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Review Article

Bioadhesive Polymeric Platforms for Transmucosal Drug Delivery Systems – a Review

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Abstract

Of the various routes of drug delivery, the oral route is often preferred by the patient. However, peroral administration of drugs has disadvantages such as hepatic first-pass metabolism and enzymatic degradation within the gastrointestinal tract which constitutes a hindrance to oral administration of certain classes of drugs, especially peptides and proteins. Consequently, other absorptive mucosae are often considered as potential sites for drug administration. Transmucosal routes of drug delivery (i.e., the mucosal linings of the nasal, rectal, vaginal, ocular, and oral cavity) offer distinct advantages over peroral administration for systemic drug delivery. These advantages include possible bypass of first-pass effect, avoidance of presystemic elimination within the GI tract, and, depending on the particular drug, better enzymatic flora for drug absorption. However, the mucosa surface as a site for drug delivery has limitations as well. Other than the low flux associated with mucosal delivery, a major limitation of the transmucosal route of administration is the lack of dosage form retention at the site of absorption. Consequently, bioadhesive polymers have extensively been employed in transmucosal drug delivery systems. If these materials are then incorporated into pharmaceutical formulations, drug absorption by mucosal cells may be enhanced or the drug may be released at the site for an extended period of time. This review describes various bio/mucoadhesive polymers used in transmucosal drug delivery. Starting with introduction of bioadhesion with theories and mechanism, history, different bioadhesive polymers, characteristics of desired bioadhesive polymers, this article then proceeds to cover the various sites suitable for mucoadhesive drug delivery system followed by the factors affecting bio/ mucoadhesion.

Keywords: *Mucosa; Tansmucosal delivery; Bioadhesion; Lectin; Polymers; Thiomer; Fimbrins.*

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INTRODUCTION

Bioadhesion may be defined as the state in which two materials, at least one of which is of biological nature, are held together for extended periods of time by interfacial forces [1]. For drug delivery purposes, the term bioadhesion implies attachment of a drug carrier system to a specific biological location. The biological surface can be epithelial tissue or the mucous coat on the surface of a tissue. If adhesive attachment is to a mucous coat, the phenomenon is referred to as mucoadhesion [2]. Mucous coat includes the mucosal linings of the nasal, rectal, oesophageal, vaginal, ocular, and oral cavity.

The idea of bioadhesive drug delivery systems was introduced as a new concept to the pharmaceutical sciences by the pioneering work of several research groups in the United States, Japan and Europe in the mid-1980s [3-6]. Since then, the idea to "stick" dosage forms to the site of application and/or drug absorption, respectively, has stimulated researchers all over the world. Originally, the advantages of bioadhesive drug delivery systems were seen in their potential (i) to prolong the residence time at the site of drug absorption (e.g., to reduce the dosing frequency for bioadhesive controlled release formulations) and (ii) to intensify contact with the underlying mucosal epithelial barrier (e.g., to enhance the epithelial transport of usually poorly absorbed drugs, such as peptides and proteins). The tight and close contact of drug delivery system (DDS) with the absorptive mucosa should generate a steeper concentration gradient, thus increasing the absorption rate [7]. This principle, in particular, supported hopes of increased bioavailability of peptide drugs.

Later, it was discovered that some mucoadhesive polymers can also modulate the permeability of epithelial tissues by loosening the tight intercellular junctions [8-9], and that some mucoadhesive polymers can also act as inhibitors of proteolytic enzymes [10-11].

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 [12]. 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 [13]. This growth can be related to the ease with which transmucosal products can be designed and administered, with mucoadhesive polymers playing a vital role.

THEORIES AND MECHANISMS OF BIOADHESION

Bioadhesion is truly an interfacial phenomenon and only differs from conventional adhesion in the special properties and characteristics of the substrate(s) being adhered. The mechanistic and structural analyses of the phenomenon of bioadhesion have been carefully outlined in several comprehensive reviews [14-15]. The mechanisms of bioadhesion are often classified into chemical and physical mechanisms with the electronic theory and adsorption theory falling under the former mechanism, while wetting, interpenetration or diffusion, and fracture theory fall under the latter.

