment. (2) The use of specific bioadhesive molecules allows for possible targeting of particular sites or tissues, for example the gastrointestinal (GI) tract. (3) Increased residence time combined with controlled API release may lead to lower administration frequency. (4) The avoidance of first-pass metabolism. (5) Additionally significant cost reductions may be achieved and dose-related side effects may be reduced due to API localisation at the disease site.[2]

## 2. Mucus: structure, function and composition

Mucus is a complex viscous adherent secretion which is synthesized by specialized 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 functions within these locations such as 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. From an engineering point of view, mucus is an outstanding water-based lubricant whose properties are extensively exploited within nature. Mucus is composed mainly of water (>95%) and mucins, which are glycoproteins of exceptionally high molecular weight (2–14 _ 106 g/mol). Also found within this ‘‘visco elastic soup” are proteins, lipids and mucopolysaccharides, which are found in smaller proportions (<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 located on the glycoprotein molecules result in mucin behaving as an anionic polyelectrolyte at neutral pH.

Other non-mucin components of mucus include secretary IgA, lysozyme, lactoferrin, lipids, polysaccharides, and various other ionic species. Some of these non-mucin components are believed to be responsible for the bacteriostatic action observed in mucus. 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 distinct regions. 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'. Mucin itself is stored in both submucosal and goblet cells, wherein the negative charges of the mucin glycoprotein are shielded by calcium ions, this allows for the compact packing of such molecules. During release into luminal space, out flux of calcium exposes these negative charges resulting in electrostatic repulsion and an approximate 400-fold expansion of the molecule. These now elongated mucin chains entangle and form non-covalent interactions such as hydrogen, electrostatic, and hydrophobic bonds leading to the development of a viscoelastic gel. In the presence of water, these mucin chains begin to overlap, interpenetrate and form a structured network that mechanically functions as mucus. The overall rheological behaviour of mucus is a result of flow resistance exerted by individual chain segments, physical chain entanglement and non-covalent intermolecular interactions. The exact composition of mucus may vary with the site of secretion, its physiological or mechanical role, and the presence of any underlying disease state. One particular point of interest is the strategic position of mucus in many disease processes in which the interactions of epithelial cells and their surroundings have gone astray such as is seen in inflammatory and infectious diseases, cancer and metastasis. Such scenarios may allow a means of targeting therapeutics to such conditions more effectively. The effect of a drug can now be reinforced as a result of the development of new release systems. Controlled release consists of techniques that make the active chemical agents available for a target, providing an adequate release rate and duration to produce the desired effect. The main controlled drug delivery systems currently available include matrices, pellets, floating systems, liposome, microemulsions, liquid crystals, solid dispersions, nanosuspensions, transdermal systems, cyclodextrin inclusion complexes, osmotic pumps and bioadhesives.[3]

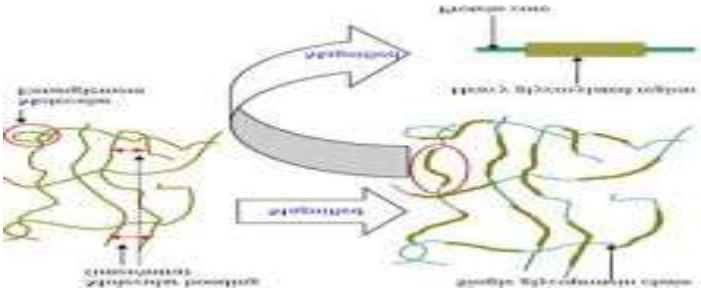

**Fig 1: The composition and interaction of glycoprotein chains within mucus**

**3. Mechanisms of mucoadhesion**

Transmucosal delivery of therapeutic agents is a popular method because mucous membranes are relatively permeable, allowing for the rapid uptake of a drug into the systemic circulation and avoiding the first pass metabolism. This efficient uptake offers several benefits over other methods of delivery and allows drugs to circumvent some of the body's natural defence mechanisms. Transmucosal products can be designed to be administered via the nasal route by using sprays, pumps and gels, via the oral/buccal route using mucoadhesives, quick dissolve tablets and solid lozenge formulations and via vaginal or urethral routes using suppositories. In the development of these drug delivery system, many theories have been proposed to describe mucoadhesion, namely electronic theory, adsorption theory, wetting theory, diffusion theory and fracture theory. Mucoadhesion is believed to occur in three stages: wetting, interpenetration and mechanical interlocking between mucin and polymer. According to electronic theory, mucoadhesion occurs from the formation of an electric double layer at the mucoadhesive interface by the transfer of electrons between the mucoadhesive polymer and the mucin glycoprotein network. Adsorption theory states that mucoadhesive systems adhere to tissue through secondary molecular interactions such as Van Der Waals forces and hydrogen bonding. Intimate molecular contact is a prerequisite for the development of strong adhesive bonds, where wetting. Equilibrium and the dynamic behavior of the bioadhesive polymeric material with the mucus is critical. The interfacial energetic is responsible for the contact of the two surfaces and the adhesive strength. Finally, diffusion theory states that interpenetration of the chains of polymer and mucus may lead to sustained mucoadhesion and by mechanical interlocking between mucin and mucoadhesives.[4]

