Designed Monomers and Polymers 12 (2009), Pages 483–495

Polymers in Mucoadhesive Drug Delivery System: A Brief Note

S. Roy[1], K. Pal[2*], A. Anis[3], K. Pramanik[2] and B.Prabhakar[1]

[1] School of Pharmacy and Technology Management, SVKM's NMIMS University, Mumbai-400056, India

[2] Department of Biotechnology & Medical Engineering, National Institute of Technology, Rourkela-769008, Orissa, India.

[3] Department of Process Engineering & Applied Science, Dalhousie University, Halifax, NS, B3J2X4, Canada.

*** Author for Correspondence:** email: pal.kunal@yahoo.com; phone: +91-661-2462289.

Abstract: Bioadhesion can be defined as the process by which a natural or a synthetic polymer can adhere to a biological substrate. When the biological substrate is a mucosal layer then the phenomena is known as mucoadhesion. The substrate possessing bioadhesive property can help in devising a delivery system capable of delivering a bioactive agent for a prolonged period of time at a specific delivery site. The current review provides a good insight on mucoadhesive polymers, the phenomenon of mucoadhesion and the factors which have the ability to affect the mucoadhesive properties of a polymer.

Keywords: Mucosa, mucoadhesion, mucoadhesive polymers, drug delivery.

1. INTRODUCTION

Bioadhesion can be defined as a phenomenon of interfacial molecular attractive forces amongst the surfaces of the biological substrate and the natural or synthetic polymers, which allows the polymer to adhere to the biological surface for an extended period of time [1-4]. Bioadhesive polymeric systems have been used since long time in the development of products for various biomedical applications which include denture adhesives and surgical glue [5-8]. The adhesion of bacteria to the human gut may be attributed to the interaction of lectin-like structure (present on the cell surface of bacteria) and mucin (present in the biological tissues) [9-12]. In general, various biopolymers show the bioadhesive properties and have been utilized for various therapeutic purposes in medicine [2, 13]. The bioadhesive polymers can be broadly classified into two groups, namely specific and nonspecific [14]. The specific bioadhesive polymers (e.g.

lectins, fimbrin) have the ability to adhere to specific chemical structures within the biological molecules while the nonspecific bioadhesive polymers (e.g. polyacrylic acid, cyanoacrylates) have the ability to bind with both the cell surfaces and the mucosal layer.

The use of mucoadhesive polymers for the development of pharmaceutical formulations dates back to 1947, when attempts were made to formulate a penicillin drug delivery system for delivering the bioactive agent to the oral mucosa using gum tragacanth and dental adhesive powders [15]. Improved results were reported when carboxymethylcellulose and petrolatum were used for the development of the formulation. Subsequent research resulted in the development of a mucoadhesive delivery vehicle which consisted of finely ground sodium carboxymethylcellulose (SCMC), pectin, and gelatin. The formulation was later marketed as Orahesive®. Another formulation which entered into the clinical trials is Orabase®, which is a blend of polymethylene/ mineral oil base. This was followed by the development of a system where polyethylene sheet was laminated with a blend of sodium carboxymethylcellulose and poly (isobutylene) which provided an added advantage of protecting the mucoadhesive layer by the polyethylene backing from the physical interference of the external environment [16-18].

Over the years, various other polymers (e.g. sodium alginate, sodium carboxymethylcellulose, guar gum, hydroxyethylcellulose, karya gum, methylcellulose, polyethylene glycol (PEG), retene and tragacanth) have been found to exhibit mucoadhesive properties. During the period of 1980s poly (acrylic acid), hydroxypropylcellulose, and sodium carboxymethylcellulose were widely explored for the development of formulations having mucoadhesive properties. Since then the use of acrylate polymers for the development of mucoadhesive formulations have increased many-fold, various authors have investigated the mucoadhesive properties of different polymers with varying molecular architecture [19-21]. After a lot of research, the researchers are of the view that a polymer will exhibit sufficient mucoadhesive property if it can form strong intermolecular hydrogen bonding with the mucosal layer, penetration of the polymer into the mucus network or tissue crevices, easy wetting of mucosal layer and high molecular weight of the polymer chain. The ideal characteristics of a mucoadhesive polymer matrix include the rapid adherence to the mucosal layer without any change in the physical property of the delivery matrix, minimum interference to the release of the active agent, biodegradable without producing any toxic byproducts, inhibit the enzymes present at the delivery site and enhance the penetration of the active agent (if the active agent is meant to be absorbed from the delivery site) [22].

Before discussing about the commonly used mucoadhesive polymers, the different theories which have been proposed to explain the phenomenon of mucoadhesion will be discussed. Furthermore, different factors affecting mucoadhesion, methods of evaluation of mucoadhesive properties of polymers and the potential biological sites where mucoadhesion can play an important role will be taken up for discussion.

THEORIES OF MUCOADHESION

The phenomena of bioadhesion occurs by a complex mechanism. Till date, six theories have been proposed which can improve our understanding for the phenomena of adhesion and can also be extended to explain the mechanism of bioadhesion. The theories include: (a) the electronic theory, (b) the wetting theory, (c) the adsorption theory, (d) the diffusion theory, (e) the mechanical theory and (f) the cohesive theory. The electronic theory proposes transfer of electrons amongst the surfaces resulting in the formation of an electrical double layer thereby giving rise to attractive forces. The wetting theory postulates that if the contact angle of liquids on the substrate surface is lower, then there is a greater affinity for the liquid to the substrate surface. If two such substrate surfaces are brought in contact with each other in the presence of the liquid, the liquid may act as an adhesive amongst the substrate surfaces. The adsorption theory proposes the presence of intermolecular forces, viz. hydrogen bonding and Van der Waal's forces, for the adhesive interaction amongst the substrate surfaces. The diffusion theory assumes the diffusion of the polymer chains, present on the substrate surfaces, across the adhesive interface thereby forming a networked structure. The mechanical theory explains the diffusion of the liquid adhesives into the micro-cracks and irregularities present on the substrate surface thereby forming an interlocked structure which gives rise to adhesion. The cohesive theory proposes that the phenomena of bioadhesion are mainly due to the intermolecular interactions amongst like-molecules [23-24].

