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Bioadhesive or Mucoadhesive Drug Delivery System: A Potential Alternative to Conventional Therapy

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ABSTRACT

The term bioadhesive describes materials that bind to biological substrates, such as mucosal membranes and in bioadhesive drug delivery systems, the term bioadhesion is used to describe the bonding or adhesion between a synthetic or natural polymer and soft tissues such as epithelial cells. The bioadhesive drug delivery formulation highlights the fact that readily accessible sites are utilized with the eye, oral cavity and vegina being targeted. The GI tract and the nasal cavity have also been extensively examined as a site for bioadhesive drug delivery. The term mucoadhesion is the subgroup of bioadhesion and in the mucoadhesion formulation attaches with the mucus membrane. The mucoadhesion can be defined as the adhesion between the two materials in which one is biological material and other one is polymeric materials with the help of interfacial forces to increase the residence time. Over the past few decades, mucosal drug delivery has received a great deal of attention. The mucoadhesion drug delivery system is better than the traditional drug delivery systems. Mucoadhesion is a useful strategy for drug delivery systems, such as tablets, patches, gels, liposomes, micro/nanoparticles, nanosuspensions, microemulsions and colloidal dispersions. The mucoadhesion bypasses the first pass metabolism and used for localized delivery of biomolecules such as peptides, proteins and oligonucleotides. Mucoadhesion drug delivery system engages much attention due to their benefits such as prolong retention time, fast uptake and increased bioavailability of active substance. Application of dosage forms to mucosal surfaces may be of benefit to drug molecules not amenable to the oral route, such as those that undergo acid degradation or extensive first-pass metabolism. The mucoadhesive ability of a dosage form is dependent upon a variety of factors, including the nature of the mucosal tissue and the physicochemical properties of the polymeric formulation. This review article aims to provide an overview of the various aspects of mucoadhesion, theories of mucoadhesion, mucoadhesive materials, factors affecting mucoadhesion, evaluating methods, mucoadhesive polymers and herbal drugs.

Keywords: Bioadhesive, bioadhesive drug delivery, Mucoadhesion, Patches, Herbal drugs

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Introduction

Since the early 1980s, the concept of mucoadhesion has gained considerable interest in pharmaceutical technology[1]. Adhesion can be defined as the bond produced by contact between a pressure -sensitive adhesive and a surface[1]. The American society of testing and materials has defined it as the state in which two surfaces are held together by interfacial forces, which may consist of valence forces, interlocking action or both[2]. The adhesion processes have demonstrated important purposes in nature and consequently, have diverse healthcare and non-biomedical implications, such as bacterial adhesion or water purification.

In pharmaceutical sciences, bioadhesion is described as the ability of a dosage form to come into close contact, by attractive interactions with a biological surface (epithelial tissue or mucus coat). If the biological environment is the mucosal surface or mucous coat, this process is termed mucoadhesion[3-6] . Bio-adhesion (or mucoadhesion) is generally understood to define the ability of a biological or synthetic material to "stick" to a mucous membrane, resulting in adhesion of the material to the tissue for a protracted period of time[7]. For a material to be bioadhesive, it must interact with mucus, which is a highly hydrated, viscous anionic hydrogel layer protecting the mucosa. The mucin is composed largely of flexible glycoprotein chains, which are crosslinked. Moreover, bio/mucoadhesion processes can be a useful approach with diverse advantages for drug delivery systems such as increased residence time at application sites, drug protection, increased drug permeation and improved drug availability[8-10]. Therefore, this strategy has been applied to several solid, semi-solid and liquid drug delivery systems, for example, buccal tablets, buccal patches or films, buccal gels for periodontitis treatment, ophthalmic liposomes, vaginal suppositories, as well as nano- or microparticles, nanosuspensions, microemulsions and

colloidal dispersions[11]. The formation of non-covalent bonds such as hydrogen bonds and ionic interactions or physical entanglements between the mucus gel layer and polymers provides a good mucoadhesion. In biological systems, four types of bio-adhesion could be distinguished

• Adhesion of a normal cell on another normal cell

• Adhesion of a cell with a foreign substance

• Adhesion of a normal cell to a pathological cell

• Adhesion of an adhesive to a biological substance.

Leung and Robinson[12]described mucoadhesion as the interaction between a mucin surface and a synthetic or natural polymer. Mucoadhesion should not be confused with bioadhesion; in bioadhesion, the polymer is attached to the biological membrane and if the substrate is mucus membrane the term mucoadhesion is used. Dosage forms designed for mucoadhesive drug delivery should be small and flexible enough to be acceptable for patients and should not cause irritation. Other desired characteristics of a mucoadhesive dosage form include high

drug loading capacity, controlled drug release (preferably unidirectional release), good mucoadhesive properties, smooth surface, tastelessness and convenient application. Erodible formulations can be beneficial because they do not require system retrieval at the end of desired dosing interval. A number of relevant mucoadhesive dosage forms have been developed for a variety of drugs. Several peptides, including thyrotropin-releasing hormone (TRH), insulin, octreotide, leuprolide, and oxytocin, have been delivered via the mucosal route, albeit with relatively low bioavailability (0.1–5%),[13] owing to their hydrophilicity and large molecular weight, as well as the inherent permeation and enzymatic barriers of the mucosa. The development of sustain release dosage form can achieve the aim of releasing the drug slowly for a long period but this is not sufficient to get sustained therapeutic effect. They may be cleared from the site of absorption before emptying the drug content. Instead, the mucoadhesive dosage form will serve both the purposes of sustain release and presence of dosage form at the site of absorption. In this regard, our review is high lighting various aspects of mucoadhesion, theories of mucoadhesion, mucoadhesive materials, factors affecting mucoadhesion, evaluating methods, mucoadhesive polymers and herbal drugs.

Structure and composition of mucous and mucus layers

The mucous membrane (mucosae) is characterized as a moist layer of connective tissue (thelamina propria), with an epithelial layer covered by mucus. According to the body cavity, these epithelia can be multilayered/stratified, such as in the vagina, cornea and esophagus, or single layered, like the small and large intestine. Moreover, this membrane has demonstrated