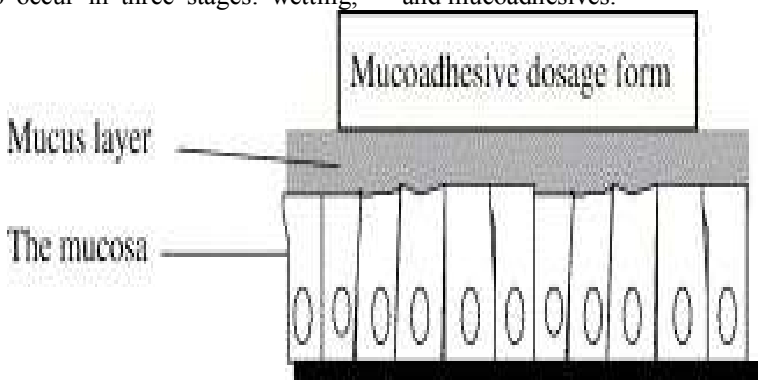


**Fig 2 The three regions within a mucoadhesive joint.**

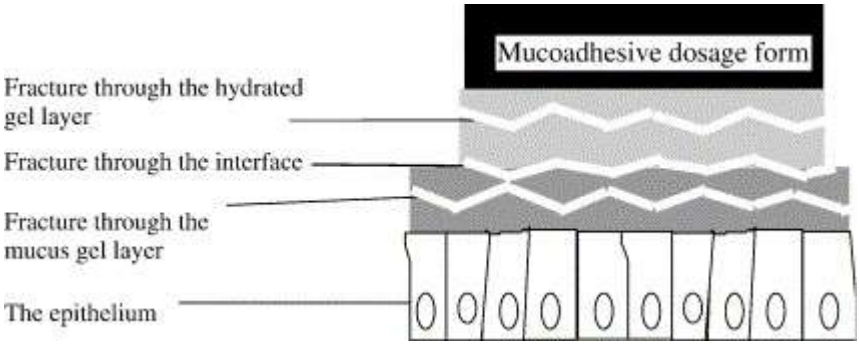


**Fig 3 the possible regions for mucoadhesive joint failure.**

**4. Mucoadhesion theories**

Although the chemical and physical basis of mucoadhesion are not yet well understood, there are six classical theories adapted from studies on the performance of several materials and polymer-polymer adhesion which explain the phenomenon.

4.1 Electronic theory

Electronic theory is based on the premise that both mucoadhesive and biological materials possess opposing electrical charges. Thus, when both materials come into contact, they transfer electrons leading to the building of a double electronic layer at the interface, where the attractive forces within this electronic double layer determines the mucoadhesive strength.

4.2 Adsorption theory

According to the adsorption theory, the mucoadhesive device adheres to the mucus by secondary chemical interactions, such as in Van Der Waals and hydrogen bonds, electrostatic attraction or hydrophobic interactions. For example, hydrogen bonds are the prevalent interfacial forces in polymers containing carboxylic acid groups. Such forces have been considered the most important in the adhesive interaction phenomenon because, although they are individually weak, a great number of interactions can result in an intense global adhesion .Fig 4 & 5

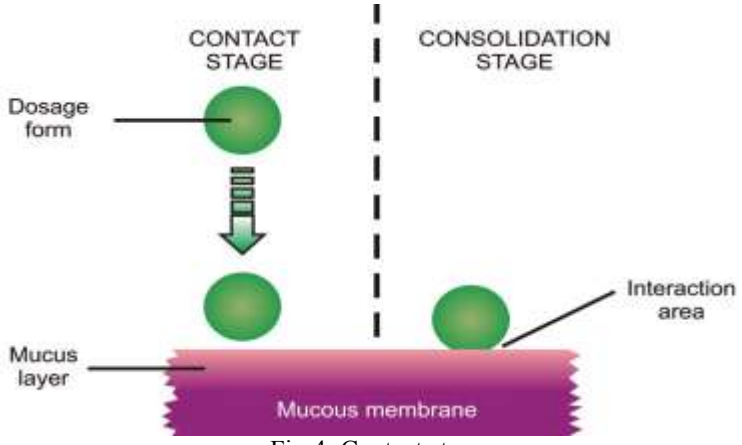


Fig 4: Contact stage

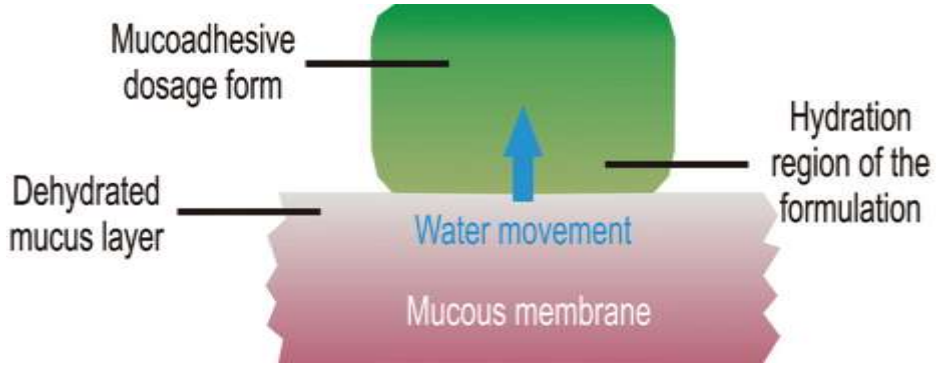


Fig 5: Hydrated stage

4.3 Wetting theory

The wetting theory applies to liquid systems which present affinity to the surface in order to spread over it. This affinity can be found by using measuring techniques such as the contact angle. The general rule states that the lower the contact angle then the greater the affinity (Figure 6). The contact angle should be equal or close to zero to provide adequate spreadability. The spreadability coefficient, SAB, can be calculated from the difference between the surface energies $\gamma_A$ and $\gamma_B$ and the interfacial energy $\gamma_{AB}$ as indicated in equation (1).

