ISSN: 2320 - 4230

Journal of Drug Discovery and Therapeutics
Available Online at www.jddt.in
CODEN: - JDDTBP (Source: - American Chemical Society)
Volume 9, Issue 06, June: 2021, 01-14

Review Article

AN OVERVIEW OF MUCOADHESIVE DRUG DELIVERY SYSTEM AND MUCOADHESIVE AGENTS

[1*]Sabuj Kumar Bhattacharya, [2]Soumya Rakshit, [3]Souvik mallik, [4]Partha Sarathi Mondal, [5]Shibam Acharya, [6]Sanjoy De, [7]Bankim Chandra Nandy

[1-6]Students of School of Pharmacy, Techno India University, Kolkata, West Bengal, India.

[7]Associate Professor, School of Pharmacy, Techno India University, Kolkata, West Bengal, India.

Address for Correspondence: [*]Sabuj Kumar Bhattacharya, School of Pharmacy, Techno India University, Kolkata, West Bengal, India.

Disclosure statement: *The authors have no conflicts of interest.*

Abstract:

Drug actions can be improved by developing new drug delivery systems, such as the mucoadhesive system. The mucoadhesive drug delivery system is a popular novel drug delivery method because mucous membranes are relatively permeable, allowing for the rapid uptake of a drug into the systemic circulation and avoiding the first pass metabolism. These systems remain in close contact with the absorption tissue, the mucous membrane, releasing the drug at the action site leading to a bioavailability increase and both local and systemic effects. Mucoadhesion is currently explained by six theories: electronic, adsorption, wettability, diffusion, fracture and mechanical. Several *in vitro* and *in vivo* methodologies are proposed for studying its mechanisms. However, mucoadhesion is not yet well understood. The aim of this study was to review the mechanisms and theories involved in mucoadhesion and mucoadhesive agents used in mucoadhesive drug delivery system.

Keywords: Mucoadhesion, Bioadhesion, mucoadhesive mechanism, natural mucoadhesive agents, systhetic mucoadhesive agents.

Introduction:

The pharmaceutical research is being steadily shifted from the development of new chemical entities to the development of Novel Drug Delivery System (NDDS) of existing drug molecule to maximize their effectiveness in terms of therapeutic action and patient protection. Extensive efforts have recently been focused on targeting a drug or drug delivery system in a particular region of the body for extended periods of time, not only for local targeting of drugs but also for better control of systemic drug delivery. There are various routes of drug administration like oral, parenterals, transdermal, nasal, rectal, intravaginal, ocular etc. Amongst these various routes of drug administration, oral route is the most preferred for its ease in administration and patient compliance [1].

In the early 1980s, the concept of mucoadhesives, was introduced into the controlled drug delivery area. Mucoadhesives are synthetic or natural polymers that interact with the mucus layer covering the mucosal epithelial surface and main molecules constituting a major part of mucus. The concept of mucoadhesives has alerted many investigators to the possibility that these polymers can be used to overcome physiological barriers in long-term drug delivery. The research on mucoadhesives, however, is still in its early stage, and further advances need to be made for the successful translation of the concept into practical application in controlled drug delivery [2] **.**

MUCOADHESIVE ORAL DRUG DELIVERY SYSTEMS

Sublingual delivery: This is systemic delivery of drugs through the mucosal membranes lining the floor of the mouth.

Buccal delivery: This is drug administration through the mucosal membranes lining the cheeks (buccal

mucosa) Local delivery: This is drug delivery into the oral cavity.

ADVANTAGES OF MUCOADHESIVE DRUG DELIVERY SYSTEM

Mucoadhesive delivery systems offer several advantages over other oral controlled release systems by virtue of prolongation of residence time of drug in gastrointestinal tract (GIT).

*Targeting and localization of the dosage form at a specific site.

*Also, the mucoadhesive systems are known to provide intimate contact between dosage form and the absorptive mucosa, resulting in high drug flux at the absorbing tissue.

Within the oral mucosal cavity, the buccal region offers an attractive route of administration for controlled systemic drug delivery. Buccal delivery is the administration of drugs through the mucosal membrane lining the cheeks. Although the sublingual mucosa is known to be more permeable than the buccal mucosa, the latter is the preferred route for systemic transmucosal drug delivery [3].

ADVANTAGES OF ORAL MUCOADHESIVE DRUG DELIVERY SYSTEMS:

- Prolongs the residence time of the dosage form at the site of absorption, hence increases the bioavailability.
- Excellent accessibility, rapid onset of action.
- Rapid absorption because of enormous blood supply and good blood flow rates.
- Drug is protected from degradation in the acidic environment in the git.
- Improved patient compliance [4].

DISADVANTAGES OF MUCOADHESIVE DRUG DELIVERY SYSTEMS:

- Occurrence of local ulcerous effects due to prolonged contact of the drug possessing ulcerogenic property.
- One of the major limitations in the development of oral mucosal delivery is the lack of a good model for in vitro screening to identify drugs suitable for such administration.
- Patient acceptability in terms to taste and irritancy.
- Eating and Drinking is prohibited [4].

COMPONENTS / STRUCTURAL FEATURES OF ORAL CAVITY

- Oral cavity is that area of mouth delineated by the lips, cheeks, hard palate, soft palate and floor of mouth. The oral cavity consists of two regions.
- Outer oral vestibule, which is bounded by cheeks, lips, teeth and gingival (gums).
- Oral cavity proper, which extends from teeth and gums back to the fauces (passage which lead to pharynx) with the roof comprising the hard and soft palate. The tongue projects from the floor of the cavity [5].

BIOADHESION

American society of testing and materials has defined ‘Adhesion’ as the state in which two surfaces are held together by interfacial forces, which may consist of valency forces, interlocking action, or both.

Good defined ‘Bioadhesion' as the state wherein two materials out of which at least one of biological origin, are held together for an extended period of time by interfacial forces. Alternatively it can also be defined as the ability of a material to adhere to biological tissue for an extended period of time.

In biological systems, four types of bioadhesion can be distinguished.