a great ability for the absorption of active substances, since it is relatively permeable, enabling the quick absorption of drugs[14-16]. Mucus is a complex and viscous fluid synthesized by goblet cells. These glandular cells are present in every epithelium layer exposed to the external environment. Mucus is found as a gel layer which adheres to surfaces, as a soluble form, or suspended within the channels, creating a fully hydrated viscoelastic gel layer. This is composed of glycoproteins, including mucin, which is responsible for the gel structure and appearance, lipids, inorganic salts, proteins, mucopolysaccharides, IgA, lysozyme and 95% water. Mucin can be bound to the mucous membrane or secreted. The latter entangles and adhesively crosslinks reversibly in order to make up the viscoelastic, shear-thinning gel, by physiological mechanisms. Although mucin is the main factor responsible for the mucus gel properties, the viscoelastic behavior is also governed by water content, and lipids and ions from the mucus, being crucial for protection and lubrication. Furthermore, mucin (Figure 1) behaves as an anionic polyelectrolyte at neutral pH due to sialic acid, which is believed to be responsible for the bacteriostatic action observed in mucus[6, 8,15,17,18]. Mucus exhibits many functions such as protection and lubrication of the epithelium, in order to impair the absorption of microorganisms and other substances. In addition, mucus allows the passage of objects and preservation of the hydrated mucous layer, while other supplementary functions depend on the epithelium being covered[14-17, 19]. Although mucus has demonstrated numerous functions, it is a dynamic system, being continuously removed from the epithelial layer and can reduce the residence time, as well as decrease the drug delivery rate at the site of administration. Additionally, their properties, composition and thickness can be influenced by pathologies[6,18]. In this context, gastrointestinal, nasal, ocular, buccal, vaginal, rectal and periodontal areas are covered by a mucous membrane and can be employed for the administration of mucoadhesive drug delivery systems. According to the site of secretion, the pH and the thickness of the mucous layer are variable. The mucus pH in the eye is slightly basic, close to 7.8. However, for the lung and nasal cavity, the pH is 5.5-6.5. Also, the balance between the rate of mucus secretion and its rate of degradation and shedding regulate the thickness of the mucus layer. For the oral cavity, this is less than 1 µm, and it is 800 µm for the gastrointestinal tract[6,14,15,18]. In this sense, the strategic position of mucus in many diseases, such as inflammatory and infectious diseases and cancers, may provide a means for targeting the therapeutics more effectively using mucoadhesive drug delivery systems[17].

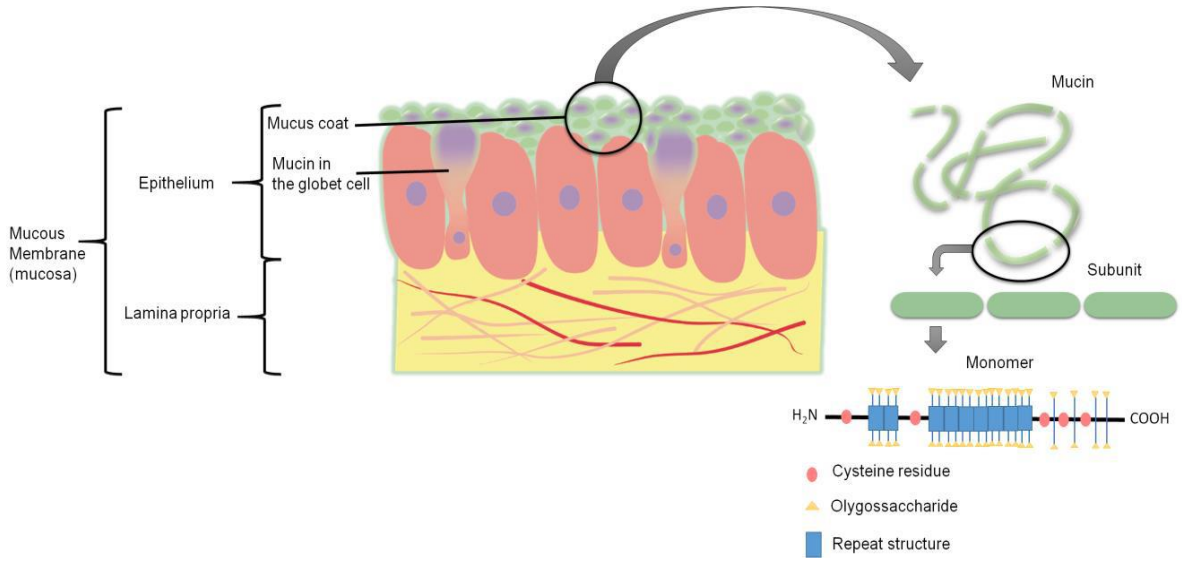

Figure 1 Mucous membrane and the structures of the mucin molecule

Mechanisms of mucoadhesion

The mechanism of mucoadhesion is generally divided into two steps: the contact stage and the consolidation stage [Figure 2]. The first stage is characterized by the contact between the mucoadhesive and the mucus membrane, with spreading and swelling of the formulation, initiating its deep contact with the mucus layer[20]. In the consolidation step [Figure 2], the mucoadhesive materials are activated by the presence of moisture. Moisture plasticizes the system, allowing the mucoadhesive molecules to break free and to link up by weak van der Waals and hydrogen bonds. Essentially, there are two theories explaining the consolidation step: the diffusion theory and the dehydration theory. According to the diffusion theory, the mucoadhesive molecules and the glycoproteins of the mucus mutually interact by means of interpenetration of their chains and the building of secondary bonds. For this to take place, the mucoadhesive device has features favoring both chemical and mechanical interactions. For example, molecules with hydrogen bond building groups (–OH, –COOH), an anionic surface charge, high molecular weight, flexible chains and surface-active properties, which help in spreading throughout the mucus layer, can present mucoadhesive properties[20].

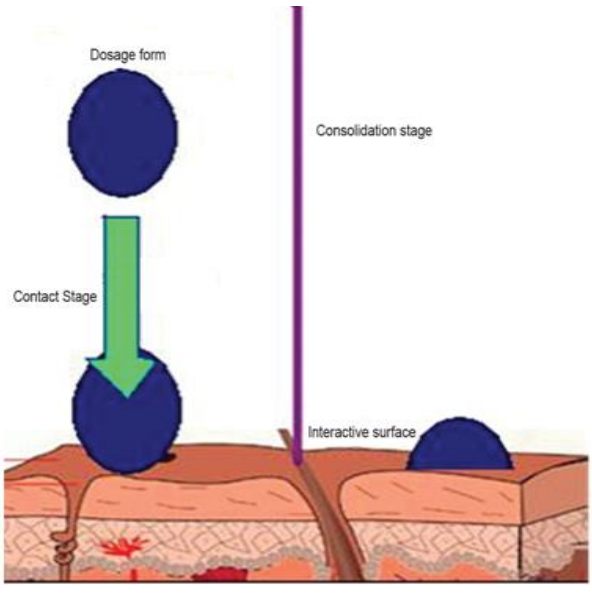

Figure 2 The process of contact and consolidation

Mucoadhesion theories

Mucoadhesion is a complex process and numerous theories have been proposed to explain the mechanisms involved. These theories include mechanical interlocking, electrostatic, diffusion interpenetration, adsorption and fracture processes.