$SAB=\gamma_A-\gamma_B-\gamma_{AB}$

(1). The greater the individual surface energy of mucus and device in relation to the interfacial energy, the greater the adhesion work, WA, i.e. the greater the energy needed to separate the two phase-

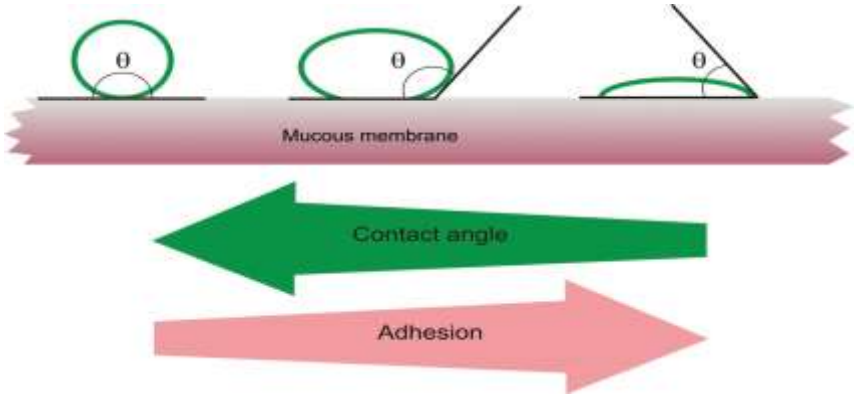


FIGURE 6. Schematic diagram showing influence of contact angle between device and mucous membrane on bioadhesion

4.4 Diffusion theory

Diffusion theory describes the interpenetration of both polymer and mucin chains to a sufficient depth to create a semi-permanent adhesive bond (Figure 4). It is believed that the adhesion force increases with the degree of penetration of the polymer chains (This penetration rate depends on the diffusion coefficient, flexibility and nature of the mucoadhesive chains, mobility and contact time. According to the literature, the depth of interpenetration required to produce an efficient bioadhesive bond lies in the range 0.2-0.5 *f*Êm. This interpenetration depth of polymer and mucin chains can be estimated by equation 3:(3) where t is the contact time, and Db is the diffusion coefficient of the mucoadhesive material in the mucus. The adhesion strength for a polymer is reached when the depth of penetration is approximately equivalent to the polymer chain size.

In order for diffusion to occur, it is important that he components involved have good mutual solubility, hat is, both the bioadhesive and the mucus have similar chemical structures. The greater the structural similarity, the better the mucoadhesive bond.

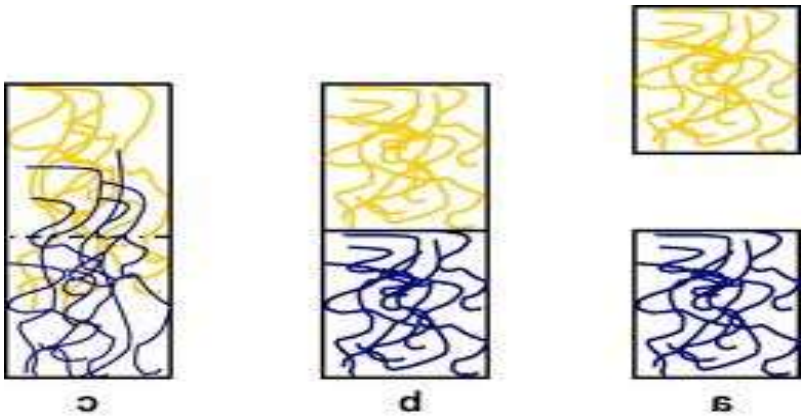


Figure 7: The diffusion theory of adhesion. (a) Top (polymer) layer and bottom (mucus) layer before contact; (b) top layer and bottom layer immediately after Contact; (c) top layer and bottom layer after contact for a period of time. Modified

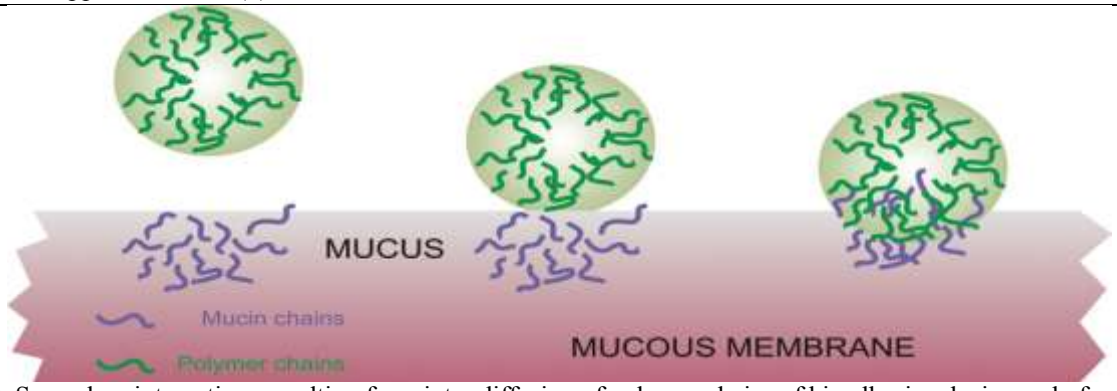


Fig 8: Secondary interactions resulting from inter diffusion of polymer chains of bioadhesive device and of mucus.