DEVELOPMENT OF MUCOADHESIVE POLYMERS - A HISTORICAL PERSPECTIVE

The development of mucoadhesive polymers may be traced back to as far as 1947, when gum tragacanth and dental adhesive powders were combined to form a vehicle for applying penicillin to the oral mucosa. An improvement in this system resulted when carboxymethylcellulose and petrolatum were combined to form the vehicle. The development of Orahesive® followed, leading to trials of Orabase® in 1959.

Table 1: Theories and mechanisms of bioadhesion [16]

Theory	Mechanism of bioadhesion	Comments
Electronic theory	Attractive electrostatic forces between glycoprotein mucin network and the bioadhesive material.	Electrons transfer occurs between the two forming a double layer of electric charge at the surface
Wetting theory	Ability of bioadhesive polymer to spread and develop intimate contact with the mucous membrane.	Spreading coefficient of polymers must be positive. Contact angle between polymer and cells must be near to zero.
Adsorption theory	Surface force resulting in chemical bonding.	*Strong primary force*: covalent bonds. *Weak secondary forces*: hydrogen bonds and van der Waal's forces
Diffusion theory	Physical entanglement of mucin strands and flexible polymer chains.	For maximum diffusion and best adhesive strength, solubility parameters of the bioadhesive polymer and the mucus glycoproteins must be similar
Mechanical theory	Adhesion arises from an interlocking of liquid adhesive into irregularities on the rough surface.	Rough surfaces provide an increased surface area available for interaction along with an enhanced viscoelastic and plastic dissipation of energy during joint failure, which are more important in the adhesion process than a mechanical effect.
Fracture theory	Analyses the maximum tensile stress developed during attachment of the transmucosal DDS from the mucosal surface	Does not require physical entanglement of bioadhesive polymer chains and mucous strands, hence it is appropriate to study the bioadhesion of hard polymers which lack flexible chains

Orahesive is a mixture of finely ground sodium carboxymethylcellulose (SCMC), pectin, and gelatin, while Orabase is a blend of these in a polymethylene/mineral oil base. A further development was the blending of sodium carboxymethylcellulose with poly (isobutylene) and laminating this mixture onto a polyethylene sheet. This system benefited from both wet-surface and dry-surface adhesion, with the added bonus of being protected from physical interference (e.g., from the tongue by polyethylene-sheet backing) [17-19].

The polymers identified as exhibiting the best adhesion were sodium alginate, sodium carboxymethylcellulose, guar gum, hydroxyethylcellulose, karya gum, methylcellulose, polyethylene glycol (PEG), retene and tragacanth. Acrylate polymers were soon recognised as useful mucoadhesive materials, and the early 1980s saw a plethora of patents in which hydroxypropylcellulose, or methylcellulose and poly (acrylic acid), were blended together to form mucoadhesive preparations. By far the most widely explored mucoadhesive polymers through the 1980s have been poly (acrylic acid), hydroxypropylcellulose, and sodium carboxymethylcellulose. The work of Chen and Cyr [20] together with Park [21] and Smart *et al*. [22], involved the

investigation of a range of polymers of varying molecular character. These studies appeared to arrive at similar conclusions as to the molecular characteristics required for mucoadhesion. The properties exhibited by such a molecule, described by Peppas and Buri [5] may be summarised as follows: (a) strong H-bonding groups (-OH; -COOH); (b) strong anionic charges; (c) sufficient flexibility to penetrate the mucus network or tissue crevices; (d) surface tension characteristics suitable for wetting mucus/mucosal tissue surfaces; and (e) high molecular weight.