1. Adhesion of a normal cell to another normal cell.
2. Adhesion of a cell with a foreign substance.
3. Adhesion of a normal cell to a pathological cell
4. Adhesion of an adhesive to a biological substrate.

Bioadhesions are classified into three types based on phenomenological observation, rather than on the mechanisms of bioadhesion:

Type I: Bioadhesion is characterized by adhesion occurring between biological objects without involvement of artificial material. e.g., cell fusion and cell aggregation.

Type II: Bioadhesion can be represented by cell adhesion onto culture dishes or adhesion to a variety of substances including metals, woods, and other synthetic materials

Type III: Bioadhesion can be described as adhesion of artificial substances to biological substrates such as adhesion of polymers to skin or other soft tissues.

A term 'Bioadhesive' is defined as a substance that is capable of interacting with biological materials and being retained on them or holding them together for extended period of time.

For drug delivery purposes, the term bioadhesion implies attachment of a drug carrier system to a specified biological location. The biological surface can either be an epithelial tissue or it can be the mucous coat on the surface of a tissue. If adhesive attachment is to a mucous coat, the phenomenon is referred to as 'Mucoadhesion'. Leung and Robinson described mucoadhesion as the interaction between a mucin and a synthetic or natural polymer [6,7,8].

Significance of Bioadhesion:

The idea of mucoadhesive was derived from the need to localize drugs at a certain site in the body. Increasing the residence time of the drug at the absorption site can enhance extent of drug absorption, for example in ocular drug delivery; less than two minutes are available for drug absorption after installation of drug solution into the eye, since it is removed rapidly through solution drainage, the ability to extend contact time of an ocular drug delivery system would undoubtedly improve bioavailability of drugs. Since many drugs are absorbed only from the upper small intestine, localizing oral drug delivery systems in the stomach or in the duodenum would significantly improve the extent of drug absorption. Also they provide intimate contact between dosage form and the absorbing tissue, which may result in high drug concentration in a local area and hence high drug flux through the absorbing tissue.

Furthermore, the intimate contact may increase the total permeability of high molecular weight drugs such as peptides and proteins. Absorption through nasal mucus is similar to the i.v. infusion, moreover buccal mucus permits the systemic entry of drugs with high first pass metabolism in stomach and a polymer used also controls drug relese [9,10].

MUCOADHESION

Good defined mucoadhesion as the state in which two materials, at least one biological in nature, are held together for an extended period of time by interfacial forces **[11].** It is also defined as the ability of a material (synthetic or biological) to adhere to a biological tissue for an extended period of time [12,13]. In case of mucoadhesion, the biological tissue is the mucous membrane. For mucoadhesion to occur, a succession of phenomena is required. The first stage involves an intimate contact between a mucoadhesive polymer and a membrane, either from good wetting of the mucoadhesive surface or from the swelling of the mucoadhesive. In the second stage, after contact is established, penetration of the mucoadhesive into the crevice of the tissue surface or interpenetration of the chains of the mucoadhesive with those of the mucus takes place. Low chemical bonds can then settle [14]. Mucoadhesive polymers Mucoadhesive polymers are water- soluble and water insoluble polymers, which are swellable networks, jointed by cross-linking agents. These polymers possess optimal polarity to make sure that they permit sufficient wetting by the mucus and optimal fluidity that permits the mutual adsorption and interpenetration of polymer and mucus to take place.

Mucoadhesive polymers that adhere to the musin epithelial surface can be conveniently divided into three broad classes-

1. Polymers that become sticky when placed in water and owe their mucoadhesion to stickiness.
2. Polymers that adhere through nonspecific, non covalent interactions that is primarily electrostatic in nature (although hydrogen and hydrophobic bonding may be significant).
3. Polymers that bind to specific receptor site on tile self surface. All three polymer types can be used for drug delivery [15].

Mucoadhesive Dosage Forms

The primary objectives of mucoadhesive dosage forms are to provide intimate contact of the dosage form with the absorbing surface and to increase the residence time of the dosage form at the absorbing surface to prolong drug action. Due to mucoadhesion, certain water-soluble polymers become adhesive on hydration [16] and hence can be used for targeting a

drug to a particular region of the body for extended periods of time .The mucosa lines a number of regions of the body including the gastrointestinal tract, the urogenital tract, the airways, the ear, nose, and eye. These represent potential sites for attachment of any mucoadhesive system and hence, the mucoadhesive drug delivery system may include the following [17].

1. Gastrointestinal delivery system.
2. Nasal delivery system.
3. Ocular delivery system.
4. Buccal delivery system.
5. Vaginal delivery System.
6. Rectal delivery system.

1. Gastrointestinal drug delivery system:

The idea of mucoadhesives began with the clear need to localize a drug at certain sites in the GI tract. Therefore, a primary objective of using mucoadhesive systems orally would be achieved by obtaining a substantial increase in residence time of the drug for local drug effect and to permit once-daily dosing. A number of mucoadhesive-based dosage forms, including sustained release tablets, semisolid forms, powders, and micro- and/or nanoparticles in the GI tract, have been widely studied. Nonetheless, successful systems that will be retained in the GI tract of humans for a desirable time have not yet been developed [18]. Matharu and Sanghavi , used carbopol 934P and poly (acrylic acid) cross-linked with 0.001% ethlene glycol to prepare mucoadhesive tablets for captopril. Decrosta et al. also used carbopol 934^P as mucoadhesive substance to prepare captopril sustained-release tablets. Captopril mixed with carbopol 934P and stearic acid (as lubricant), tableted, and could sustain the release of the drug for up to 16 h ormore [19].

2. Nasal drug delivery system:

Histologically, the nasal mucosa provides a potentially good route for systemic drug delivery. With a surface area of 150 cm^2, a highly dense vascular network, and a relatively permeable membrane structure, the nasal route has good absorption potential. One of the most important features of the nasal route is that it avoids first-pass hepatic metabolism, thereby reducing metabolism. The use of dry powder formulations containing mucoadhesive polymers for nasal administration of peptides and proteins was first investigated by Nagai *et al.* [19] Mucoadhesive microspheres are another way of prolonging the residence time in the nasal cavity.[20] reported that small volumes of liquid and powder particles have almost the same clearance rate. The addition of mucoadhesive excipient such as chitosan results in a decreased clearance rate. Morimoto *et al.* [21] developed a mucoadhesive system for nasal administration of nifedipine. Using a mixture of drug, PEG 400, and carbopol 931, they obtained a relatively high and sustained drug plasma concentration.

