Journal of Applied Pharmaceutical Science Vol. 7 (05), pp. 195-203, May, 2017
Available online at http://www.japsonline.com
DOI: 10.7324/JAPS.2017.70533
ISSN 2231-3354

Mucoadhesive Polymers and Their Mode of Action: A Recent Update

Bappaditya Chatterjee[1*], Nursazreen Amalina[1], Pinaki Sengupta[1], Uttam Kumar Mandal[2]

[1]Pharmaceutical Technology, Kulliyyah of Pharmacy, International Islamic University Malaysia, Kuantan 25200, Malaysia.
[2]Department of Pharmacy, Maharaja Ranjit Singh Punjab Technical University (MRSPTU), Bathinda, India.

ARTICLE INFO

Article history:
Received on: 17/02/2017
Accepted on: 23/04/2017
Available online: 30/05/2017

Key words:
Mucoadhesive drug delivery system, Bioadhesion, Sustained delivery, Polymers, Mucoadhesison mechanism

ABSTRACT

The potential of mucoadhesive delivery system for sustained delivery of drug has been established few decades back. Different polymeric systems such as single or combined, substituted, conjugated, pre-activated polymer (s) etc. are used to develop such delivery platform. To explain the mucoadhesion mechanism, several possible theories namely electronic theory, adsorption theory, wetting theory, diffusion theory, fraction theory and mechanical theory have been proposed. But none of these theories alone can explain the mechanism of mucoadhesion. Various mechanisms of mucoadhesion or bioadhesion between polymer and mucin such as H bonding, electrostatic interactions, di-sulfide linkage, van Der Waals attraction etc have been evidenced. Researches are focused to enrich such interaction between the mucous layer and the delivery platform by modifying the system. Wide varieties of polymers such as cationic, anionic, non-ionic, thiolated polymers etc have been used to design and develop mucoadhesive drug delivery system. Therefore reviewing and analyzing the mucoadhesive polymeric system and their mechanism of action is still relevant and necessary. The aim of this current review is to highlight the polymers which are being used under recent scientific researches with emphasis on their mechanism of mucoadhesion. The result of this critique will assist researchers to screen the mucoadhesive polymers for their designated purpose.

INTRODUCTION

Mucoadhesive formulation contains one or more hydrophilic polymers along with drug. When it comes in contact to saliva, due to the aqueous nature of saliva it becomes wet and the drug releases from the system. Simultaneously modified drug delivery system (MDDS) adheres to the mucous with some physical interaction. Mucous, secreted from salivary gland or epithelial glands is an aqueous based viscoelastic complex mixture of proteins, nucleic acid, immunoglobulins, enzymes, lipids and several ionic species (Russo *et al.*, 2016). Functionally mucus membrane or mucosa provides a protective barrier, an adhesive function and lubricant effect (Bader and Putnam, 2013). The success of MDDS depends on the ability of the polymer/s to retain at the mucous layer and to sustain the drug release.

This indicates the importance of polymeric properties for successful development of mucoadhesive preparation. In general polymers consisting carboxyl, amine or hydroxyl groups with certain molecular weight have potential to prolong retention of the system with mucous layer (Bader and Putnam, 2013). Cellulose derivatives, chitosan, pectin, hyaluronic acids, alginates, thiolated derivatives are few examples of commonly applicable mucoadhesive polymers. In different published reviews the construction or composition of mucous layer, the theory of mucoadhesison has been addressed extensively (Smart, 2014). In this review different polymers that are used in recent times to design and develop MDDS are discussed with special emphasis on the mechanism of mucoadhesion exerted by respective polymer (s).

* *Corresponding Author*
Bappaditya Chatterjee, Pharmaceutical Technology, Kulliyyah of Pharmacy, International Islamic University Malaysia, Kuantan 25200, Malaysia. Email: bdpharmaju @ gmail.com

CHALLENGES BY MUCUS MEMBRANE TO DRUG DELIVERY

Mucus layer, also known as mucosal membrane creates challenges to the drug delivery system and drug absorption due to its physicochemical nature and composition. Mucus is a complex secretion of mucus layer which consist of water and mucin. It forms a gel like layer on the epithelial membrane of the oral cavity, nose or some other body cavities. Chemically mucin is glycoprotein which is composed of single chain amino acid backbones (mainly serine, threonine and proline) with branched oligosaccharide chains containing N-acetyl galactosamine, N acetyl glucosamine, fructose, galactose etc. (Bader and Putnam, 2013). The dynamic formation and fate of mucin has made a non-stagnant mucin composition in the body cavities. This dynamic nature influences the mucus composition which in turn creates a challenge to prolonged muacoadhesion by the drug delivery system and drug absorption. The formation and fate of mucus are a major biological factor behind the retention of delivery system on the mucus membrane (Russo *et al.,* 2016). The mucus formation rate may also suffer from patient variation, fasted state-fed state, and disease conditions such as peptic ulcer, ulcerative colitis, bacterial or fungal infection etc. The thickness of gel like mucus layer also varies in such conditions. Therefore to design an optimized MDDS for all type of patients is really challenging. The soluble mucin molecule may react with the adhesive delivery system prior to attaching to the mucus membrane which may limit the bio-adhesion. Moreover, mucus layer itself causes decrease in drug absorption by reducing diffusion through it and by binding with the drug molecules (Khanvilkar *et al*., 2001; Lai *et al*., 2009).

MUCOADHESION THEORIES AND MECHANISMS

There are several general theories that can explain mucoadhesion such as electronic theory, adsorption theory, wetting theory, diffusion theory, fraction theory and mechanical theory. For an overview, the theories explained by different researchers are summarized by Table 1.

Combination of all the possible theories together helps in explaining several mechanisms about mucoadhesion. The dosage form needs to become swell and spread on the mucus, which explains the wetting theory.

Next, within the mucus-polymer interface due to electric charges distribution (electronic theory) linkages might be created (adsorption theory). Following that, the polymer and protein chains diffuse together (diffusion theory) and entangle together, forming further bonding (electronic and adsorption theories) for longer adhesion. These mechanisms also can be categorized into two, which are contact stage and consolidation stage, explained by Fig 1.