CLASSES OF POLYMERS WITH BIOADHESIVE PROPERTIES

Hydrophilic polymers

These are water-soluble polymers that swell when they come in contact with water and eventually undergo complete dissolution. Systems coated with these polymers show high bioadhesiveness to the mucosa in dry state but the bioadhesive nature deteriorates as they start dissolving. As a result, their bioadhesiveness is short-lived. An example is poly (acrylic acid).

Hydrogels

These are three-dimensional polymer networks of hydrophilic polymers which are cross-linked either by chemical or physical bonds. These polymers swell when they come in contact with water. The extent of swelling depends upon the degree of cross-linking. Examples are polycarbophil, carbopol and polyox [23].

Co-polymers/Interpolymer complex

A block copolymer is formed when the reaction is carried out in a stepwise manner, leading to a structure with long sequences or blocks of one monomer alternating with long sequences of the other. There are also graft copolymers, in which entire chains of one kind (*e.g.,* polystyrene) are made to grow out of the sides of chains of another kind (*e.g.,* polybutadiene), resulting in a product that is less brittle and more impact-resistant. Hydrogen bonding is a major driving force for interpolymer interactions.

Thiolated polymers (Thiomers)

These are hydrophilic macromolecules exhibiting free thiol groups on the polymeric backbone. Based on thiol/disulfide exchange reactions and/or a simple oxidation process disulfide bonds are formed between such polymers and cysteine-rich subdomains of mucus glycoproteins building up the mucus gel layer. So far, the cationic thiomers, chitosan–cysteine, chitosan–thiobutylamidine as well as chitosan–thioglycolic acid, and the anionic thiomers, poly (acylic acid)–cysteine, poly (acrylic acid)–cysteamine, carboxy-methylcellulose–cysteine and alginate–cysteine, have been generated. Due to the immobilisation of thiol groups on mucoadhesive basis polymers, their mucoadhesive properties are 2- up to 140-fold improved [24].

APPLICATION OF SECOND GENERATION BIOADHESIVE POLYMERS

Mucosal immunization

The majority of pathogens initially infect their hosts through mucosal surfaces. Moreover, mucosal administration of vaccine avoids the use of needles and is thus an attractive approach for development of new generation vaccines. Current research in vaccine development has focused on treatment requiring a single administration, since the major disadvantage of many currently available vaccines is that repeated administrations are required. The ability to provide controlled release of antigens through bioadhesive DDS has given an impetus to research in the area of mucosal immunisation. Intravaginal immunisation has been tried in sheep for the influenza virus haemagglutinin [26].

Table 2: Rank order of mucoadhesive force for various polymers [25]

Mucoadhesive polymers	Mean adhesive force (%) with standard deviation
Poly(acrylic acid)	185.0 ±10.3
Tragacanth	154.4 ±7.5
Poly(methylvinylether co-maleic anhydride)	147.7 ±9.7
Poly(ethylene oxide)	128.6 ±4.0
Methylcellulose	128.0 ±2.4
Sodium alginate	126.2 ±12.0
Hydroxypropylmethyl cellulose	125.2 ±16.7
Karaya gum	125.2 ±4.8
Methylethyl cellulose	117.4 ±4.2
Soluble starch	117.2 ±3.1
Gelatin	115.8 ±5.6
Pectin	100.0 ±2.4
Poly (vinyl pyrrolidone)	97.6 ±3.9
Poly (ethylene glycol)	96.0 ± 7.6
Poly (vinyl alcohol)	94.8 ±4.4
Poly(hydroxyethylmethacrylate)	88.4 ±2.3
Hydroxypropylcellulose	87.1 ±13.3

Site-targeted drug delivery

Bioadhesive DDS lack specificity, a factor that is especially important for orally delivered formulations that are targeted to sites within the GI tract. This lack of specificity targeting results in polymer adhering to the first mucosal surface that is encountered leading to localised tissue damage. Another issue with lack of specificity is that the formulation may interact with the loose mucus within the GI tract and be coated with this material and then pass through the GI tract when it comes into close contact with absorbing mucosal membrane. Therefore, developing a bioadhesive polymer which interacts with a particular target is a very attractive potential for targeted delivery. Examples of molecules with specific adhesion include *lectins*, bacterial *fimbrins* and *invasions* [27].