3. Ocular drug delivery system:

Mucin is secreted by conjunctival globlet cells, but there are no globlet cells on the cornea. On this basis, a mucoadhesive polymer will firmly attach to conjunctival mucus but only loosely, if at all, to corneal mucus [22] .Opthalmic dosage forms can be improved by increasing the time the active ingredients remain in contact with eye tissues. There are several mucoadhesive dosage forms that have been developed to this end: liquid systems, in situ gelling systems, dispersed, systems and solid systems [23,24].

4. Buccal drug delivery system:

Because of the presence a smooth and relatively immobile surface for placement of a mucoadhesive dosage form, the buccal region appears to be more suitable for sustained delivery of therapeutic agents using mucoadhesive systems. The buccal and sublingual routes avoid first- pass metabolism. These regions consist of a nonkeratinized epithelium, resulting in a somewhat more permeable tissue than the skin. Therefore, drugs with a short biological half-life requiring a sustained release effect and exhibiting poor permeability, sensitivity to enzymatic degradation, or poor solubility may be good candidates to be delivered via the oral cavity. Relevant mucoadhesive dosage forms for the oral cavity include gels, patches, tablets, and ointments [25,26], Nagai *et al.* Formulated a highly viscous gel containing carbopol and hydroxypropyl cellulose for ointment dosage forms that were maintained on

the tissue for up to 8 h. Robinson et al. showed that a three-layer buccal patch, composed of an impermeable backing membrane, a rate-limiting middle membrane, and a basement membrane containing polycarbophil, can remain in place for up to 15 h in humans, regardless of eating or drinking [27].

5. Vaginal drug delivery system:

Recently, vaginal mucoadhesive preparations have been developed as a new type of controlled release form for the treatment of both topical and systemic diseases. For drugs that are susceptible to gut or hepatic metabolism or which cause GI side effects, vaginal delivery may offer a number of advantages over the other routes of administration. The greatest advantage of such dosage forms is the possibility of maintaining them in the vagina for extended periods of time including daytime and nighttime, thereby enabling lower dosing frequencies. The vagina is a fibromuscular tube connecting the uterus to the exterior of the body. The surface area of the vagina is increased by numerous folds in the epithelium and by microridges covering the epithelial cell surface [28] .Among the polymers, polyacrylic acid and hydroxypropyl methyl cellulose are the ideal excipient in mucoadhesive strength. In general, traditional vaginal dosage forms include solutions, suspensions, gels, microparticles, suppositories, creams, foams, and tablets [28-34] and all have a relatively short contact time. Robinson et al. reported on a system of treatment using a gel containing the mucoadhesive polycarbophil that remained on vaginal tissue for 3-4 days and hence served as a platform for delivery of drug such as progesterone.

6. Rectal drug delivery system:

Another way to deliver the drug by using mucoadhesive polymers is through the mucous membrane of the rectum. Hydrogels administered rectally have proven to be useful for drug delivery. Leede et al. [**35]** proposed that hydrogels using hydroxy ethyl methacrylate cross- linked with ethylene glycol dimethacrylate and including antipyrine and theophyiline as model drugs provided rate-controlled drug delivery.

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 mass of the polymer chain there is an increase in the mucoadhesiveness of a polymer.

In general, polymers having a molecular mass ≥100 kDa have been found to haveadequate mucoadhesive property for biomedical applications. A typical example is PEG. PEG of 20 kDa molecular mass shows negligible mucoadhesive property while PEG of 200 kDa exhibits improved mucoadhesiveness and PEG of 400 kDa has got excellent mucoadhesiveness [35]. Similarly, polyoxyethylene of 7000 kDa exhibits excellent mucoadhesive property and could be tried for the development of buccal delivery systems. Dextrans of 19 500 and 200 kDa, poly(acrylic acid) of approx. 750 kDa and poly(ethylene oxide) of 4000 kDa also exhibit good bioadhe- sive properties [36].Polymer chain length plays an important role in bioadhesive- ness. With the increase in the chain length of the polymers there is an increase in the mucoadhesive property of the polymer. Having 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 cross-linking reactions and the hydration of the polymer network, the higher the cross-linking density, the lower the flexibility of the polymer chains. Keeping this in mind, teethering of long flexible chains onto the polymer matrices, with high cross-linking density, appears to be an excellent idea to improve the bioadhesive property. In a recent study, this phenomenon was utilized to develop tethered PEG–poly(acrylic acid) hydrogels with improved mucoadhe- sive properties [37]. In addition to the reduced flexibility of the polymer chains, cross-

linking results in the reduced diffusion of water into the cross-linked polymer matrix. 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 [38]. Hence, highly cross-linked polymeric ma- trix limits the interpenetration of polymer and mucin chains amongst themselves which in turn results in the decrease in the mucoadhesive strength [39].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 and 200 kDa exhibit good mucoadhesive properties. The efficiency of both the dextrans and PEG (200 kDa) have been found to possess similar bioadhesive strength [40, 41].

Formation of hydrogen bonds amongst the functional groups of the polymers and mucosal layer also plays an important role. In general, stronger the hydrogen bond- ing 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 [42]. Apart from the hydrogen bond formation, the presence of functional groups within the polymer structure may render the poly- mer 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 a cell-culture-fluorescent probe technique [43, 44]. Anionic poly- electrolytes have been found to form stronger adhesion when compared with neutral polymers [45].

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 poly- mer and the mucosal layer resulting in poor mucoadhesive properties. In general, polymer concentration in the range of 1–2.5 wt% may exhibit sufficient mucoad- hesive 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 [46].