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, the greater is the affinity [Figure 3]. 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 γB and γA and the interfacial energy γAB, as indicated in the equation given below[15]. This theory explains the importance of contact angle and reduction of surface and interfacial energies to achieve good amount of mucoadhesion.

$$SAB = \gamma B - \gamma A - \gamma AB$$

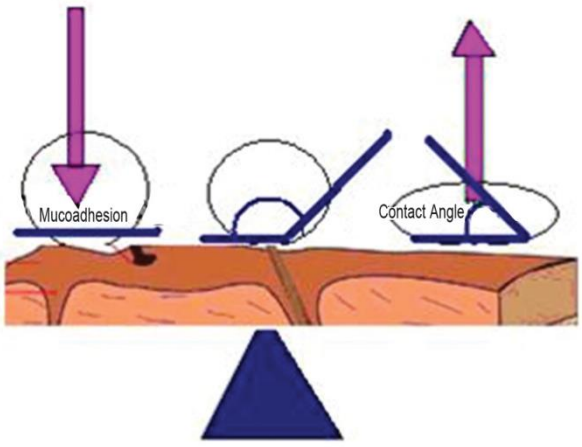

Figure 3 Influence of contact angle on mucoadhesion

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 µm. This interpenetration depth of polymer and mucin chains can be estimated by the following equation:

$$l = (tD_b)^{½}$$

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 the components involved have good mutual solubility, that is, both the bioadhesive and the mucus have similar chemical structures. The greater the structural similarity, the better is the mucoadhesive bond[15].

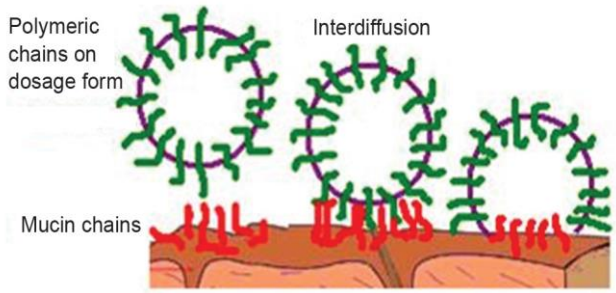

Figure 4 Secondary interaction between mucoadhesive device and of mucus

Fracture theory

This is perhaps the most used theory in studies on the mechanical measurement of mucoadhesion. It analyzes 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, *A*0, involved in the adhesive interaction

$$S_m = F_m / A_0$$

Since the fracture theory [Figure 5] 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 polymer chains do not penetrate into the mucus layer[15, 20].

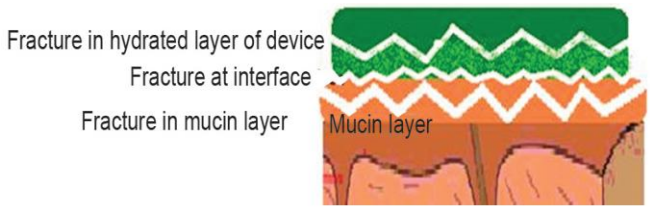

Figure 5 Fractures occurring for mucoadhesion

The electronic theory

This theory describes adhesion occurring by means of electron transfer between the mucus and the mucoadhesive system, arising through differences in their electronic structures. The electron transfer between the mucus and the mucoadhesive results in the formation of double layer of electrical charges at the mucus and mucoadhesive interface. The net result of such a process is the formation of attractive forces within this double layer[21].

The adsorption theory

In this instance, adhesion is the result of various surface interactions (primary and secondary bonding) between the adhesive polymer and mucus substrate. Primary bonds due to chemisorptions result in adhesion due to ionic, covalent and metallic bonding, which is generally undesirable due to their permanency[22]. Secondary bonds arise mainly due to van der Waals forces, hydrophobic interactions and hydrogen bonding. Whilst these interactions require less energy to "break", they are the most prominent form of surface interaction in mucoadhesion processes as they have the advantage of being semi-permanent bonds[23].

Mechanical theory

This theory considers the adhesion of mucoadhesive liquids systems (mucoadhesive liquids or particulate systems) which happens when the liquid fills the irregularities of a rough surface, since the adhesion is facilitated due to roughness on the substrate surface. These irregularities increase the area available to interact and improve the humectant characteristics.

In this way, the mechanical theory has a close contact with the wetting theory, described previously, since both are adequate and complementary with regard to describing the adhesion of liquid systems. Moreover, with increased roughness there is higher viscoelasticity and plastic dissipation of the energy at the interface[11].

All these numerous theories should be considered as supplementary processes involved in the different stages of the mucus/substrate interaction, rather than individual and alternative theories. Each and every theory is equally important to describe the mucoadhesion process. There is a possibility that there will be initial wetting of the mucin, and then diffusion of the polymer into mucin layer, thus causing the fracture in the layers to effect the adhesion or electronic transfer or simple adsorption phenomenon that finally leads to the perfect mucoadhesion. The mechanism by which a mucoadhesive bond is formed will depend on the nature of the mucus membrane and mucoadhesive material, the type of formulation, the attachment process and the subsequent environment of the bond. It is apparent that a single mechanism for mucoadhesion proposed in many texts is unlikely for all the different occasions when adhesion occurs.

Mucoadhesive polymers

Different polymers have been explained by the researchers for the drug delivery. However, polymers having mucoadhesive nature should possess same specific characteristics and act as drug delivery system. An ideal mucoadhesive polymer has the following characteristics[24,25]:

1. It must be loaded substantially by the active compound.

2. It must swell in the aqueous biological environment of the site of absorption.

3. It must interact with mucus or its components for adequate adhesion.

4. It must allow controlled release of the active compound when swelled.

5. It must be excreted unaltered or biologically degraded to inactive, nontoxic oligomers.

6. It must possess sufficient quantities of hydrogen bonding chemical groups.

7. It must possess high molecular weight.

8. It must possess high chain flexibility.

9. It must have the surface tension that may induce spreading into mucous layer.

Effect of polymer properties on mucoadhesive drug delivery system

Different polymers exhibit different mucoadhesive properties depending on their physical and chemical strength. For example, a more flexible polymer exhibits higher degree of mucoadhesive property[26]. Mucoadhesive polymers possessing hydrophilic functional groups such as COOH, OH, NH_2 and SO_4H are more favorable candidates for the formulation of targeted drug delivery. These polymers bearing the desired functional group interact with mucus through physical entanglement as well as through chemical bonds resulting in formation of cross-linked network. For example, urea is a well-accepted hydrogen-bonding disruptor which decreases mucoadhesion of mucin/pectin samples. Other properties which may affect the mucoadhesive nature of the polymer include chain length, degree of hydration, degree of cross-linking, polymer concentration, charge, etc. (Table 1).

Table 1 Effect of polymer properties on mucoadhesion[27]

Properties	Effect
Functional group	COOH, OH, NH2 , SO4 H groups favor mucoadhesion
Molecular weight	More is molecular weight (above 100,000) more is the bioadhesion
Flexibility	Higher is the flexibility of the polymer more is the diff usion and hence more mucoadhesion
Chain length	With decrease in chain length interpenetration increases
Degree of hydration	Excessive hydration leads to decreased mucoadhesion
Degree of cross-linking	Increased cross-linking decreased mucoadhesion
Polymer concentration	For semisolid: increase in concentration decrease mucoadhesion. For solid dosage form: increase in concentration increase mucoadhesion
Charge	Nonionic polymers posses less mucoadhesion than ionic and cationic polymers exhibits more mucoadhesion than anionic

Polymers used for mucoadhesive drug delivery

The rheology of the mucoadhesion is a typical topic and it deals with a number of forces, factors of the components, state of the material and its derived properties. Different polymers and their mucoadhesive strength are listed in Table 2.

