INTRODUCTION

In recent years, delivery of therapeutic agents through various transmucosal routes has gained significant attention owing to their presystemic metabolism or instability in the acidic environment associated with oral administration. Mucoadhesive materials from natural sources are nowadays gaining more importance for spatial placement of mucoadhesive dosage devices. If they are biocompatible and biodegradable, provides added advantages for formulating various controlled-release pharmaceutical formulations and avoids patient noncompliance, especially for chronically ill patients. The advantages of such materials include their natural origin, ready availability, low cost, biodegradability and capability of a multitude of chemical modifications. Mucoadhesive controlled-drug delivery systems are very beneficial, since they provide a controlled drug release over time and localize the drug to a specific site of the body. The prolonged residence time of the drug in the body is believed to prolong the duration of action. Mucoadhesive drug delivery devices can be applied to any mucosal tissue in the body, including the gastrointestinal, ocular, respiratory, buccal, nasal, rectal, urethral and vaginal path. Oral administration of drugs is the preferred administration route for the purpose sustained-release of a drug. Since, the GI tract is covered by a mucus layer, localization of a mucoadhesive drug delivery system to a specific site is very beneficial.

1.1. Bioadhesion

Bioadhesion can be defined as the process by which a natural or a synthetic polymer can adhere to a biological substrate. When the biological substrate is a mucosal layer then the phenomena is known as “mucoadhesion”. In the pharmaceutical sciences, when the adhesive attachment is to mucus or a mucous membrane, the phenomenon is referred to as mucoadhesion\(^1\). Over the last two
decades mucoadhesion has become of interest for its potential to optimize localized drug delivery, by retaining a dosage form at the site of action (e.g. within the gastrointestinal tract) or systemic delivery, by retaining a formulation in intimate contact with the absorption site (e.g. the nasal cavity). The need to deliver ‘challenging’ molecules such as Biopharmaceuticals (proteins and oligonucleotides) has increased interest in this area. Mucoadhesives materials could also be used as therapeutic agents in their own right, to coat and protect damaged tissues (gastric ulcers or lesions of the oral mucosa) or to act as lubricating agents (in the oral cavity, eye and vagina). This chapter will consider the basic mechanisms by which mucoadhesives can adhere to a mucous membrane in terms of the nature of the adhering surfaces and the forces that may be generated to secure them together.

1.1.1 Mucous membranes

Mucous membranes (mucosa) are the moist surfaces lining the walls of various body cavities such as the gastrointestinal and respiratory tracts. They consist of a connective tissue layer (the lamina propria) above which is an epithelial layer, the surface of which is made moist usually by the presence of a mucus layer. The epithelia may be either single layered (e.g. the stomach, small and large intestine and bronchi) or multilayered/stratified (e.g. in the oesophagus, vagina and cornea). The former contain goblet cells which secrete mucus directly onto the epithelial surfaces, the latter contain, or are adjacent to tissues containing, specialized glands such as salivary glands that secrete mucus onto the epithelial surface. Mucus is present as either a gel layer adherent to the mucosal surface or as a luminal soluble or suspended form. The major components of all mucus gels are mucin glycoproteins, lipids, inorganic salts and water, the latter accounting for more than 95% of its weight,
making it a highly hydrated system. The mucin glycoproteins are the most important structure-forming component of the mucus gel, resulting in its characteristic gel-like, cohesive and adhesive properties. The thickness of this mucus layer varies on different mucosal surfaces, from 50 to 450 Åm in the stomach to less than 1 Åm in the oral cavity. The major functions of mucus are that of protection and lubrication (they could be said to act as anti-adherents).

1.1.2. Mucoadhesives

The most widely investigated group of mucoadhesives is hydrophilic macromolecules containing numerous hydrogen bonds forming groups, the so-called ‘first generation’ mucoadhesives. Their initial use as mucoadhesives was in denture fixative powders or pastes. The presence of hydroxyl, carboxyl or amine groups on the molecules favours adhesion. They are called ‘wet’ adhesives in that they are activated by moistening and will adhere non-specifically to many surfaces. Once activated, they will show stronger adhesion to dry inert surfaces than those covered with mucus. Unless water uptake is restricted, they may over hydrate to form slippery mucilage. Like typical hydrocolloid glues, if the formed adhesive joint is allowed to dry then, they can form very strong adhesive bonds. Typical examples are a. carbomers, b. chitosan and c. sodium alginate (Fig. 1.1). These were used initially largely as they were available ‘off-the-shelf’ with regulatory approval, but in the last few years, new enhanced materials have been developed.

\[
\begin{align*}
\text{a) Poly(acrylic acid), } R &= \text{ allyl sucrose or allyl pentaerythritol (Carbopols) or divinyl glycol (polycarbophil)}
\end{align*}
\]
1.1.3. Mucosa interaction

Chemical bonds

For adhesion to occur, molecules must bond across the interface. These bonds can arise in the following way\textsuperscript{13}.