During contact stage, wetting will occur between dosage form and mucus surface. During consolidation stage the plasticizing and adhesion activity of the polymers are activated by the moisture that promotes formation of hydrogen bonds and van Der Waals force. Diffusion theory also explains the consolidation phase where the glycoprotein of mucus layer and the polymer molecules inter-diffuses and form secondary bonds. This will strengthen and prolong the adhesion. It can be said that bioadhesion or mucoadhesion cannot be explained by a single theory rather it is better explained by combining all or some of the above mentioned mechanisms.

Table 1: Theories of mucoadhesion.

Theory	Explanation
Electronic theory	Formation of electrostatic attraction from electron transfer between mucoadhesive polymer and mucous membrane that possess different electronic charges [Smart,2014, Smart, 2005].
Adsorption theory	Adhesion between mucus and polymer that is achieved via intermolecular interactions [Smart, 2014].
Wetting theory	Capability of mucoadhesive polymer to spread on the mucus with respect to its surface tension [Smart, 2014].
Diffusion theory	Diffusion of polymer into the mucus and vice versa, resulting in formation of an interpenetration layer [Smart, 2014].
Fracture theory	Strength required detaching two surfaces after adhesion [Leung and Robinson, 1990].
Mechanical theory	Considers the effect of surface roughness, which favors the adhesion due to an increased contact area [Leung and Robinson, 1990].

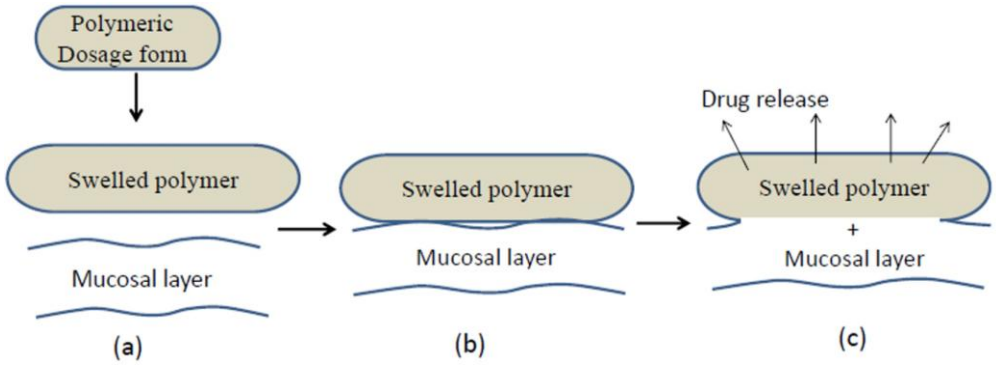

Fig. 1: Mechanism of mucoadhesion.
(a) Polymer layer and mucosal layer before contact:
(b) Both layers upon contact (starting to create bonds):
(c) Interpenetration and entanglement (bonds created for a period of time).

There are three major factors that affect mucoadhesion in a broader sense, which include environmental factor, physiological factor and polymeric factor. These factors are described in detail by different researchers earlier (Burgalassi *et al.,* 2015). In this review, we have concentrated on the polymeric factors because polymer is the most important component of a mucoadhesive drug delivery system. Environmental factor such as pH at the mucoadhesion site affects ionizable functional group of ionic polymers that are used as an adhesive layer in the formulation such as a carboxylic group for anionic polymers. Ionic polymer provides a higher degree of mucoadhesion by interaction of the ionizable functional group with charged component of mucin layer thus promoting a strong adhesiveness. Polymer will be largely ionized if the pH at the mucoadhesion site is above the pKa value of the polymer whereas it will be largely unionized if pH at mucoadhesion site is below pKa (Shaikh *et al.,* 2011). Other factor that can affect mucoadhesion is physiological factor specifically mucin turnover factor which has been discussed earlier in this article. Apart from environmental and physiological factors, major responsible factor from the formulation point of view is the polymeric nature that present in the formulation. Polymeric factors that may affect mucoadhesion include hydrogen bonding capacity and hydrophilicity, molecular weight, cross-linking, spatial conformation and concentration of polymer.

Hydrogen bonding capacity and hydrophilicity

Hydrophilic functional groups such as carboxyl and hydroxyl allow hydrogen bonding between the polymer and mucous membrane. More hydrophilic functional groups enable the formation of more hydrogen bonding. The degree of hydration of a polymer depends on its molecular structure. Hydration is important for polymer to swell on mucus layer, creating a maximal exposure for interpenetration between polymer and mucin as well as providing entanglement between them. However, excess hydration may reduce mucoadhesion and slippery mucilage will form instead (Perioli *et al.,* 2004).

Molecular weight

In general, the interpenetration of polymer molecules is better in low molecular weight polymers, while higher molecular weight polymer can entangle better (Jain *et al.,* 2012). For maximum mucoadhesion, optimum molecular weight of polymer is needed. However, it depends on the type of polymer used. Different type of polymer used will have different optimum molecular weight to achieve better bioadhesion (Edsman and Hägerström, 2005).

Cross-linking

More cross-linking provides less flexibility of the chain, thus limiting interpenetration as well as entanglement hence reducing mucoadhesion. In addition, greater cross-linking density will provide lesser swelling (Laffleur, 2014). This will reduce area for interpenetration between polymer and mucin resulting weaker adhesion. Thus, for maximum mucoadhesion, lesser cross-linking density of polymer is favored with addition of higher hydration rate and flexibility which will promote greater swelling.

Spatial conformation

Conformation of polymer molecules may affect mucoadhesion because some of the conformation may hinder functional groups that responsible for bonding with mucin. For example, helical conformation (e.g. Dextran) of a polymer may require higher concentration to produce same mucoadhesive strength as liner conformation such as polyethylene glycol (Hombach and Bernkop-Schnurch, 2010).

Concentration of polymer

This factor depends on type of dosage form. In case of solid dosage form, the higher the concentration of polymer, the stronger the mucoadhesion. However, for liquid dosage form, maximum mucoadhesion is shown when there is an optimum polymer concentration (Duchene and Peppas, 1988).

Other factor that may affect mucoadhesion is pressure applied initially during application. By giving higher pressure, it will increase the depth of interpenetration and prolong initial contact between polymer and mucous membrane resulting stronger mucoadhesion (Hombach and Bernkop-Schnurch, 2010).