Based on the rheological aspects, we can categorize the mucoadhesive polymers into two broad categories: materials which undergo matrix formation or hydrogel formation by either a water swellable material or a water soluble material. These carriers are generally polymers and classified as given in Table 3.

Table 2 Bioadhesive property of different polymers

Polymer	Bioadhesive property
CMC sodium	Excellent
Carbopol	Excellent
Polycarbophil	Excellent
Tragacanth	Excellent
Sodium alginate	Excellent
HPMC	Excellent
Gum karaya	Very good
Gelatin	Very good
Guar gum	Very good
Pectin	Good
Acacia	Good
Chitosan	Good
Hydroxypropyl cellulose	Good

Table 3 Classification of bioadhesive polymers[27]

Polymers	Examples
Hydrophilic polymers	Methyl cellulose, Hydroxyethyl cellulose, HPMC, Na CMC, Carbomers
Thiolated polymers	Chitosan-iminothiolane, PAA-cysteine, PAA-homocysteine, Chitosan-thioglycolic acid, Chitosan- thioethylamidine, Alginate- cysteine, Poly (methacrylic acid)-cysteine and Sodium carboxymethylcellulose- cysteine
Lectin-based polymers	Lentil lectin, Peanut agglutinin, Ulex europaeus agglutinin
Polyox WSR	WSR N-10, WSR N-80, WSR N-205, WSR N-750.
Novel polymers	Tomato lectin, PAA-co-PEG, PSA

Hydrophilic polymers contain carboxylic group and possess excellent mucoadhesive properties. Matrices developed with these polymers swell when put into an aqueous media with subsequent dissolution of the matrix, for example, methyl cellulose, hydroxyethyl cellulose, hydroxypropyl methylcellulose (HPMC), sodium carboxymethyl cellulose, carbomers, chitosan and plant gums. Polyelectrolytes extend greater mucoadhesive property when compared with neutral polymers[28]. Anionic polyelectrolytes, for example, PAA and carboxymethyl cellulose have been extensively used for designing mucoadhesive delivery systems based on their ability to exhibit strong hydrogen bonding with the mucin present in the mucosal layer[17]. Chitosan, a cationic polymer, is widely used for its biodegradable and biocompatible properties and it undergoes electrostatic interactions with the negatively charged mucin chains thereby exhibiting mucoadhesive property[29]. The ionic polymers may be used to develop ionic complex with the counter-ionic drug molecules so as to have a drug delivery matrix exhibiting mucoadhesive property. Nonionic polymers, for example, poloxamer, HPMC, methyl cellulose, polyvinyl alcohol (PVA), and polyvinylpyrrolidone (PVP), have also been used for mucoadhesive properties[28]. The hydrophilic polymers form viscous solutions when dissolved in water and hence may also be used as viscosity modifying/enhancing agents in the development of liquid ocular delivery systems so as to increase the bioavailability of the active agents by reducing the drainage of the administered formulations[28,30].

Hydrogels: Hydrogels can be defined as three-dimensional cross-linked polymer chains which have the ability to hold water within its porous structure. The water-holding capacity of the hydrogels is mainly due to the presence of hydrophilic functional groups such as hydroxyl, amino and carboxyl groups. These include hydrogels prepared by thermal crosslinking of PAA and methyl cellulose[31]and hydrogels prepared by condensation reaction of PAA and sucrose[32]. In addition to the drug targeting, mucoadhesive hydrogel-based formulations improve the bioavailability of the poorly water-soluble drug.

Novel polymers: With the advancement in the technology a large number of novel polymers have come into picture. Tomato lectin showed that it has binding selectivity to the small intestinal epithelium[33]. Shajaei and Xiaoling have designed and characterized a copolymer of PAA and polyethylene glycol (PEG) monoethyl ether mono methacrylate (PAA-co-PEG) for exhibiting optimal buccal adhesion[34]. Lele Hoff man (2000) investigated novel polymers of PAA complexed with PEGylated drug conjugate[35]. A new class of hydrophilic pressure sensitive adhesives (PSA) has been developed by Corium Technologies. A complex has been prepared by noncovalent hydrogenbonding cross-linking of a film forming hydrophilic polymer with a short chain plasticizer having reactive OH groups at chain ends. Similarly, Bogataj et al. (1999) prepared and studied mucoadhesive microspheres prepared using different polymers by solvent casting method for application in urinary bladder[36]. Chen and Langer (1998) investigated the benefit of thiolated polymers for the development of buccal drug delivery systems[37].

Some important bioadhesive polymers used in drug delivery

Chitosan

Chitosan is a biodegradable, nontoxic polymer obtained by deacetylation of the N-acetyl glucosamine units of chitin, generally by hydrolysis under alkali conditions at high temperature[38]. Due to its positive charge it shows ionic interaction with the negative charge of the sialic acid residues of mucus thus possessing very good bioadhesive properties. It is a biocompatible, pH-dependent cationic polymer, which is soluble in water up to pH 6.2. Basification of chitosan aqueous solutions above this pH leads to the formation of a hydrated gel-like precipitate. Chitosan being linear polymer provides greater polymer chain flexibility[39]. Many chitosan derivatives have been synthesized with improved mucoadhesion such as thiolated polymers, quaternized chitosan, fatty acid derivatives and different copolymers of chitosan[40]. Chitosan and its derivatives have been used in the formulation of various mucoadhesive controlled drug delivery systems.

Carbopol

Carbopol or carbomer are high molecular weight polymers of acrylic acid cross-linked with either allyl sucrose or allyl ethers of pentaerythritol. These contain 56% and 68% of carboxylic acid groups calculated on the dry bases[41]. These are used as suspending agent or viscosity increasing agent, dry and wet binder, as well as rate controlling agent in tablets, enzyme inhibitor of intestinal protease in peptide containing dosage form, etc. Carbomer is a pH-dependent polymer which stays in solution form at acidic pH but forms a low viscosity gel at alkaline pH. Carbopol offers the advantage of exhibiting excellent mucoadhesive properties in comparison with other polymers (e.g., cellulose derivatives and polyvinyl alcohol). Different mucoadhesive formulations containing carbopol have been developed and it was found that these demonstrated excellent mucoadhesive property and release the drug in controlled manner for a longer period of time.