Apart from the above-mentioned physico-chemical properties of the polymeric network, various environmental factors also play an important role in mucoadhe- sion. 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, chi- tosan (cationic polyelectrolyte) exhibit excellent mucoadhesive property in neutral or alkaline medium [47]. 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 properties of a polymer matrix include texture and thickness of the mucosa [48].

MECHANISM OF MUCOADHESION

The mechanism of mucoadhesion is generally divided into two steps: the contact stage and the consolidation stage [Figure 1]. The first stage is characterized by the contact between the mucoadhesive and the mucus membrane, with spreading and swelling of the formulation, initiating its deep contact with the mucus layer.

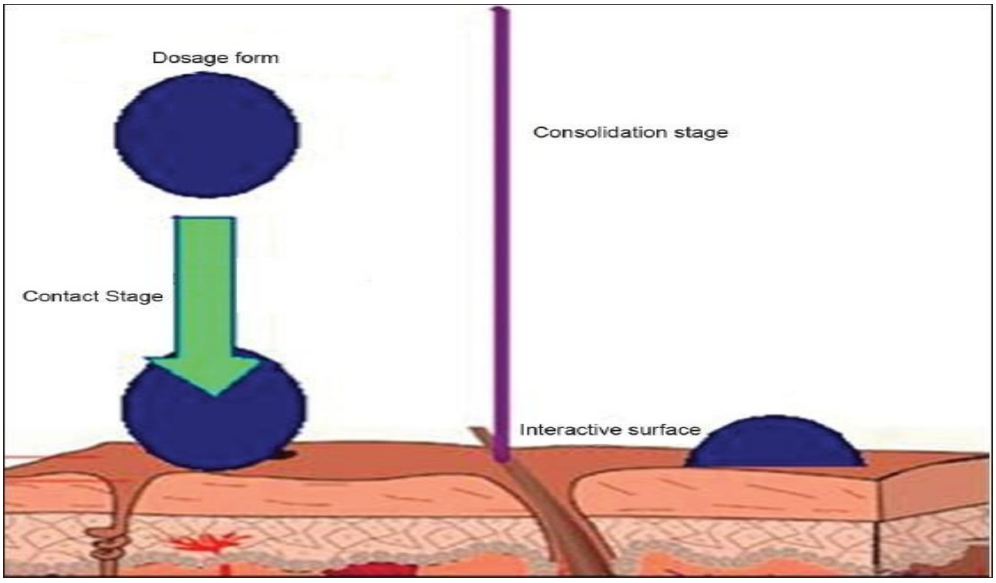

Figure 1: The process of contact and consolidation[49]

In the consolidation step [Figure 1], the mucoadhesive materials are activated by the presence of moisture. Moisture plasticizes the system, allowing the mucoadhesive molecules to break free and to link up by weak van der Waals and hydrogen bonds. Essentially, there are two theories explaining the consolidation step: the diffusion theory and the dehydration theory. According to the diffusion theory, the mucoadhesive molecules and the glycoproteins of the mucus mutually interact by means of interpenetration of their chains and the building of secondary bonds. For this to take place, the mucoadhesive device has features favoring both chemical and mechanical interactions. For example, molecules with hydrogen bond building groups (–OH, –COOH), an anionic surface charge, high molecular weight, flexible chains and surface-active properties, which help in spreading throughout the mucus layer, can present mucoadhesive properties[50].

Theories of Mucoadhesion

The process of mucoadhesion is mainly based on formation of two types of bond between bio adhesive system and mucus membrane and they are:

Chemical bond

It may include covalent bonds, Weak secondary bonds, ionic bond and hydrogen bond etc.

Mechanical bond

This bond can be arising from the physical connection between two surfaces. It is similar to that of the interlocking system.

On the basis of nature and strength of these two kinds of bonds, there are following five theories of mucoadhesion that are been postulated [51].

Electronic theory

According to the electronic theory, there is difference in the electronic structure of mucin surfaces and bio adhesive system which results in attaining a electronic gradient. Due to presence this electronic structure difference, the transfer of electrons occurs in these two systems (mucin surface and bioadhesive system) when they come in contact with each. As a result of this electron transfer there is the formation of an electronic bi-layer at the interface of the two surfaces. This interfacial bi-layer exerts an attractive force in the interface of two surfaces that may produce an effective mucoadhesion [52].

Adsorption theory

This theory describes the involvement of both type of chemical bond, that is, primary and secondary bond in the bio adhesion mechanism. Both the surface that is mucin and drug delivery system has their own surface energy. When they come in contact, the adhesion occurs due to the surface energy and results

in the formation of two types of chemical bond. Primary chemical bond such as covalent bond, which is strong in nature, thus produces a permanent bonding, whereas secondary chemical bond involves Vander-Waals forces, hydrophobic interaction and hydrogen bonding, which are weak in nature, thus produces a semi-permanent bond [52].

Wetting theory

This theory is based on the mechanism of spreadability of drug dosage form across the biological layer. This theory is mainly applicable to liquids or low viscous mucoadhesive system. According to this theory, the active components penetrate in to the surface irregularities and gets harden it that finally results in mucoadhesion [53].

Diffusion interlocking theory

This theory describes the involvement of a mechanical bond between the polymeric chain of drug delivery system and polymeric chain of mucus membrane, that is, glycol proteins. When two surfaces are in intimate contact, the polymeric chain of drug delivery system penetrates in to the glycoprotein network. According to this theory, the bioadhesion basically depends on the diffusion coefficient of both polymeric chains. The other factors that may influence the inter movement of polymeric chain are molecular weight, cross linking density, chain flexibility, and temperature in order to achieve a good bio adhesion, the bio adhesive medium should have a similar solubility with glycoprotein resulting in effective mucoadhesion [53].