POLYMERS USED IN MUCOADHESIVE DRUG DELIVERY SYSTEM

Huge numbers of polymers have been used to design and develop MDDS which are categorized as cationic, anionic, non-ionic, thiolated polymers etc. Among the chemical groups evaluated extensively for mucoadhesion, acrylate polymers, cellulose derivatives, chitosan, alginates are most prevalent. Different composite materials, chemically modified polymers and combination of two or more than polymers are also applied to design the system (Russo *et al.,* 2016). Due to lack of any compendial assay method and wide variety of experimental evaluations it is very difficult to categorize the polymers based on their mucoadhesion strength. The polymers cannot be categorized based on the source also. Because the boundary between synthetic and semi-synthetic is very narrow and often is a matter of debate. Based on the mechanism of mucoadhesion also, the classification of polymers is very difficult because either the polymers act by more than one mechanisms or the mechanism is not fully understood. Based on these considerations in this review we have described the polymers used for mucoadhesive delivery system with respect to the main chemical groups. The mechanism of mucoadhesion for each type is especially emphasized.

Acrylic acid derivative/Poly acrylate

Chemically polyacrylate is cross linked polymers of acrylic acid with divinyl glycol or polyalkenylether substitution. Methyl group substituted acrylate is a common type of plastic available at present. Among the polyacrylates, polycarbophil and carbomer have been extensively studied for polymeric platform of

MDDS. Polycarbophil and carbomer differs in the cross linked pattern and viscosity. Carbomer grades with non-residual benzene content like 934P, 971P etc are extensively studied for mucoadhesion nature (Singla *et al.,* 2000). The functional carboxylic acid groups of carbomers become ionized at moderately higher pH (around 6.2). The resultant electrostatic repulsion causes uncoiling of polymeric chain. Such uncoiling promotes mechanical entanglement and interaction of polymers with the mucus glycoprotein. Presence of numerous carboxylic groups in carbomer create favorable macromolecular conformation and increase accessibility of H bond forming groups (Mortazavi, 2002). Polycarbophil is insoluble in aqueous medium but has high swelling capacity. It was also reported enhanced H bonding by polycarbophil with glycoprotein of mucus after relaxation in intestine by Zhu *et al*. (2013). This bonding promotes penetration and interlinking of the polymer with mucus network, causing better adhesion.

Despite excellent mucoadhesive properties polyacrylates swells upon hydration resulting patient inconveniences. To overcome this drawback polyacrylates were modified by methyl group substitution forming poly methacrylate or polymethyl methacrylate. Polymethyl methacrylate (Eudragit® S100) has shown no swelling with satisfactory bioadhesion after salification with sodium salt. Drug release pattern was governed by erosion from the patch and tablets prepared from those methacrylate salts (Elhady *et al.,* 2003).

Another modification of polyacrylate was done by thiolation or cysteine conjugation targeting better bioadhesion. Thiolated polycarbophil is derived by neutralizing its carboxyl group with sodium hydroxide (NaOH) and covalent bonding with cysteine amino groups (Wasnik and Godse, 2014). The thiolated polymer forms disulfide bond (S=S) with cysteine moiety of sub-domains of mucus glycoprotein by either thio/disulfide exchange or oxidation of thiol group, resulting increased mucoadhesion. These mucoadhesive features prevented all thiolated formulations from reaching and/or adhering to the epithelial cell membrane and inhibited their absorption-enhancing effects. Therefore, sustained drug release pattern might be achieved from this backbone. Sustained drug release from thiolated polyacrylate was also demonstrated by Wasnik *et al*. (2014) where they observed higher drug release retardant property of polyacrylate-cysteine conjugate compared to non-thioalted polyacrylte. It is to note that both type of polymers were used to deliver antiparkisonism drug via buccal mucoahesive patch.

Cellulose derivative

Cellulose derivatives such as hydroxyl propyl cellulose (HPC), hydroxyl propyl methyl cellulose (HPMC), hydroxyl ethyl cellulose (HEC), carboxy methyl cellulose (CMC) are considered as first generation mucoadhesive polymers (Bader Putnam, 2013). The mechanism of adhesion involves formation of H bond between caroboxylic acid group of cellulosic polymers and glycoprotein of mucin. Stronger H bond causes deeper and stronger attachment of the delivery system with the mucous layer.

HPMC are extensively used not only for mucoadhesison properties but also for its controlled release mechanism. It has been applied to deliver various drugs via different type of dosage forms. The list includes but not limited to delivery of mebeverine HCl by thermoresponsive mucoadheisve gel incorporating poloxamer in the system (Baloğlu *et al.,* 2010), delivery of valsartan by mucoadheisve microsphere (Pardeshi *et al.,* 2012), delivery of carvedilol by mucoadhesive patch (Meher *et al.,* 2013)etc. In the last mentioned example, the researchers have combined HPMC K4M, HPMC K15M, eudragit, carbopol and methyl cellulose together to achieve better mucoadhesion along with sustained release profile. However the combination of so many polymers in a dosage form has been rarely observed.

CMC, more specifically sodium salt of CMC (Na-CMC) is also very extensively used as mucoadhesive polymer. Some recently published researches on mucoahdesive delivery system with Na-CMC include localized delivery of imiquimod by the buccal patch (Ramineni *et al.,* 2013), delivery of lysozyme by gelatin-CMC mucoadhesive films (Dekina *et al.,* 2016). In terms of mucoadhesion, CMC possesses better property than HPMC. HPMC is a non-ionic polymer and lacking of proton donating carboxylic group which causes lesser H bonding than CMC. CMC is anionic polymer which causes higher H bonding than nonionic cellulose polymers. But the mucoadhesion nature depends on the pH of the medium used for testing. In a published report, Prajapati *et al* (2008) demonstrated that mucoadhesive microcapsule prepared with gelatin showed almost the same period (hour) of adhesion to rat intestinal tissue when tested in pH 7.4 phosphate buffer solutions (Prajapati *et al.,* 2008). However, in 0.1 N HCl solution the HPMC microcapsules showed a little higher period of mucoadhesison than Na-CMC capsule. The reason behind this was not explained by the author. But it can be assumed that at higher pH, anionic polymer like CMC was not ionized and hence could not form sufficient number of H bond with tissue glycoprotein. Thiolation of CMC shows better mucoadhesion due to disulfide bond formation like thiolated polyacrylate. Thiolated CMC, prepared by cysteine conjugation showed 1.6 folds improved mucoadhesion in buccal cavity compared to non-thiolated one (Flavia & Alexie, 2016).

