BIOADHESIVE DRUG DELIVERY SYSTEM: AN OVERVIEW

*JADHAV KHANDERAO R. [1], PAWAR ASHISH Y. [2] & TALELE GOKUL S. [3]

[1]Department of Pharmaceutical Sciences, JJT University, Rajasthan, India.,[2]Department of Pharmaceutics, MGV's Pharmacy College, Panchavati, Nashik, Maharashtra, India.,[3]Department of Pharmaceutical Chemistry, NGSPM's,College of Pharmacy, Anjaneri, Nasik, Maharashtra, India. E-mail: krjadhav25@gmail.com

ABSTRACT

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. 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 release. Because of these several advantages there is enormous development was taking place in the field of bioadhesive drug delivery system. The article summarizes in detail about theories of bioadhesion, significance of bioadhesion & factors affecting mucoadhesion.

Keywords: Mucoadhesive, Bioadhesion, Mucin, Controlled release.

INTRODUCTION

Oral controlled release systems continue to be the most popular one among all the drug delivery systems due to their several advantages over the conventional systems like:

1. Improved patient compliance and convenience due to less frequent dosing of drug required.
2. Reduction in fluctuation of steady state plasma level and therefore helps in better control of disease condition.
3. Better control of plasma levels of high potency drugs.
4. Maximum utilization of drug enabling reduction in total amount of dose administered.
5. Reduction in health care cost through improved therapy, shorter treatment period and less frequency of dosing.[1, 2]
6. Patentability, and opportunity for extending product life-cycle.[3]

However, the problem frequently encountered with controlled release dosage forms is the inability to increase the residence time of the dosage form in the stomach and proximal portion of the small intestine, due to the rapid gastrointestinal transit phenomenon of the stomach which may consequently diminish the extent of absorption of many drugs since almost most of the drug entities are mostly absorbed from the upper part of the intestine. Therefore it would be beneficial to develop sustained release formulations which remain at the absorption site for an extended period of time. Several approaches have been immerged to prolong the residence time of the dosage forms at the absorption site and one of these is the development of oral controlled release bioadhesive system.

In the early 1980's, Professor Joseph R. Robinson at the University of Wisconsin pioneered the concept of bioadhesion as a new strategy to prolong the residence time of various drugs on the ocular surface.[4]

Various gastrointestinal mucoadhesive dosage forms, such as discs, microspheres, and tablets, have been prepared and reported by several research groups**.**[5]

Bioadhesion: [5,6,7]

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.

Significance of Bioadhesion: [8, 9]

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 rele

THEORIES OF BIOADHESION:[5,6,7]

For adhesion to occur, molecules must bond across the interface of mucus. These bonds can arise in the following ways:[11]

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

Covalent bonds— electrons are shared, in pairs, between the bonded atoms in order to fill the orbital in both. These are also strong bonds.

Hydrogen bonds— a hydrogen atom, when covalently bonded to electronegative atoms such as oxygen, fluorine or nitrogen, carries a partial positive charge and is therefore is attracted to other electronegative atoms. The bond formed is generally weaker than ionic or covalent bonds.

Van der-Waals bonds— 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.

For bioadhesion to occur, a succession of following phenomena is required. The first stage involves an intimate contact between a bioadhesive and a membrane, either from a good wetting of the bioadhesive surface or from the swelling of the bioadhesive. In second stage, once contact is established, penetrations of the bioadhesive into the crevice of tissue surface or interpenetration of the chains of the bioadhesive with that of the mucus take place.

On a molecular level, mucoadhesion can be explained on the basis of molecular interactions. The interaction between two molecules is composed of attraction and repulsion. Attractive interactions arise from van der Waals forces, electrostatic attraction, hydrogen bonding, and hydrophobic interaction. Repulsive interactions occur because of electrostatic and steric repulsion. For mucoadhesion to occur, the attractive interaction should be larger than nonspecific repulsion.

Several theories have been proposed to explain the fundamental mechanisms of adhesion.

Electronic Theory

Electron transfer occurs upon contact of an adhesive polymer with a mucus glycoprotein network because of difference in the electronic structures. This results in the formation of electrical double layer at the interface. Adhesion occurs due to attractive forces across the double layer.

Adsorption Theory

According to the adsorption theory, after an initial contact between two surfaces, the material adheres because of surface forces acting between the atoms on the two surfaces. Two types of chemical bonds resulting from these forces can be distinguished,

Primary chemical bonds of covalent nature, which are undesirable in bioadhesion because of their high strength, which may result in permanent bonds.

Secondary chemical bonds having many different forces of attraction, including

Wetting Theory

Wetting theory is predominantly applicable to liquid bioadhesive systems. It analyzes adhesive and contact behavior in terms of the ability of a liquid or paste to spread over a biological system.

The work of adhesion (W_a) is defined as the energy per square centimeter released when an interface is formed and is expressed in terms of surface and interfacial tension Y. The work of adhesion is given by,

$$W_a = Y_A + Y_B - Y_{AB}$$

Where A and B refer to the biological membrane and the bioadhesive formulation respectively. The work of cohesion is given by,

$$W_c = 2Y_A \text{ or } 2Y_B$$

For a bioadhesive material B spreading on a biological substrate A, the spreading coefficient is given by,

$$S_{B/A} = Y_A - Y_B + Y_{AB}$$

$S_{B/A}$ should be positive for a bioadhesive material to adhere to a biological membrane.

Diffusion Theory

According to diffusion theory, the polymer chains and the mucus mix to a sufficient depth to create a semi-permanent adhesive bond .The exact depth to which the polymer chain penetrates the mucus depends on the diffusion coefficient and the time of contact.