4.5 Fracture theory

This is perhaps the most-used theory in studies on the mechanical measurement of mucoadhesion. It analyses the force required to separate two surfaces after adhesion is established. This force, Sm, is frequently calculated in tests of resistance to rupture by the ratio of the maximal detachment force, Fm, and the total surface area, A0, involved in the adhesive interaction Sm=Fm/A0

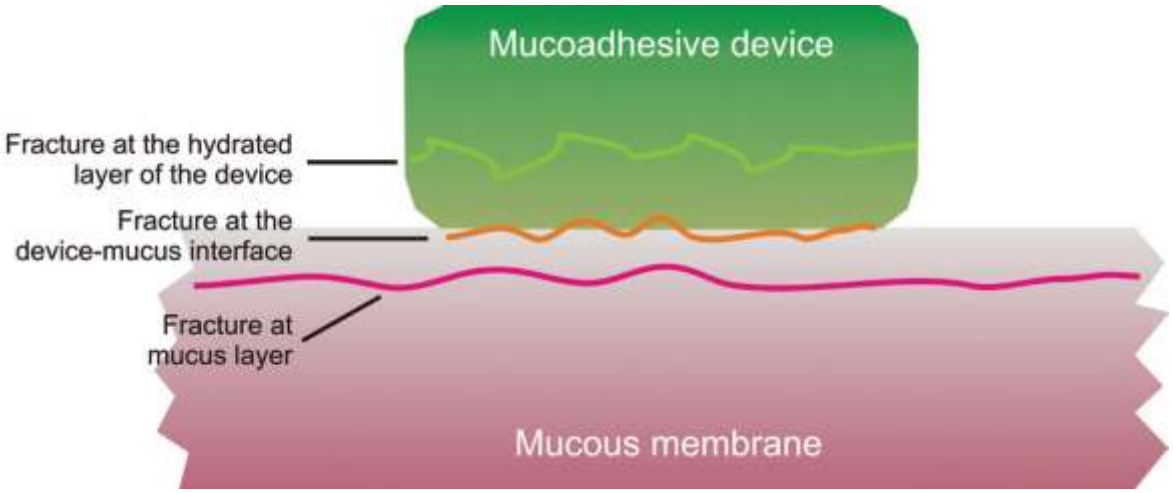


Fig 9 Regions where the mucoadhesive bond rupture can occur.

A criticism of this analysis is that the system under investigation must have known physical dimensions and should be constituted by a single and uniform material. In-virtue of this, the relationship obtained cannot be applied to analyze the fracture site of a multiple component bioadhesive. In this case, the equation should be expanded to accommodate elastic dimensions and modules for each component. Besides, it must be considered that a failure of adhesion will occur at the bioadhesive interface. However, it has been demonstrated that the rupture rarely occurs at the surface, but near it or at the weakest point, which can be the interface itself, the mucus layer or the hydrated region of the mucus, as illustrated in Figure 9. Since the fracture theory is concerned only with the force required to separate the parts, it does not take into account, the interpenetration or diffusion of polymer chains. Consequently, it is appropriate for use in the calculations for rigid or semi-rigid bioadhesive materials, in which the e polymer chains do not penetrate into the mucus layer.

4.6 Mechanical theory

Mechanical theory considers adhesion to be due to the filling of the irregularities on a rough surface by a mucoadhesive liquid. Moreover, such roughness increases the interfacial area available to interactions thereby aiding dissipating energy and can be considered the most important phenomenon of the process. It is unlikely that the mucoadhesion process is the same for all cases and therefore it cannot be described by a single theory. In fact, all theories are relevant to identify the important process variables.

The mechanisms governing mucoadhesion are also determined by the intrinsic properties of the formulation and by the environment in which it is applied. Intrinsic factors of the polymer are related to its molecular weight, concentration and chain flexibility. For linear polymers, mucoadhesion increases with molecular weight, but the same relationship does not hold for nonlinear polymers. It has been shown that more concentrated mucoadhesive dispersions are retained on the mucous membrane for longer periods, as in the case of systems formed by in situ gelification. After application, such systems spread easily, since they present rheological properties of a liquid, but gelify as they come into contact the absorption site, thus preventing their rapid removal. Chain flexibility is critical to consolidate the interpenetration between formulation and mucus.

Environment-related factors include pH, initial contact time, and swelling and physiological variations. The pH can influence the formation of ionizable groups in polymers as well as the formation of charges on the mucus surface. Contact time between mucoadhesive and mucus layer determines the extent of chain interpenetration. Super-hydration of the system can lead to build up of mucilage without adhesion. The

thickness of the mucus layer can vary from 50 to 450 ƒÊm in the stomach to less than 1ƒÊm in the oral cavity. Other physiological variations can also occur with diseases. None of these mechanisms or theories alone can explain the mucoadhesion which occurs in an array of different situations. However, the understanding of these mechanisms in each instance can help toward the development of new mucoadhesive products.[5]

**5. Polymer properties affecting mucoadhesion**

With reference to the theories of mucoadhesion, various polymer structural and functional groupings can have an effect on the likelihood and degree of polymer/mucus interaction. As such the potential for the modification or control of such polymer properties may allow for specific tailoring of mucoadhesive delivery systems.

