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Gastro Retentive Bioadhesive Drug Delivery System: A Review

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Abstract: Bioadhesion is a topic of current interest in the design of drug delivery systems. The gastroretentive bioadhesive drug delivery system prolong the residence time of the dosage form at the site of absorption and facilitate an intimate contact of the dosage form with the underline absorption surface and thus contribute to improved and / or better therapeutic performance of the drug. The process of bioadhesion involving a polymeric drug delivery platform is a complex one that includes wetting, adsorption and interpenetration of polymer chains amongst various other processes. There is various factor influences the Gastroretention and bioadhesion. This paper describes some aspects of bioadhesion such as mucus layer, mucoadhesion, and theories of bioadhesion to explain the adhesion mechanism .The factors important to bioadhesion and different type's bioadhesive polymers are described.
Key words: Gastro Retentive ,Bioadhesive Drug Delivery System.

Introduction

Historically, oral drug administration has been the predominant route for drug delivery. During the past two decades, numerous oral delivery systems have been developed to act as drug reservoirs from which the active substance can be released over a defined period of time at a predetermined and controlled rate. From a pharmacokinetic point of view, the ideal sustained and controlled release dosage form should be comparable with an intravenous infusion, which supplies continuously the amount of drug needed to maintain constant plasma levels once the steady state is reached.[1]

However, the problem frequently encountered with sustained 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. Therefore it would be beneficial to develop sustained release formulations which remain at the absorption site for an extended period of time. One of the feasible approaches for achieving prolonged and predictable drug delivery profile in GIT is to control Gastric Retention time (GRT) of the formulation. Dosage form with prolonged GRT i.e. Gastro Retentive Dosage Forms (GRDFs) will offer new and important therapeutic options.

Gastro Retentive Drug Delivery System: [2, 3, 4]

The relatively short gastric emptying time in humans, which normally averages 2-3 hrs through the major absorption zone (stomach or upper part of the intestine), can result in incomplete drug release from the drug delivery system leading to diminished efficiency of the administered dose. Thus, localization of a drug delivery system in a specific region of the GIT offers numerous advantages, especially for drugs having narrow absorption window. The intimate contact of the dosage form with the absorbing membrane has the potential to maximize drug absorption and may also influence the rate of drug absorption. These considerations have lead to the development of oral sustained release dosage forms possessing gastric retention potential. The primary concern in the development of once daily oral sustained release dosage form is not just to prolong the delivery of drugs for 24hrs but also to prolong the presence of dosage forms in the stomach or somewhere in the upper small intestine.

Gastroretentive dosage forms through local drug release will greatly enhance the pharmacotherapy of the stomach leading to high drug concentrations at the gastric mucosa, which are sustained over a long period of time. This is mainly beneficial for eradication of Helicobacter pylori, which requires the administration

of various drugs.
several times a day according to a complicated regimen and which frequently is unsuccessful as a consequence of insufficient patient compliance, could possibly be achieved more reliably using gastroretentive dosage form. Finally, gastroretentive dosage form can be used as potential delivery system for drugs with narrow absorption windows; these substances are taken up only from very specific sites of the gastrointestinal tract, often from the stomach and the proximal region of the intestine. Conventional sustained release dosage forms pass the absorption window although they still contain a large fraction of the drug which is consequently lost and not available for absorption. In contrast, an appropriate gastroretentive dosage form would slowly release Gastroretentive dosage forms through local drug release will greatly enhance the pharmacotherapy the complete dose over its defined GRT and thus make it continuously available at the site of absorption.

Need For Gastro Retention: [1]

- Drugs that are absorbed from the proximal part of the gastrointestinal tract (GIT).
- Drugs that are less soluble or are degraded by the alkaline pH they encounters at the lower part of GIT.
- Drugs that are absorbed due to variable gastric emptying time.
- Local or sustained drug delivery to the stomach and proximal Small intestine to treat certain conditions.
- Particularly useful for the treatment of peptic ulcers caused by H. Pylori Infections.

Advantages of Gastroretentive Delivery Systems:

- Improvement of bioavailability and therapeutic efficacy of the drugs and possible reduction of dose e.g. Furosemide
- Maintenance of constant therapeutic levels over a prolonged period and thus reduction in fluctuation in therapeutic levels minimizing the risk of resistance especially in case of antibiotics. e.g. Beta-lactam antibiotics (penicillin's and cephalosporin's)
- Retention of drug delivery systems in the stomach prolongs overall.
- Gastrointestinal transit time thereby increasing bioavailability of sustained release delivery systems intended for once-a-day administration. e.g. Ofloxacin

Approaches to Gastroretentive drug delivery system: [5, 6.]

1. High density (sinking) systems
2. Low density (floating) systems
3. Expandable systems
4. Superporous hydrogel systems
5. Mucoadhesive (bioadhesive) systems
6. Magnetic systems

Mucoadhesive (bioadhesive) systems:

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[7]. Various gastrointestinal mucoadhesive dosage forms, such as discs, microspheres, and tablets, have been prepared and reported by several research groups[8].