Fracture Theory

Fracture theory attempts to relate the difficulty of separation of two surfaces after adhesion. Fracture theory equivalent to adhesion strength is given by,

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

Where E is Young's modulus of elasticity, Δ is fracture energy and L is critical crack length when two surfaces are separated.

Different approaches:[5]

Mucoadhesive drug delivery systems utilize the property of bioadhesion of certain water-soluble polymers, which become adhesive on hydration and hence can be used for targeting a drug to a particular region of the body for extended period of time. The potential sites for attachment of any bioadhesive system lead to the development of various mucoadhesive drug delivery systems such as buccal sublingual, vaginal, rectal, nasal, ocular and gastrointestinal drug delivery systems. Anatomy and physiology of GI tract is presented in the following section.

ANATOMY OF THE GASTROINTESTINAL TRACT: [12-15]

The gastrointestinal tract can be divided into three main regions namely

1. Stomach
2. Small intestine- Duodenum, Jejunum and Ileum
3. Large intestine

The entire gastrointestinal tract (figure 1) is lined by a relatively thick, dense and multi–layered mucous membrane of a highly vascularized nature. Drug penetrating into the membrane can find access to the systemic circulation via the capillaries and arteries lying underneath.

Mucin is secreted mainly from the goblet cells that lie on the epithelium layer and form a thick mucus layer over the epithelial surface, which protects the epithelium cells from the acidic environment of the stomach and also protects the epithelium against gastric enzymes.
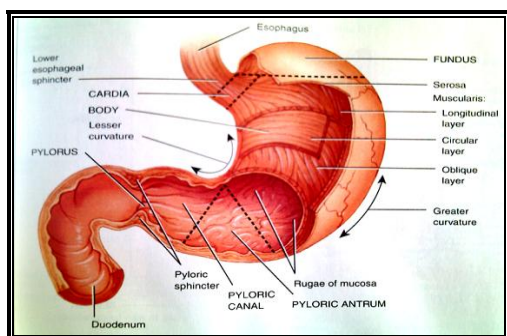

Figure 1: Anatomy of the gastrointestinal tract

Mucus layer

The target for interactions of most of the bioadhesive polymers is mucus. In higher organisms mucus is a highly viscous product, which forms a protective coating over the lining of hollow organs in contact with external media. Mucus is mixture of large glycoproteins (Mucin), water, electrolytes, sloughed epithelial cells, enzymes, bacteria and bacterial products and various other materials, depending on its source and location. Mucin is synthesized either by goblet cells lining the mucus epithelium or by special exocrine glands with mucus cell acini. The main component of mucus secretion is the glycoprotein fraction, which is responsible for its gel like characteristics. The mean thickness of mucus layer varies from 50 to 450μm in humans and about half of this in rats.

The primary functions of mucus are lubrication and protection of underlying epithelial cells. Continuous secretion of mucus from the goblet cells is necessary to compensate for the removal of the mucus layer due to digestion, bacterial degradation and solubilization of mucin molecules.

Based on the structure of mucin, there are four characteristics of the mucus layer that relate to mucoadhesion:

1. It is a network of linear, flexible, and random coil mucin molecules.
2. It is negatively charged due to the presence of sialic acid, which has a pKa of 2.6 and sulfate residues on the mucin molecules.
3. It is a cross-linked network because of disulfide bonds and physical entanglement between mucin molecules.It is highly hydrated.

The main components of mucous layer include water (up to 95% by weight), mucin (generally no more than 5% by weight), inorganic salts (about 1% by weight), carbohydrates and lipids. Mucin represents more than 80% of the organic components of mucus and controls the gel-like structure. Mucins are O-linked glycoproteins. From a polymer science viewpoint, mucins are block copolymers with branched and un-branched blocks. Both types of blocks have protein backbone chains, but the branched blocks have highly branched oligosaccharide chains attached to them. The main amino acids in the branched protein blocks are serine, threonine and proline. The serine and threonine residues dominate the amino acid composition, together making up 25–40% of the total amino acids.

The oligosaccharide side chains have sugar residues such as galactose, fucose, N-acetylglucosamine, N-acetylglactosamine and sialic acid (Figure 2).

In most cases, the branch point is made of N-acetylgalactosamine (GAlNAc) attached to the protein backbone through an ether bond, which is the result of the reaction between the α-1 position hydroxyl group and the hydroxyl group from serine or threonine residues. The number of sugar residues in each of the branched chains ranges from 2 to 19; in addition, branched chains may have sub-branches.

The terminal groups of the sugar chains are often fucose, sialic acid, sulfate esters of galactose and N-acetylglucosamine. In the non-branched blocks, the composition of amino acid residues is normal compared with the concentrated serine and threonine composition in the branched blocks.