5.1 Functional group contribution

The attachment and bonding of bioadhesive polymers to biological substrates occurs mainly through interpenetration followed by secondary non-covalent bonding between substrates. Given that secondary bonding mainly arises due to hydrogen bond formation, it is well accepted that mucoadhesive polymers possessing hydrophilic functional groups such as, carboxyl (COOH), hydroxyl (OH), amide (NH2) and sulphate groups (SO4H) may be more favorable in formulating targeted drug delivery platforms. Typically, physical entanglements and secondary interactions (hydrogen bonds) contribute to the formation of a strengthened network; therefore polymers that exhibit a high density of available hydrogen bonding groups would be able to interact more strongly with mucin glycoproteins. Mucoadhesive polymers are generally hydrophilic networks that contain numerous polar functional groups. Consequently, such functionalized polymers interact with the mucus not only through physical entanglements but also through secondary chemical bonds, thus resulting in the formation of weakly cross-linked networks. The key sites for mucoadhesive interactions appear to be on the carbohydrate residues, via electrostatic interaction or through hydrophobic bonding of fructose clusters [30].The significance of hydrogen bonding within mucoadhesion processes has been recently reported. Urea, a well-accepted hydrogen bonding disruptor significantly decreased the mucoadhesiveness of various mucus/pectin samples. The authors reported decreased cohesiveness and a loss of synergy within the combined pectin/mucin mixture.

5.2 Degree of hydration

Another important factor affecting the mucoadhesive strength of polymeric components is the degree of hydration. In this respect many polymers will exhibit adhesive properties under conditions where the amount of water is limited. However in such a situation, adhesion is thought to be a result of a combination of capillary attraction and osmotic forces between the dry polymer and the wet mucosal surface which act to dehydrate and strengthen the mucus layer. Although this kind of ‘‘sticking” has been referred to as mucoadhesion, it is important to clearly distinguish such processes from ‘‘wet-on-wet” adhesion in which swollen mucoadhesive polymers attach to mucosal surfaces . Whilst hydration is essential for the relaxation and interpenetration of polymer chains, excess hydration could lead to decreased mucoadhesion and/or retention due to the formation of slippery mucilage. In this situation cross-linked polymers that only permit a certain degree of hydration may be advantageous for providing a prolonged mucoadhesive effect.

5.3 Polymer molecular weight, chain length, conformation, and degree of cross-linking

It is well accepted that structural polymeric components significantly influence the extent of diffusion, entanglement and hence mucoadhesion. A large molecular weight is essential for entanglement; however, excessively long polymer chains lose their ability to diffuse and interpenetrate mucosal surfaces. Research within this field has shown that each polymeric system is unique preventing the definition of an optimum molecular weight. Dextrans, for example, with molecular weights of 19,500,000 and 200,000 possess similar bioadhesive strength which may be explained in terms of the helical conformation resulting in shielding of potential bioadhesive sites inside coiled conformers at higher molecular weights. Conversely poly (acrylic) acid has an optimal MW of about 750,000, whereas polyethylene oxide has an optimum MW closer to 4,000,000 While a critical length is necessary to produce bioadhesive interactions, additionally the size and shape of the interpenetrating polymeric chains must be considered .The degree of cross-linking within a polymer system significantly influences chain mobility and resistance to dissolution. Cross-linked hydrophilic polymers swell in the presence of water allowing them to retain their structure, whereas similar high molecular weight linear hydrophilic polymers are swellable and readily dispersible. In mucoadhesive terms swelling is favorable as it not only allows greater control of drug release, but also additionally the swelling process increases the surface area for polymer/mucus interpenetration. As cross-link density increases, chain mobility decreases and hence the effective chain length, which can penetrate into the mucus layer decreases, reducing mucoadhesive strength. Chain flexibility is critical for interpenetration and entanglement with the mucus gel. Increased chain mobility leads to increased inter-diffusion and interpenetration of the polymer within the mucus network Fig. 3. 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.

5.4 pH and charge

The charge density of macromolecules is an important factor for bioadhesion with polyanions preferred to polycations when considering both toxicity and bioadhesion. Macromolecular charge is affected by the pH of the physiological environment due to the dissociation of functional groups. Undoubtedly there is the greatest potential for polymer mucus hydrogen bonding with undissociated anionic pendant functional groups. In relation to carboxylated polymers, pH values below the respective pKa value would then be more favorable. An article published almost 20 years ago] suggests that approximately 80% protonation of carboxyl groups is necessary for mucoadhesion within polyacrylic acid systems. This theory has been more recently discussed with the suggestion that carboxylic groups in polyacrylic acids are only effective as interaction sites when in their acidic form. Whilst it is recognized that mucoadhesion processes are optimized in low pH environments, mucoadhesion may not be completely lost at higher pH values. At higher pH levels, repulsion of ‘‘like”

COO_ functional groups changes the spatial conformation from a coiled state into a ‘‘rod-like” structure making them more readily available for inter-diffusion and interpenetration. Interestingly, above the pKa of mucin a net negative charge may result in the repulsion of anionic species such as observed in ionized polyacrylic acid systems. At such elevated pH values, positively charged polymers, such as chitosan, may form polyelectrolyte complexes with negatively charged mucins and exhibit strong mucoadhesion.