Adhesion: *Adhesion* can be defined as the bond produced by contact between a pressure-sensitive adhesive and a surface[9].

The American Society of Testing and Materials has defined it as the state in which two surfaces are held together by interfacial forces which may consist of valence forces, interlocking action, or both[10].

A ***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 periods of time.

According to Good defined *bioadhesion* as the state in which two materials, at least one biological in nature, are held together for an extended period of time by interfacial forces. It is also defined as the ability of a material (synthetic or biological) to adhere to a biological tissue for an extended period of time[8].

In biological systems, four types of bioadhesion can be distinguished

Adhesion of a normal cell on another normal cell
Adhesion of a cell with a foreign substance
Adhesion of a normal cell to a pathological cell
Adhesion of an adhesive to a biological substrate[9]

Bioadhesive 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 materials. Cell fusion and cell aggregation are good examples.

***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[8].

The mucoadhesive/mucosa interaction:

1. Chemical bonds:

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

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

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

(3) 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.

(4) 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.

(5) 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

GASTROINTESTINAL TRACT:

1. Anatomy of the gastrointestinal tract:

The gastrointestinal tract can be divided into three main regions namely

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

The GIT is a continuous muscular tube, extending from the mouth to the anus, which functions to take in nutrients and eliminate waste by such physiological processes as secretion, motility, digestion, absorption and excretion. The organization of the GIT, from stomach to large intestine, is shown in Fig.1. The stomach is a J-shaped enlargement of the GIT which can be divided into four anatomical regions: cardia, fundus, body and antrum. The main function of the stomach is to store and mix food with gastric secretions before emptying its load (chyme) through the pyloric sphincter and into the small intestine at a controlled rate suitable for digestion and absorption. When empty, the stomach occupies a volume of about 50 ml, but this may increase to as much as 1 liter when full [12].

The walls of the GIT, from stomach to large intestine, have the same basic arrangement of tissues, the different layers, from outside to inside, comprising serosa, longitudinal muscle, intermuscular plane, circular muscle, submucosa, muscularis mucosae, lamina propria and epithelium. In addition to longitudinal and circular muscle, the stomach has a third muscle layer known as the "oblique muscle layer", which is situated in the proximal stomach, branching over the fundus and higher regions of the gastric body. The different smooth muscle layers are responsible for performing the motor functions of the GIT, i.e. gastric emptying and intestinal transit [13].

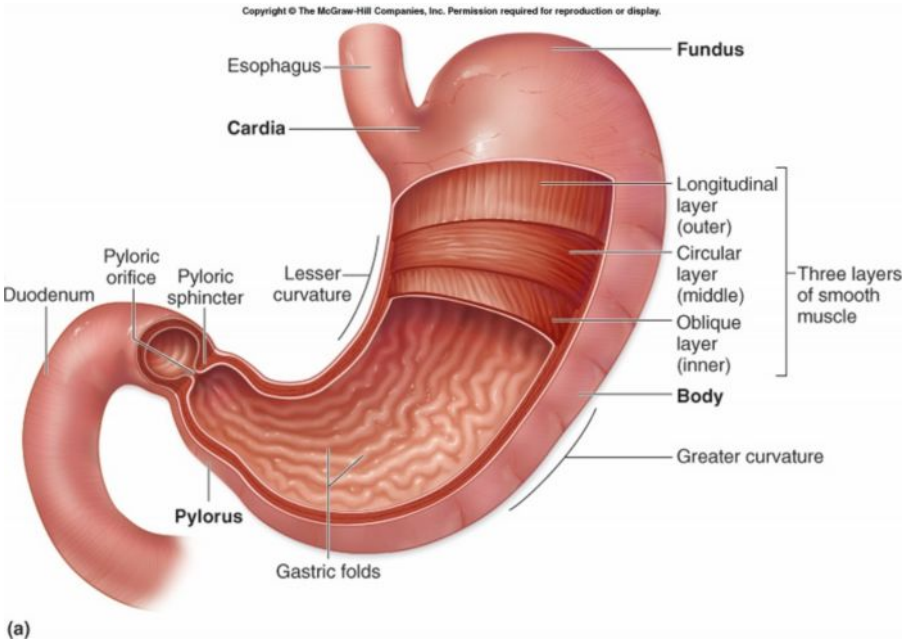

Figure 1: Anatomy of the gastrointestinal tract

Mucus: structure, function and composition:

Mucus is a complex viscous adherent secretion which is synthesized by specialized goblet cells. These goblet cells are glandular columnar epithelium cells and line all organs that are exposed to the external environment. Mucus is found to serve many functions within these locations such as lubrication for the passage of objects, maintenance of a hydrated epithelium layer, a barrier function with regard to pathogens and noxious substances and as a permeable gel layer allowing for the exchange of gases and nutrients to and from underlying epithelium[14]. From an engineering point of view, mucus is an outstanding water-based lubricant whose properties are extensively exploited within nature[15].