(a) Bacterial adhesion

Bacterial *fimbriae* adhere to the binding moiety of specific receptors. The attractiveness of this approach lies in the potential increase in the residence time of the drug on the mucus and its receptor-specific interaction, similar to those of the plant lectins [27].

(b) Amino acid and Antibodies

Certain amino acid sequences have complementary parts on the cell and mucosal surfaces and, when attached to microparticles, can promote binding to specific cell surface glycoproteins. The cell surface glycoproteins are altered in the presence of disease conditions and these altered protein sequences can be targeted by complementary amino acid sequences attached to the drug delivery device. Due to their high specificity, antibody can be a rational choice as a polymeric ligand for designing site-specific mucoadhesives. This approach can be useful for targeting drugs to tumour tissues [28].

Ion-exchange resins

Ion-exchange resins (IER) have been extensively studied in the development of novel DDSs and other biomedical applications. Prolonged gastric retention of the drug formulations could improve the bioavailability and reduce drug wastage, especially for those predominantly absorbed from the stomach. Floating dosage forms are one of the alternatives designed to prolong gastric residence of drugs. Some IER, such as cholestyramine, possess bio/muco-adhesive properties, which might be caused by their electrostatic interaction with mucin and epithelial cell surface. The use of such bioadhesive IER is another attractive approach in the development of targeted formulations for the GIT. This approach would enhance the localized delivery of antibiotics, such as tetracycline, to the sites of *Helicobacter pylori* colonisation (fundus), which conventional dosage forms fail to reach [29].

Cell adhesion and bone formation

Cell adhesion to extracellular matrices is essential to the development and maintenance of bones. Adhesive interactions with extracellular matrix components play critical roles in osteoblast survival, proliferation, differentiation and bone formation. Cell adhesion to extracellular matrix ligands is primarily mediated by integrins, a widely expressed family of transmembrane adhesion receptors which bind to specific amino acid sequences, such as the arginine-glycine-aspartic acid (RGD) recognition motif present in many extracellular matrix proteins. Over the last decade, biomimetic approaches have sought to convey biofunctionality to synthetic materials by presenting bioadhesive motifs derived from extracellular matrix components, such as RGD for fibronectin. These biomolecular strategies mostly focus on immobilising short peptides onto synthetic or natural materials to produce biofunctional surfaces that bind adhesion receptors and promote cell adhesion [30].

Protein and peptide drug delivery

Protein and peptide drugs offer formidable challenges for peroral delivery due to their relatively large size, enzymatic degradation and very low permeability across the absorptive epithelial cells. The luminal enzymatic degradation of proteins and peptides can be effectively minimised by direct contact with the absorptive mucosa and avoiding exposition to body fluids and enzymes. Specific enzyme inhibitors can be attached to the surface of bioadhesive formulation. Moreover, certain polymers, e.g., chitosan have been reported to possess permeability enhancing properties. Senel *et al.* observed a six- to seven-fold enhancement of permeability by chitosan for the bioactive peptide transforming growth factor (TGF-β) to which the oral mucosa was reported to be relatively impermeable [31].

Tissue engineering

The replacement of blood vessels is one of the most important procedures in cardiovascular surgery. The surgical insertion of arterial implants with an inner diameter of **>** 6 mm is possible with good long-term results but venous and arterial implants with a narrow lumen of **<** 4 mm, present current limitations. The blood coagulation cascade recognizing the synthetic surface occludes the blood vessels prosthesis after a short period. The lining of analogous endothelial cells (ECs) to prosthetic polytetra-fluoroethylene (PTFE)–grafts has been promoted as a method of improving graft potency. However, the performance of simple coating with extracellular matrix proteins is insufficient, in that the cells were washed away under perfusion. Thus, the researchers covalently coupled a specific cell-adhesion molecule to the polymer surface. Only PTFE–grafts covalently modified with the mentioned specific adhesion molecules showed a regular cell lining even under perfusion. The researchers were able to show that EC adhere on formerly inert PTFE surfaces and allow a complete lining of the graft. This cell monolayer was physiologically active and was able to withstand sheer stress in perfusion [32].