Fracture theory

The fracture theory is mainly based on the fact that, the force required detaching the polymeric chain from the mucin layer is the strength of their adhesive forces. This strength may be also called as fracture strength. The fracture strength can be determined by using the formula given below

$G=(E.\ e/L)^{1/2}$

G-Fracture strength,

E-Young's modules of electricity, e-Fracture energy,

L-Critical crack length

NATURAL MUCOADHESIVE AGENTS

Dellinia indica

The scientists reviewed on oxytocin nasal gel using fruit extracts of Dellinia indica. L. A new nasal gel formulation has been developed using a natural mucoadhesive agent obtained from the fruit of Dellinia indica L. The Mucoadhesive strength and viscosity of this natural mucoadhesive agent were found to be higher in comparison to the synthetic polymers, namely hydroxy propyl methyl cellulose (HPMC) and carbopol 934, which are conventionally used for a similar purpose. In-vitro drug release characteristics using a Franz-diffusion cell and excised bovine nasal membrane were also found to be better in comparison to the above synthetic polymers [54].

Trigonella foenum-graecum L

Works on fenugreek seeds for development of new drug delivery system of diazepam. Mucoadhesive agent obtained from fenufreek seeds exhibits high adhesion with high molecular weight and viscosity, better mucoadhesive properties comparision to other synthetic polymers. This may be due to presence of numerous carboxyl and hydroxyl groups, which adopt more favourable macromolecule conformation and accessibility of its hydrogen binding group, while compare with other polymers. It is edible, easily biodegradable and non-allergic. Diazepam is routinely administered parenterally and causes hazardous with least patient compliance. This nasal drug delivery system may substitute the conventional diazepam injection [55].

Cumin (Cuminum cyminum)

Cumin prefers areas with low atmospheric humidity during the period of flowering, seed formation and ripening. Bitter cumin (Cuminum nigrum L.) locally known as 'Shahijeera' or'Kashmiri' cumin belongs to the family Apiaceae and grows mainly in Central Asia and India. It is used in spicemix or garam masala, pickles,wheat and rice dishes. It is bitterin taste compared to other two varietiesof cumin viz., normal cumin and black cumin. In traditional ayurvedic medicine,it is used as a stimulant, carminative, astringent and useful in dyspepsia and diarrhea. As a result of our work, the yield of

Cuminum cyminum is higher than *Trigonella foenum graecum and Foeniculum vulgare.*The pH and loss on drying of three extracts was found to be same. The amount of starch is high for *Cuminum cyminum* which shows it, has high binding activity. The percentage bitters was found to be high in *Cuminum cyminum* only. It has a high preservative action [56].

Ficus carica

The mucilage extracted from F.carica fruits was found to possess better mucoadhesive properties than the synthetic polymers HPMC and Carbopol 934 that are widely used in preparation of nasal gels. The in situ nasal gels prepared from FCM showed better rheological,mechanical and mucoadhesive properties than the gels prepared from synthetic polymers. Histopathological study confirmed that this natural mucilage had no adverse impact on the structural integrity of the nasal mucosa. Further, in vivo study proves that bioavailability of midazolam from FCM gels was far better than those prepared from HPMC and Carbopol 934 gels. Results obtained from the present study show that nasal gel prepared from 0.5% w/v F. carica mucilage containing 0.5% sodium taurocholate as enhancer gave reproducible results. This type of nasal in situ gel of midazolam prepared from natural mucilage extracted from F. carica fruits will undoubtedly provide a cheaper dosage form of midazolam and will thus add a new dimension in this regard[57].

Chitosan

On the basis of the fact that chitosan and HP$ CD can enhance the intranasal permeation of drug moiety, we formulated an Optimized thermoreversible gel for intranasal delivery of FXD HCl. They showed enhanced not only the permeation of FXD HCl in HNE cell monolayers but also the intranasal bioavailability of FXD HCl in rabbits. Thus, P407-based thermoreversible nasal gel could open a way to the design of new controlled delivery for the FXD HCl administration via nasal route [58].

Xanthan gum

Gellan gum is an anionic deacetylated, Exocellular polysaccharide secreted by *Pseudomonas elodea* with atetrasaccharide repeating unit of 1â-l- rhamnose, 1â-dglucuronic acid and 2â d- glucose. The mechanism of gelation involves the formation of double-helical junction zones followed by aggregation of the double helical segments to form a 3- D network by complexation with cations and hydrogen bonding with water. Since human nasal mucosa is covered with approximately 0.1mlmucus, which consists of sodium, potassium, and calcium ions, a solution-gel phasetransition can be expected.

Metoclopramide Hydrochloride was successfully formulated as an in situ gelling system using Gellan gum. The formulated systems provided sustained release of the drug over an 8 hour period in vitro and the developed formulations were devoid of any deleterious effect on the nasal tissues. Hence, this can be viewed as a viable alternative to conventional nasal drops by virtue of its ability to enhance nasal residence time and thereby intranasal bioavailability. The ease of administration coupled with its ability to provide sustained release could probably result in less frequent administration, thus enhancing patient compliance [59].

***Artocarpus heterophyllus* Lam**

It is popular fruit crop that is originated in India at the foot of the Western Ghats, and is now very popular throughout South East Asia. It is a nutritious fruit,rich in vitamins A, B and C, potassium, calcium, iron, proteins and carbohydrates. Different concentrations of the mucoadhesive agent solution, a such as, 1%, 2%, and 3% w/v, using Methocel K4M, Carbopol 974P, and a natural isolated mucilage from jackfruit were prepared. Shear stress was calculated by self-fabricated apparatus made of wooden board with scale and two glass slides having two pans on the both sides mounted on a pulley. An excess of prepared solution was placed between two glass slides and 1000 g weight was placed on glass slide for 5 min to compress the sample to uniform thickness. Weight (250 g) was added to the pan. The weight required to separate two slides was taken as a measure of shear stress. Jackfruit yielded 12-15% w/w [60].

Gliclazide

Based on swelling behaviour, mucoadhesivity and release studies, it can be concluded that the composition(2:3) of alginate-ispaghula mucoadhesive beads (F1) can be considered as an optimized

formulation among the compositions studied. It can be recommended for further evaluation in suitable animal models for oral delivery of GCD for the treatment of noninsulin dependent diabetes mellitus [61].