This region is rich in charged amino acids, such as aspartic acid. The branched blocks constitute 75% of the length of the protein backbone chains, whereas the oligosaccharide branch chains make up 50% by weight of the mucin.
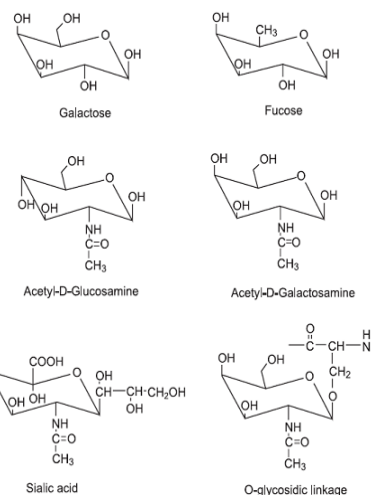

Figure 2: Chemical structures of the sugar units generally found in mucin molecules

One mucin molecule consists of about four subunits, and each subunit is composed of a few so-called ''T-domains''. T-domains include one branched and one or two terminal peptide blocks. The molecular weight of the subunits is about 5×10^5. Due to their highly branched nature, mucin subunits can be modeled by a polymer bottle-brush model. According to this model, the local chain conformation of the backbone chain is much more extended than those of chains without branches; sometimes even a lyotropic liquid crystalline mesophase can occur. Moreover, the branched chains and the backbone chains are charged in suitable environments, and this furthers the extent of stretched conformation. Electron microscopic results suggest that the persistence length of mucin in solution is about 100 nm, while the effective diameter of mucin molecules is about 5 nm.

In an aqueous solution, the backbone proteins are neutral if not hydrophobic, but the branched sugar chains are highly hydrophilic. Thus, if the branched density is very high and the branched chains are long enough, other molecules only contact the hydrophilic sugar chains, while the backbone segments are shielded. For the subunits of a branched block, about 25% of the amino acids have sugar branch chains. Moreover, the function of branch sugar chains on the extended conformation is believed mainly due to the first one or two sugar residues, and the other sugar residues are less important.

The conformation of the unglycosylated peptide region of the subunits is dependent on the local amino acid composition and the solution environment. The following three conformations are possible: rigid helix, random coil and compact globules.[14]

Gel structure of the mucus layer: [14]

Four to six subunits are linked together to form a mucin molecule with a molecular weight of $0.5– 40 \times 10^6$. The subunits are assembled end-to-end into large, linear and flexible macromolecules. The cystein residues in the unglycosylated peptide regions may form disulfide bridges and link the linear mucin molecules together.

The conformation of isolated mucin molecules in solution takes the form of highly expanded spheres and extended filamentous structures. Though paradoxical, these descriptions suggest the feature of the mucin conformation: local rod-like and global coil-like.

The appearance of loops, kinks and turns in microscopy pictures suggests that mucin chains have considerable flexibility. The overall radius of gyration of isolated mucins in solution is about 50–200 nm.

The mechanism of formation of gel-like mucous layers by mucin macromolecules is still under investigation. The intermolecular interaction is believed to be non-covalent in nature since the gel structure can be disrupted by small shear forces, and the disulfide bridges may be only intramolecular. Proposed intermolecular interactions include hydrogen bonding, hydrophobic interactions and physical entanglements. In order to understand the interaction between mucus and polymer, it is important to understand the interactions between mucins first.

The mucin molecules have both glycosylated hydrophilic blocks and unglycosylated hydrophobic peptide blocks. Hence, the blocks prefer to form segregated domains. The intermolecular domains act as physical crosslinks leading to spontaneous gel formation. Experimentally, if the bare peptide blocks are disrupted both by breaking disulfide bridges or peptide proteolytic enzymes, the mucins are no longer able to form gels and they dissolve into aqueous solutions.

The intermolecular entanglements are also able to form transient gels. Mucins in the native state are well entangled. The entanglements consist of transient entanglements as well as those formed by intermolecular aggregation of hydrophobic blocks.

Another proposed mechanism for gel formation is by locally ordered regions. The localized regions are formed by the cooperative interactions of several weak bonds, since no single weak bond is strong enough for a stable gel. Observations of Bell et al. suggest that non-specific entanglements or simple hydrophobic interactions cannot completely determine the gel structure of the native mucus. Bell et al suggested a stable interdigitation of the sugar side chains from different mucins. These interactions may be topological in nature and are formed in the mucin secretion process. The topological interactions are lost in the purification process and are not reformed spontaneously. This kind of 3-dimensional intermolecular interaction is more stable than the transient entanglements. The detailed structure of mucus layers is not clear.

Physiological Considerations

The major factors determining bioavailability of the drug are:

1. Drug (the intrinsic properties of the drug molecule),

2. Delivery (dosage form) and

3. Destination (the target environment for delivery). [16,17]

Factors such as pH, enzymes, nature and volume of secretions, residence time, and effective absorbing surface area of the site of delivery play an important role in drug liberation and absorption.

In stomach there are several types of cells that secrete up to 2–3 liters of gastric juice daily. For example, goblet cells secrete mucus, parietal cells secrete hydrochloric acid, and chief cells secrete pepsinogen.

The contraction forces of the stomach churn the chyme and mix it thoroughly with the gastric juice. The average length of the stomach is about 0.2 meter, and the apparent absorbing surface area is about 0.1m². The physiological features that pose challenge to the development of an effective gastroretentive delivery system have been reviewed by Deshpande et al[16] and Talukder et al[17] A brief survey is presented here.

Gastric pH

The gastric pH is not constant. It is influenced by various factors like diet, disease, presence of gases, fatty acids, and other fermentation products. In addition, the gastric pH exhibits intra-as well as inter-subject variation. This variation in pH may significantly influence the performance of orally administered drugs. It has been reported that the mean value of gastric pH in fasted healthy subjects is 1.1 ± 0.15. [On the contrary, the mean gastric pH in fed state in healthy males has been reported to be 3.6±0.4, and the pH returns to basal level in about 2 to 4 hours. However, in fasted state, basal gastric secretion in women is slightly lower than that of in men.