Chitosan

Among all mucoadhesive agents, chitosan is the most abundant polysachharide after cellulose in the world. It is one of the extensively studied polymers under countless scientific reports since early 80s (He *et al.,* 1998). Chitosan, a cationic mucoadhesive agent is basically a polysachharide derived from chitin by means of deacetylation. This is a co-polymer of glucosamine and N-acetyl-glucosamine. Chitosan is insoluble in water but soluble in dilute weak acid (Lehr *et al.,* 1992). The biocompatibility, biodegradation and low toxic nature probably has made chitosan an attractive polymeric component (He *et al.,* 1998). The mucoadhesion nature of chitosan is attributed to several mechanisms. The abundant mechanism is H bonding with glycoprotein of mucin due to presence of –OH and -NH_2 groups.

The conformational flexibility of the linear chitosan molecule also contributes to the mucoadhesion property (Alhalaweh *et al.,* 2011). Besides this, electrostatic interaction between positively charged amines of chitosan and negatively charged sialic acid residue of the mucin is considered a factor for adhesion (Jacobsen *et al.,* 2014). All these interactions cause strong mechanical fusion of polymeric chain into the mucous layer. The interaction of chitosan with mucous and its mucoadhesive phenomena is affected by both physiological factor and physicochemical properties of chitosan. The extent of mucin adsorption by chitosan increases with increasing sialic acid in mucin (Sandri *et al.,* 2012). Since the amounts of sialic acid in mucosal secretions vary, the force of adhesion of chitosan to mucus may also vary depending on the mucosa considered.

Chitosan is used for successful development of the different mucoadhesive delivery system. However, the oral delivery with chitosan containing devices is not very popular because at higher pH (6-6.5) chitosan precipitates. So in the distant region of the gastrointestinal tract chitosan may lose its mucoadhesive and permeation enhancing property (Sandri *et al.,* 2012). But chitosan is very popular in some other routes of delivery. Ocular delivery of cyclosporine A by chitosan nanoparticle showed an improved drug delivery to the ocular mucosa and also enhances drug permeation to the inner eye (Hermans *et al.,* 2014). Sound mucoadhesion along with permeation enhancing nature has made chitosan a promising component for buccal delivery also as retardation of the delivery system in the buccal mucosa increases sustainability of drug action. For instance, trimethylated chitosan was shown to deliver hydrophilic macromolecule successfully to the buccal cavity (Sandri *et al.,* 2005). Apart from these routes, nasal delivery or vaginal delivery using chitosan as a component of the system is also reported (El-Kamel *et al.,* 2002; Na *et al.,* 2010).

Modified chitosan

Thiolated chitosan (TC) is a disulfide substituted chitosan that might be prepared by reacting chitosan with thioglycolic acid or by cysteine conjugation. It is evidenced from many scientific literatures that TC possesses improved mucoadhesion and permeation properties compared to chitosan (Peh *et al.,* 2000). Advantages of TC over chitosan include more hydrophilicity due to disulfide bonds, more efficient uptake process for macromolecules delivered, enzyme inhibitory activity, opening of tight cellular junction for improved drug permeation etc (Anitha *et al.,* 2011). Thiolated chitosan is extensively evaluated for use in buccal or oral cavity with prolonged mucoadhesion and hydration effect (Laffleur *et al.,* 2015). Apart from this route, a cysteine conjugated thiolated chitosan nanoparticle was developed and studied by Yin *et al*. for oral delivery of insulin (Yin *et al.,* 2009). The authors reported 1.8-2.6 folds of improvement of insulin transport through rat intestine compared to insulin solution. In a recent research, a pH responsive thiolated chitosan nanoparticle is developed and successfully applied to deliver low molecular weight heparin orally with improved bioavailability (Fan *et al.,* 2016).

Apart from thiolation, different substituted or cross-linked chitosan is also used by the researchers in order to improve its mucoadhesion efficiency such as N-trimethyl chitosan which is a partially quaternized chitosan made from reaction of chitosan and EDTA (Sandri *et al.,* 2005) or cross-linked catecholized chitosan hydrogel for buccal delivery of lidocaine (Xu *et al.,* 2015).

Alginates

Alginate is a natural and biodegradable anionic polymer that is typically obtained from brown seaweed. It has low toxicity and relatively low cost thus making it extensively being investigated in numerous studies to prepare microparticles, beads with excellent bioadhesive features (Lee and Mooney, 2012). Mostly sodium or calcium salt of alginate is used in pharmaceutical research (Tønnesen and Karlsen, 2002). Alginate has good mucoadhesion property due to the presence of carboxylic acid moiety which causes H bonding with the glycoprotein of mucin (Patil and Sawant, 2009). In acidic pH alginate does not swell much resulting much coiling of the polymeric chain. Uncoiling of polymeric chains raises possibilities of entanglement with mucous layer and hence more mucoadhesion occurs. Therefore alginate gives comparatively less mucoadhesion in acidic pH (Kesavan *et al.,* 2010). In most of the cases alginate is used to formulate beads or microsphere by crosslinked with divalent cation commonly Ca^{++}. But if concentration of Ca^{++} is increased more alginate becomes crosslinked with Ca^{++} and polymer chain flexibility reduces. This in turn reduces mucoadhesion strength (Patil and Sawant, 2009).

Combination of alginate with different other bioadhesive carrier to design drug delivery system is very popular in pharmaceutical researchers, for example; chitosan-alginate bead for vaginal delivery of chlorhexidine digluconate (Abruzzo *et al.,* 2013), jackfruit seed starch-alginate microsphere of metformin HCl (Nayak and Pal, 2013), tamarind seed polysachharide-alginate beads for gliclazide oral delivery (Pal and Nayak, 2012) etc. Strength of mucoadhesion by alginate depends on its molecular weight. It has been shown that low molecular weight alginate chain remains comparatively rigid than high molecular weight alginate. This nature makes low molecular weight alginate less susceptible to bridge with mucin molecule resulting lower bioadhesion than high molecular weight alginate (Menchicchi *et al.,* 2015).