Glycin

Glycin seed extract is a better mucoadhesive agent than carbapol and NaCMC with respect to inbuilt mucoadhesive and mucoretentive properties. Since this natural mucoadhesive agent is edible, it is easily biodegradable and not an allergen and may provide an alternative to conventional synthetic and natural mucoadhesive agents [62].

Synthetic mucoadhesive agents

Synthetic polymers:

Cellulose derivatives (methylcellulose, ethyl cellulose, hydroxy-ethylcellulose, Hydroxyl propyl cellulose, hydroxyl propyl methylcellulose, sodium carboxymethylcellulose, Poly (acrylic acid) polymers (carbomers, polycarbophil), Poly (hydroxyethyl methylacrylate), Poly (ethylene oxide), Poly (vinyl pyrrolidone), Poly (vinyl alcohol).

Synthetic mucoadhesive agents used by various researchers

HPMC

The HPMC based gels showed good surface morphology with higher drug loading efficiency. The viscosities of the preparations were found to be within suitable range for nasal administration. The permeation was more controlled due to higher viscosities of the formulations at higher concentration of HPMC. A higher permeation flux was observed with the formulations containing PEG 400 than with the formulations containing Tween 80. The FT-IR analysis and DSC scans confirmed no interaction between Felodipine and HPMC. It may be concluded that bioavailability of felodipine can be increased by nasal delivery of the drug [63].

Pluronic F-127 and Pluronic F-68

Study revealed that the temperature sensitive gelling system can be formulated using optimum concentration of PF-127 and PF-68 that can gel at the body temperature. Addition of bioadhesive polymers can prolong therelease of zolmitriptan that may behelpful for migraine treatment [64].

Carbopol 974 P

The characterization of domperidone dispersion demonstrated that the prepared domperidone dispersion were amorphous and in the nanometer size range. Solubility of domperidone in the dispersion showed a marked increase. The domperidone hydrogel was prepared by directly incorporating the domperidone dispersion in Carbopol hydrogel. As a result of the mucoadhesive properties and improved solubility, a statistically significant improvement in bioavailability and prolonged propulsion efficacy of domperidone in hydrogel group were observed compared to that in Motilium tablet group in beagle dogs and mice. In addition, these results indicate that dispersion incorporating with hydrogel can be an effective tool to improve the bioavailability of poor water soluble drugs [65].

Polyacrylic acid

Covalently attached a fimbrial protein (antigen K99 from E. coli) to poly (acrylic acid) polymer and substantially improved the adhesion of the drug delivery system to the GI epithelium [66].

Polyacrylate

Thiolated polyacrylate microparticles were generated for the nasal delivery of human growth hormone (hGH). The intranasal administration of this microparticulate formulation to rats resulted in a relative bioavailability of 8.11 ± 2.15% that represents a 3-fold improvement compared to microparticles comprising the corresponding unmodifiedpolymer [67].

Polyethylene glycol

Alginate Polyethylene glycol Acrylate is also known by the acronym Alginate- PEGAc. It has an alginate backbone with acrylated polyethylenglycol groups attached to it. This polymer meshes the properties of alginates (strength, simplicity and gelation) with characteristics specific to the acrylate functionality of PEG like mucoadhesion. PEG's have the ability to penetrate the mucus surface while the acrylate group of the polymer reacts with the sulphide group of glycoproteins present in the mucus. This results in a

strong interactionbetween the mucus and the polymer [68].

Polycarbophil

PLGA nanoparticles were prepared by the solvent deposition method and were characterized as "mucoadhesive" by coating with mucoadhesive polymer, polyacrylic acid (polycarbophil). The application of factorial design gave a statistically systematic approach for the formulation of nanoparticles with the desired particle size, high entrapment efficiency and sustained drug release Drug: polymer ratio and concentration of surfactant were found to influence the particle size and % drug release of acyclovir-loaded PLGA mucoadhesive nanoparticles. *In vitro* intestinal mucoadhesion of nanoparticles showed that the adhesion properties of nanoparticles increased with increasing concentration of mucoadhesive polymer (polycarbophil). These preliminary resultsindicate that acyclovir-loaded mucoadhesive PLGA nanoparticles couldbe effective in sustaining drug release for a prolonged period [69].

Poly-N-vinyl-2-pyrrolidone

The PVP gels were prepared with the assistance of radiation that imparted the crosslinking with a radiation dose of 15 kGy being as efficient as 20 kGy. Considering the mucoadhesive force, chitosan gel and gel prepared with 3% PVP in presence of PEG 600 showed the mucoadhesive potential. The release characteristics of hydrogels revealed higher release rates from PVP gels with the release rate increasing further in presence of PEG or glycerol. Histopathological investigations proved that the PVP was a safe hydrogel to be used for mucosal delivery. The nasal mucosal damages were less severe with the presence of PEG in gel formulations as compared to that produced by the formulations containing glycerol [70].

Polyvinyl Alcohol

The Phase separation emulsification technique for obtainingPVA microspheres has proved to be a useful tool in thepreparation of microspheres for nasal drug delivery. By virtueof prolonged drug residence at the site of absorption,improved bioavailability can be achieved in contrast to oraldosage form prone for first-pass metabolism [71].

CONCLUSION

Studies on mucoadhesive systems have focused on a broad setting of aspects. It is a growth area whose goal is the development of new devices and more "intelligent" polymers, as well as the creation of new methodologies that can better demonsrate the mucoadhesion phenomenon. The use of mucoadhesive polymers has made this delivery system of controlled release application. There are significant advancements have been achieved in the field of mucoadhesives, but there are still many challenges are not been sought out in this field. However, a lot of research has been done of this drug delivery system. But, these novel mucoadhesive formulations require much more research work to understand how to deliver drug clinically for the treatment of both systemic and topical diseases .With the great influx of new molecules stemming from drug research, mucoadhesive systems may play an increasing role in the development of new pharmaceuticals. Mucoadhesive dosage forms provide prolonged contact time at the site of attachment, having high patient compliance and are economic as compare to other dosage forms.