**Ionic bonds** - where two oppositely charged ions attract each other via electrostatic interactions to form a strong bond (e.g. in a salt crystal).

**Covalent bonds** - where electrons are shared, in pairs, between the bonded atoms in order to ‘fill’ the orbitals in both. These are also strong bonds.

**Hydrogen bonds** - here a hydrogen atom, when covalently bonded to electronegative atoms such as oxygen, fluorine or nitrogen, carries a slight positively charge and is
therefore is attracted to other electronegative atoms. The hydrogen can therefore be thought of as being shared, and the bond formed is generally weaker than ionic or covalent bonds.

**Van-der-Waals bonds**-these are some of the weakest forms of interaction that arise from dipole–dipole and dipole-induced dipole attractions in polar molecules, and dispersion forces with non-polar substances.

**Hydrophobic bonds**-more accurately described as the hydrophobic effect, these are indirect bonds (such groups only appear to be attracted to each other) that occur when non-polar groups are present in an aqueous solution. Water molecules adjacent to non-polar groups form hydrogen bonded structures, which lowers the system entropy. There is therefore an increase in the tendency of non-polar groups to associate with each other to minimize this effect.

### 1.1.4. Theories of adhesion

There are six general theories of adhesion, which have been adapted for the investigation of mucoadhesion.\textsuperscript{11, 14, 15}

**The electronic theory** suggests that electron transfer occurs upon contact of adhering surfaces due to differences in their electronic structure. This is proposed to result in the formation of an electrical double layer at the interface, with subsequent adhesion due to attractive forces.

**The wetting theory** is primarily applied to liquid systems and considers surface and interfacial energies. It involves the ability of a liquid to spread spontaneously onto a surface as a prerequisite for the development of adhesion. The affinity of a liquid for a surface can be found using techniques such as contact angle goniometry to measure
the contact angle of the liquid on the surface, with the general rule being that the lower the contact angle, the greater the affinity of the liquid to the solid. The spreading coefficient ($S_{AB}$) can be calculated from the surface energies of the solid and liquids using the equation:

$$S_{AB} = \gamma_B - \gamma_A - \gamma_{AB}$$

Where $\gamma_A$ is the surface tension (energy) of the liquid A, $\gamma_A$ is the surface energy of the solid B and $\gamma_{AB}$ is the interfacial energy between the solid and liquid. $S_{AB}$ should be positive for the liquid to spread spontaneously over the solid. The work of adhesion ($W_A$) represents the energy required to separate the two phases, and is given by:

$$W_A = \gamma_A + \gamma_B - \gamma_{AB}$$

The greater the individual surface energies of the solid and liquid relative to the interfacial energy, the greater the work of adhesion.

The adsorption theory describes the attachment of adhesives on the basis of hydrogen bonding and van der Waals’ forces. It has been proposed that these forces are the main contributors to the adhesive interaction. A subsection of this, the chemisorption theory, assumes an interaction across the interface occurs as a result of strong covalent bonding.

The diffusion theory describes interdiffusion of polymers chains across an adhesive interface. This process is driven by concentration gradients and is affected by the available molecular chain lengths and their mobilities. The depth of interpenetration depends on the diffusion coefficient and the time of contact. Sufficient depth of penetration creates a semi-permanent adhesive bond.
**The mechanical theory** assumes that adhesion arises from an interlocking of a liquid adhesive (on setting) into irregularities on a rough surface. However, rough surfaces also provide an increased surface area available for interaction along with an enhanced viscoelastic and plastic dissipation of energy during joint failure, which are thought to be more important in the adhesion process than a mechanical effect.\(^{15}\)

**The fracture theory** differs a little from the other five in that it relates the adhesive strength to the forces required for the detachment of the two involved surfaces after adhesion. This assumes that the failure of the adhesive bond occurs at the interface.

### 1.1.5. Ideal properties for mucoadhesive polymers

An ideal polymer for mucoadhesive drug delivery system should have the following characteristics;

- **a)** The polymer and its degradation products should be non-toxic and non-absorbable from the GI tract.
- **b)** It should be non-irritant to the mucus membrane.
- **c)** It should preferably form a strong non-covalent bond with the mucin-epithelial cell surfaces.
- **d)** It should adhere quickly to moist tissue and should possess some site specificity.
- **e)** It should allow easy incorporation of the drug and offer no hindrance to its release.
- **f)** The polymers should not decompose on storage or during the shelf life of the dosage form.
- **g)** The cost of the polymers should not be high so that the prepared dosage form remains competitive.
Due to its relative complexity, it is likely that the process of mucoadhesion cannot be described by just one of these theories. In considering the mechanism of mucoadhesion, a whole range “scenarios” for in vivo mucoadhesive bond formations are possible and shown in Fig. 1.2.