Alginate

Alginates are random anionic, linear polymers consisting of varying ratios of glucuronic and manuronic acid units. Salts of alginate are formed when metal ion reacts with glucuronicor manuronic acid residue. Alginate has been used in many biomedical applications, including drug delivery systems, as they are biodegradable, biocompatible and mucoadhesive[43]. These delivery systems are formed when they are in monovalent, water-soluble state. Alginate salts undergo an aqueous sol-gel transformation to water-insoluble salts due to the addition of divalent ions such as calcium, strontium and barium[44]. Mainly calcium alginate matrix is used for drug delivery systems including beads, gels, films, microparticles and sponges. Alginates with a high glucuronic acid contents form more rigid, porous gel due to their orientation within the egg-box structure and conversely gel with low glucuronic content are more randomly packed and less porous[45].

Sodium carboxymethyl cellulose (Na CMC)

It is a low-cost, commercial, soluble and polyanionic polysaccharide derivative of cellulose that has been employed in medicine, as an emulsifying agent in pharmaceuticals and in cosmetics. The solution characteristics depend upon the average chain length and degree of polymerization. High and medium viscosity solutions of Na CMC possess thixotropic behavior[46]. The bioadhesive properties of the Na CMC are remarkable and it has been used in the development of various bioadhesive formulations such as matrix tablets, microspheres, buccal patches and nanoparticles. Going to the literature, a vast study has been carried out on Na CMC and various formulations have been prepared.

Hydroxypropyl methyl cellulose

HPMC, a semisynthetic, inert, viscoelastic polymer used as an ophthalmic lubricant, emulsifi er, suspending agent, thickening agent and controlled-delivery component in oral medicaments, is found in a variety of commercial products. Also known as hypermellose, it is a thermosenstive polymer whose aqueous solution sets into gel when heated up to critical temperature[47]. It also shows good bioadhesive property due to its ability to exhibit strong hydrogen bonding with the mucin present in the mucosal layer. Various films, tablets and gels formulations have been formulated using HPMC as mucoadhesive polymer. The formulation shows very good mucoadhesion and provided sustained release.

Factors affecting mucoadhesion

Mucoadhesion may be affected by a number of factors, including

1. ***Polymer related factors:***

i) Molecular weight

ii) Concentration of active polymer

iii) Flexibility of polymer chains

iv) Spatial conformation

v) Swelling

vi) Hydrophilicity

2. ***Environment related factors:***

i) pH of polymer - substrate interface

ii) Applied strength

iii) Initial contact time

3. ***Physiological factors:***

i) Mucin turns over

ii) Disease state

Hydrophilicity

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

Molecular weight

The interpenetration of polymer molecules is favored by low molecular-weight polymers, whereas entanglements are favored at higher molecular weights. The optimum molecular weight for the maximum mucoadhesion depends on the type of polymer, with bioadhesive forces increasing with the molecular weight of the polymer up to 100,000. Beyond this level, there is no further gain[48].

Cross-linking and swelling

Cross-link density is inversely proportional to the degree of swelling[49]. The lower the cross-link density, the higher the flexibility and hydration rate; the larger the surface area of the polymer, the better the mucoadhesion. To achieve a high degree of swelling, a lightly cross-linked polymer is favored. However, if too much moisture is present and the degree of swelling is too great, a slippy mucilage results and this can be easily removed from the substrate[50]. The mucoadhesion of cross-linked polymers can be enhanced by the inclusion in the formulation of adhesion promoters, such as free polymer chains and polymers grafted onto the preformed network[51].

Spatial conformation

Besides molecular weight or chain length, spatial conformation of a polymer is also important. Despite a high molecular weight of 19,500,000 for dextrans, they have adhesive strength similar to that of polyethylene glycol (PEG), with a molecular weight of 200,000. The helical conformation of dextran may shield many adhesively active groups, primarily responsible for adhesion, unlike PEG polymers, which have a linear conformation[52].

pH

The pH at the bioadhesive to substrate interface can influence the adhesion of bioadhesives possessing ionizable groups. Many bioadhesives used in drug delivery are polyanions possessing carboxylic acid functionalities. If the local pH is above the pK of the polymer, it will be largely ionized; if the pH is below the pK of the polymer, it will be largely unionized. The approximate pKa for the poly(acrylic acid) family of polymers is between 4 and 5. The maximum adhesive strength of these polymers is observed around pH 4-5 and decreases gradually above a pH of 6. A systematic investigation of the mechanisms of mucoadhesion clearly showed that the protonated carboxyl groups, rather than the ionized carboxyl groups, react with mucin molecules, presumably by the simultaneous formation of numerous hydrogen bonds[53].

Concentration of active polymer

Ahuja[54] stated that there is an optimum concentration of polymer corresponding to the best mucoadhesion. In highly concentrated systems, beyond the optimum concentration the adhesive strength drops significantly. In concentrated solutions, the coiled molecules become solvent-poor and the chains available for interpenetration are not numerous. This result seems to be of interest only for more or less liquid mucoadhesive formulations. It was shown by Duchêne[55] that, for solid dosage forms such as tablets, the higher the polymer concentration, the stronger the mucoadhesion.

Drug/excipient concentration

Drug/excipient concentration may influence the mucoadhesion. Blanco Fuente [56] studied the effect of propranolol hydrochloride to Carbopol® (a lightly cross-linked poly(acrylic acid) polymer) hydrogels adhesion. Author demonstrated increased adhesion when water was limited in the system due to an increase in the elasticity, caused by the complex formation between drug and the polymer. While in the presence of large quantities of water, the complex precipitated out, leading to a slight decrease in the adhesive character. Increasing toluidine blue O (TBO) concentration in mucoadhesive patches based on Gantrez® (poly(methylvinylether/maleic acid) significantly increased mucoadhesion to porcine cheek tissue[57]This was attributed to increased internal cohesion within the patches due to electrostatic interactions between the cationic drug and anionic copolymer.

Other factors affecting mucoadhesion

Mucoadhesion may be affected by the initial force of application[58]. Higher forces lead to enhanced interpenetration and high bioadhesive strength[59]. In addition, the greater the initial contact time between bioadhesive and substrate, the greater the swelling and interpenetration of polymer Physiological variables can also

affect mucoadhesion. The rate of mucus turnover can be affected by disease states and also by the presence of a bioadhesive device[61]. In addition, the nature of the surface presented to the bioadhesive formulation canvary significantly depending on the body site and the presence of local or systemic disease[60].

Evaluation of mucoadhesive drug delivery systems

Mucoadhesive drug delivery systems can be evaluated by testing their adhesion strength. Various *in vitro* and *in vivo* tests (Figure 6) are available to determine the adhesion strength of the mucoadhesive polymers.