REFERENCE

1. KPR Chowdary; RY Srinivasa. *AAPS PharmSci Tech(* **2003)**; 4 (3): 39.
2. KR Kamath, K Park. Mucosal Adhesive Preparations. In Encyclopedia of
3. Shojaei Amir H. (2003), Buccal Mucosa as A Route for Systemic Drug Delivery: A Review, J Pharm Pharm Sci., 1(1):15-33.
4. Tangri P., Khurana S., Madhav N.V.S. (2011), Mucoadhesive Drug Delivery System: Material and Method, Int. J. Of Pham. Bio. Sci., 2(1):34-46.
5. Amanpreet Kaur "Mucoadhesive Drug Delivery System: A Review" Int. J. Drug Dev. & Res., January- March 2013, 5(1):11-20. doi: doi number.
6. Ahuja, R.P.K, & Khar, J.A. Mucoadhesive Drug Delivery System. Drug Dev. Ind. Pharm, (1997); 23 (5): 489-515.
7. Duchene, D., Touchard, F., & Peppas, N.A. Pharmaceutical and medical aspects of bioadhesive systems for drug administration. Drug Dev. Ind. Pharm., (1988); 14 (2): 283-318

8. Dominique, D., & Gilles, P. Bioadhesion of solid dosage forms, why and how? Eur. J. Pharm. Biopharm., (1997); 44: 15-23.
9. Jin, W.L., & Jae, H.P. Bioadhesive based dosage forms: the next generation. J. Pharm. Sci., (2000); 89(7): 850-861
10. Kamath, K. R., & Park, K. Mucosal adhesive preparations. In J. Swarbrick, & J.C. Boylan (Eds.). Encyclopedia of pharmaceutical technology
11. Ketousetuo.K, Bandyopadhyay. A.K., Development of Oxytocin Nasal Gel using Mucoadhesive Agent obtained from the Fruits of Dellinia indica L. ScienceAsia. (2007); 33: 57-60.
12. RJ Good.*J. Adhesion (*1976); 8: 1-5.
13. NA Peppas; PA Buri. *J Control, Rel.(*1985)l (2): 257.
14. MA Longer; JR Robinson. *Phar-Int (*1987*)*7:114.
15. D Duchene; F Touchard ; NA Peppos. *Drug Dev 1nd Pharm(*1988) 14: 283.
16. K P R Choudary; L Srinivas . *Indian Drugs (2000*); 37 (9):400.
17. NA Peppas; PA Buri. *J Control, Rel.(*1985); l (2): 257.
18. A Ahuja; RK Khar; J Ali. *Drug Dev. Ind Pharm.(*1997*)*23 (5): 489-497.
19. C M Lehr; J A Bouwstra; W Kok; A G De Boer; J J Tukker; J C Verboet; D D Breimer; Junginger HE Junginger. *J. Pharm Pharmacol (*1992) 44: 402.
20. C M Lehr. *Eur J. Drug Metab Pharmacokinet (*1996)21: 139 R S Matharu; N M Sanghavi. *Drug Dev Ind Pharm,(*1992)18:1567.
21. M T Decrosta; N B Jain; E M Rudnic. *U.S. Patent* 4666705, (1987)
22. L Illum; H Jorgensen; H Bigaard; O Krogsgaard; N Rossing. *Int. J. Pharm (*1987);310:189.
23. K Morimoto; H Tabata; K Mosisaka. *Chem Pharm Bull (*1997); 35: 3041.
24. J Liaw; Y Rojansakul; J R Robinson. *Int. J. Pharm. (*1992); 88:111.
25. J L Greaves; C G Wilson. *Adv. Drug Deliv. Rev(* 1993); 11:349.
26. H Hui; J R Robinson. *Int. J. Pharm(* 1985) 26: 203 A K Zimmer; P Chetoni; M F Sattone; Zerbe ; J Kreuter. *J Control. Rel (*1995); 33: 31
27. .A K Zimmer; P Chetoni; M F Sattone; Zerbe ; J Kreuter. *J Control. Rel (*1995); 33: 31.
28. R B Gandhi; J R Robinson. *Adv. Drug Deliv Rev (*1994) 13: 43.
29. M Shiozaki; N Nambu; TJ Nagai. *Pharm Sci. Technol. JPN(*1982) 42: 10. M
30. M Ishida ;N Nambu; T Nagai. *Chem Pharm Bull (*1983)31:4561.
31. J R Robinson; M A Longer; M Veillard. *Ann. NYA Cad Sci. (*1987); 507,307.
32. J R Robinson; W J Bologna. *J Control Rel (*1994)*;* 28: 87.
33. A D Woolfson; D F McCafferty ; P A McCarron ;J H Price. *J Control. Rel (*1995); 35: 49.
34. D T O'Hagan; D Rafferty; S Wharton;L Illum . *Vaccine (*1993)*;* 11: 660.
35. E Bonuci; P Ballanthi; PA Ramires;JL Richardson; LM Benedetti. *Calcify Tissue Int,(*2005)*;* 56: 274.
36. LGJ Leede; AG Boer; E Portzgen; J Feijen; D D Bremier. *J Control Rel (*1986);4: 17.
37. D. L. Middleton, S. S. Leung and J. R. Robinson, in: *Bioadhesive Drug Delivery* Systems,V. Lenaerts and R. Gurny (Eds), p. 189. CRC Press, Boca Raton, FL (1990).
38. D.Tiwari, D.Goldman, R.Sause and P.L.Madan, AAPSPharm.Sci.1, E13 (1999).
39. G.P.Andrew, T.P.Laverty and D.S.Jones, Eur.J.Pharm.Biopharm.71,505 (2009).
40. Y.Huang, W.Leobandung, A.Foss and N.A.Peppas, J.Control.Rel.65, 63 (2000
41. N.S.Miller,M.Chittchang and T.P.Johnston, Adv.Drug Deliv.Rev.57,1666(2005).
42. P.J.Flory, in: Principles of Polymer Chemistry, p. 541. Cornell University Press, Ithaca, NY (1953).
43. D. L. Middleton, S. S. Leung and J. R. Robinson, in: Bioadhesive Drug Delivery Systems,V. Lenaerts and R. Gurny (Eds), p. 189. CRC Press, Boca Raton, FL (1990).
44. J. W. Lee, J. H. Park and J. R. Robinson, J. Pharm. Sci. 89, 850 (2000).
45. K. Park, H. S. Ch'ng and J. R. Robinson, in: Recent Advances in Drug Delivery Systems, J. M. An- derson and S. W. Kim (Eds), p. 163. Plenum Press, New York, NY (1984).