These include:

1. Dry or partially hydrated dosage forms contacting surfaces with substantial mucus layers (typically particulates administered into the nasal cavity).

2. Fully hydrated dosage forms contacting surfaces with substantial mucus layers (typically particulates of many ‘First Generation’ mucoadhesives that have hydrated in the luminal contents on delivery to the lower gastrointestinal tract).

3. Dry or partially hydrated dosage forms contacting surfaces with thin/discontinuous mucus layers (typically tablets or patches in the oral cavity or vagina).

4. Fully hydrated dosage forms contacting surfaces with thin/discontinuous mucus layers (typically aqueous semisolids or liquids administered into the oesophagus or eye).

It is unlikely that the mucoadhesive process will be the same in each case.

In the study of adhesion generally, two steps in the adhesive process have been identified\(^1\) which have been adapted to describe the interaction between mucoadhesive materials and a mucous membrane\(^1,17\) shown in Fig. 1.3.

Step 1 - **Contact stage:** An intimate contact (wetting) occurs between the mucoadhesive and mucous membrane.
Step 2- **Consolidation stage:** Various physicochemical interactions occur to consolidate and strengthen the adhesive joint, leading to prolonged adhesion.

**The contact stage**

The mucoadhesive and the mucous membrane have initially come together to form an intimate contact. In some cases these two surfaces can be mechanically brought together, e.g. placing and holding a delivery system within the oral cavity, eye or vagina. In others the deposition of a particle is encouraged via the aerodynamics of the organ. For example within the nasal cavity or bronchi of the respiratory tract deposition onto the ‘sticky’ mucus coat is encouraged by processes such as inertial impaction, in order to ‘filter out’ particles from the airstream. The gastrointestinal tract is an example of an inaccessible mucosal surface where the adhesive material cannot be placed directly onto the target mucosal surface, or delivered to the surface by organ design. In general, adhesion and possible blockage of the gastrointestinal tract would be potentially catastrophic. For larger particles, peristalsis and other gastrointestinal movement would help to force the dosage form into contact with the mucosa. However little evidence of successful adhesion of larger dosage forms has yet been reported in the literature, other than the potentially dangerous case of oesophageal adhesion. For smaller particles in suspension, adsorption onto the gastrointestinal mucosa would be an essential prerequisite for the adhesion process. Other examples where an adsorption step would be required would be the administration of nanoparticle suspensions to the precorneal region, or mouthwashes containing microparticles.

The principles of the DLVO theory described in the 1940’s by Derjaguin and Landau, and separately by Verwey and Overbeek to explain the stability of colloids.
have been used to describe the physicochemical processes involved in the adsorption of Bacteria onto surfaces.\textsuperscript{20, 21}

a. Dry or partially hydrated dosage forms contacting surfaces with substantial mucus layers

b. Fully hydrated dosage forms contacting surfaces with substantial mucus layers (e.g. particle suspensions in the gastrointestinal tract).

c. Dry or partially hydrated dosage forms contacting surfaces with thin/discontinuous mucus layers (e.g. a tablet placed onto the oral mucosa)

d. Fully hydrated dosage forms contacting surfaces with thin/discontinuous mucus layers (e.g. aqueous microparticles administered into the vagina).

**Fig. 1.2: Scenarios of mucoadhesion.**

**Fig. 1.3: Two stages in mucoadhesion**
The theory may therefore also be used in the consideration of the adsorption process for small particles. Within the body a particle will move due to Brownian motion, the flow of liquids within a body cavity and body movements such as peristalsis. If a particle approaches a surface it will experience both repulsive and attractive forces.

Repulsive forces arise from osmotic pressure effects as a result of the interpenetration of the electrical double layers, steric effects and also electrostatic interactions when the surface and particle carry the same charge. Attractive forces arise form van der Waals’ interactions, surface energy effects and electrostatic interactions if the surface and particles carry opposite charges.