Pectin

Pectin is a natural, biodegradable, biocompatible, non-toxic heterogenous polysaccharide that is extracted from citrus peel or apple pomace. It contains linear chains of (1–4)-linked a-D-galacturonic acid residues that have carboxyl groups (Sharma and Ahuja, 2011). Mucoadhesion mechanism of pectin has been explained in two ways; formation of H bond with mucin and electrostatic interaction between pectin and mucin molecule

(Sriamornsak *et al.,* 2010). H bonding occurs due to the presence of carboxylic acid group in pectin. If pectin is mixed with mucin in aqueous solution it showed formation of aggregates which increase with increasing amount of pectin (Russo *et al.,* 2016). This established increasing adhesion with mucin molecule. Mucin and pectin both are negatively charged. Therefore increasing concentration of pectin in aqueous medium causes increase in electrostatic repulsion with mucin. This repulsion causes uncoiling of polymer chain facilitating more entanglement and adhesion. Interesting fact is that the theories of physical adsorption by formation of H bonding and electrostatic repulsion are contradictory to each other. But both are described by different researchers. Better mucoadhesion was reported by Jorgensen *et al* (2011) with low molecular weight pectin compared to high molecular weight (Joergensen *et al.,* 2011). The author explained low molecular weight pectin can penetrate mucin layer easily and form intermolecular bonding better than high molecular weight pectin.

To characterize pectin the degree of amidation (DA) and the degree of esterification (DE) is very important. Sometimes the carboxylic acid groups of galacturonic acid are substituted by methyl group naturally or are reacted with ammonia to form carboxamide group. A study was made to prepare and evaluate the pectin-based mucoadhesive buccal disc containing carbenoxolone sodium for treatment of aphthous ulcers (Wattanakorn *et al.,* 2010). The pectin buccal discs were prepared by direct compression. The discs were categorized into two main categories following DE which were low-DE (38%) pectin and high-DE (70%) pectin. It was found that low-DE pectin showed higher mucoadhesion strength compared to high-DE pectin. It might be due to the difference in molecular weight of esterified pectin and presence of methoxy groups. A higher MW and the presence of hydrophobic moieties in pectin structure may result in the lower thermodynamic work of adhesion (Wattanakorn *et al.,* 2010). Not only as a single mucoadhesive component, pectin was also combined with other polymers to exploit the mucoadhesion property by many researchers, for example: pectin-gellan gum beads (Prezotti *et al.,* 2014), modified pectin-acrylate combined carrier, pectin - jackfruit seed starch beads (Pal and Nayak, 2012) etc. Thiolation of pectin was shown to possess superior mucoadhesion than normal pectin. In a study by Sharma and Ahuja (2011), a comparison between metformin loaded gel beads made up of pectin esterified by thioglycolic acid and normal pectin showed that the former had 2.5 folds higher strength of bioadhesion with respect to ex-vivo bioadhesion study. The mechanism lies behind is the stronger disulfide linkage between –SH group of thiolated pectin and mucin compared to H bonding between –OH group of pectin and mucin (Sharma and Ahuja, 2011).

Hyaluronic acid

Hyaluronic acid (HA), an anionic biopolymer with high molecular weight is composed of alternating disaccharide units of D-glucuronic acid and N-acetyl-Dglucosamine with β (1→4) inter-glycosidic linkage (Oh *et al.,* 2010). This is biodegradable as well as highly biocompatible in nature. The random coil structure in solution might be behind the bioadhesive property of HA by entanglement with the mucous layer (Russo *et al.,* 2016). Low molecular weight HA was shown to form superior mucoadhesion compared to the high molecular weight (Mayol *et al.,* 2008) A thermosensitive and mucoadhesive polymeric platform was designed by Mayol *et al.* (2008) by incorporating low molecular weight HA with poloxamer. The model showed good mucoadhesion behavior with sustained drug release (Mayol *et al.,* 2008).

Sodium hyaluronate was used as component of MDDS in order to deliver drugs to the brain via intra-nasal administration. In a recent study a comparison is done between HA, thiolated HA and pre-activated thiolated HA (pre-activation by mercaptonicotinamide) with respect to bioadhesion to vaginal mucosa (Nowak *et al.,* 2015). The order of adhesion time is as follows; HA<thiolated HA<pre-activated thiolated HA. Presence of disulphide bonds between thiolated HA and glycoprotein of mucin is attributed to the stronger adhesion than normal HA where the formation of H bonding is the responsible factor for adhesion. In contrast to HA and thiolated HA, preactivated thiolated HA did not detach from the mucosa during the whole experiment. This can be explained by the moderate swelling behavior and by preactivation with MNA which led to higher stability because of less oxidation of thiol groups and higher attendance to form disulfide bonds with the mucus (Nowak *et al.,* 2015).

Use of polymers in newer MDDS

Conventionally mucoadhesive polymers are used to design and develop different drug delivery platforms such as gel, patch, microspheres, beads etc via buccal, nasal, vaginal, oral etc routes. Examples of such systems are widely available under current scientific domain. Other than these, few relatively newer delivery systems are also reported and becoming popular among the researchers. The most prevalent is mucoadhesive nano-carriers. As a recent example; Luo, Teng, Li and Wang designed and developed a solid lipid nanoparticle coated with chitosan. Due to chitosan the nanoparticle showed improved mucoadhesive property following oral delivery (Luo *et al.,* 2015). In another recent work, Oh and Borros (2016) studied mucoadhesion as well as mucous permeability of thiolated chitosan made nanoparticle and observed significant results with respect to both properties (Oh and Borrs, 2016). A nanogel was prepared using conjugated chitosan and carboxymethyl chitosan by electrostatic interaction (Feng *et al.,* 2015). It was shown that the nanogel adhered to the intestinal mucosa for prolonged duration of time which in turn results into better drug action in colorectal cancer. In a recent review by Sosnik *et al.* (2014) the usage of mucoadheisve polymers for non-parenteral delivery system has been described. As per the authors, all the three types of polymers such as natural (pectin, alginate, chitosan, hyaluronic acid etc), synthetics (acrylic acid derivatives) and semi-synthetic (cellulose derivatives) are used for the nanoparticulate mucoadhesive delivery system. In

another interesting work Abd-Elbarry *et al* (2016) has explained the formulation of HPMC coated buccal sponge loaded with carvedilol nanoemulsion. Carvedilol by their developed delivery system showed more sustained release profile and 1.5 folds higher relative bioavailability in human volunteer compared to conventional tablet. In another non-conventional mucoadhesive approach, an in-situ ocular mucoadhesive gel was developed by Horvat *et al* (2015) where the authors have used thiolated poly aspartic acid which can also be considered as a non-conventional mucoadhesive carrier. The thio groups of poly aspartic acid are able to from disulphide linkage with mucin glycoprotein and hence cause mucoadhesion.