Based on the above theories, the process of bioadhesion can be broadly classified into two categories, namely chemical (electronic and adsorption theories) and physical (wetting, diffusion and cohesive theory) methods [25-26]. The process of adhesion may be divided into two stages. During the first stage (also known as contact stage), wetting of mucoadhesive polymer and mucous membrane occurs followed by the consolidation stage, where the physico-chemical interactions prevail [27-28].

As mentioned above, bioadhesion may take place either by physical or by chemical interactions. These interactions can be further classified as hydrogen bonds, Van der Waals force and hydrophobic bonds which are considered as physical interactions while the formation of ionic and covalent bonds are categorized as chemical interactions. Hydrogen bonds are formed due to the interaction of the electronegative and electropositive atoms though there is no actual transfer of electrons. Example of this kind of interaction includes formation of gelled structure when aqueous solutions of polyvinyl alcohol and glycine are mixed. Van der Waals forces are either due to presence of the dipole-dipole interactions in polar molecules or due to the dispersion forces amongst non-polar substrates. Hydrophobic bonds are formed due to the interaction of the non-polar groups when the polymers are dispersed in an aqueous solution. Freeze-thawing of polyvinyl alcohol solution in water exhibits this kind of interaction. Ionic bonds are formed due to the electrostatic interactions amongst the polymers (e.g. instantaneous formation of gelled structure when alginate and chitosan solutions in water are mixed) while covalent bonds are formed due to the sharing of electrons amongst the atoms (e.g. crosslinking reaction amongst genipin and amino groups).

The term “mucoadhesion” was coined for the adhesion of the polymers with the surface of the mucosal layer [29]. The mucosal layer is made up of mucus which is secreted by the goblet cells (glandular columnar epithelial cells) and is a viscoelastic fluid. It lines the visceral organs, which are exposed to the external environment. The main components constituting the mucosa include water and mucin (an anionic polyelectrolyte), while the other components include proteins, lipids and mucopolysaccharides. Water and mucin constitute > 99% of the total composition of the mucus and out of this > 95% is water. The gel-like structure of the mucus can be attributed to the intermolecular entanglements of the mucin glycoproteins along with the non-covalent interactions (e.g. hydrogen, electrostatic and hydrophobic bonds) which results in the formation of a hydrated gel-like structure and explains the viscoelastic nature of the mucus [24].

FACTORS AFFECTING MUCOADHESION

Based on the theories of the adhesion, it can be summarized that the mucoadhesive property of a polymer can be tailored by changing the parameters which has the capacity to alter the interaction among the polymer and the mucosal layer. In this section, attempts will be made to analyze some of the parameters which can tailor the mucoadhesive property of a given polymer.

Polymers usually diffuse into the mucosal layer and thereafter adhere to the layer by forming intermolecular entanglements. With the increase in the molecular weight (MW) of the polymer chain there is an increase in the mucoadhesiveness of a polymer. In general, polymers having $MW \geq 100,000$ have been found to have adequate mucoadhesive property for biomedical applications. A typical example is polyethylene glycol (PEG). PEG of 20,000 MW shows negligible mucoadhesive property while PEG of 200,000 MW exhibits improved mucoadhesiveness and the PEG of 400,000 MW has got excellent mucoadhesiveness [30]. Similarly, polyoxyethylene of 7,000,000 MW has exhibited excellent mucoadhesive property and could be tried for the development of buccal delivery systems [31]. Dextrans of 19,500,000 and 200,000 MW, poly(acrylic) acid of ~750,000 MW and polyethylene oxide of 4,000,000 MW also exhibit good bioadhesive property [24]. Polymer chain length plays an important role in bioadhesiveness. With the increase in the chain length of the polymers there is an increase in the mucoadhesive property of the polymer. Flexible polymer chains helps in the better penetration and entanglement of the polymer chains with that of mucosal layer thereby improving the bioadhesive property. The flexibility of the polymer chains is generally affected by the crosslinking reactions and the hydration of the polymer network. Higher the crosslinking density, lower is the flexibility of the polymer chains. Keeping this in mind, teethering of long flexible chains onto the polymer matrices, with high crosslinking density, appears to be an excellent idea to improve the bioadhesive property. In a recent study, this phenomenon was utilized to device tethered poly (ethylene glycol)–poly (acrylic acid) hydrogels with improved mucoadhesive properties [24, 32]. In addition to the reduced flexibility of the polymer chains, crosslinking results in the reduced diffusion of water into the crosslinked polymer matrix. But sufficient hydration of the polymer network is necessary for the complete opening of the interpolymeric pores within the polymer matrix in addition to the mobilization of the polymer chains [33]. Hence highly crosslinked polymeric matrix limits the interpenetration of polymer and mucin chains amongst themselves which in turn results in the decrease in the mucoadhesive strength [34]. Apart from the MW and chain length of the polymer chains, spatial arrangement of the polymer chains may also play an important role. As mentioned above, dextrans of 19,500,000 and 200,000 MW exhibit good mucoadhesive properties. The efficiency of both the dextrans and PEG (MW: 200,000) have been found to possess similar bioadhesive strength [24, 30, 35].