Gastric pH may be influenced by age, pathological conditions and drugs. About 20% of the elderly people exhibit either diminished (hypochlorhydria) or no gastric acid secretion (achlorohydia) leading to basal pH value over 5.0. Pathological conditions such as pernicious anemia and AIDS (Acquired Immuno Deficiency Syndrome) may significantly reduce gastric acid secretion leading to elevated gastric pH. In addition, drugs like H_2 receptor antagonists and proton pump inhibitors significantly reduce gastric acid secretion.

Gastric pH is an important consideration in selecting a drug substance, excipients, and drug carrier(s) for designing intragastric delivery systems.

Gastrointestinal Motility and Transit Time

Based on fasted and fed states of the stomach, two distinct patterns of gastrointestinal motility and secretions have been identified. In the fasting state, the stomach usually contains saliva, mucus, and cellular debris. The fasted state is associated with some cyclic contractile events commonly known as migrating myoelectric complex (MMC). Liquid components easily pass through the partially constricted sphincter. On the contrary, the large undigested materials are retained by an "antral-sieving" process and are retropulsed into the main body of stomach and remain in the fed state. In the fed state, gastric contractions move the contents towards the antrum and the pyloric sphincter. Usually a series of interdigestive events take place in the stomach. However, feeding disrupts this cycle causing a period of irregular contractile pattern. The MMC, which governs the gastrointestinal motility pattern has been described as an alternating cycles of activity and quiescence. Apparently there are four consecutive phases of activity in the MMC (Table 1 and Figure 3).

Table 1: Four phases in migrating myoelectric complex (MMC)

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Phase I	It is a quiescent period lasting from 30 to 60 minutes with no contractions.
Phase II	It consists of intermittent contractions that gradually increase in intensity as the phase progresses, and it lasts about 20 to 40 minutes. Gastric discharge of fluid and very small particles begins later in this phase.
Phase III	This is a short period of intense distal and proximal gastric contractions (4–5 contractions per minute) lasting about 10 to 20 minutes; these contractions, also known as "house-keeper wave," sweep gastric contents down the small intestine.
Phase IV	This is a short transitory period of about 0 to 5 minutes, and the contractions dissipate between the last part of phase
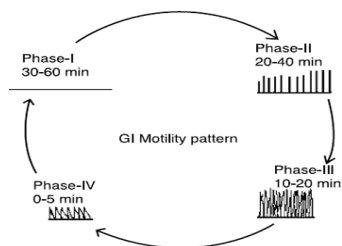
Figure 3: A simplified schematic representation of the interdigestive motility pattern, frequency of contraction forces during each phase, and average time period for each period.

The different phases originating in the foregut continue to the terminal ileum cycle in about 2 hours. Therefore, when one phase III reaches the terminal ileum, another begins in the stomach and duodenum.

As mentioned before, feeding disrupts this cycle resulting in a period of irregular contractile activity, which may last for many hours (i.e.,

3 to 4 hours). Thus frequent feeding may prolong gastric retention time.

One of the important factors that influence the gastric emptying is the caloric content of the meals. Usually fats tend to form an oily layer on the other gastric contents, as such; fatty substances are emptied later than the others. Also, increased acidity and osmolality slow down gastric emptying. Stress appears to cause an increase in gastric emptying rate, while depression slows it down. In general, women and elderly have a slower gastric emptying rate than men and young people respectively. In addition, exercise, and body posture may influence the gastric emptying. However, there is no significant effect of posture (standing vs. flat on back) on gastric residence time (GRT).

It has been reported that drugs taken before meals usually exit from the stomach within an hour; but when taken after meals, the GRT especially for non-disintegrating tablets may be as high as 10 hours. Nevertheless, it has been suggested that small size tablets of less than 7 mm in diameter may exit from the fed stomach regardless of its emptying pattern. However, the two most important parameters that influence the gastric emptying of sustained release dosage forms are the size of the delivery system, and the state of the stomach, i.e., whether the drug is administered in fed or fasted state. In the fasted state, the gastric emptying of large single unit dosage forms is erratic and it is dependent on the time of arrival in the stomach in relation to activity of MMC.

As far as the size is concerned, it has been reported that differences in gastric emptying of various sizes tablets up to 11 mm in diameter, under fed conditions, are insignificant. However, the much discussed 2mm cutoff size for gastric emptying of indigestible solids during the digestive phase in canines may not be applicable to human. In addition, the relationship between the tablet size and its gastric emptying appear to vary significantly among the subjects. Also, the non-disintegrating systems of a size in excess of the mean diameter of the pylorus (in man, 12.8±7 mm) appear to be retained in the stomach for as long as the digestive phase is maintained.

Multiple-unit systems containing 1-mm pellets have been found to pass through the constricted pylorus with a gradual emptying. When the pellets are administered with a light meal, an initial short lag phase followed by a linear emptying pattern is observed. On the other hands, when encapsulated pellets are taken with a heavy meal, prolonged gastric emptying of pellets is observed. However, in most cases, tablets are emptied before all the pellets are emptied. This phenomenon has been explained by two theories. Upon dispersion in the stomach, the pellets may be lodged within the folds of stomach wall prolonging their gastric emptying time. Secondly, gastric contractions during the digestive mode may empty large particles fortuitously as compared to the smaller ones. Under certain circumstances, especially in fasted state, multiparticulate systems may empty from the stomach as a bolus.

Therefore, the state of the stomach, i.e., fed or fasted state in relation to drug administration is the primary consideration for modulating gastric residence time. Along with that, the original size and where applicable expanded size after administration of the dosage form play a significant role in its GRT.

IMPORTANT FACTORS AFFECTING MUCOADHESION: [15, 16]

Polymer Related Factors

Molecular weight

The interpenetration of polymer molecules into the mucus layer is variable, for low molecular weight polymers penetration is more than high molecular weight polymers because entanglements are favored in high molecular weight polymers.