5.5 Polymer concentration

Polymer concentration has also been shown to significantly influence the strength of mucoadhesion. Optimal polymer concentration is dependent on physical state of the delivery system, with observational differences between semisolid and solid-state platforms. In the semisolid state, an optimum concentration exists for each polymer beyond which reduced adhesion occurs because a lower number of polymer chains are available for interpenetration with mucus. On the other hand, solid dosage forms such as buccal tablets exhibit increased adhesive strength as the mucoadhesive polymer concentration increases.

5.6 Environmental and physiological factors

There are numerous environmental and physiological factors that will have a marked effect on the mucoadhesive strength of polymer systems. Most of these factors such as pH and the amount of fluid at the biologically targeted area have been discussed previously. One significant factor not mentioned thus far is the variable mucus turnover at the applied surface/site throughout the body. Undoubtedly the most critical aspect is the time required to replenish the mucus layer. Such a shedding process is paramount in the body’s fight against pathogens and will eventually lead to the shedding and eventual excretion of even the most adhesive drug delivery systems. The maximum duration in which a mucoadhesive system may adhere to the mucosal tissue will therefore be limited by the turnover time of the mucus gel layer. For some mucosal tissues, where mucus turnover is relatively low e.g. mouth or vagina, this may be of less critical importance. However, in areas of markedly high mucus turnover such as in the intestines, adherence time is probably not longer than a couple of hours .Mucus gel layer viscosity can vary throughout the body, with variability increasing in certain disease states. Low mucus viscosity results in a weak, easily detachable polymer/mucus bond, making targeted drug delivery extremely difficult. In contrast an extremely viscous mucus layer, such as those thickened due to white blood cell DNA, dead cells and inflammatory mediators limits the degree of interpenetration and also increases the diffusion pathway through which the active agent must pass. Furthermore, the ionic strength of the surrounding medium may also have a significant role in defining the mucoadhesive bond force. In general mucoadhesion strength is decreased in the presence of ions due to shielding of functional sites that are pertinent for adhesion processes and importantly, gel network expansion. It is worth to note that this generalization is not always applicable, and indeed certain polymer systems such as gellan are dependent upon the presence of divalent cations for in situ gelatin.[6]

**6. Mucoadhesive polymer drug delivery 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 favorable. 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 as (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 that is primarily electrostatic in nature (although hydrogen and hydrophobic bonding may be significant). (3) Polymers that bind to specific receptor sites on the cell surface.

Traditional non-specific 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. Consequently; such charged polymeric systems will now be examined in more depth.

6.1 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 characterized 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 mucoadhesive characteristics due to the formation of strong hydrogen bonding interactions with mucin. Polycarbophil (Noveon_) and carbomer (Carbopol), PAA derivatives have been studied extensively as mucoadhesive platforms for drug delivery to the GI tract. 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 mass100 times in aqueous media at neutral pH. Additionally the non-ionized carboxylic acid groups bind to the mucosal surfaces via hydrogen bonding interactions. PAA polymers are available in a wide range of molecular weights, form transparent, easily modified gel networks, are non-irritant, non-toxic and are considered safe (GRAS (Generally Recognized As Safe) status) for oral use by the FDA . Furthermore, gel formation in such platforms is well understood, occurring as a result of electrostatic repulsion between anionic groups. One clear distinction between carbomer and polycarbophil is the level of cross-linking and the cross linking agent itself. Carbomers are cross-linked with allyl sucrose or allylpentaerythritol, whereas polycarbophil polymers are cross-linked with divinyl glycol. Both compounds have the same acrylic backbone but vary in their cross-link density that is often tailored to suit pharmaceutical and/or cosmetic performance.

6.2 Cationic polymers

Of 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 abundant polysaccharide in the world,next to cellulose. 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 utilized as an antipathogenic and from an industrial standpoint investigated as a metal-recovering agent. Chitosan has been noted for its film-forming properties and has used extensively in cosmetics. Furthermore, chitosan has been employed as a dye binder for textiles, a strengthening additive in paper and as a hypolipidic material in diets Among presently explored mucoadhesive polymers, chitosan is gaining increasing importance due to its good biocompatibility, biodegradability and due to their favorable toxicological properties Whereas PAAs bind to mucus via hydrogen bonds chitosan has been reported to bind via ionic interactions between primary amino functional groups and the sialic acid and sulphonic acid substructures of mucus Additionally, the hydroxyl and amino groups may interact with mucus via hydrogen bonding. The linearity of chitosan molecules also ensures sufficient chain flexibility for interpenetration. 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 neutralization of fixed anionic sites within the tight junctions between mucosal cells. As previously 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. 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. It 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.

6.3 Novel second-generation mucoadhesives

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 hypothesized 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.

6.4 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 glycoprotein that can bind reversibly to specific carbohydrate residues. After initial mucosal cell-binding, lectins can either remain on the cell surface or in the case of receptor-mediated adhesion possibly become internalized via a process of endocytosis. 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 via active cell-mediated drug uptake. 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. 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 individuals susceptible to systemic anaphylaxis on subsequent exposure.

6.5 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, has been covalently attached to polyacrylic acid networks. The formulated polymer–fimbriae platform exhibited a significant increase in adhesion in vitro in comparison to the control (unmodified polymer).