The delivery system showed promising drug release up to 24 hrs (Horvát *et al.,* 2015). Apart from these few more researches on newer type of MDDS are highly prevalent in the pharmaceutical or bio-engineering field for example; delivery of insulin via intestinal device (Gupta *et al.,* 2016) or floating bioadhesive multiparticulate delivery via hollow structure (Zhang *et al.,* 2016).

CONCLUSION

This review presents the mucoadhesive or bioadhesive polymers, both conventional and substituted or conjugated emphasizing their mechanism of mucoadhesion. It can be concluded from the current study that research with conventional MDDS with conventional polymer is already a past trend. The reason is the maximum mucoadhesion occupancy with a single conventional polymer is already being achieved or studied. It is found from the current study that use of composite material, combined polymer systems, substituted or conjugated polymers are more popular to design a MDDS with desired criteria. Among the substituted polymers, it can be assumed, although not exclusively, that thiolated polymer is more prevalently explored by the researchers than other substituted mucoadhesive polymers. The reason is prolonged mucoadhesion due to the presence of the thiol group.

Thiolated chitosan is one of the most abundant mucoadhesive polymers among the substituted or conjugated system. Mucoadhesive platform loaded with nanoparticulate dosage form is one of the recent advancements of mucoadhesive research. But the physiological challenges and the constraints on in-vivo pharmacokinetic studies are required to overcome in order to make mucoadhesive delivery platform more successful in future.

Financial support and sponsorship: NIL.

Conflict of Interests: There are no conflicts of interest.

REFERENCES

Abruzzo A, Bigucci F, Cerchiara T, Saladini B, Gallucci MC, Cruciani F. Chitosan/alginate complexes for vaginal delivery of chlorhexidine digluconate. Carbohydr Polym, 2013;91(2):651–8.

Ahmed A-E, Amna M, Mina Ibrahim, Tadrosa Ahmed AA-E. Laminated sponges as challenging solid hydrophilic matrices for the buccal delivery of carvedilol microemulsion systems: Development and proof of concept via mucoadhesion and pharmacokinetic assessments in healthy human volunteers. Eur J Pharm Sci, 2016;82:31–44.

Alhalaweh A, Vilinska A, Gavini E, Rassu G, Velaga SP. Surface thermodynamics of mucoadhesive dry powder formulation of zolmitriptan. AAPS PharmSciTech, 2011;12(4):1186–92.

Anitha A, Deepa N, Chennazhi KP, Nair S V., Tamura H, Jayakumar R. Development of mucoadhesive thiolated chitosan nanoparticles for biomedical applications. Carbohydr Polym, 2011; 83(1): 66–73.

Bader RA, Putnam DA. 2013. Engineering Polymer Systems for Improved Drug Delivery. New Jersy, USA: Wiley.

Baloğlu E, Karavana SY, Hyusein IY, Köse T. Design and formulation of mebeverine HCl semisolid formulations for intraorally administration. AAPS PharmSciTech, 2010;11(1):181–8.

Burgalassi S, Monti D, Tampucci S. Chetoni P. In vitro evaluation of some parameters involved in mucoadhesion of aqueous polymeric dispersions. Pharm Dev Tech, 2015; 20(8): 927-34.

Chatterjee B, Almurisi SH, Dukhan AA, Mandal UK, Sengupta P. Controversies with self-emulsifying drug delivery system from pharmacokinetic point of view. Drug Deliv, 2016; 23(9): 3639-52.

Choudhury H, Gorain B, Chatterjee B, Mandal UK, Sengupta P, Tekade RK. Pharmacokinetic and Pharmacodynamic Features of Nanoemulsion Following Oral, Intravenous, Topical and Nasal Route. Curr Pharm Design. (2016) [Online] Available at http://www.eurekaselect.com/147857/article. [Accessed on 02 Feb 2017]

Dekina S, Romanovska I, Ovsepyan A, Tkach V, Muratov E. Gelatin/carboxymethyl cellulose mucoadhesive films with lysozyme: Development and characterization. Carbohydr Polym, 2016;147:208–15.

Duchene D, F T, Peppas N. Pharmaceutical and medical aspects of bioadhesive systems for drug administration. Drug Dev Ind Pharm, 1988;14(2–3):283–318.

Edsman K, Hägerström H. Pharmaceutical applications of mucoadhesion for the non-oral routes. J Pharm Pharmacol, 2005;57(1):3–22.

Elhady SSA, Mortada ND, Awad GS, Zaki NM, Taha R. Development of in Situ Gelling and Mucoadhesive Mebeverine Hydrochloride Solution for Rectal Administration. Saudi Pharm J,2003;11(4): 159-71.

El-Kamel A, Sokar M, Naggar V, Al Gamal S. Chitosan and sodium alginate-based bioadhesive vaginal tablets. AAPS PharmSci, 2002;4(4):224-30.

Fan B, Xing Y, Zheng Y, Sun C, Liang G. pH-responsive thiolated chitosan nanoparticles for oral low-molecular weight heparin delivery: in vitro and in vivo evaluation. Drug Deliv, 2016;23(1):238–47.

Feng C, Li J, Kong M, Liu Y, Cheng XJ, Li Y, *et al*. Surface charge effect on mucoadhesion of chitosan based nanogels for local anti-colorectal cancer drug delivery. Colloids Surfaces B Biointerfaces, 2015;128:439–47.