Concentration of active polymer

For solid dosage forms such as tablets, the higher the concentration of polymer, the stronger the bioadhesion force.

Spatial Conformation

Bioadhesive force is also dependent on the conformation of polymers, i.e., helical or linear. The helical conformation of polymers may shield many active groups, primarily responsible for adhesion, thus reducing the mucoadhesive strength of the polymer.

Chain flexibility of polymer

Chain flexibility is important for interpenetration and enlargement. As water-soluble polymers become more and more cross linked, the mobility of the individual polymer chain decreases, also as the cross linking density increases, the effective length of the chain which can penetrate into mucus decrease even further and mucoadhesive strength is reduced.

Environmental – Related Factors

pH: pH influences the charge on the surface of both mucus and polymers. Mucus will have a different charge density depending on pH, because of difference in dissociation of functional groups on carbohydrate moiety and amino acids of the polypeptide backbone, which may affect adhesion.

Applied strength: To place a solid bioadhesive system, it is necessary to apply a defined strength. Whichever the polymer may be, the adhesion strength of those polymers increases with the increase in the applied strength.

Initial contact time: The initial contact time between mucoadhesive and the mucus layer determines the extent of swelling and the interpenetration of polymer chains. The mucoadhesive strength increases as the initial contact time increases.

Selection of the model substrate surface: The handling and treatment of biological substrates during the testing of mucoadhesive is an important factor, since physical and biological changes may occurs in the mucus gels or tissues under the experimental conditions.

Swelling

The swelling characteristic is related to the polymer itself, and also to its environment. Inter-penetration of chains is easier as polymer chains are disentangled and free of interactions.

Physiological variables:

Mucin turnover and disease state of mucus layer are physiological variables, which may affect bioadhesion

Controlled drug delivery by hydrophilic matrix system:

The earliest studies in the field of modified drug delivery date back to the 1950s. Since then, a large number of drug products, mainly in the form of tablet and capsule with controlled release characteristics, have been introduced. Das and Das predicted a minimum growth of 9% per year for this market through 2007. [18] This incredible growth can be attributed to several advantages that these products offer as discussed at the start.

Various technologies have been investigated in order to achieve different aims of modified release, e.g. sustained, delayed, pulsatile, targeted, and programmed release. Among different technologies used in controlled drug delivery, hydrophilic matrix systems are the most popular because of the simplicity of formulation, ease of manufacturing, low cost, FDA acceptance, and applicability to drugs with wide range of solubility. [3]

Drug release from this type of system is controlled by hydration of the polymer, which forms a gelatinous barrier layer at the surface of the tablet through which the drug diffuses. The consistency and strength of the gel layer formed at the tablet surface are crucial factors in determining drug release mechanism and the rate of drug delivery from the polymeric system. Mixtures of polymers are thus useful in regulating the drug release properties of a dosage form. In matrix tablets, polymer mixtures can be used to control the drug release rate by producing gel barriers of varying consistency. This effect is often due to interactions between the excipients that modify the matrix viscosity and/or polarity as well as the internal structure of the tablet through which the drug must diffuse. [19,20]

Polymer swelling and drug release control:

Thermoplastic polymers, which are sufficiently hydrophilic, are water soluble. A sharp advancing front divides the unpenetrated core from a swollen and dissolving shell. Under stationary conditions, a constant thickness surface layer is formed by the swollen polymer and by a high concentration polymer solution.

If the dissolution occurs normally, the steady-state surface layer consists of four different sub layers as liquid sublayer (adjacent to the pure solvent), gel sublayer, solid swollen sublayer and infiltration sublayer (adjacent to the polymer base into which the solvent has not yet migrated). The dissolution rate strongly depends on hydrodynamic conditions, temperature, polymer molecular weight and crystallinity level.[21]

Although outwardly simple, drug release from hydrophilic matrices is a complex phenomenon resulting from the interplay of many different physical processes. In particular, the formation and physical properties of the hydrated surface barrier are important determinants of subsequent behaviour and drug release performance. This gel layer formation and its stability, which defines the kinetics of drug delivery from matrix systems, are controlled by the concentration, viscosity and chemical structure of the polymer(s).

In short, drug release from these systems is the consequence of controlled matrix hydration, followed by gel formation, textural/rheological behavior, matrix erosion, and/or drug dissolution and diffusion, the significance of which depends on drug solubility and concentration and changes in matrix characteristics as illustrated in
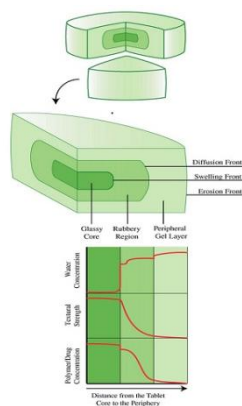
Figure 4 [22, 23].

Figure 4: Water concentration gradient, textural behaviour and polymer drug concentration gradient in swelling polymer matrix.