6.6 Thiolated polymers

Thiolated polymers (thiomers) are a type of second-generation mucoadhesive derived from hydrophilic polymers such as polyacrylates, chitosan or deacetylated gellan gum. Lists typical hydrophilic polymers that have been thiolated and the subsequent effect on mucoadhesive bond strength. The presence of thiol groups allows the formation of covalent bonds with cysteine-rich sub domains of the mucus gel layer, leading to increased residence time and improved bioavailability. In this respect thiomers mimic the natural mechanism of secreted mucus glycoprotein that are also covalently anchored in the mucus layer by the formation of disulphide bonds. Whilst first-generation mucoadhesive platforms are facilitated via non-covalent secondary interactions, the covalent bonding mechanisms involved in second- generation systems lead to interactions that are less susceptible to changes in ionic strength and/or the pH. Moreover the presence of disulphide bonds may significantly alter 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 anomalous transport of API into bulk solution is more common. 7,8.

**7. Common sites of application for engineered mucoadhesive drug delivery platforms**

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

7.1 Buccal drug delivery

The buccal cavity offers many advantages for drug delivery application, the most pertinent being high accessibility and low, enzymatic activity. Additionally, buccal drug delivery can be promptly terminated in cases of toxicity through the removal of dosage form thereby offering a safe and easy method of drug utilization. Whilst first-generation mucoadhesives, such as sodiumcarboxymethylcellulose, hydroxypropylcellulose and polycarbophil have been extensively examined, particularly for the treatment of periodontal disease .more recent investigations have focused on the controlled delivery of macromolecular therapeutic agents, such as peptides, proteins and polysaccharides. Although gel and ointments are the most patient convenient; tablets, patches and films have also been examined. Drug delivery to accessible cutaneous sites such as the buccal cavity is often associated with high patient compliance, low levels of irritation and offers significant ease of administration. Other less reported advantages include rapid onset of action due to a highly vascularised buccal mucosa and avoidance of hepatic first pass metabolism.

Orabase_, a first-generation mucoadhesive paste, has long been used as barrier system for mouth ulcers. More recently, formulationdevelopment has resulted in a combined corticosteroid (triamcinoloneacetonide) Orabase_ product (Adcortyl in Orabase_), that provides local relief of mouth ulcers via a twofold mechanism; a barrier function and an anti-inflammatory function (due to triamcinoloneacetonide). Although semisolid systems offer ease of administration and comfort tablets and patches typically offer greater active ingredient stability (typically solid state), improved 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. 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 principal factors for the dominance of semisolid and flexible patch-based systems in buccal drug delivery.

7.2Ophthalmic applications

The delivery of therapeutic agents to the eye may be achieved using various types of dosage forms including liquid drops, gels, ointments and solid ocular inserts (both degradable and nondegradable). Another interesting delivery platform is in situ gelling polymer that undergoes a phase transition after application. Pre-application these systems are in the liquid state and are easily administered, whereas post-application they are transformed in highly viscous rheologically structured networks. Transitional stimuli include temperature, pH, and the presence of certain ions (calcium ions) within the ocular fluid. One of the major 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. Additionally 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. Further consideration should also be given to normal ocular clearance mechanisms (blinking) as well as lacrimation, both of which will enhance leakage from the applied site. Undoubtedly the most common dosage form for application at this site is ophthalmic solutions. Interestingly, such drug delivery platforms typically exhibit poor bioavailability and therapeutic response because high tear fluid turnover results in rapid precorneal elimination of the active agent. Consequently, high-frequency dosing is required and patient non-compliance is a major 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. Furthermore, the rigidity of ophthalmic inserts is often extremely uncomfortable for patients. User acceptance and compliance may subsequently be limited by physical and psychological barriers surrounding such dosage forms.

7.3. Vaginal drug delivery systems

Vaginal drug delivery offers many advantages; the avoidance of hepatic first-pass metabolism, a reduction 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 parenteral drug delivery routes of administration. Whilst 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. However, residence times within the vagina tend to be much higher than at other absorption sites such as the rectum or intestinal mucosa. Another important consideration is the change in the vaginal membrane during the menstrual cycle and post-menopausal period. Furthermore, cultural sensitivity, personal hygiene, gender specificity, local irritation and influence of sexual intercourse are significant in determining the performance and success of the applied dosage form. Additionally, considerable variability in the rate and extent of absorption of vaginally administered drugs is observed by changes in thickness of vaginal epithelium.

Typical bioadhesive polymers that have been in vaginal formulations include polycarbophil, hydroxypropylcellulose and polyacrylic acid. Although the major challenge for vaginal formulations is maximizing coverage in vivo whilst minimizing leakage other important factors such as ease of use, absence of odour and lack of colour have been shown to significantly influence formulation acceptability. There are several marketed formulations currently available, but undoubtedly the most difficult 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_). Moreover, after dilution with vaginal fluids and semen, ACIDFORM retained its viscoelasticity to a greater extent. More recently ACIDFORM_ has been shown to be present intra-vaginally 12 h after insertion. Whilst mucoadhesive polymeric platforms provide longevity within the vagina it is extremely important 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 [100]. Although 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 viable using such platforms. Oral bromocriptine used in the treatment of hyperprolactinemia, gives rise to a high proportion of gastrointestinal side effects. Therefore alternative routes of delivery with a much lower occurrence of side effects would be highly beneficial. More recently research has focused on the placement of commercial tablets in the vagina as a logical alternative for patients who cannot tolerate oral treatment. Many studies have demonstrated the superiority of the vaginal placement over the oral route in terms of dramatic minimization of general and gastrointestinal side effects