Formation of hydrogen-bonds amongst the functional groups of the polymers and mucosal layer also plays an important role. In general, stronger the hydrogen bonding stronger is the adhesion. The functional groups responsible for such kind of interaction include hydroxyl, carboxyl and amino groups. Various polymers which have the ability to form strong hydrogen bonds include poly (vinyl alcohol), acrylic derivates, celluloses and starch [36]. Apart from the hydrogen bond formation, the presence of functional groups within the polymer structure may render the polymer chains as polyelectrolytes. The presence of charged functional groups in the polymer chain has a marked effect on the strength of the bioadhesion and can be demonstrated by cell-culture-fluorescent probe technique [37-38]. Anionic polyelectrolytes have been found to form stronger adhesion when compared with neutral polymers [13, 39].

In addition to the above facts, the concentration of the polymer also plays a significant role in the process of mucoadhesion. At lower concentrations of the polymer chains, there is an inadequate and unstable interaction amongst the polymer and the mucosal layer resulting in poor mucoadhesive properties. In general, polymer concentration in the range of 1-2.5 wt % may exhibit sufficient mucoadhesive property for biomedical applications. However for certain polymers, like poly (vinyl pyrrolidone) and poly (vinyl alcohol), solvent diffusion into the polymer network decreases at very high polymer concentration due to the formation of the highly coiled structure thereby limiting interpenetration of the polymer and mucin chains with the subsequent reduction in the mucoadhesive property [40].

Apart from the above-mentioned physico-chemical properties of the polymeric network, various environmental factors also play an important role in mucoadhesion. As mentioned previously, mucoadhesive property is dependent on the presence of functional groups which can ionize so as to give a charge distribution on the polymer chains. The ionization of the functional group is dependent on the pH of the external medium. Hence change in the pH of the external environment may play an important role in tailoring mucoadhesive property. As for example, chitosan (cationic polyelectrolyte) exhibit excellent mucoadhesive property in neutral or alkaline medium [41]. The contact time amongst the polymer matrix and the mucosal layer can also govern the mucoadhesive property. With the initial increase in the contact time there is an increase in the hydration of the polymer matrix and subsequent interpenetration of the polymer chains. The physiology of the mucosal layer may vary depending on the patho-physiological

nature of the human body. The physiological factors which play an important role in governing the mucoadhesive property of a polymer matrix include texture and thickness of mucosa [36].

EVALUATION OF MUCOADHESIVE PROPERTIES

Various in vivo and in vitro methods are used for testing the efficacy of the mucoadhesive nature of a polymer matrix. Commonly used in vitro/ ex vivo methods include tensile strength measurement, shear strength measurement and chip based systems whereas various imaging techniques are used for the evaluation of the delivery systems under in vivo conditions. This section will describe various methods used to study the mucoadhesive properties.

In vitro tensile strength measurement is done by dipping a filter paper in 8% mucin dispersion. Thereafter, the mucin coated filter paper is placed in contact with the hydrated polymeric samples (in physiological solutions) for a definite period of time, followed by the determination of the maximum force required to detach the filter-paper and polymer surfaces after the mucoadhesive bonding [42]. Similarly, ex vivo experimentations are also done with the exception that the mucin coated filter-paper is replaced with excised mucosal tissues (e.g. buccal mucosa, intestinal mucosa, vaginal mucosa) [43-45]. The mucoadhesive properties can also be determined by incubating the hydrated polymer matrix surface kept in contact with a viscoelastic 30 % (w/w) mucin solution in water with the subsequent determination of the maximum detachment force required to separate the polymer matrix and mucin solution surfaces after the adhesion [46]. Wash-off test may also be used to determine the mucoadhesive property of delivery systems. In the test, the mucosal tissue is attached onto a glass slide with the help of a double-sided cyanoacrylate tape. Thereafter, the delivery system is put on the surface of the tissue (exposed mucosal surface) with the subsequent vertical attachment of the system into the USP tablet disintegrator apparatus, which contains 1 L of physiological solution maintained at 37^{o}C. The operation of the equipment gives an up-and-down movement to the tissue-delivery matrix system. In this study, the time for the complete detachment of the delivery system from the mucosal layer is determined [47]. For the relative measurement of mucoadhesive nature of powder polymer samples modified Du Noüy tensiometer may be used, while in the shear strength determination method the force required to slide the polymer matrix over the mucus layer is determined [45]. Recently mucoadhesion studies have been reported by using BIACORE® integrated chip (IC) systems. The method involves immobilization of the polymer

(powder) on to the surface of the IC with the subsequent passage of the mucin solution over the same. This results in the interaction of the mucin with that of the polymer surface. The polymer-mucin interaction is measured by an optical phenomenon called Surface Plasmon Resonance (SPR), which measures the change in the refractive index when mucin binds on the polymer surface [48]. The in vivo experiments involve the administration of radioactive labeled delivery system with the subsequent measurement of radioactivity in the tissues, at regular intervals of time, where the delivery system is supposed to adhere. The higher the radioactivity, the higher is the mucoadhesive property of the designed delivery system [48-50].

SITES FOR MUCOADHESIVE DRUG DELIVERY SYSTEMS

The common sites of application where mucoadhesive polymers have the ability to delivery pharmacologically active agents include oral cavity, eye conjunctiva, vagina, nasal cavity and gastrointestinal tract. The current section of the review will give an overview of the above-mentioned delivery sites.