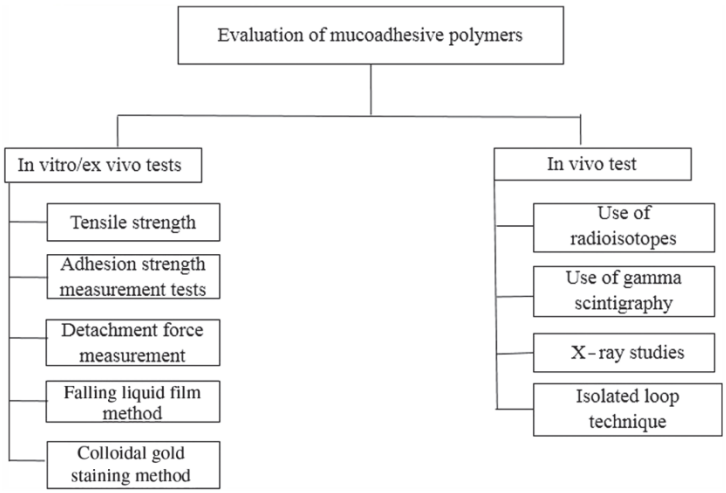

Figure 6 Different methods for evaluation of mucoadhesive polymers

Natural polymers

The polymers within this category are soluble in water. Matrices developed with these polymers swell when they come in contact an aqueous media with subsequent dissolution of the matrix. The polyelectrolytes widen greater mucoadhesive property such as. poloxamer, hydroxypropyl methyl cellulose, methyl cellulose, poly (vinyl alcohol) and poly (vinyl pyrrolidone), have been used for mucoadhesive properties. The natural polysaccharides and its derivatives like chitosan, methyl cellulose, hyaluronic acid, hydroxy propyl methylcellulose, hydroxy propyl cellulose, Xanthan gum, gellan gum, guar gum, and Carrageenan have been utilized in development of ocular drug delivery systems. Cellulose and its derivates have been reported to have surface active property in addition to its film forming capability. Cellulose derivatives with lower surface acting property are normally preferred in ocular delivery systems as they cause reduced eye irritation. Cationic cellulose derivatives (e.g. cationic hydroxyethyl celluloses) have been used in conjunction with various anionic polymers for the development of sustained delivery systems[62,63].

List of natural polymers

- Karya gum
- Xanthan gum
- Guar gum
- Tragacanth
- Pectin
- Chitosan
- Gum Arabic
- Locust bean gum
- Grewia gum
- Bhara Gum
- Mango Gum
- Gelatin
- Fenugreek gum
- Tamarind gum

Reported herbal patches

Bhattacharjee et al prepared and characterizing mucoadhesive buccal patches with the incorporation of herbal extract. Buccal patches were prepared with herbal (Neem) extract with two polymers such as methyl cellulose and hydroxy propyl methyl cellulose in a respective solvent such as ethanol with propylene glycol as the plasticizer[64].

Kanjani et al formulated transdermal patch incorporating herbal bioactive *azadirachta indica.* Transdermal patch was formulated by solvent casting method and was evaluated for organoleptic distinctiveness, stratification, weight consistency, flopping fortitude, dampness content, drug content and exterior morphology by scanning electron microscopy (SEM) [65].

Saleem and Idris formulated and evaluate a Unani transdermal patch that could be used for antiemetic therapy. The incorporation of Unani ingredients, namely, Khardal (*Brassica nigra*), Zanjabeel (*Zingiber officinale*), Podina (*Mentha arvensis*), and Sirka (Vinegar) were envisaged. The TP was prepared by solvent evaporation technique and was evaluated for organoleptic characteristics and other physicochemical properties, such as thickness, weight uniformity, folding endurance, moisture content, drug content, and tolerability and acceptability of patch[66].

Das et al prepared and evaluate the transdermal patches of *Cissus Quadrangularis* extract by the solvent evaporation method using hydroxy propyl ethyl cellulose (HPMC E-15) in different concentrations. Di butyl phthalate and DMSO were used as plasticizers and permeation enhancer[67].

Patel et al developed the transdermal patch of curcumin using polymer blends so that minimize the side effects and maximize the therapeutic efficacy[68].

Jasuja et al formulated matrix type transdermal patches of a potent anti atherosclerotic botanical Emblica officinalis on a mercury substrate and evaluated for physicochemical parameters like thickness, % flatness, weight variation, moisture uptake, moisture content, folding endurance, elongation and drug content values. Further, in vivo drug release was also observed by HPLC in rabbit serum[69].

Moghadamnia et al evaluated the efficacy of licorice bioadhesive hydrogel patches to control the pain and reduce the healing time of recurrent aphthous ulcer[70].

Hashemi et al developed *Myrtus communis L. (Myrtle*) containing oral patches and applied box-behnken design to evaluate the effect of polymers such as polyvinyl pyrrolidone (PVP), gelatin, methylcellulose (MC) and pectin. The patches properties such as tensile strength, folding endurance, swelling index, thickness, mucoadhesive strength and the pattern of myrtle release were evaluated as dependent variables. Then, the model was adjusted according to the best fitted equation with box behnken design[71].

Savula et al formulated and evaluate *Nelumbo nucifera* herbal patches*. Nelumbo nucifera* Gaertn (Nymphaeaceae), a perennial aquatic plant, has been used as a medicinal herb in China and India[72].

Bhutkar formulated and evaluate mucoadhesive buccal patch for systemic drug delivery of drug like flavonoid which is isolated from the leaves of Psidium guajava in which system avoid first pass effect of hepatic metabolism[73].

Suksaeree et al studied the preparation, physicochemical characterization, and in vitro characteristic of Zingiber cassumunar blended patches. The Z. cassumunar blended patches incorporating Z. cassumunar Roxb also known as Plai were prepared from chitosan and polyvinyl alcohol with glycerin as plasticizer[74].

Conclusion

Today, drug delivery systems designed with the aim to improve patient compliance and convenience is more important than ever. Therefore huge work is going on to develop novel dosage forms to satisfy increased patient demands of more convenient dosage forms. This overview about the mucoadhesive dosage forms might be a useful tool for the efficient design of novel mucoadhesive drug delivery systems. Mucoadhesive drug delivery systems have applications from different angles, including development of novel mucoadhesive, design of the device, mechanisms of mucoadhesion and permeation enhancement. With the influx of a large number of new drug molecules due to drug discovery, mucoadhesive drug delivery will play an even more important role in delivering these molecules. The mucoadhesive dosage forms offer prolonged contact at the site of administration, low enzymatic activity, and patient compliance. However, these novel mucoadhesive formulations require much more work, to deliver clinically for the treatment of both topical and systemic diseases.