Flavia L, Alexie M. Development of mucoadhesive thio-carboxymethyl cellulose for application in buccal delivery of drugs. Ther Deliv, 2016;7(2):63–71.

Gupta V, Hwang BH, Doshi N, Banerjee A, Anselmo AC, Mitragotri S. Delivery of Exenatide and Insulin Using Mucoadhesive Intestinal Devices. Ann Biomed Eng, 2016;44(6):1993–2007.

He P, Davis SS, Illum L. In vitro evaluation of the mucoadhesive properties of chitosan microspheres. Int J Pharm, 1998;166(1):75–88.

Hermans K, Van Den Plas D, Kerimova S, Carleer R, Adriaensens P, Weyenberg W, *et al*. Development and characterization of mucoadhesive chitosan films for ophthalmic delivery of cyclosporine A. Int J Pharm, 2014;472(1–2):10–9.

Hombach J, Bernkop-Schnurch A. Mucoadhesive drug delivery systems. Handb Exp Pharmacol, 2010;46(197):251–66.

Horvát G, Gyarmati B, Berkó S, Szabó-Révész P, Szilágyi BÁ, Szilágyi A, *et al*. Thiolated poly(aspartic acid) as potential in situ gelling,

ocular mucoadhesive drug delivery system. Eur J Pharm Sci, 2015;67:1–11.

Jacobsen J, Meng-Lund E, Muff-Westergaard C, Sander C, Madelung P. A mechanistic based approach for enhancing buccal mucoadhesion of chitosan. Int J Pharm, 2014;461(1–2):280–5.

Jain N, Gulati N, Kumar D, Nagaich U. Microspheres: Mucoadhesion Based Controlled Drug Delivery System. RGUHS J Pharm Sci, 2012;2(3):28–40.

Joergensen L, Klosgen B, Simonsen AC, Borch J, Hagesaether E. New insights into the mucoadhesion of pectins by AFM roughness parameters in combination with SPR. Int J Pharm, 2011;411(1–2):162–8.

Kesavan K, Nath G, Pandit JK. Preparation and in vitro antibacterial evaluation of gatifloxacin mucoadhesive gellan system. DARU, 2010;18(4):237–46.

Khanvilkar K, Donovan MD, Flanagan DR. Drug transfer through mucus. Vol. 48, Adv Drug Deliv Rev. 2001; 48(2-3): 144-99.

Kumar K, Dhawan N, Sharma H, Vaidya S, Vaidya B. Bioadhesive polymers: novel tool for drug delivery. Artif cells, nanomedicine, Biotechnol, 2014;42(4):274–83.

Kyaw OM, Mandal UK, Chatterjee B. Polymeric behavior evaluation of PVP K30-poloxamer binary carrier for solid dispersed nisoldipine by experimental design. Pharm Dev Tech, 2017; 22(1) :2-12.

Laffleur F, Fischer A, Schmutzler M, Hintzen F, Bernkop-Schn??rch A. Evaluation of functional characteristics of preactivated thiolated chitosan as potential therapeutic agent for dry mouth syndrome. Acta Biomater, 2015;21:123–31.

Laffleur F. Mucoadhesive polymers for buccal drug delivery. Drug Dev Ind Pharm, 2014;40(5):591–8.

Lai SK, Wang YY, Hanes J. Mucus-penetrating nanoparticles for drug and gene delivery to mucosal tissues. Adv Drug Deliv Rev, 2009; 61(2):158–71.

Lee KY, Mooney DJ. Alginate: Properties and biomedical applications. Prog Polym Sci, 2012;37(1):106–26.

Lehr CM, Bouwstra JA, Schacht EH, Junginger HE. In vitro evaluation of mucoadhesive properties of chitosan and some other natural polymers. Int J Pharm, 1992;78(1–3):43–8.

Leung SH, Robinson JR. Polymer Structure Features Contributing to Mucoadhesion.J Control Rel, 1990; 12:187–194.

Luo Y, Teng Z, Li Y, Wang Q. Solid lipid nanoparticles for oral drug delivery: Chitosan coating improves stability, controlled delivery, mucoadhesion and cellular uptake. Carbohydr Polym, 2015;122:221–9.

Mayol L, Quaglia F, Borzacchiello A, Ambrosio L, Rotonda MI La. A novel poloxamers/hyaluronic acid in situ forming hydrogel for drug delivery: Rheological, mucoadhesive and in vitro release properties. Eur J Pharm Biopharm, 2008;70(1):199–206.

Meher JG, Tarai M, Yadav NP, Patnaik A, Mishra P, Yadav KS. Development and characterization of cellulose-polymethacrylate mucoadhesive film for buccal delivery of carvedilol. Carbohydr Polym, 2013;96(1):172–80.

Menchicchi B, Fuenzalida JP, Hensel A, Swamy MJ, David L, Rochas C, *et al*. Biophysical Analysis of the Molecular Interactions between Polysaccharides and Mucin. Biomacromolecules, 2015;16(3):924–35.

Mortazavi SA. A comparative study between the strength and duration of mucosa-adhesion of transbuccal carbomer based aqueous gels. Iran J Pharm Res, 2002;1(1):7–13.

Na L, Mao S, Wang J, Sun W. Comparison of different absorption enhancers on the intranasal absorption of isosorbide dinitrate in rats. Int J Pharm, 2010;397(1–2):59–66.

Nayak AK, Pal D. Formulation optimization and evaluation of jackfruit seed starch-alginate mucoadhesive beads of metformin HCl. Int J Biol Macromol, 2013;59:264–72.

Nowak J, Laffleur F, Bernkop-Schnrch A. Preactivated hyaluronic acid: A potential mucoadhesive polymer for vaginal delivery. Int J Pharm, 2015;478(1):383–9.

Oh EJ, Park K, Kim KS, Kim J, Yang JA, Kong JH. Target specific and long-acting delivery of protein, peptide, and nucleotide therapeutics using hyaluronic acid derivatives.J Control Rel, 2010; 141: 2–12.

Oh S, Borrs S. Mucoadhesion vs mucus permeability of thiolated chitosan polymers and their resulting nanoparticles using a quartz crystal microbalance with dissipation (QCM-D). Colloids Surfaces B Biointerfaces, 2016;147:434–41.