The buccal cavity has a very limited surface area of around 50 cm^2 but the easy access to the site makes it a preferred location for delivering active agents. The site provides an opportunity to deliver pharmacologically active agents systemically by avoiding hepatic first-pass metabolism in addition to the local treatment of the oral lesions. The sublingual mucosa is relatively more permeable than the buccal mucosa (due to the presence of large number of smooth muscle and immobile mucosa), hence formulations for sublingual delivery are designed to release the active agent quickly while mucoadhesive formulation is of importance for the delivery of active agents to the buccal mucosa where the active agent has to be released in a controlled manner. This makes the buccal cavity more suitable for mucoadhesive drug delivery [51]. The various mucoadhesive polymers used for the development of buccal delivery systems include cyanoacrylates, polyacrylic acid, sodium carboxymethylcellulose, hyaluronic acid, hydroxypropylcellulose, polycarbophil, chitosan and gellan [24, 52]. The delivery systems are generally coated with a drug and water impermeable film so as to prevent the washing of the active agent by the saliva [24].

Like buccal cavity, nasal cavity also provides a potential site for the development of formulations where mucoadhesive polymers can play an important role. The nasal mucosal layer has a surface area of around 150-200 cm^2. The residence time of a particulate matter in the nasal

mucosa varies between 15 and 30 min, which have been attributed to the increased activity of the mucociliary layer in the presence of foreign particulate matter. The polymers used in the development of formulations for the development of nasal delivery system include copolymer of methyl vinyl ether, hydroxypropylmethylcellulose, sodium carboxymethylcellulose, carbopol-934P and Eudragit RL-100 [53-54].

Due to the continuous formation of tears and blinking of eye lids there is a rapid removal of the active medicament from the ocular cavity, which results in the poor bioavailability of the active agents. This can be minimized by delivering the drugs using ocular insert or patches [24]. The mucoadhesive polymers used for the ocular delivery include thiolated poly(acrylic acid), poloxamer, celluloseacetophthalate, methyl cellulose, hydroxy ethyl cellulose, poly(amidoamine) dendrimers, poly(dimethyl siloxane) and poly (vinyl pyrrolidone) [55-57].

The vaginal and the rectal lumen have also been explored for the delivery of the active agents both systemically and locally. The active agents meant for the systemic delivery by this route of administration bypasses the hepatic first-pass metabolism. Quite often the delivery systems suffer from migration within the vaginal/rectal lumen which might affect the delivery of the active agent to the specific location. The use of mucoadhesive polymers for the development of delivery system helps in reducing the migration of the same thereby promoting better therapeutic efficacy. The polymers used in the development of vaginal and rectal delivery systems include mucin, gelatin, polycarbophil and poloxamer [58-60].

Gastrointestinal tract is also a potential site which has been explored since long for the development of mucoadhesive based formulations. The modulation of the transit time of the delivery systems in a particular location of the gastrointestinal system by using mucoadhesive polymers has generated much interest among researchers around the world [61]. The various mucoadhesive polymers which have been used for the development of oral delivery systems include chitosan, poly (acrylic acid), alginate, poly (methacrylic acid) and sodium carboxymethyl cellulose [62].

POLYMERS IN MUCOSAL DRUG DELIVERY

Mucoadhesive delivery systems are being explored for the localization of the active agents to a particular location/ site. Polymers have played an important role in designing such systems so as to increase the residence time of the active agent at the desired location. Polymers used in

mucosal delivery system may be of natural or synthetic origin. In this section we will briefly discuss some of the common classes of mucoadhesive polymers.

Hydrophilic polymers

The polymers within this category are soluble in water. Matrices developed with these polymers swell when put into an aqueous media with subsequent dissolution of the matrix. The polyelectrolytes extend greater mucoadhesive property when compared with neutral polymers [63]. Anionic polyelectrolytes, e.g. poly (acrylic acid) and carboxymethyl cellulose, have been extensively used for designing mucoadhesive delivery systems due to their ability to exhibit strong hydrogen bonding with the mucin present in the mucosal layer [24, 64]. Chitosan provides an excellent example of cationic polyelectrolyte, which has been extensively used for developing mucoadhesive polymer due to its good biocompatibility and biodegradable properties [65]. Chitosan undergoes electrostatic interactions with the negatively charged mucin chains thereby exhibiting mucoadhesive property [63]. 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. In a recent study, partially neutralized poly (acrylic acid) complex was developed in the presence of levobetaxolol hydrochloride, a potent cardiac β-blocker. The delivery system was prone to dissolution as the time progressed due to the release of the incorporated drug [66]. Mucoadhesive microcapsules can be designed with same principle by using orifice-ionic gelation method. This technique has been used to design a delivery system of gliclazide, an anti-diabetic drug, using sodium alginate, sodium carboxymethyl cellulose, carbopol 934P and hydroxy propylmethyl cellulose. The delivery system showed the release of gliclazide for an extended period of time due to its mucoadhesive properties [67]. Non-ionic polymers, e.g. poloxamer, hydroxypropyl methyl cellulose, methyl cellulose, poly (vinyl alcohol) and poly (vinyl pyrrolidone), have also been used for mucoadhesive properties [63]. 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 [63, 68]. These polymers may be directly compressed in the presence of drugs so as to have a mucoadhesive delivery system [69].

Numerous polysaccharides and its derivatives like chitosan, methyl cellulose, hyaluronic acid, hydroxypropyl methylcellulose, hydroxypropyl cellulose, xanthan gum, gellan gum, guar gum, and carrageenan have found applications in ocular mucoadhesive delivery systems [63]. Cellulose and its derivates have been reported to have surface active property in addition to its film forming capability [65, 70]. Cellulose derivatives with lower surface acting property are generally preferred in ocular delivery systems as they cause reduced eye irritation. Of the various cellulose derivates, sodium carboxymethyl cellulose has been found to have excellent ocular mucoadhesive property. Cationic cellulose derivatives (e.g. cationic hydroxyethyl celluloses) have been used in conjunction with various anionic polymers for the development of sustained delivery systems [63, 71].