CHARACTERISTICS OF AN IDEAL MUCOADHESIVE POLYMER [33]

1. Rapid adherence to mucosa.
2. Exhibit strong interaction with the mucin epithelial tissue.
3. Minimum impact on drug release.
4. Good spreadability, wetting, swelling and solubility and biodegradability properties.
5. Unaffected by the hydrodynamic conditions, food and pH changes.
6. Easy to incorporate in various dosage forms.
7. Possess peel, tensile and shear strengths at the bioadhesive range.
8. Show bioadhesive properties in both dry and liquid state.

9. Demonstrate local enzyme inhibition and penetration enhancement properties.
10. Demonstrate acceptable shelf life.
11. Optimum molecular weight.
12. Possess adhesively active groups.
13. Possess required spatial conformation.
14. Sufficiently cross-linked but not to the degree of suppression of bond forming groups.
15. Possess good viscoelastic properties and no breakdown at the mucosa.

FACTORS AFFECTING MUCOADHESION IN ORAL CAVITY

Polymer-related factors

Molecular weight

Generally, the threshold molecular weight required for successful bioadhesion is at least 100,000. For example, polyethylene glycol (PEG) with a molecular weight (MW) of 20,000, has little adhesive character, whereas PEG with MW of 200,000 and 400,000 has improved and superior adhesive properties, respectively. Tiwari *et al*. have shown the direct correlation between the bioadhesive strength of polyoxyethylene polymers and their molecular weights in the range of 200,000 to 7,000,000 [34].

Spatial conformation

In general, it has been shown that the bioadhesive strength of a polymer increases with molecular weights above 100,000. Interestingly, adhesiveness of non-linear molecular structure follows a quite different trend. The adhesiveness of dextran, with a very high molecular weight of 19,500,000, is similar to that of PEG with a molecular weight of 200,000 [2]. The reason for this similarity may be that the helical conformation of dextran may shield many of the adhesive groups, which are primarily responsible for adhesion, unlike the conformation of PEG.

Chain flexibility

Chain flexibility is critical for interpenetration and entanglement of mucoasadhesive polymers. As water soluble polymers become cross-linked, mobility of individual polymer chains decrease and thus the effective length of the chain that can penetrate into the mucous layer decreases, which reduces bioadhesive strength. The increased chain interpenetration was attributed to the increased structural flexibility of the polymer upon incorporation of poly (ethylene glycol) [35].

Hydrogen bonding capacity

Park and Robinson found that in order for mucoadhesion to occur, the desired polymers must have functional groups that are able to form hydrogen bonds [36]. The hydrophilic functional groups responsible for forming hydrogen bonds are the hydroxyl (-OH) and carboxylic groups (-COOH). A major reason behind the selection of hydrophilic polymers for oral transmucosal drug delivery systems is the water-rich environment of the oral cavity owing to the presence of saliva.

Cross-linking density

The average pore size, the number average molecular weight of the cross-linked polymers, and the density of cross-linking are three important and interrelated structural parameters of a polymer network. Therefore, it seems reasonable that with increasing density of cross-linking, diffusion of water into the polymer network occurs at a lower rate which, in turn, causes an insufficient swelling of the polymer and a decreased rate of interpenetration between polymer and mucin. Flory has reported this general property of polymers, in which the degree of swelling at equilibrium has an inverse relationship with the degree of cross-linking of a polymer [37].