The relative strength of these opposing forces will vary depending on the nature of the particle, the aqueous environment, and the distance between the particle and surface. For example, the smaller the particle, the greater the surface-area-to-volume ratio and therefore the greater the attractive forces. Particles can be weakly held at a secondary minimum (circa 10 nm separation), a region where the attractive forces are balanced by the repulsive forces allowing the particles to be easily dislodged. For stronger adsorption to occur, particles have to overcome a repulsive barrier (the potential energy barrier) to get closer to the surface (circa 1 nm). If this barrier is sufficiently small, or if the particle has sufficient energy, then adsorption into the primary minimum can occur. This type of adsorption would be required to allow a strong adhesive bond to form. This situation is made more complex by the fact that the surface in question is usually a mucus gel rather than a solid, and the particles in-vivo may become hydrated and/or coated with biomolecules, significantly altering their physicochemical properties.\textsuperscript{22–24} The adhesive interaction necessary to retain a dosage form may only need to be weak if the forces promoting displacement.
are also small. A consideration of many physicochemical models of liquids at solid interfaces suggests that the liquid adjacent to the interface is stationary, with the rate of flow increasing with distance from the surface.\textsuperscript{25} Many texts also refer to the presence of an unstirred water layer at the surface of the gastrointestinal mucosae.\textsuperscript{26} Mucous membranes typically have a highly irregular topography on both the macroscopic and microscopic level so it is possible for small particulates to become lodged in these surface folds and crevasses. Small particles may therefore be subjected only to minor dislodging stresses so only small adhesive interactions would be required to keep them in place. This might explain how apparently inert materials have been reported to be Mucoadhesive.\textsuperscript{27–29}

**The consolidation stage**

It has been proposed that if strong or prolonged adhesion is required, for example with larger formulations exposed to stresses such as blinking or mouth movements, then a second ‘consolidation’ stage is required. Mucoadhesive materials adhere most strongly to solid dry surfaces\textsuperscript{30} as long as they are activated by the presence of moisture. Moisture will effectively plasticize the system allowing mucoadhesive molecules to become free, conform to the shape of the surface, and bond predominantly by weaker van der Waal and hydrogen bonding. In the case of cationic materials such as chitosan, electrostatic interactions with the negatively charged groups (such as carboxyl or sulphate) on the mucin or cell surfaces are also possible. The mucoadhesive bond is by nature very heterogenous making it extremely difficult to use spectroscopic techniques to identify the type of bonds and groups involved although hydrogen bonds have been identified as being important.\textsuperscript{1,31} Polymer/mucosae interactions have been investigated by evaluating surface energies\textsuperscript{32–34}. Although of interest, these studies have met with varying degrees of
success, which is unsurprising considering the heterogeneous nature of mucosal surfaces and biopolymer solutions relative to the normally pure solvents and surfaces required in surface energy measurements. Polymers and biopolymers in solution tend to rapidly accumulate at interfaces producing a significant reduction in the surface energy. It is also noticeable when undertaking tensiometer studies with these systems that the high affinity of materials like carbomers for water almost appears to have a ‘suction-like’ effect, helping to hold to formulation onto a solid surface. For surfaces with only limited amounts of mucus, a dry mucoadhesive polymer will almost certainly collapse the mucus layer by extracting the water component of the gel, allowing the polymer molecules the freedom to interact by hydrogen bonding with the epithelial surface.

However, when a substantial mucus layer is present then the anti adherent properties of mucus will need to be overcome if a strong adhesive joint is to be formed. In this case the adhesive joint can be considered to contain three regions are shown in Fig. 1.4, the mucoadhesive, the mucosa and an interfacial region, consisting at least initially of mucus. To achieve strong adhesion, a change in the physical properties of the mucus layer will be required otherwise it will readily fail on application of a dislodging stress. There are essentially two theories as to how gel strengthening/consolidation occurs. One is based on a macromolecular interpenetration effect, which has been dealt with in a theoretical basis by Peppas and Sahlin.

![Fig. 1.4: Three regions within a mucoadhesive joint](image-url)
In this theory, based largely on the diffusion theory described by Voyutskii\textsuperscript{35} for compatible polymeric systems, the mucoadhesive molecules interpenetrate and bond by secondary interactions with mucus glycoproteins were shown in Fig. 1.5. In an earlier study a thin crosslinked film of poly (acrylic acid) was formed on an ATR crystal. A mucin solution was placed into contact with this film and ATR-FTIR spectra collected over a period of time. Deconvolution of these spectra revealed a peak after 6 min at 1550 cm\(^{-1}\) (which manifested itself as a small shoulder in the original spectrum) which was attributed to mucin dimeric carboxylic CMO stretching and it was proposed that this indicated the presence of interpenetrating mucin molecules within the poly (acrylic acid) film\textsuperscript{36}. Another study suggested that evidence of substantial interpenetration was apparent for poly (acrylic acid) labelled with fluoresceinamine. This was size dependent but even the largest polymer (polycarbophil) showed penetration to a depth of 60 Am after 4 hr\textsuperscript{37}. However, the model mucus used was a commercial mucin which is thought to be degraded and therefore of limited value as a model of native mucus.\textsuperscript{38, 39} The porcine intestinal mucosa also used in this study had been frozen prior to experimentation, a procedure likely to result in significant damage to the mucus gel layer. Further indirect evidence for interpenetration is based on the rheological effects of mixing mucus with mucoadhesive gels.\textsuperscript{40, 41}