Hydrogels

Hydrogels can be defined as three-dimensionally crosslinked 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 like hydroxyl, amino and carboxyl groups. In general, with the increase in the crosslinking density there is an associated decrease in the mucoadhesion [72]. Thielmann et al. reported the thermal crosslinking of poly (acrylic acid) and methyl cellulose. They reported that with the increase in the crosslinking density, there was a reduction in the solubility parameters and swelling which resulted in a reduction of mucoadhesion [72]. Hydrogels prepared by the condensation reaction of poly (acrylic acid) and sucrose indicated an increase in the mucoadhesive property with the increase in the crosslinking density and was attributed to increase in the poly (acrylic acid) chain density per unit area [73]. Acrylates have been used to develop mucoadhesive delivery systems which have the ability to deliver peptide bioactive agents to the upper small intestine region without any change in the bioactivity of the peptides. In a typical experimentation, Wood and Peppas developed a system in which ethylene glycol chains were grafted on methacrylic acid hydrogels and were subsequently functionalized with wheat germ agglutinin. Wheat germ agglutinin helped in improving the intestinal residence time of the delivery system by binding with the specific carbohydrate moieties present in the intestinal mucosa [74]. In addition to the drug targeting, mucoadhesive hydrogel based formulations for improving the bioavailability of the poorly water soluble drug. Muller and Jacobs prepared a nanosuspension of buparvaquone, a poorly water soluble drug, by

incorporating it within carbopol and chitosan based hydrogels. The mucoadhesive delivery systems showed improved bioavailability of the drug when compared over the nanosuspension. This was attributed to the increased retention time of the delivery system within the gastrointestinal tract [75].

Thiolated polymers:

The presence of free thiol groups in the polymeric skeleton helps in the formation of disulphide bonds with that of the cysteine-rich sub-domains present in mucin which can substantially improve the mucoadhesive properties of the polymers (e.g. poly (acrylic acid) and chitosan) in addition to the paracellular uptake of the bioactive agents [76-80]. Various thiolated polymers include chitosan–iminothiolane, poly(acrylic acid)–cysteine, poly(acrylic acid)–homocysteine, chitosan–thioglycolic acid, chitosan–thioethylamidine, alginate–cysteine, poly(methacrylic acid)–cysteine and sodium carboxymethylcellulose–cysteine [24].

Lectin-based polymers:

Lectins are proteins which have the ability to reversibly bind with specific sugar / carbohydrate residues and are found in both animal and plant kingdom in addition to various microorganisms [81-83]. Many lectins have been found to be toxic and immunogenic which may lead to systemic anaphylaxis in susceptible individuals on subsequent exposure [24]. The specific affinity of lectins towards sugar or carbohydrate residues provides them with specific cyto-adhesive property and is being explored to develop targeted delivery systems. Lectins extracted from legumes have been widely explored for targeted delivery systems. The various lectins which have shown specific binding to the mucosa include lectins extracted from *Ulex europaeus* I, soybean, peanut and *Lens culinarius* [84]. The use of wheat germ agglutinin has been on the rise due to its least immunogenic reactions, amongst available lectins, in addition to its capability to bind to the intestinal and alveolar epithelium and hence could be used to design oral and aerosol delivery systems [85].

CONCLUSION

Of late, scientists are trying to improve the bioavailability of active agents by tailoring the properties of the delivery systems instead of designing new active agents. Mucoadhesive

polymers may provide an important tool to improve the bioavailability of the active agent by improving the residence time at the delivery site. The various sites where mucoadhesive polymers have played an important role include buccal cavity, nasal cavity, rectal lumen, vaginal lumen and gastrointestinal tract. Development of novel mucoadhesive delivery systems are being undertaken so as to understand the various mechanism of mucoadhesion and improved permeation of active agents. Many potential mucoadhesive systems are being investigated which may find their way into the market in near future.

References:

1. Webster's Encyclopedic Unabridged Dictionary of the English Language. Thunder Bay Press, Avenel (NJ, USA), 2001.
2. Kaelbe D H and Moacanin J. A surface energy analysis of bioadhesion. Polym., 18, 1977, pp. 475-481.
3. Gu J M, Robinson J R and Leung S. Binding of acrylic polymers to mucin/epithelial surfaces; Structure-property-relationship. Crit. Rev. Ther. Drug Car. Sys. 5, 1998, pp. 21-67.
4. Duchene D, Touchard F and Peppas N A. Pharmaceutical and medical aspects of Bioadhesive system for drug administration. Drug Dev. Ind. Pharm., 14, 1998, pp. 283-381.
5. Hollingsbee D A and Timmins P. Topical adhesive system, in Bioadhesion Possibilities and Future Trends, Gurny R and Junginger H E Eds., Wissenchaftliche verlag Gesellschaft, Stuttgart, 1990, pp. 140-164.
6. Wang P Y. Surgical adhesive and coating in medical engineering. Ray C D Eds., Year book Medical Publisher, Chicago, USA, 1974, pp. 1123-1128.
7. Harper C M and Ralston M. Isobutyl 2-cyanoacrylate as an osseous adhesive in the repair of osteochondral fracture. J. Biomed Mat. Res., 17, 1983, pp. 167-177.
8. Silver T H, Librizzi J, Pins G, Wang M C and Benedetto D. Physical properties of hyaluronic acid and hydroxypropylmethylcellulose in sol; Evaluation of coating abilities. J. Appl. Biomat. l5, 1979, pp. 89-98.
9. Beachy E H. Bacterial adherence, series B, Vol 6, Chapman and Hall, London and New York, 1980.