At the molecular level, drug release is determined by water penetration, polymer swelling, drug dissolution, drug diffusion and matrix erosion. These phenomena depend upon the interaction among water, polymer, matrix content and the drug. Water has to penetrate the polymer matrix, leading to polymer swelling and drug dissolution, before the drug can diffuse out of the system. In effect, water decreases the glass transition temperature of the polymer to the experimental temperature resulting in a transformation of the glassy polymer into a rubbery phase. The enhanced mobility of the polymeric chains favours the transport of water and consequently of the dissolved drug.[24]

Mucoadhesive controlled release drug delivery system:

One method of optimizing drug delivery is by the use of adhesive dosage forms.[25] Mediated by mucoadhesive polymers, the residence time of dosage forms on the GI-mucosa should be prolonged, which allows a sustained drug release at a given target site to maximize the therapeutic effect. Furthermore, drug delivery systems can be localized on a certain surface area for the purpose of local therapy or of drug liberation at the 'absorption window' representing the GI-segment, where drug absorption takes place. For example, the absorption of riboflavin, which has its 'absorption window' in the stomach and upper segment of the small intestine, could be strongly

improved in human volunteers by oral administration of mucoadhesive microspheres versus non-adhesive microspheres. In addition, mucoadhesive polymers can guarantee an intimate contact with the absorption membrane providing the basis for a high concentration gradient as driving force for a passive drug uptake, for the exclusion of a presystemic metabolism such as the degradation of orally given (poly)peptide drugs by luminally secreted intestinal enzymes, and for interactions of the polymer with the epithelium such as a permeation-enhancing effect or the inhibition of brush border membrane bound enzymes.[26, 27]

In Mucoadhesive drug delivery systems, the ability of certain water-soluble polymers, which become adhesive on hydration, has been utilized. The most important goals in mucoadhesion consist of drug targeting, controlled and sustained releasing, increasing of residence time, decreasing of adverse effects and minimizing of the first pass effect and long-term drug delivery.[28]

Bioadhesive polymers in addition of bioadhesion effects, decrease release rate and change kinetic of drug release from mucoadhesive tablets due to their swelling properties as discussed above. Thus, mucoadhesive controlled release drug delivery system can be developed by using hydrophilic polymers.[24,25] this introductory chapter is followed by a brief review of mucoadhesive polymers including their classification, ideal characteristics and other aspects.

MUCOADHESIVE POLYMERS

A bioadhesive has been defined as a synthetic or biological material, which is capable of adhering to a biological substrate or tissue. When the biological substrate is mucus, the term "mucoadhesive" has been employed. Mucosal-adhesive materials are hydrophilic macromolecules containing numerous hydrogen bond-forming groups.[25]

Over the years, mucoadhesive polymers were shown to be able to adhere to various other mucosal membranes. The capability to adhere to the mucus gel layer, which covers epithelial tissues, makes such polymers very useful excipients in drug delivery.[29]

1. Polymers that adhere to the mucin-epithelial surface can be divided into three broad categories: [5]
2. Polymers that become sticky when placed in water and owe their mucoadhesion to stickiness.
3. Polymers that adhere through nonspecific, noncovalent interactions that are primarily electrostatic in nature (although hydrogen and hydrophobic bonding may be significant).
4. Polymers that bind to specific receptor sites on the cell surface.

These polymers could be either natural such as gelatin, sodium alginate, and guar gum or synthetic and semi-synthetic such as hydroxypropylmethyl cellulose (HPMC), Carbopol 934 and Sodium carboxy methyl cellulose (Sodium CMC).[30-33] Also different blends of two or more adhesive polymers may be used as mucoadhesive systems. [33-40]

Characteristics of ideal mucoadhesive polymer to be used in drug delivery system: [5, 28]

1. The polymer and its degradation products should be nontoxic and nonabsorbable from the gastrointestinal tract.
2. It should be nonirritant to the mucous membrane.
3. It should preferably form a strong noncovalent bond with the mucin-epithelial cell surfaces.
4. It should adhere quickly to soft tissue and should posses some site specificity.
5. It should allow some easy incorporation of the drug and offer no hindrance to its release.
6. The polymer must not decompose on storage or during shelf life of the dosage form.
7. The cost of the polymer should not be high, so that the prepared dosage form remains competitive.
8. The polymer should not interfere in drug analysis.

Well-established mucoadhesive polymers are for instance poly (acrylates) and chitosans. Poly (acrylates) such as carbomers are believed to bind via hydrogen bonds, whereas chitosans seem to bind via ionic interactions between their primary amino

substructures and sialic acid and sulfonic acid substructures of the mucus. These polymers are able to provide therefore only a weak adhesive force being in many cases insufficient to guarantee the localization of the delivery system on the GI-mucosa for prolonged time periods.

Recently, a novel promising strategy to improve mucoadhesion has been introduced into the pharmaceutical literature. The most commonly bridging structure in biological systems, the disulfide bond, is thereby utilized to improve adhesion of polymeric carrier systems to mucosal membranes. Thiolated polymers, designated as thiomers, are believed to interact with cysteine-rich subdomains of mucus glycoproteins forming disulfide bonds between the mucoadhesive polymer and the mucus layer. [27]

According to Robinson: [5]

1. Cationic and anionic polymers bind more effectively than neutral polymers.
2. Polyanions are better than polycations in terms of binding/potential toxicity; and further, that water-insoluble polymers give greater flexibility in dosage form design compared to rapidly or slowly dissolving water-soluble polymers.
3. Anionic polymers with sulphate groups bind more effectively than those with carboxylic groups.
4. Degree of binding is proportional to the charge density on the polymer.
5. In comparison to anionic and cationic polymers, the mucoadhesive properties of hydroxypropyl cellulose, hydroxyethyl cellulose, polyethylenglycol 6000 and polyvinylpyrrolidone 44000 (non-ionic polymers) are not affected by electrolytes.[41] This section is followed by the review of two nonionic mucoadhesive polymers - Polyethylene oxide (PEO) and hydroxypropylmethyl cellulose (HPMC).