7.4. Nasal

From a histological point of view, the nasal mucosa provides an attractive route for systemic drug delivery. The total area of the human nasal mucosa is about 150 cm2, which is surrounded by a dense vascular network, thus providing an excellent absorptive interface. The nasal epithelium exhibits a relatively high permeability, with only two cell layers separating the nasal lumen from the dense vasculature within the lamina propriety. Such factors make the nasal cavity an attractive route for drug delivery, but they also result in nasal mucosa cells being vulnerable to adverse effects of drugs and excipients delivered intranasally. One of the key 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. 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. 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. Whilst 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. Polymeric components such as hydroxypropylcellulose (HPC), chitosan, carbomer, NaCMC, hyaluronic acid and polyacrylic acid have all shown promise as mucoadhesive agents for use in controlled drug delivery to pulmonary andnasal sites. Such polymeric delivery platforms may be used either alone or as synergistic combination systems. Poloxamers and polyethylene oxide have also found use in drug delivery o this region.

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 due to absorption through the nasal-associated lymphoid tissue (NALT). In this respect a large body of research has been conducted using microparticulate systems. Whilst inhaled particulate systems impacting on the mucus layer may be cleared rapidly by ciliary motion, they may also be selectively delivered to the organized NALT structures via the overlying specialized lympho epithelium and induce an immune response . Significant advantages in using such an approach include ease of administration and the generation of both systemic and mucosal immunities. Despite 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.

7.5. GI tract

Oral ingestion is the predominant and most preferable route for drug delivery. 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. Principally mucoadhesive polymers may offer increased intimacy with the lining of the GI tract and hence bioavailability. Furthermore, ‘‘absorption windows” within the GI tract such as those making up the gastro-associated lymphatic tissue (GALT) may be targeted allowing for the absorption of larger poorly soluble therapeutic agents. Despite 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. Targeted drug delivery systems in this respect have focused on mucoadhesive patches and microparticles using first-

generation polymers. The significant problem with large mucoadhesive solid dosage forms such as tablets is the poor adherence to mucosal surfaces due to large dosage form mass combined with the vigorous movement of the gastrointestinal tract. Although first-generation polymers have had limited success, second-generation vehicles are now receiving increased attention. A thiolated chitosan tablet has recently been reported by Kraulan det al. for the oral delivery of insulin significantly decreased glucose levels in non-diabetic rats compared to unmodified polymer insulin tablets were reported. This was attributed to the presence of two enzyme inhibitors (chitosan and thiol groups), a penetration enhancing effect of the polymer system and the mucoadhesive potential of the system. Further advances in this field have included the attachment of second-generation mucoadhesives to the surface of microspheres. Furthermore, Säkkinenet al. have examined the potential of microcrystalline chitosan granules for the delivery of furosemide. Gamma scintigraphy revealed that gastrointestinal transit in vivo was extremely erratic, with adhesion to the gastric mucosa in only one-third of the granules administered. Although the use of mucoadhesive delivery platforms may result in altered pharmacokinetic profiles, there is limited evidence to suggest that such a phenomenon is directly related to increased adhesion within the gastrointestinal tract. Although in principal such dosage forms may provide increased adhesion and thus improved bioavailability; peristalsis, high mucus turnover and encasement of the delivery vehicle within a mucus shell are significant factors limiting their success.[10, 11, and 12.]

## 8. Conclusion

The complex procedure of mucoadhesion can allow for the target-controlled delivery of a range of APIs. Certain polymer properties such as charge, hydrophilicity, molecular weight amongst other parameters can affect the success and strength of adhesive bond. Furthermore, environmental factors such as the tonicity and mucus turnover rate must also be considered prior to formulation. Taking such considerations into account, polymers can be chemically structured and engineered to fit a particular pharmaceutical application. Despite the lack of a universal test for mucoadhesion, numerous techniques are available that allow for mucoadhesive ranking of polymer systems. Such systems are usually in vitro in nature due to their relative ease of implementation and cost-effectiveness and as such may present an efficient way of selecting candidate delivery systems for further more intensive in vivo testing. The most successful first-generation mucoadhesive polymer systems have been centered on hydrophilic, high molecular weight, anionic species such as carbomers. Such polymeric networks have found widespread use within the mucus-lined organelles of the nose, buccal cavity and the vagina to name but a few. Despite the controlled release of pharmaceutical actives such systems offer, the specific targeting of particular mucosal sites has fallen short. In particular the holy grail of mucoadhesive drug delivery has been centered around delayed transit and/or targeting of adhesive polymer drug delivery platforms to particular ‘‘absorption windows”. Such a system could have numerous potential applications, not least improvement in the bioavailability of current poorly absorbed GI drugs, but to date results in the literature have been mixed. More recently attention has shifted away from these more traditional mucoadhesive polymers towards systems based on the new second-generation mucoadhesives. These second-generation mucoadhesives usually involve the attachment of lectin, thiol or various other adhesion functional groupings to traditional first-generation polymers networks. As such the binding of these types of platforms offer, the possibility of controlled release and a greater degree of attachment specificity, perhaps even within the GI tract. Despite the promise of these advanced formulations more work is required, not least on toxicity profiling, before the true potential of such engineered formulations may be realized.

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