Charge

In a study of polymer adhesiveness, using a cell-culture-fluorescent probe technique, it was found that the charge sign of polymer is an important element for bioadhesion [3, 38]. The strength of mucoadhesion of polymers with carboxyl groups was much stronger than that of those with neutral groups [39]. Some generalizations about the charge of bioadhesive polymers have been made previously, where nonionic polymers appear to undergo a smaller degree of adhesion compared to anionic polymers. Peppas and Buri have demonstrated that strong anionic charge on the polymer is one of the required characteristics for mucoadhesion [5]. It has been shown that some cationic polymers, such as chitosan, exhibit superior mucoadhesive properties, especially in a neutral or alkaline medium [40].

Concentration

At low concentration of the polymer, the number of penetrating polymer chains per unit volume of the mucus is small and the interaction between polymer and mucus is unstable. A more concentrated polymer leads to longer penetrating chain length and better adhesion. Increased concentration of bioadhesive polymer, usually from 1.0 - 2.5 wt%, in principle, increased the binding potential. However, for each polymer, there is a critical concentration, above which the polymer produces an “unperturbed” state due to a significantly coiled structure. As a result, the accessibility of the solvent to the polymer decreases, and chain penetration of the polymer is drastically reduced [41].

Hydration (swelling)

A sufficient amount of water appears necessary to properly hydrate and expand the mucoadhesive network to expose available bioadhesive sites for bond formation by creating pores, channels or macromolecular mesh of sufficient size for diffusion of solutes or polymer chains, as well as mobilizing the polymer chain for interpenetration. Thus, polymer swelling permits a mechanical entanglement by exposing the bioadhesive sites for hydrogen bonding and/or electrostatic interaction between the polymer and the mucous network. However, a critical degree of hydration of the mucoadhesive polymer exists where optimum swelling and bioadhesion occurs [42].

Environment-related factors

pH

pH can influence the formal charge on the surface of mucus as well as certain ionisable bioadhesive polymers. Mucus will have a different charge density depending on pH due to difference in dissociation of functional groups on the carbohydrate moiety and the amino acids of the polypeptide backbone. For example, polycarbophil does not show a strong bioadhesive property above pH 5 because uncharged rather than ionised, carboxyl groups react with mucin molecules, presumably through numerous hydrogen bonds. However, at higher pH, the chains are fully expanded due to electrostatic repulsion of carboxylate anions [43].

Initial contact time

Contact time between the bioadhesive and mucus layer determines the extent of swelling and interpenetration of the bioadhesive polymer chains. Moreover, bioadhesive strength increases as the initial contact time increases [44].

Table 3: Some currently available commercial bioadhesive drug formulations [58]

Brand name	Company	Bioadhesive polymer	Pharmaceutical form
Buccastem	Reckitt Benckiser	PVP, Xanthum gum and locust bean gum	Buccal tablet
Corlan Pellets	ElITech	Acacia gum	Oromucosal pellets
Suscard	Forest	HPMC	Buccal tablet
Gaviscon Liquid	Reckitt Benckiser	Sodium alginate	Oral liquid
Orabase	Conva Tech	Pectin, gelatin	Oral paste
Corsodyl gel	Glaxo Smith Kline	HPMC	Oromucosal gel
Nyogel	Novartis	Carbomer and PVA	Eye gel
Pilogel	Alcon	Carbomer	Eye gel
Timoptol –LA	Merc, Sharpe and Dohme	Gellan gum	Eye gel- solution
Aci-jel	Janseen-Cilag	Tragacanth and Acacia	Vaginal gel
Crinone	Serono	Carbomer	Vaginal gel
Gynol-II	Janseen-Cilag	SCMC and PVP	Vaginal gel
Zidoval	3-M	Carbomer	Vaginal gel

Mucin turnover rate

Estimation of mucin turnover varies widely, depending on location and method of measurement. Values ranging from a few hours to a day have been reported. However, residence times of bioadhesives that are thought to attach to mucin are typically longer than the reported mucin turnover, suggesting that the presence of bioadhesive polymer on mucin may alter the turnover of this biopolymer. The residence time of dosage forms is limited by the mucin turnover time, which has been calculated to range between 47 and 270 min in rats and 12 – 24 h in humans [45].