Pal D, Nayak AK. Novel tamarind seed polysaccharide-alginate mucoadhesive microspheres for oral gliclazide delivery: In vitro-in vivo evaluation. Drug Deliv, 2012;19(3):123–31.

Pardeshi C V., Rajput P V., Belgamwar VS, Tekade AR. Formulation, optimization and evaluation of spray-dried mucoadhesive microspheres as intranasal carriers for Valsartan. J Microencapsul, 2012;29(2):103–14.

Park H, Robinson JR. Mechanisms of Mucoadhesion of Poly(acrylic Acid) Hydrogels. Pharm Res, 1987;4(6):457–64.

Patil SB, Sawant KK. Development, optimization and in vitro evaluation of alginate mucoadhesive microspheres of carvedilol for nasal delivery. J Microencapsul, 2009;26(5):432–43.

Peh K, Khan T, Ch'ng H. Mechanical, bioadhesive strength and biological evaluations of chitosan films for wound dressing. J Pharm Pharm Sci, 2000;3(3):303–11.

Perioli L, Ambrogi V, Angelici F, Ricci M, Giovagnoli S, Capuccella M, *et al*. Development of mucoadhesive patches for buccal administration of ibuprofen. J Control Rel, 2004;99(1):73–82.

Prajapati SK, Tripathi P, Ubaidulla U, Anand V. Design and development of gliclazide mucoadhesive microcapsules: in vitro and in vivo evaluation. AAPS PharmSciTech, 2008;9(1):224–30.

Prezotti FG, Cury BSF, Evangelista RC. Mucoadhesive beads of gellan gum/pectin intended to controlled delivery of drugs. Carbohydr Polym, 2014;113:286–95.

Ramineni SK, Cunningham Jr. LL, Dziubla TD, Puleo DA, Cunningham LL, Dziubla TD, *et al*. Competing properties of mucoadhesive films designed for localized delivery of imiquimod. Biomater Sci, 2013;1(7):753.

Russo E, Selmin F, Baldassari S, Gennari CGM, Caviglioli G, Cilurzo F, *et al*. A focus on mucoadhesive polymers and their application in buccal dosage forms. J Drug Deliv Sci Technol, 2016;32:113–25.

Sandri G, Rossi S, Bonferoni MC, Ferrari F, Mori M, Caramella C. The role of chitosan as a mucoadhesive agent in mucosal drug delivery. JDrug Deliv Sci and Tech, 2012; 22: 275–84.

Sandri G, Rossi S, Bonferoni MC, Ferrari F, Zambito Y, Di Colo G, *et al*. Buccal penetration enhancement properties of N-trimethyl chitosan: Influence of quaternization degree on absorption of a high molecular weight molecule. Int J Pharm, 2005;297(1–2):146–55.

Shaikh R, Raj Singh TR, Garland MJ, Woolfson a D, Donnelly RF. Mucoadhesive drug delivery systems. J Pharm Bioallied Sci, 2011;3(1):89–100.

Sharma R, Ahuja M. Thiolated pectin: Synthesis, characterization and evaluation as a mucoadhesive polymer. Carbohydr Polym, 2011;85(3):658–63.

Singla AK, Chawla M, Singh A. Potential Applications of Carbomer in Oral Mucoadhesive Controlled Drug Delivery System: A Review. Drug Dev Ind Pharm, 2000;26(9):913–24.

Smart JD. 2014.Theories of Mucoadhesion. In: Khutoryanskiy VV, ed. Mucoadhesive Materials and Drug Delivery Systems. Sussex, UK: John Wiley & Sons .

Smart JD.The basics and underlying mechanisms of mucoadhesion. Adv Drug DelivRev,

2005;57(11): 1556–68.

Sosnik A, Das Neves J, Sarmento B. Mucoadhesive polymers in the design of nano-drug delivery systems for administration by non-parenteral routes: A review. Progress in Polymer Science, 2014; 39:2030–75.

Sriamornsak P, Wattanakorn N, Takeuchi H. Study on the mucoadhesion mechanism of pectin by atomic force microscopy and mucin-particle method. Carbohydr Polym, 2010;79(1):54–9.

Tønnesen HH, Karlsen J. Alginate in drug delivery systems. Drug Dev Ind Pharm, 2002;28(6):621–30.

Wasnik MN, Godse RD, Nair HA. Development and evaluation of buccoadhesive tablet for selegiline hydrochloride based on thiolated polycarbophil. Drug Dev Ind Pharm, 2014;40(5):632–8.

Wattanakorn N, Asavapichayont P, Nunthanid J, Limmatvapirat S, Sungthongjeen S, Chantasart D, *et al*. Pectin-based bioadhesive delivery of carbenoxolone sodium for aphthous ulcers in oral cavity. AAPS PharmSciTech, 2010;11(2):743–51.

Wen H, Park K. 2011. Oral Controlled Release Formulation Design and Drug Delivery: Theory to Practice. Sussex, UK: John Wiley & Sons.

Xu J, Strandman S, Zhu JXX, Barralet J, Cerruti M. Genipin-crosslinked catechol-chitosan mucoadhesive hydrogels for buccal drug delivery. Biomaterials, 2015;37:395–404.

Yin L, Ding J, He C, Cui L, Tang C, Yin C. Drug permeability and mucoadhesion properties of thiolated trimethyl chitosan nanoparticles in oral insulin delivery. Biomaterials, 2009;30(29):5691–700.

Zhu Z, Zhai Y, Zhang N, Leng D, Ding P. The development of polycarbophil as a bioadhesive material in pharmacy. Asian J Pharm Sci, 2013;8(4):218–27.

Zhang C, Tang J, Liu D, Li X, Cheng L, Tang X. Design and evaluation of an innovative floating and bioadhesive multiparticulate drug delivery system based on hollow structure. Int J Pharm, 2016;503(1–2):41–55.

How to cite this article:

Chatterjee B, Amalina N, Sengupta P, Mandal UK. Mucoadhesive Polymers and Their Mode of Action: A Recent Update. J App Pharm Sci, 2017; 7 (05): 195-203.