Rheological synergism, an increase in the resistance to elastic deformation (i.e. mucus gel strengthening) is evident, and this would undoubtedly help consolidate the adhesive joint. The second theory is the dehydration theory.\textsuperscript{17} When a material capable of rapid gelation in an aqueous environment is brought into contact with a second gel water movement occurs between gels until equilibrium is achieved. A
polyelectrolyte gel, such as a poly(acrylic acid) will have a strong affinity for water, therefore a high “osmotic pressure” and a large swelling force.\textsuperscript{42,43}

![Diagram](image)

**Fig. 1.5: Interpenetration theory - three stages in the interaction between a mucoadhesive polymer and mucin glycoproteins**

When brought into contact with mucus gel it will rapidly dehydrate that gel and force intermixing and consolidation of the mucus joint until equilibrium is reached are shown in Fig. 1.6. The movement of water from mucus into a poly (acrylic acid) film was observed.\textsuperscript{36} A mucus gel on dehydration, goes from having a lubricant to the opposite adhesive properties, as observed in studies.\textsuperscript{44,45}

The latter theory explains why mucoadhesion arises very quickly, within a matter of seconds, while the former requires two large macromolecules to interpenetrate several aims within a short time.

![Diagram](image)

**Fig. 1.6: Dehydration theory of mucoadhesion**
The rheological synergy study suggests that as soon as mucus and mucoadhesive interpenetrate they are likely to interact and form a surface gel layer that will substantially inhibit any further interpenetration. In an electron microscopy study\textsuperscript{46} no evidence of interpenetration could be seen in the micrometer range when fresh rat intestinal mucus was used. Clear evidence of rapid mucus gel dehydration has been observed using light microscopy.\textsuperscript{44} However, the dehydration theory is limited to explaining the adhesion arising when a dry or partially hydrated formulation are brought into contact with a substantial mucus gel, and will not apply to the occasions where hydrated gels are involved.

**Removal mechanisms**

Adhesive failure will normally occur at the weakest component of the joint were shown in Fig. 1.7. For weaker adhesives this would be the mucoadhesive–mucus interface, for stronger adhesives this would initially be the mucus layer, but later may be the hydrating mucoadhesive material\textsuperscript{47}. On application of a constant tensile stress to compacts of mucoadhesive polymers, joint failure was found by Mortazavi and Smart\textsuperscript{48} to be a cohesive failure of the swelling polymer for all but the weakest adhesives. The strength and durability of the adhesive joint will therefore depend on the cohesive nature of the weakest region. The mucoadhesive polymer in an aqueous environment can over hydrate to form slippery mucilage, which is readily removed\textsuperscript{7}. Controlling the rate and extent of hydration is required to produce prolonged adhesion and strategies such as cross-linking\textsuperscript{49–51} and introducing hydrophobic entities\textsuperscript{52} has been tried to achieve this. In all cases, eventually all formulations will be displaced by mucus or cell turnover\textsuperscript{53–55}.
Factors affecting mucoadhesion

Several factors have been identified as affecting the strength of the solid mucoadhesive joint\textsuperscript{1, 9, 11}. Many studies have indicated an optimum molecular weight for mucoadhesion, ranging from circa $10^4$ Da to circa $4 \times 10^6$ Da, although accurately characterizing the molecular weight of large hydrophilic polymers is very difficult. Larger molecular weight polymers will not hydrate readily to free the binding groups to interact with a substrate, while lower molecular weight polymers will form weak gels and readily dissolve. The flexibility of polymer chains is believed to be important for interpenetration and entanglement, allowing binding groups to come together. As the cross-linking of water-soluble polymers increases, the mobility of the polymer chains decrease, although this could also have a positive effect in restricting over hydration. Studies have shown that the mucoadhesive properties of polymers containing ionisable groups are affected by the pH of the surrounding media\textsuperscript{1}. For example, mucoadhesion of poly (acrylic acid) is favoured when the majority of the carboxylate groups are in the unionised form, which occurs at pHs below the pKa. However, in systems with a high density of ionisable groups (e.g. carbomers or chitosans), the local pH within or at the surface of a formulation will differ significantly from that of the surrounding environment\textsuperscript{56}.