Physiological considerations

In many routes of administration, surface mucus is encountered by the bioadhesive before it reaches the tissue. The extent of interaction between the polymer and the mucus depends on mucus viscosity, degree of entanglement, and water content. Physiological considerations such as texture of mucosa, thickness of the mucous layer, its turnover time, and other factors, are to be considered in designing the dosage forms [46].

SITES FOR MUCOADHESIVE DRUG DELIVERY SYSTEMS

Buccal cavity

At this site, first-pass metabolism is avoided, and the non-keratinized epithelium is relatively permeable to drugs. Due to flow of saliva and swallowing, materials in the buccal cavity have a short residence time and so it is one of the most suitable areas for the development of bioadhesive devices that adhere to the buccal mucosa and remain in place for a considerable period of time

Vagina

The vagina is a highly suitable site for bioadhesive formulations and it is here that the success of the concept can be seen convincingly. The bioadhesion increases the retention time (up to 72 h) and a smaller amount of the active ingredient can be used, reducing any adverse effects [27].

Nasal cavity

Ease of access, avoidance of first-pass metabolism and a relatively permeable and well-vascularised membrane, contribute to make the nasal cavity an attractive site for

drug delivery. Although the surface area is not large (between 150-200 cm^2), one major disadvantage of nasal mucosa is the rapid removal of substances by mucociliary action (with a residence time half-life of 15 - 30 min) [47]. This makes it a prime target for bioadhesive formulations to prolong the residence time to allow drug release and absorption.

Eye

One major problem for drug administration to the eye is rapid loss of the drug and or vehicle as a result of tear flow, and so it is a target for prolonging the residence time by bioadhesion. The bioadhesive polymers are finding increasing use in ophthalmic formulations, but often as viscosity enhancers rather than as bioadhesives *per se* [27].

Gastrointestinal tract

The gastrointestinal tract has been the subject of intense study for the use of bioadhesive formulations to improve drug bioavailability. The problem associated is that the polymeric bioadhesive formulations bind the intestinal mucus, which is constantly turning over and are transported down the gut by peristalsis. Another problem is that with conventional formulations such as tablets, the active ingredient may diffuse relatively rapidly away from the bioadhesive [27].

Oesophagagus

Tablets or capsules lodging in the oesophagus leads to delayed absorption and therefore delayed onset of action, as the oesophageal epithelial layer is impermeable to most drugs. In addition, adhesion at such a site may cause problems if localisation of the drug or dosage form leads to irritation of the mucosa. Development of a DDS that adheres to the oesophagus has implications in both the protection of the epithelial surface from damage caused by reflux and as a vehicle to deliver drugs for local action within the oesophagus. Bioadhesive dosage forms that adhere to the oesophageal mucosa and prolong contact have been investigated to improve the efficacy of locally acting agents [48-49].

TECHNIQUES FOR EVALUATING BIOADHESIVE PROPERTIES

In vitro techniques

Tensile stress measurement

(i) Wilhelmy plate technique: The Wilhelmy plate technique is traditionally used for the measurement of dynamic contact angles. The instrument measures the bioadhesive force between mucosal tissue and the dosage form [50]. By using the CAHN software system, parameters such as fracture strength, deformation to failure and work of adhesion can be analysed.

(ii) Electromagnetic force transducer (EMFT): The EMFT uses a calibrated electromagnet to detach a magnetic loaded polymer DDS from a tissue sample [51]. It has the unique ability to record remotely and simultaneously the tensile force information as well as high magnification video images of bioadhesive interactions at near physiological conditions. EMFT measures tissue adhesive forces by monitoring the magnetic force required to exactly oppose the bioadhesive force.