46. K. Park and J. R. Robinson, Int. J. Pharm. 19, 107 (1984).
47. H. S. Ch'ng, K. Park, P. Kelly and J. R. Robinson, J. Pharm. Sci. 74, 399 (1985)
48. D. Solomonidou, K. Cremer, M. Krumme and J. Kreuter, *J. Biomater. Sci. Polymer Edn* 12, 1191(2001).
49. Fig1: https://www.japtr.org/viewimage.asp?img=JAdvPharmTechRes_2010_1_4_381_76436_f2.jpg
50. H. Park, M. Amiji and K. Park, *Proc. Int. Symp. Control. Rel. Bioact. Mater.* **16**, 217 (1989).
51. Hägerström H, Edsman K, Strømme M. Low-frequency dielectric spectroscopy as a tool for studying the compatibility between pharmaceutical gels and mucus tissue. *J Pharm Sci. (*2003);92:1869–81.
52. Bhowmik D, Niladry C (2013) Mucoadhesive Buccal Drug Delivery System-An over view. J of Advance Pharm Edu And Res 3: 319-331
53. Varma N, Chattopadyay P (2011) Polymeric Platform for Muco Adhesive Buccal Drug Delivery System: a Review. Int Journal of Current Pharmaceutical Research.
54. Review on Mucoadhesive Drug Delivery System with Special Emphasis on Buccal Route: An Important Tool in Designing of Novel Controlled Drug Delivery System for the Effective Delivery of Pharmaceuticals
55. Datta Rimi, Bandyopadhyay AK, Development of a new nasal drug delivery system of diazepam with natural mucoadhesive agent from Trigonella foenum- graecum L, Journal of Scientific & Industrial research Vol. 64,(2005):973-977.
56. Niraimathi K L et al. Standardization studies on herbal binders and preservatives Journal of Pharmacy Research (2012), 5(4),2091-2093.
57. Basu Shyamoshree, Bandyopadhyay AK Development and Characterization of Mucoadhesive i*n situ* Nasal Gel of Midazolam Prepared with *Ficus carica* Mucilage AAPS PharmSciTech. (2010) September; 11(3): 1223–1231.
58. Hyun-Jong Cho,P.Balakrishnan,et al, Poloxamer/Cyclodextrin/Chitosan-Based Thermoreversible Gel for Intranasal Delivery of Fexofenadine Hydrochloride Journal of Pharmaceutical Sciences, (2011), Vol. 100, 681–691.
59. Viram Parmar, A.N.Lumbhani et al Development and evaluation of ion- dependent *in- situ* nasal gelling systems of metoclopramide hydrochloride as an antimigraine model drug International Journal of Latest Research in Science and Technology,2012 Vol.1,Issue 2 :Page No.80-89.
60. Sabale Vidya, Patel Vandana, Paranjape Archana, Isolation and characterization of jackfruit mucilage and its comparative evaluation as a mucoadhesive and controlled release component in buccal tablets deetu journal of pharmaceutical science 2012, vol.2, Issue.2: page 61-69.
61. Nayak A.K., M. Saquib Hasnain, Sarwar Beg, M. Intakhab Alam Mucoadhesive beads of gliclazide: Design, development and evaluation ScienceAsia 36 (2010): 319–325
62. Ali Md Sajid, Alam Md Sarfaraz, Siddiqu Raza Masoom A Novel Mucoadhesive Biomaterial from Natural Source Glycine Max Research Journal of Pharmaceutical, Biological and Chemical SciencesOctober -December 2012 Volume 3 Issue 4 Page No. 1020
63. Sahu P Shanu , H. K. Sharma ,Das Malay K, Nasal delivery of Felodipin using hydrogel matrix Journal of Global Trends in Pharmaceutical Sciences 2011 Vol.2, Issue 3,pp -296-309.
64. Kolsure Pramod K, Kapoor Raj B. Develpoment of Zolmitriptan Gel for Nasal Admonistration Asian Journal of Pharmaceutical and Clinical Research 2012 Vol 5, Issue 3,p.g no. 88-94.
65. Zhang Chun-Hui, Huang Yue et al, A Novel Domperidone Hydrogel: Preparation, Characterization, Pharmacokinetic, and Pharmacodynamic Properties Journal of Drug Delivery Volume 2011, pages 09.
66. Schnurch A. B., Gabor F., Szostak M.P., Lubitz W., An adhesive drug delivery system based on K99-fimbriae, Eur. J. Pharm. Sci. 1995, 3, 293–299.
67. Leitner V, Guggi D, Bernkop-Schnürch A

(2004) Thiomers in non-invasive peptide delivery: in vitro and in vivo characterisation of a polycarbophil–cysteine/glutathione gel formulation for hGH. J Pharm Sci. 93(7):1682-91.

68. Bhosale UV, Kusum V Devi, and Jain N Formulation and Optimization of Mucoadhesive Nanodrug Delivery System of Acyclovir J Young Pharm. 2011 Oct-Dec; 3(4): 275–283.
69. Davidovich-Pinhas M, Bianco-Peled H (2011) Alginate–PEGAc: A new mucoadhesive polymer. Acta Biomater. 7(2):625-33.
70. Alsarra Ibrahim. A, Hamed Amel Y, Mucoadhesive Polymeric Hydrogels for Nasal Delivery of Acyclovir Drug Development and Industrial Pharmacy (2009), 35:352–362.
71. Swamy N.G.N. Abbas Z, Preparation and In Vitro Characterization of Mucoadhesive PolyvinylAlcohol Microspheres Containing Amlodipine Besylate for Nasal Administration Indian Journal of Pharmaceutical Education and Research Jan-Mar, 2012.