The strength of adhesion has been found to change with the initial “consolidation” force applied to the joint, or the length of contact time prior to testing. The presence of metal ions, which can interact with charged polymers, may also affect the adhesion process.
18

Chapter 1

Introduction

Mucoadhesive dosage form
Fracture through the hydrated gel layer
Fracture through the interface
Fracture through the mucus gel layer
The Epithelium

Fig. 1.7: The possible regions for mucoadhesive joint failure.

1.1.6. Liquid and Semisolid adhesion

Water soluble polymer adsorption

Mucoadhesive polymers (Chitosan, Polycarbophil and Carbopol 934) in dilute solutions were shown to bind to buccal cells in-vitro\(^57\), and to bind and be retained in vivo for over 2 h\(^58\). The mechanism by which this occurs is that of polymer adsorption at an interface, where polymers will naturally collect to reduce the surface energy and can then bind by the formation of many weak bonds, mimicking the natural role of mucins in saliva. The scenario is complicated by the presence of mucins on the mucosae, which means that polymers are adsorbing onto a hydrated gel. In the case of cationic polymers like chitosan, the positive charge will favour binding to a negatively charged surface although, in-vivo binding to soluble luminal mucins may inhibit this effect\(^59\).

Retention of liquids and gels

More concentrated mucoadhesive dispersions have been shown to be retained on mucosal surfaces for extended periods\(^60\), \(^61\). The process by which polymeric dispersions spread and are retained on mucosae will depend principally on the surface energy of the solid and liquid (a positive spreading coefficient), along with the
rheology of the liquid. The dispersion will need to be sufficiently mobile to allow spreading and interaction while not being so mobile as to be readily dislodged. Systems that allow in situ gelation will clearly favour retention in this case\textsuperscript{62, 63}. The interaction of the liquid or semisolid with biological fluids in terms of the rate and extend of mixing and dissolution, will also be key factors influencing retention.

**New materials**

In order to overcome the limitations of first generation “off-the-shelf” mucoadhesive materials, new types of materials have been investigated that allow specificity, or prolong and strengthen the mucoadhesion process. In some cases, existing mucoadhesive polymers have been modified, while in others, new materials are developed.

One approach to produce improved mucoadhesives has been to modify existing materials. For example thiol groups (by coupling cysteine, thioglycolic acid, cysteamine) have been placed into a range of mucoadhesive polymers such as the carbomers, chitosans and alginates by Bernkop-Schnurch et al.\textsuperscript{64, 65} The concept is that in-situ they will form disulphide links not only between the polymers themselves thus inhibiting overhydration and formation of the slippery mucilage, but also with the mucin layer/ mucosa itself, thus strengthening the adhesive joint and leading to improved adhesive performance. This interesting approach appears to be meeting with some success.

The incorporation of ethyl hexyl acrylate into a copolymer with acrylic acid in order to produce a more hydrophobic and plasticized system was considered by Shojaei et al.\textsuperscript{68}. This would reduce hydration rate while allowing optimum interaction with the mucosal surface, and the mucoadhesive force was found to be greater with
the copolymer than with poly (acrylic acid) alone. The grafting of polyethylene glycol (PEG) onto poly (acrylic acid) polymers and copolymers has also been investigated\textsuperscript{69,71}. These copolymers were shown to have favourable adhesion relative to poly (acrylic acid) alone, in that the polyethylene glycol is proposed to promote interpenetration with the mucus gel\textsuperscript{72}. Poly (acrylic acid)/PEG complexes have also been developed as mucoadhesive materials\textsuperscript{73}. Pluronics have also been chemically combined with poly (acrylic acid) to produce systems with enhanced adhesion\textsuperscript{74} and retention in the nasal cavity\textsuperscript{75}. Dihydroxyphenylalanine (DOPA), an amino acid found in mussel adhesive protein that is believed to lend to the adhesive process, has also been combined with pluronics to enhance their adhesion\textsuperscript{76}.

Glyceryl monooleate/water liquid crystalline phases have also been found to be mucoadhesive using a range of mucosal surfaces, although the mechanism will differ somewhat from that of other mucoadhesives\textsuperscript{77}. Lectins are proteins or glycoproteins that have been considered second-generation bioadhesives, and differ significantly from the polymeric systems described above. There is a range of lectins available that interact with specific sugar residues via relatively weak (secondary) interactions and have been considered for use in targeted drug delivery\textsuperscript{78}.