10. Boedecker E C. Attachment of organism to the gut mucosa. Vol I and II, CRC Press, Boca Raton, Florida, 1984.
11. Mergenhagen, S. E. and Rosan, B., Molecular basis of oral microbial adhesion. Am. Soc. Microbio., 1985, Washington D.C.
12. Horstedt P, Danielsson A, Nyhlin H, Stenling R and Suhr O. Adhesion of bacteria to the human small intestinal mucosa. Scandinavian J. Gastroenterology, 24, 1989, pp. 877-885.
13. Peppas N A and Buri P A. Surface, interfacial and molecular aspects of polymer bioadhesion on soft tissues. J. Control. Release., 2, 1985, pp. 257-275.
14. Woodley J. Bioadhesion: New Possibilities for Drug Administration. Clin. Pharmacokinet., 40 (2), 2001, pp. 77-84.
15. Harding SE, Davis SS, Deacon MP and Fiebrig I. Biopolymer mucoadhesives. Biotechnol. Genet. Eng. Rev. 16, 1999, pp. 41-86.
16. Scrivener C A and Schantz C W. Penicillin: new methods for its use in dentistry. J. Am. Dental Assoc., 35, 1947, pp. 644-647.
17. Rothner J T, Cobe H M, Rosenthal S L and Bailin J. Adhesive penicillin ointment for topical application. J. Dent. Res., 28, 1949, pp. 544-548.
18. Keutscher A H, Zegarelli E V, Beube F E, Chiton N W. A new vehicle (Orabase) for the application of drugs to the oral mucus membranes, Oral Pathol., 12, 1959, pp. 1080-1089.
19. Chen J L and Cyr G N. Compositions producing adhesion through hydration, in Adhesion in Biological Systems, Manly R S Eds, Academic Press, New York, 1970, pp.163-167.
20. Park J B. Acrylic bone cement: in vitro and in vivo property-structural relationship: a selective review. Ann. Biomed. Eng., 11, 1983, pp. 297–312.
21. Smart J D, Kellaway I W and Worthington H E C. An in vitro investigation of mucosa adhesive materials for use in controlled drug delivery. J. Pharm. Pharmacol., **36**, 1984, pp. 295-299.
22. Sudhakar Y, Kuotsu K and Bandyopadhyay A K. Review: Buccal bioadhesive drug delivery - A promising option for orally less efficient drugs. J. Control. Release, 114, 2006, pp. 15-40.
23. Smart J D. The basics and underlying mechanisms of mucoadhesion. Adv.Drug Del. Rev., 57, 2005, pp. 1556-1568.

24. Andrew G P, Laverty T P and Jones D S. Mucoadhesive polymeric for controlled drug delivery. European Journal of Pharmaceutics and Biopharmaceutics, 71 (3), 2009, pp. 505-518.
25. Hubbell J A. Biomaterials in tissue engineering. Biotechnology, 13, 1995, pp. 565-576.
26. Peppas N A and Sahlin J J. Hydrogels as mucoadhesive and bioadhesive materials: a review. Biomaterials, 17, 1996, pp. 1553–1561.
27. Wu S. Formation of adhesive bond; Polymer Interface and Adhesion. Marcel Dekker Inc, New York, 1982, pp. 359-447.
28. Smart J D. The role of water movement and polymer hydration in mucoadhesion, in Bioadhesive Drug Delivery Systems: Fundamentals, Novel Approaches and Development, Mathiowitz E, Chickering D E and Lehr C M Eds, Marcel Decker, New York, 1999, pp. 11-23.
29. Robinson J R. Rationale of bioadhesion/ mucoadhesion. In Bioadhesion Possibilities and Future Trends. Gurny R and Junginger H E Eds., Wissenchaftliche verlag Gesellschaft, Stuttgart, 1990, pp. 13-28.
30. Middleton D L, Leung S S and Robinson J R. Ocular Bioadhesive Delivery Systems: in Bioadhesive Drug Delivery Systems, Lenaerts V and Gurny R Eds., CRC Press, 1990, pp. 189-192.
31. Tiwari D, Goldman D, Sause R and Madan P L. Evaluation of polyoxyethylene homopolymers for buccal bioadhesive drug delivery device formulations. AAPS Pharm Sci. 1**,** 1999, pp. E13.
32. Huang Y, Leobandung W, Foss A and Peppas N A. Molecular aspects of muco- and bioadhesion: tethered structures and site-specific surfaces. J. Control. Release., 65, 2000, pp. 63-71.
33. Miller N S, Chittchang M and Johnston T P. The use of mucoadhesive polymers in buccal drug delivery. Adv. Drug De.l Rev., 57, 2005, pp. 1666– 1691.
34. Flory P J. Principle of Polymer Chemistry, Cornell University Press, Ithaca, New York, 1953, pp. 541-556.
35. Lee J W, Park J H, Robinson J R. Bioadhesive-based dosage forms: The next generation. Journal of Pharmaceutical Sciences. 89 Issue 7, 2000, pp. 850 – 866.