References

1. Chickering DE III, Mathiowitz E. Fundamentals of bioadhesion. In: Lehr CM, editor. Bioadhesive drug delivery systems- Fundamentals, Novel Approaches and Development. New York: Marcel Dekker; 1999;1-85.
2. Asane GS. Mucoadhesive Gastro intestinal drug delivery system: an overview, Pharmainfonet.com. 2007, 5(6).
3. Mansuri S, Kesharwani P, Jain K, et al., Mucoadhesion: A promisingapproach in drug delivery system. React Funct Polym. 2016; 100:151-72.
4. Grabovac V, Guggi D, Bernkop-Schnürch A. Comparison of the mucoadhesive properties of various polymers. Adv Drug Deliv Rev 2005; 57(11):1713-23.
5. De Souza Ferreira SB, Moço TD, Borghi-Pangoni FB, et al., Rheological, mucoadhesive and textural properties of thermoresponsive polymer blends for biomedical applications. J Mech Behav Biomed Mater. 2015; 55:164-78.
6. Khutoryanskiy VV. Advances in mucoadhesion and mucoadhesive polymers. Macromol Biosci 2011; 11(6):748-64.
7. Lubrizol Pharmaceutical Bulletin 23, Edition: October 29, 2008;1-20.
8. Cook MT, Khutoryanskiy VV. Mucoadhesion and mucosa-mimetic materials-A mini-review. Int J Pharm 2015; 495(2):991-8.
9. Hägerström H. Polymer gels as pharmaceutical dosage forms. Acta Universitatis Upsaliensis 2003.
10. Bruschi ML, Francisco LMB, Toledo LAS, Borghi FB. An overview of recent patents on composition of mucoadhesive drug delivery systems. Recent Pat Drug Deliv Formul. 2015; 9:79-87.
11. Bassi da Silva J, Ferreira SBS, de Freitas O, et al., A critical review about methodologies for the analysis of mucoadhesive properties of drug delivery systems. Drug Dev Ind Pharm. 2017; 43(7):1053-1070.
12. Leung SH, Robinson JR. The Contribution of anionic polymer structural features related to mucoadhesion. J Control Release 1988; 5:223-31.
13. Veuillez F, Kalia YN, Jacques Y, et al., Factors and strategies for improving buccal absorption of peptides. Eur J Pharm Biopharm 2001; 51:93-109.
14. Carvalho FC, Bruschi ML, Evangelista RC, et al., Mucoadhesive drug delivery systems. Brazilian J Pharm Sci 2010;46(1):1-18
15. Smart JD. The basics and underlying mechanisms of mucoadhesion. Adv Drug Deliv Rev. 2005; 57(11):1556-68.
16. Khan AB, Mahamana R, Pal E. Review on mucoadhesive drug delivery system: novel approaches in modern era. Rajiv Gandhi Univ Heal Sci J Pharm Sci. 2015; 4(4):128-41.
17. Andrews GP, Laverty TP, Jones DS. Mucoadhesive polymeric platforms for controlled drug delivery. Eur J Pharm Biopharm. 2009; 71(3):505-18.
18. Carvalho FC, Chorilli M, Gremião MPD. Plataformas Bio Adesivas Poliméricas Baseadas em Nanotecnologia para Liberação Controlada de Fármacos - Propriedades , Metodologias e Aplicações. Polímeros. 2014; 24(2):203-13.
19. Varum FO, Basit AW, Sousa J, Veiga F. Mucoadhesion studies in the gastrointestinal tract to increase oral drug bioavailability. Braz J Pharm Sci 2008; 44(4):535-48.
20. Hägerström H, Edsman K, Strømme M. Low-frequency dielectric spectroscopy as a tool for studying the compatibility between pharmaceutical gels and mucus tissue. J Pharm Sci 2003; 92:1869-81.
21. Dodou D, Breedveld P, Wieringa P. Mucoadhesives in the gastrointestinal tract: Revisiting the literature for novel applications. Eur J Pharm Biopharm 2005; 60:1-16.
22. Kinloch AJ. The science of adhesion. J Mater Sci 1980; 15:2141-66.
23. Jiménez-Castellanos MR, Zia H, Rhodes CT. Mucoadhe-sive drug delivery systems. Drug Dev Ind Pharm 1993; 19:143-94.
24. Vinod KR, Reddy R, Sandhya S, et al., Critical review on mucoadhesive drug delivery systems. Hygeia J D Med 2012; 4: 7-28.
25. Sudhakar Y, Kuotsu K, Bandyopadhyay AK. Buccal bioadhesive drug delivery - a Promising option for orally less effi cient drugs. J Control Release 2006; 114: 15-40.
26. Gu JM, Robinson JR, Leung SH. Binding of acrylic polymers to mucin/epithelial surfaces: structure-property relationships. Crit Rev Ther Drug Carrier Syst 1988;5: 21-67.
27. Kumar K, Dhawan N, Sharma H, Vaidya S, Vaidya B. Bioadhesive polymers: novel tool for drug delivery, artificial cells, nanomedicine, and biotechnology 2014; 42:4, 274-283.
28. Ludwig A. The use of mucoadhesive polymers in ocular drug delivery. Adv Drug Del Rev 2005; 57: 1595-1639.