1.2. Controlled release drug delivery system

As the name implies, controlled-release drug delivery systems serve two functions. The first, drug delivery, involves the transport of the drug to a particular part of the body. This may be accomplished in a number of ways: intravenously, transdermally, or orally. This paper focuses on oral delivery systems. The second function is that of controlled release. This describes the rate at which the drug is made available to the body once it has been delivered. Traditionally, delivery systems have
not incorporated means of controlled release. The problem, however, is that with each
dose of a non controlled-release drug, the concentration of drug available to the body
immediately peaks and then declines rapidly. At times, the drug concentration is very
high, contributing to adverse side effects. At other times, the concentration is too low
to provide therapeutic benefit. It is desirable to release drugs at a constant rate,
thereby maintaining drug concentration within the therapeutic range and eliminating
the need for frequent dosages\textsuperscript{79-82}. Taking four doses of a drug in a day, for instance,
would yield an absorption pattern similar to one time of control release drug in a day.
And a number of controlled-release systems have been developed in recent years. To
control and to prolong the GIT transit of oral controlled delivery system for all kind
of drugs are through the polymers mainly, and the polymers may be of either natural
or synthetic mucoadhesive in character to sustain the drug release. Hence it may be
emphasized that the polymers are playing a key role in all types of
controlled/sustained release dosage formulations especially mucoadhesive polymer
and requires utmost importance in the selection of polymers, which should be
therapeutically and chemically inert so that the untoward effects may not occur, when
administered in to the human system. The main objective of this is that polymers can
be used to overcome physiological barriers in long-term drug delivery.\textsuperscript{83}

1.2.1. Potential advantages of controlled drug delivery

1. Avoid patient compliance problems.

2. Employ less total drug
   a. Minimize or eliminate local side effects.
   b. Minimize or eliminate systemic side effects.
   c. Obtain less potentiation or reduction in drug activity with chronic use.
   d. Minimize drug accumulation with chronic dosing.
3. Improve efficiency in treatment
   a. Cure or control condition more promptly
   b. Improve control of condition, i.e., reduce fluctuation in drug level.
   c. Improve bioavailability of some drugs.
   d. Make use of special effects, e.g., sustained release aspirin for morning relief of arthritis by dosing before bedtime.

4. Economy.

5. A greater selectivity of pharmacological activity.

1.2.2. Factors influencing the design and performance of controlled release products

1. Drug properties
2. Route of drug delivery
3. Target sites
4. Acute or chronic therapy
5. The disease
6. The patient

1.2.3. Drugs suited for formulation into the controlled release products for oral administration

1. Drugs having fairly rapid rate of absorption and excretion.
2. Drugs which are uniformly absorbed in GI tract.
3. Drugs which require relatively smaller doses for therapeutic effect.
4. Drugs which are used for chronic rather than acute conditions.

1.2.4. Characteristics which make a drug unsuitable for controlled release dosing via oral route

1. Short elimination half life. i.e. less than 1hr.
2. Longer elimination half life. i.e. greater than 12hr.
3. Narrow therapeutic index.
4. Large doses.
5. Poor absorption.
6. Low or slow solubility.
7. Active absorption.
8. Time course of circulating drug level different to that of pharmacological effect.
1.3. Conventional drug delivery

To gain an appreciation for the value of controlled drug therapy it is useful to review some fundamental aspects of conventional drug delivery. Consider single dosing of a hypothetical drug that follows a simple one-compartment pharmacokinetic model for disposition. Depending on the route of administration, a conventional dosage form of the drug, example solution, suspension, capsule, tablet, etc can produce a drug blood level versus time profile. The term drug blood level refers to the concentration of drug in blood or plasma, but the concentration in any tissue could not be equalized in distribution. In this case the drug blood level reached and time required to reach that level depend on the dose and the dosing interval. There are several potential problems inherent in conventional therapy:

a. If the dosing interval is not appropriate for the biological half life of the drug, a sudden increase of blood drug level may results. For example, drugs with short half lives require frequent dosing to maintain constant therapeutic levels.

b. The drug blood level may not be within the therapeutic range at sufficiently early times, an important consideration for certain disease states.

c. Patient noncompliance with the conventional dosage regimen can result in the failure of approach.

In many instances, potential problems associated with conventional drug therapy can be overcome. When this is the case, drugs given in conventional dosage forms by multiple-dosing can produce the desired drug blood level for extended periods of time. Frequently, however, these problems are significant enough to make drug therapy with conventional dosage forms less desirable than controlled release drug therapy. This fact, coupled with the intrinsic inability of conventional dosage
forms to achieve spatial placement, is a compelling motive for investigation of controlled release drug delivery systems. There are numerous potential advantages of controlled release drug therapy that are discussed below.

1.4. **Natural pharmaceutical excipients**

Today we have a number of pharmaceutical excipients from plant origin, like starch, agar, alginites, carrageenan, guar gum, xanthan gum, gelatin, pectin, acacia, tragacanth and celluloses. These natural excipients find applications in pharmaceutical industry as binding agents, disintegrates, sustaining agents, protectives, colloids, thickening agents, gelling agents, bases in suppositories, stabilizers and coating materials.