WIDELY USED MUCOADHESIVE POLYMERS

Polyethylene oxide (PEO)

Introduction of PEO

Polyethylene oxide (PEO) resins are non-ionic, high molecular weight, thermoplastic[42] and water-soluble synthetic polymers.[3] These can be synthesized by anionic or cationic polymerization of ethylene oxide. [23]

PEOs are widely used in medicine and biotechnology. These have been proposed as alternatives to cellulose or other ethylene glycol derivatives in the production of tablets or granules.[43]

All this attention to PEOs is a consequence of their following properties:[23, 43, 44]

1. High biocompatibility (lack of immunogenicity) and low cytotoxicity. PEO has been approved by the Food and Drug Administration (FDA) for several medical applications. It is generally regarded as safe (GRAS) for use in solid oral human dosage forms.[44, 45, 46]
2. Physical and chemical stability[43]
3. Compressibility [47]
4. High swelling ability[43]
5. Good solubility in water and in many organic solvents. When bounded to a water insoluble compound, the resulting PEO conjugate generally displays increased water solubility or dispersibility .[48]
6. One desirable characteristic of PEO is the relatively narrow molecular weight distribution that can be achieved compared with many other polymers. PEO prepared by anionic ring-opening polymerization generally has a polydispersity (Mw/Mn) less than 1.1.
7. Inert to many chemical agents.
8. PEO is clear, colorless and odorless.

Stability of PEO

Hassouna et al observed no significant oxidation of PEO even after exposure to radiation for 900 hours at room temperature (20–25 °C). [49] They concluded that the photostability of PEO was dramatically reduced in the presence of metal ions and a significant formation of carbonyl, carboxyl and hydroxy/hydroperoxy groups was observed.

According to Thompson et al, although aliphatic polyethers such as PEO are resistant to hydrolytic degradation or attack by nucleophiles or acids, the relatively labile C-H bonds adjacent to the ether oxygens are susceptible to oxidative degradation through a radical mechanism. [48]

Mucoadhesive property of PEO

Due to the linear flexible structure of the PEO macromolecule, this polymer shows a particular ability to form entangled physical bonds by interpenetrating deeply and rapidly into mucous substratum networks.

The mucoadhesive properties of PEO reported in the literature are strongly dependent on the polymer molecular weight and are more pronounced in the case of the high molecular weight materials. In particular PEO shows a behaviour ranging from no bioadhesion at molecular weight 20000 to very good bioadhesion at molecular weight 4 000 000.[21]

To calculate the size of the penetrating PEO chains the analysis of Merrill et al can be employed.[66] The expanded (solvated) correlation length or end-to-end distance of the PEO, ξ, could be calculated from equation (1)

$$\xi = \alpha C_n^{1/2} n^{1/2} l \dots\dots\dots\dots\dots\dots(1)$$

Here, C_n is the characteristic ratio of PEO ($C_n = 4$), l is the bond length of the C---C bonds (l= 1.54 A) and n is the number of links per PEO molecule.

$$n = 3M / M_r \dots\dots\dots\dots\dots\dots\dots\dots\dots(2)$$

Where, M is the molecular weight of PEO and M_r is the molecular weight of

$$\text{--CH}_2\text{--CH}_2\text{--O-- } (M_r = 44).$$
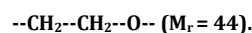
Finally, the expansion coefficient , appearing in equation (1), α can be calculated from equation (3).

$$\alpha^5 - \alpha^3 = 2C_M \Psi_1 (1 - \theta/T) \dots\dots\dots\dots \dots(3)$$

Where, $C_M = 0.105$ in water at 25°C, Ψ_1 is the entropic Flory interaction parameter

($\Psi_1 = - 0.5$), θ is the theta temperature of the system, and M is the PEO molecular weight. Using these values, the size of penetrating PEO with known molecular weight can be calculated.

To further examine this effect, the characteristic depth of penetration of such chains in time period, t, with a typical diffusion coefficient of

D =10^{-9} cm²/s can be calculated using equation (4) as follows.

$$\lambda = (\Box Dt)^{1/2} \dots\dots\dots\dots\dots\dots\dots\dots\dots(4)$$

It should be noted that the size of the penetrating long PEO chains might become detrimental if it is too long.

Unique behaviors of PEO in aqueous solution:

Incorporation of water in low molecular weight PEO has been shown to decrease the degree of crystallinity and increase the mobility of the PEO.[50]

PEO is very hydrophilic.[23] The polyether chains of PEO can form strong hydrogen bonds with water; therefore, when solid matrices are brought into contact with an aqueous medium, the polymer tends to hydrate, forming a superficial gel which eventually erodes as the polymer dissolves.[51]

When exposed to water, the structure and mobility of the semi-crystalline PEO are altered. The structural changes of PEO affect the mobility of water in PEO-water systems.

Water molecules interact simultaneously with two PEO ether

oxygens on different PEO segments and consequently hindering separation of the PEO segments. In addition, strained conformations in the rigid amorphous phase surrounding the undisturbed amorphous phase may obstruct the separation of the PEO segments in the amorphous phase to some extent.

The free volume hole size, V_h, in the PEO-water system decreases when the amount of water increases. The densification of the PEO-water system may be due to certain water molecules interacting simultaneously with two ether oxygens on different PEO segments, causing them to come closer together.