29. Portero A, Osorio DT, Alonso MJ, Lopez CR. Development of chitosan sponges for buccal administration of insulin. Carbohyd Polym 2007; 68: 617- 625 .
30. Hui HW, Robinson JR. Ocular delivery of progesterone using a bioadhesive polymer. Int J Pharm 1985;26: 203-213.
31. Dubolazov AV, Nurkeeva ZS, Mun GA, et al., Design of mucoadhesive polymeric films based on blends of poly(acrylic acid) and (hydroxypropyl)cellulose. Biomacromolecules 2006; 7: 1637- 164.
32. Warren SJ, Kellaway IW. The synthesis and in vitro characterization of the mucoadhesion and swelling of Poly (acrylic acid) hydrogels. Pharm Dev Tech 1998; 3: 199-208.
33. Carreno-Gomez B, Woodley JF, Florence AT. Studies on the uptake of tomato lectin nanoparticles in everted gut sacs. Int J Pharm 1999; 183: 7-11.
34. Shojaei AH, Xiaoling L. Mechanism of buccal mucoadhesion of novel copolymers of acrylic acid and polyethylene glycol monomethylether monometh-acrylate. J Control Release 1997; 47: 151-161.
35. Lele BS, Hoff man AS. Mucoadhesive drug carriers based on complexes of poly(acrylic acid) and PEGylated drugs having hydrolysable PEG-anhydride-drug linkages . J Control Release 2000; 69: 237-248.
36. Bogataj M, Mrhar A, Korosec L. Influence of physicochemical and biological parameters on drug release from microspheres adhered on vesical and intestinal mucosa. Int J Pharm 1999; 177: 211-220.
37. Chen H, Langer, R. Oral particulate delivery: status and future trends. Adv Drug Deliv Rev 1998; 34: 339-350.
38. Bagheri KS, Taghizadeh SM, Mirzadeh H. An investigation on the short-term biodegradability of chitosan with various molecular weights and degrees of deacetylation . Carbohyd Polym 2009; 78: 773- 77.
39. Chenite A , Chaput C , Wang D , et al., Novel injectable neutral solutions of chitosan form biodegradable gels in situ, Biomaterials 2000; 21: 2155-2161.
40. Riva R, Ragelle H, des Rieux A, et al., Chitosan and chitosan derivatives in drug delivery and tissue engineering. In: Jayakumar R, Prabaharan M, Muzzarelli RAA, Eds. Chitosan for Biomaterials II. Berlin, Heidelberg: Springer 2011.
41. Barry BW, Meyer MC. The rheological properties of carbopol gels I. Continuous shear and creep properties of carbopol gels. Int J Pharm 1978; 2: 1-25.
42. Davies NM, Farr SJ, Hadgraft J, et al., Evaluation of mucoadhesive polymers in ocular drug delivery. II. Polymer-coated vesicles. Pharm Res 1992; 9: 1137-1144.
43. Rajaonarivony M, Vauthier C, Couarraze G, et al., Development of a new drug carrier made from alginate. J Pharm Sci 1993; 82: 912-917.
44. Kesavan K, Nath G, Pandit JK. Sodium alginate based mucoadhesive system for gatifl oxacin and its in vitro antibacterial activity. Sci Pharm 2010; 78: 941-957.
45. Wee S, Gombotz WR. Protein release from alginate matrices. Adv Drug Deliv Rev 1998; 31: 267-285.
46. Elliot JH, Ganz AJ. Some rheological properties of sodium carboxymethylcellulose solutions and gels. Rheologica Acta 1974; 13: 670-674.
47. Silva DJ, Olver JM. Hydroxypropyl methylcellulose (HPMC) lubricant facilitates insertion of porous spherical orbital implants. Ophthal Plast Reconstr Surg 2005; 21: 301-302.
48. Gurny R, Meyer JM, Peppas NA. Bioadhesive intraoral release systems: Design, testing and analysis. Biomaterials 1984; 5:336-40.
49. Gudeman L, Peppas NA. Preparation and characterisation of ph- sensitive, interpenetrating networks of poly (vinyl alcohol) and poly(acrylic acid). J Appl Polym Sci 1995; 55:919-28.
50. McCarron PA, Woolfson AD, Donnelly RF, et al., Influence of plasticiser type and storage conditions on the properties of poly(methyl vinyl ether-co-maleic anhydride) bioadhesive films. J Appl Polym Sci 2004; 91:1576-89.
51. Peppas NA, Little MD, Huang Y. Bioadhesive Controlled Release Systems. In: Wise DL, editor. Handbook of pharmaceutical controlled release technology. New York: Marcel Dekker; 2000; 255-69.
52. Jimenez-Castellanos MR, Zia, H, Rhodes CT. Mucoadhesive drug delivery systems. Drug Dev Ind Pharm 1993; 19:143-94.
53. Park H, Robinson JR. Physicochemical properties of water soluble polymers important to mucin/epithelium adhesion. J Control Release 1985; 2:47-7.
54. Ahuja A, Khar RK, Ali J. Mucoadhesive drug delivery systems. Drug Dev Ind Pharm 1997; 23:489-515.
55. Duchene D, Touchard F, Peppas NA. Pharmaceutical and medical aspects of bioadhesive systems for drug administration. Drug Dev Ind Pharm 1988; 14:283-18.
56. Blanco Fuente H, AnguianoIgea S, OteroEspinar FJ, BlancoMendez J. *Invitro* bioadhesion of carbopol hydrogels. Int J Pharm 1996; 142:169-74.
57. Donnelly RF, McCarron PA, Tunney MM, Woolfson AD. Potential of photodynamic therapy in treatment of fungal infections of the mouth. design and characterisation of a mucoadhesive patch containing toluidine Blue O. J Photochem Photobiol B 2007;86:59-69.
58. Smart JD. An *in vitro* assessment of some mucoadhesive dosage forms. Int J Pharm 1991; 73:69-74.
59. Peppas NA, Buri PA. Surface, interfacial and molecular aspects of polymer bioadhesion on soft tissues. J Control Release 1985;2:257-75.
60. Kamath KR, Park K. Mucosal Adhesive Preparations. In: Swarbrick J, Boylan JC, editors. Encyclopedia of Pharmaceutical Technology. New York: Marcel Dekker; 1992;133.
61. Lehr CM, Poelma FG. An Estimate of turnover time of intestinal mucus gel layer in the Rat *in situ* Loop. Int J Pharm 1991; 70:235.
62. Shukla AK, Kumar M, Bishnoi RS, Jain CP. Review article application of fenugreek seed gum: in novel drug delivery. Asian J Biomat Res 2017; 3(6):1-10
63. Shukla AK, Bishnoi RS, Kumar M, et al., Applications of tamarind seeds polysaccharide-based copolymers in controlled drug delivery: An overview. Asian J Pharm Pharmacol 2018; 4(1):23-30.
64. Bhattacharjee S, Nagalakshmi S, Shanmuganathan S. Formulation characterization and in-vitro diffusion studies of herbal extract loaded mucoadhesive buccal patches Int J Pharm Sci Res 2014; 5(11): 4965-4970.
65. Kanjani B, Rai G, Gilhotra R, et al., Formulation design, optimization and characterization of herbal bioactive loaded transdermal patch: the state of the art. SGVU J Pharm Res Edu 2018; 3(1): 279-288
66. Saleem MN, Idris M. Formulation design and development of a unani transdermal patch for antiemetic therapy and its pharmaceutical evaluation. Scientifica 2016; 7602347.
67. Das R, Kolhe S, Patil A, et al., Development and evaluation of transdermal patches with cissus quadrangularis plant extract. Int J Life Sci Pharm Res 2018; 8(2):29-34.
68. Patel DK, Gidwani B, Gupta A, et al., Formulation and evaluation of transdermal patch using antioxidant phytoconstituent. J Biol Sci 2016; 4(2):1-9.
69. Jasuja ND, Sharma PR, Sharma S, Joshi SC. Development of non-invasive transdermal patch of Emblica officinalis for anti atherosclerotic activity. Int J Drug Deliv 2013; 5: 402-411.
70. Moghadamnia AA, Motallebnejad M, Kantian M. The efficacy of the bioadhesive patches containing licorice extract in the management of recurrent aphthous stomatitis. Phytother Res 2009; 23: 246-250.
71. Hashemi M, Ramezani V, Seyedabadi M, et al., Formulation and optimization of oral mucoadhesive patches of myrtus communis by box behnken design. Adv Pharm Bull 2017; 7(3): 441-450
72. Savula J, Krishna KSM, Anwesh H, Prashanth K. Formulation and evaluation of herbal transdermal patches. World J Pharm Res 2017;6(13); 365-374.
73. Bhutkar KG. Formulation and evaluation of mucoadhesive herbal buccal patch of *Psidium Guava L.* J Curr Pharm Res 2014; 5 (1): 1372-1377.
74. Suksaeree J, Charoenchai L, Madaka F, Monton C, et al., Zingiber cassumunar blended patches for skin application: Formulation, physicochemical properties and in vitro studies. Asian J Pharm Sci 2015; 10:341-349.