Shear stress measurement

The shear stress technique measures the force that causes a mucoadhesive to slide with respect to the mucous layer in a direction parallel to their plane of contact [52]. Adhesion tests based on the shear stress measurement involve two glass slides coated with polymer and a film of mucus. Mucus forms a thin film between the two polymer coated slides, and the test measures the force required to separate the two surfaces. For this purpose, Mikos and Peppas designed the *in vitro* method of flow chamber [53].

Rheological approach

The rheological properties of the mucoadhesive interface (*i.e.* of the hydrated gel) are influenced by the occurrence of interpenetration step in the process of bioadhesion. Chain interlocking, conformational changes and chemical interaction, which occur between bioadhesive polymer and mucin chains, produce changes in the rheological behaviour of the two macromolecular species. The rheological studies provide an acceptable *in vitro* model representative of the *in vivo* behaviour of mucoadhesive polymers [54].

Colloidal gold staining method

This technique employs red colloidal gold particles, which are stabilized by the adsorbed mucin molecule by forming mucin–gold conjugates [55]. Upon interaction with mucin–gold conjugates, bioadhesive hydrogels develop a red colour on the surface. Thus, the interaction between them can easily be quantified, either by the measurement of the intensity of the red colour on the hydrogel surface or by the measurement of the decrease in the concentration of the conjugates from the absorbance changes at 525 nm.

Viscometeric method

A simple viscometric method was used by Hassan and Gallo to quantify mucin–polymer bioadhesive bond strength [56]. Viscosities of 15 %w/v porcine gastric mucin dispersion in 0.1M HCl (pH 1) or 0.1M acetate buffer (pH 5.5) were measured with a Brookefield viscometer in the absence or presence of selected neutral, anionic, and cationic polymers. Viscosity components and the forces of bioadhesion were calculated.

Fluorescent probe method

Park and Robinson studied polymer interaction with the conjunctival epithelial cell membrane using fluorescent probes [3]. The study was done in an attempt to understand structural requirements for bioadhesion in order to design improved bioadhesive polymers for oral use. The membrane lipid bilayer and membrane proteins were labelled with pyrene and fluorescein isothiocyanate, respectively. The cells were then mixed with candidate bioadhesive, and the changes in fluorescence spectra were monitored. This gave a direct indication of polymer binding and its influence on polymer adhesion.

In vivo techniques

GI transit using radio-opaque technique

It involves the use of radio-opaque markers, *e.g.,* barium sulfate, encapsulated in bioadhesive DDS to determine the effects of bioadhesive polymers on GI transit time. Faeces collection (using an automated faeces collection machine) and x-ray inspection provide a non-invasive method of monitoring total GI residence time without affecting normal GI motility. Mucoadhesives labelled with Cr-^{51}, Tc-^{99m}, In-^{113m}, or I-^{123} have been used to study the transit of the DDS in the GI tract [57].

Gamma scintigraphy technique

It is a valuable tool used in the development of pharmaceutical dosage forms. With this methodology, it is possible to obtain information non-invasively. This technique gives information in terms of oral dosage forms across the different regions of GI tract, the time and site of disintegration of dosage forms, the site of drug absorption, and also the effect of food, disease, and size of the dosage form on the *in vivo* performance of the dosage forms.

CONCLUSION

Improvements in bioadhesive-based drug delivery and, in particular, the delivery of novel, highly-effective and mucosa-compatible polymer, are creating new commercial and clinical opportunities for

delivering narrow absorption window drugs at the target sites to maximise their usefulness. Mucoadhesive drug delivery systems are being studied from different angles, including development of novel mucoadhesives, design of the device, mechanisms of mucoadhesion and permeation enhancement. With the influx of a large number of new drug molecules from drug discovery, mucoadhesive drug delivery will play an even more important role in delivering these molecules. Gains due to bioadhesion in the mucosal cavity are less obvious, but many potential systems are under investigation, and some of these may bear fruit in future.

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