36. Lee J W, Park J H and Robinson J R. Bioadhesive Dosage Form: The Next Generation. J.Pharm. Sci., 89 (17), 2000, pp. 850-866.
37. Park K, Ch'ng H S and Robinson J R. Alternative approaches to oral-controlled drug delivery: bioadhesive and in situ systems. In Recent advances in Drug Deliverty System Anderson JM and Kim SW Eds, Plenum Press, New York, 1984, pp.163
38. Park K and Robinson J R. Bioadhesive polymers as platforms for oral controlled drug delivery; methods to study bioadhesion. Int. J. Pharm., 19, 1984, pp. 107.
39. Ch'ng H S, Park K, Kelly P and Robinson J R. Bioadhesive polymers as platform for oral controlled drug delivery. II Synthesis and evaluation of some swelling, water insoluble bioadhesive polymers. J. Pharm. Sci., 74, 1985, pp. 399-404.
40. Solomonidou D, Cremer K, Krumme M and Kreuter J. Effect of carbomer concentration and degree of neutralization on the mucoadhesive properties of polymer films. J. Biomater. Sci., 12, 2001, pp. 1191-1205.
41. Park H, Amiji M and Park K. Mucoadhesive hydrogels effective at neutral pH. Proc. Int. Symp. Control. Release Bioact. Mater., 16 , 1989, pp. 217-218.
42. Bonferoni M C, Chetoni P, Giunchedi P, Rossi S. Carrageenan–gelatin mucoadhesive systems for ion-exchange based ophthalmic delivery: in vitro and preliminary in vivo studies. European Journal of Pharmaceutics and Biopharmaceutics, 57, 2004, pp. 465–472.
43. Eouani C, Piccerelle P, Prinderre P, Bourret E, Joachim J. In-vitro comparative study of buccal mucoadhesive performance of different polymeric films. European Journal of Pharmaceutics and Biopharmaceutics, 52, 2001, pp. 45-55
44. Ndesendo V M K, Pillay V, Choonara Y E, Khan R A, Meyer L, Buchmann E, Rosin U. In vitro and ex vivo bioadhesivity analysis of polymeric intravaginal caplets using physicomechanics and computational structural modeling. International Journal of Pharmaceutics, 370, 2009, pp. 151–159.
45. Thirawong N, Nunthanid J, Puttipipatkhachorn S, Sriamornsak P. Mucoadhesive properties of various pectins on gastrointestinal mucosa: An in vitro evaluation using texture analyzer. European Journal of Pharmaceutics and Biopharmaceutics. 67 (1), 2007, pp. 132-140.

46. Perumal V A, Lutchman D, Mackraj I, Govender T. Formulation of monolayered films with drug and polymers of opposing solubilities. International Journal of Pharmaceutics, 358, 2008, pp. 184–191
47. Chowdary K P R and Srinivasa Rao Y. Design and In Vitro and In Vivo Evaluation of Mucoadhesive Microcapsules of Glipizide for Oral Controlled Release: A Technical Note. AAPS PharmSci Tech, 4 (3), 2003, Article 39.
48. Takeuchi H, Thongborisute J, MatsuiY, Sugihara H, Yamamoto H and Kawashima Y. Novel mucoadhesion tests for polymers and polymer-coated particles to design optimal mucoadhesive drug delivery systems. Advanced Drug Delivery Reviews, 57(11), 2005, pp. 1583-1594
49. Durrer C , Irache J M, Puisieux F, Duchêne D, Ponchel G. Mucoadhesion of Latexes. II. Adsorption Isotherms and Desorption Studies. Pharmaceutical Research, 11 (5), 1994, pp. 680-683.
50. Kreuter J, Müller U and Munz K. Quantitative and microautoradiographic study on mouse intestinal distribution of polycyanoacrylate nanoparticles. International Journal of Pharmaceutics, 55 (1), 1989, pp. 39-45.
51. Shojaei A H. Buccal Mucosa As A Route For Systemic Drug Delivery: A Review. J Pharm Pharmaceut Sci (www.ualberta.ca/~csps) 1 (1),1998, pp. 15-30
52. Remuñán-López C, Portero A, Vila-Jato J L, Alonso M J. Design and evaluation of chitosan/ethylcellulose mucoadhesive bilayered devices for buccal drug delivery. Journal of Controlled Release. 55 (2-3), 1998, pp. 143-152.
53. http://www.nsti.org/Nanotech2009/abs.html?i=262
54. Semalty M, Semalty A, Kumar G. Formulation and characterization of mucoadhesive buccal films of glipizide. Indian Journal of Pharmaceutical Sciences, 70 (1), 2008, pp. 43-48.
55. Hornof M, Weyenberg W, Ludwig A, Bernkop-Schnürch A. Mucoadhesive ocular insert based on thiolated poly(acrylic acid): development and in vivo evaluation in humans. Journal of Controlled Release, 89 (3), 2003, pp. 419-428
56. Sultana Y, Aqil M and Ali A. Ocular inserts for controlled delivery of pefloxacin mesylate: Preparation and evaluation. Acta Pharm., 55, 2005, pp. 305-314.