Water absorption reduces the degree of crystallinity of PEO and that PEO is almost completely molten at room temperature at a water weight fraction of 0.50 w/w. Dry PEO is partly constituted of a rigid amorphous phase. The amount of this phase decreases as water is incorporated in the PEO, leading to essentially no rigid amorphous phase remaining at a water weight fraction of 0.13 w/w. The rigid amorphous phase seems to be depleted just before the absorption of water in the PEO started to increase drastically. This, in turn, renders an accelerating decrease in crystallinity and probably a reorganization of the crystalline structure. The decrease in glass

Applications of PEO

PEO is widely used in many applications such as detergents, paints, drug delivery, etc. [49,51] It has been extensively used for preparation of biologically relevant conjugates, including stabilization of proteins and surface modification.[23] When bounded to an immunogenic substrate having a desirable function in the body, PEO tends to reduce or eliminate immune response so that the organism can tolerate the substance.[48] Various PEO-based copolymers have been reported and used, especially in drug delivery applications. One representative copolymer is a triblock copolymer of PEO and poly(propylene oxide) (PEO-b-PPO-b-PEO), which is commercially available as Pluronic or Poloxamer in various lengths and compositions.[23]

In recent years poly (ethylene oxide) (PEO) has attracted much attention as a polymeric excipient that can be used in formulations for different purposes.[47] However, PEOs are mostly used to produce controlled release solid dosage forms such as matrices, reservoirs, or coated cores.[43, 52]

PEOs in controlled release drug delivery

Drug release from polymer matrices may be controlled by polymer swelling or erosion, or drug diffusion in the hydrated gel or by these processes altogether. A variety of release patterns can be obtained, depending on the PEO molecular mass and the drug's physicochemical properties.[47]

Due to their chemical structure, PEOs are among various hydrophilic polymers that, in the presence of water, control the release of the active moiety either by swelling (large molecular weight, >2 MDa) or by eroding and swelling (small molecular weight, <0.9 MDa), forming a hydrogel.[43, 42]

Several studies on PEO-based controlled-release matrices for oral application have been reported.[22, 47] (Table 2) They have been extensively studied as a polymer material for controlled release and several oral drug delivery systems are already in the market.[53, 54] Pinto et al have reported PEO-303 as better polymer excipients for tablets than PEO-301.[43] PEOs are suitable materials for use in sustained-release preparations as tablets. PEO proved to be a good direct compression material for the production of tablets of different sizes, although different mechanical properties were observed between tablets prepared from PEO-301 and PEO-303. Pinto et al attributed the difference in mechanical properties to possible different compaction mechanisms. They observed an increase in the axial relaxation of the tablets with increase in the amount of PEO in the formulation. These conclusions were based on the determined tensile strengths of the tablets.[43]

Table 2: Polyethylene oxide in recent literature

Sr. No.	Application	Year	References
1	As the central hydrophilic matrix material containing drug molecules	2008	3
2	In wound healing	2007	55
3	In electrospun biodegradable fibers for controlled protein delivery	2007	56
4	Linked with thiourea	2007	57
5	Cross-linked with chitosan to improve swelling ability of the chitosan	2007	58
6	As block co-polymer in gene delivery	2007	60
7	In the production of beads by extrusion–spheronization.	2006	46
8	For coarse extrusion for tableting	2004	43
9	As a wet granulation binder for immediate and sustained release tablets	2004	45
10	As a bioadhesive for oral drug delivery	2003,2001,1995	62, 63, 64
11	An ocular products	2002	65
12	As an aid in hot melt extrusion	2000	61
13	In buccoadhesive tablets by direct compression and compression moulding	1999	59
14	Peo loaded phema particles with improved mucoadhesion	1995	66

Hydroxypropylmethyl cellulose (HPMC)

Among a large variety of polymers, which have been utilized in the formulation of controlled release oral dosage forms, HPMC has received the most attention due to its very low toxicity and ease of manufacture.

HPMC is a non-ionic polymer, which has a cellulose backbone, a natural carbohydrate containing a basic repeat unit of

anhydroglucose. HPMC is a polar polymer with hydrogen bonding ability.[67] There are three established 'chemistries' or substitution classes for HPMC, according to the percentage of methoxy or

hydroxypropyl groups on the main cellulose chain.

The USP defines, among others, HPMC 2901 (Methocel E), HPMC 2906 (Methocel F) and HPMC 2208 (Methocel K).[68] The ratios and degree of substitution vary between grades. Variations in the

molecular weights of various HPMC grades are reflected in the viscosities of aqueous solutions prepared at a standard concentration. In discussions regarding controlled release, the terms

'viscosity' or 'viscosity grade' and the associated value for a 2% (w/w) aqueous solution are frequently used to refer to the molecular weight of the HPMC grade being used. [69]

It is approved by the FDA for use as an "inactive ingredient"(21CFR 210.32, 3) in numerous oral, ophthalmic, and even topical nasal drug product preparations. A theoretical safety factor of >100,000 exists. [70]

Applications

Hydroxypropylmethyl cellulose (HPMC) belongs to the industrially important class of hydrogel-forming polymers with different applications, among them the production of controlled-release drugs.

It is widely used in the pharmaceutical industry (Table 3) in oral and topical formulations as a coating agent, film-former, rate controlling polymer for sustained release, stabilizing and suspending agent,

tablet binder and viscosity-increasing agent. [67]

Table 3: HPMC in recent literature

Sr. No.	Applications	Year	References
1	Nanoparticles of insulin	2007	72
2	Hydrophilic matrix	2006	73
3	Female controlled drug delivery system (fcdds) in combination with carbopol and peg	2006	74
4	Sustained release formulation of theophylin	2005	71
5	Buccoadhesive tablets of piroxicam with carbopol	2004	38
6	Bioadhesive gels	2003	75
7	Capsules advantageous over gelatin capsules	2002	76

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