The advantages of natural plant based excipients include low cost, natural origin, free from side effects, biocompatible, bioacceptable, renewable source, environmental friendly processing, local availability, better patient tolerance as well as public acceptance. They improve the national economy by providing inexpensive formulations to people, using locally available material.

1.4.1. **Disadvantages of synthetic materials**

The synthetic material have certain disadvantages such as high cost, time consumption, toxicity, environmental pollution by chemical industry, non renewable sources, more side effects and hence, less patient compliance.

1.4.2. **Polysaccharides, gums and mucilages from plant source**

Plants are the sources of many polysaccharide hydrocolloids. Gums and mucilage’s are the most commonly available plant polysaccharide hydrocolloids.
These are complexes formed from sugar and uronic acid units. They are insoluble in alcohol but dissolve or swell in water. They are usually formed from the cell wall (e.g., tragacanth) or deposited on it in successive layer. Gums are natural plant colloids that may be classified as anionic or nonionic polysaccharides. They are translucent, amorphous substances that are frequently produced in higher plants as a protective after injury. Gums are either hydrophobic or hydrophilic in nature. An effort has been made to distinguish between mucilages and gums on the basis that gums readily dissolve in water, where as mucilages from slimy masses. Other investigators have tried to distinguish pathological products. Another difference is that the mucilages contain pectin. Gums and mucilages are typically heterogeneous in composition. Upon hydrolysis, arabinose, galactose, glucose, mannose, xylose and various uronic acids are the most frequently observed components. The uronic acid may form salts with calcium, magnesium and sulfate ester substituents.\(^{87,88}\)

1.4.3. **Classification of gums and mucilages**

Gums and mucilages are present in high quantities in varieties of plants, animals, seaweeds, fungi and other microbial sources, where they perform a number of structural and metabolic functions, plant sources provide the largest amounts. The different available gums and mucilages can be classified as follows: \(^{89}\)

**a. According to the charge**

**Non-ionic seed gums** : Guar, Locust bean, Tamarind, Xanthan, Amylose, Arabinans, Cellulose, Galactomannans.

**Anionic gums** : Arabic, Karaya, Tragacant, Gellan, Agar, Algin.

**b. According to the source**

**Marine origin** : Algae, Agar, Carrageenans, Alginic acid, Laminarin.
Plant Origin:

i. Shrubs/Tree exudates: Gum arabica, Gum ghatti, Gum karaya, Gum tragacanth, Khaya and Albizia gums.

ii. Seed gums: Guar gum, Locust bean gum, Starch, Amylose and Cellulose.

iii. Extracts: Pectin, Larch gum,

iv. Tuber and roots: Potato starch.

Animal origin: Chitosan, Chondroitin sulfate, Hyaluronic acid.

Microbial origin: Xanthan, Dextran, Curdian, Pullulan.

c. Semi-synthetic

Starch: Hetastarch, Starch acetate, Starch phosphates.

Cellulose: Carboxymethylcellulose, Hydroxyethylcellulose, Hydroxypropylmethyl cellulose, Methylcellulose, Microcrystalline cellulose.

d. According to shape

Linear: Algins, Amylose, Cellulose, Pectins.

Branched: Xanthan, Xylan, Amylopectin, Gum Arabic.

e. According to manomeric units in chemical structure

Homoglycans: Amylase, Arabinanas, Cellulose

Diheteroglycans: Aligns, Carragennans, Galactomannans.

1.4.4. Pharmaceutical applications of gums and mucilages

The plant agents may have a linear or branched structure. They may have acidic, basic or neutral characteristics. Among them the hydrocolloids with basic characteristics have limited commercial importance, where as acidic and neutral
polymers have wide pharmaceutical applications. They are ingredients in dental and other adhesives and as bulk laxatives. These hydrophilic polymers are useful as tablet binders, disintegrants, emulsifiers, suspending agents, gelling agents, stabilizing agents, thickening agents and sustaining agents.

1.4.5. Natural material as retarding agent in oral tablets

The natural material can be used for retardation of the drug release. They have been used in tablets, suspensions or as a matrix system for sustaining the drug release. These polymers, when comes in contact with water, get hydrated and gel form. The drug release from this gel will be usually diffusion controlled and hence the release will be sustained over a prolonged time. Many hydrocolloids such as guargum, xanthan gum, karaya gum and mucilages from cassia tora, ocimum canum, ledidium sativum, asparagus racemosus, aloe vera, althea rosea and althea officinalis have been reported to sustain the drug release from matrix tablets.