57. Wagh V D, Inamdar B, Samanta M K. Polymers used in ocular dosage form and drug delivery systems. Asian Journal of Pharmaceutics, 2 (1), 2008, pp. 12-17.
58. Elhadi S S A, Mortada N D, Awad G A S, Zaki N M and Taha R A. Development of in situ gelling and mucoadhesive mebeverine hydrochloride solution for rectal administration. Saudi Pharm. Journal, 11 (4), 2003, pp. 150-171.
59. Neves J d, Amaral M H, Bahia M F. Vaginal Drug Delivery: in Pharmaceutical Manufacturing Handbook, Gad S C Ed., John Willey & Sons Inc, NJ, USA, 2007, pp. 809-878.
60. Choi H G, Oh Y K, Kim C K. In situ gelling and mucoadhesive liquid suppository containing acetaminophen: enhanced bioavailability. International Journal of Pharmaceutics. 165 (1), 1998, pp. 23-32.
61. Asane G S. Mucoadhesive Gastro Intestinal Drug Delivery System: An Overview. Pharmainfo.net, 5 (6), 2007. Available at: http://www.pharmainfo.net/reviews/mucoadhesive-gastro-intestinal-drug-delivery-system-overview
62. Schnürch A B. Mucoadhesive systems in oral drug delivery. Drug Discovery Today: Technologies, 2 (1), 2005, pp. 83-87.
63. Ludwig A. The use of mucoadhesive polymers in ocular drug delivery. Advanced Drug Delivery Reviews. 57 (11), 2005, pp. 1595-1639.
64. Rossi S, Bonferoni M C, Ferrari F and Caramella C. Drug release and washability of mucoadhesive gels based on sodium carboxymethylcellulose and polyacrylic acid. Pharmaceutical development and technology, 4 (1), 1999, pp. 55-63.
65. Portero A, Osorio D T, Alonso M J and López C R. Development of chitosan sponges for buccal administration of insulin. Carbohydrate Polymers. 68 (4), 2007, pp. 617-625.
66. Lele BS and Hoffman AS. Insoluble ionic complexes of polyacrylic acid with a cationic drug for use as a mucoadhesive, ophthalmic drug delivery system. J Biomater Sci Polym Ed., 11(12), 2000, pp. 1319-31.
67. Prajapati S K, Tripathi P, Ubaidulla U and Anand V. Design and Development of Gliclazide Mucoadhesive Microcapsules: In Vitro and In Vivo Evaluation. AAPS PharmSciTech, 9 (1), 2008, pp. 224-230.

68. Hui Hand Robinson J R. Ocular delivery of progesterone using a bioadhesive polymer. International Journal of Pharmaceutics. 26 (3), 1985, pp. 203-213.
69. Juliano C, Gavini E, Cossu M, Bonferoni M.C, Giunchedi P. Mucoadhesive alginate matrices containing sodium carboxymethyl starch for buccal delivery: In vitro and in vivo studies. Journal of Drug Delivery Science and Technology, 14 (2), 2004, pp. 159-163.
70. Benedetto D A, Shah D O, Kaufman H E. The instilled fluid dynamics and surface chemistry of polymers in the preocular tear film. Investigative Ophthalmology, 14 (12), 1975, pp. 887-902.
71. Marlin L and Yamamoto R K. Muco-adhesive polymers. United States Patent 5358706. Available at: http://www.freepatentsonline.com/5358706.html
72. Thielmann1 F, Naderi1 M, Khutoryanskiy V, Khutoryanskaya O. Mucoadhesive hydrogel films based on blends of poly(acrylic acid) and methylcellulose. Available at: http://www.aapsj.org/abstracts/NBC_2007/NBC07-000679.PDF**.**
73. Warren S J and Kellaway I W. The synthesis and in vitro characterization of the mucoadhesion and swelling of poly(acrylic acid) hydrogels. Pharm Dev Technol., 3(2), 1998, pp. 199-208.
74. Kristy M. Wood and Nicholas A. Peppas. Mucoadhesive Oral Insulin Delivery Systems Using Lectin Functionalized Complexation Hydrogels. Available at: http://aiche.confex.com/aiche/2005/preliminaryprogram/abstract_31567.htm
75. Müller R H and Jacobs C. Buparvaquone mucoadhesive nanosuspension: preparation, optimisation and long-term stability. International Journal of Pharmaceutics, 237 (1-2), 2002, pp. 151-161.
76. Soo P L, Luo L, Maysinger D and Eisenberg A. Incorporation and release of hydrophobic probes in biocompatible polycaprolactone-block-poly (ethylene oxide) micelles: implications for drug delivery. Langmuir, 18, 2002, pp. 9996-10004.
77. Saviae R, Eisenberg L L A and Maysinger D. Micellar nanocontainers distributeto defined cytoplasmic organelles. Science, 300, 2003, pp. 615-618.
78. Allen C, Maysinger D and Eisenberg A. Nano-engineering block copolymer aggregates for drug delivery. Col. Surf. B: Biointerfaces, 16, 1999, pp. 3-27.
79. Kast C E, Guggi D, Langoth N and Bernkop-Schnürch A. Pharm. Res., 20, 2003, pp. 931 936.

80. Leitner V M, Guggi D and Bernkop-Schnürch A. 5th Central Eur. Symp. Pharm. Technology, Ljubljana, Slovenia, 2003.
81. Lehr C M. Lectin-mediated drug delivery: the second generation of bioadhesives. J. Control. Release, 65, 2000, pp. 19– 29.
82. Haltner E, Easson J H and Lehr C M. Lectins and bacterial invasion factors for controlling endo and transcytosis of bioadhesive drug carrier system. Euro. J. Pharm. Biopharm, 44, 1997, pp. 3-13.
83. Smart J D. Lectin-mediated drug delivery in the oral cavity. Advanced Drug Delivery Reviews. 56 (4), 2004, pp. 481-489.
84. Hietanen J and Salo O P. Binding of four lectins to normal human oral mucosa. European Journal of Oral Sciences, 92 (5), 2007, pp. 443 – 447.
85. SharmaA, Sharma S and Khuller G K. Lectin-functionalized poly (lactide-co-glycolide) nanoparticles as oral/aerosolized antitubercular drug carriers for treatment of tuberculosis. The Journal of Antimicrobial Chemotherapy, 54 (4), 2004, pp. 761-766.