Mucus is composed mainly of water (>95%) and mucin, which are glycoprotein's of exceptionally high molecular weight (2–14 $X10^6$ g/mol). Also found within this ''viscoelastic soup" are proteins, lipids and mucopolysaccharides, which are found in smaller proportions (<1%). The mucin glycoprotein's form a highly entangled network of macromolecules that associate with one another through non covalent bonds. Such molecular association is central to the structure of mucus and is responsible for its rheological properties. Furthermore, pendant sialic acid (pKa = 2.6) and sulphate groups located on the glycoprotein molecules result in mucin behaving as an anionic polyelectrolyte at neutral pH[16]. Other non-mucin components of mucus include secretory IgA, lysozyme, lactoferrin, lipids, polysaccharides, and various other ionic species. Some of these non-mucin components are believed to be responsible for the bacteriostatic action observed in mucus[17].

Basic Gastrointestinal Tract Physiology: [18]

Anatomically the stomach is divided into 3 regions: fundus, body, and antrum pylorus. The proximal part made of fundus and body acts as a reservoir for undigested material, whereas the antrum is the main site for mixing motions and acts as a pump for gastric emptying by propelling actions. Gastric emptying occurs during fasting as well as fed states. The pattern of motility is however distinct in the 2 states.

During the fasting state an interdigestive series of electrical events take place, which cycle through both stomach and intestine every 2 to 3 hours. This is called the interdigestive myloelectric cycle or migrating myloelectric cycle (MMC), which is further divided into following 4 phases.

1. Phase I (basal phase)
2. Phase II (preburst phase)
3. Phase III (burst phase)
4. Phase IV

Table1: Four phases in migrating myoelectric complex (MMC):[19]

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 III and quiescence of phase I.

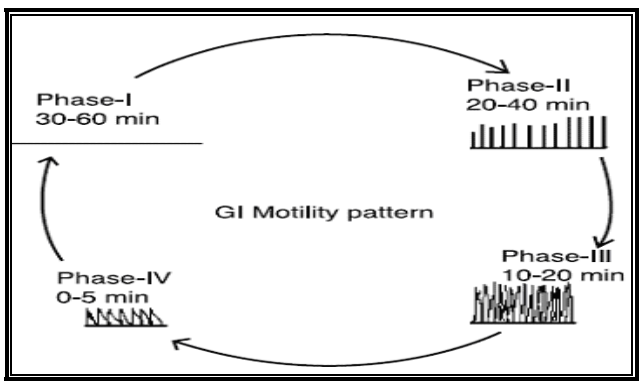

Figure 2: A simplified schematic representation of the interdigestive motility pattern, frequency of contraction forces during each phase, and average time Period for each period.

Theories of Bioadhesion:

Several theories have been proposed to explain the fundamental mechanisms of adhesion. In a particular system, one or more theories can equally well explain or contribute to the formation of bioadhesive bonds[5, 6, 11]

Electronic Theory:

According to the electronic theory, electron transfer occurs upon contact of an adhesive polymer with a mucus glycoprotein network because of differences in their electronic structures. This results in the formation of an 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 in the two surfaces. Two types of chemical bonds resulting from these forces can be distinguished.

1. Primary chemical bonds of covalent nature, which are undesirable in bioadhesion because their high strength may result in permanent bonds.
2. Secondary chemical bonds having many different forces of attraction, including electrostatic forces, van der Waals forces, and hydrogen and hydrophobic bonds.

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 (expressed in terms of surface and interfacial tension, Y, is defined as the energy per square centimeter released when an interface is formed.

The work of adhesion is given by:

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

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

$W_C = 2Y_A$ or Y_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 chains penetrate the mucus depends on the diffusion coefficient and the time of contact. This diffusion coefficient, in turn, depends on the value of molecular weight between cross-links and decreases significantly as the cross-linking density increases.

Fracture Theory:

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

$G = (E/L)l\ h$

where E is the Young's modulus of elasticity, **6** is the fracture energy, and L is the critical crack length when two surfaces are separated.

Mechanical Theory:

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[20].

FACTORS AFFECTING GASTRIC RETENTION:

Gastric residence time of an oral dosage form is affected by several factors. To pass through the pyloric valve into the small intestine the particle size should be in the range of 1 to 2 mm. The pH of the stomach in fasting state is ~1.5 to 2.0 and in fed state is 2.0 to 6.0. A large volume of water administered with an oral dosage form raises the pH of stomach contents to 6.0 to 9.0. Stomach doesn't get time to produce sufficient acid when the liquid empties from the stomach; hence generally basic drugs have a better chance of dissolving in fed state than in a fasting state[18].

The rate of gastric emptying depends mainly on viscosity, volume, and caloric content of meals. Nutritive densities of meals help to determine gastric emptying time. It does not make any difference whether the meal has high protein, fat, or carbohydrate content as long as the caloric content is the same. However, increase in acidity and caloric value slows down gastric emptying time. Biological factors such that acidity and caloric value slows down gastric emptying time. Biological factors such as age, body mass index (BMI), gender, posture, and diseased states (diabetes, Chron's disease) influence gastric emptying. In the case of elderly persons, gastric emptying is slowed down. Generally females have slower gastric emptying rates than males. Stress increases gastric emptying rates while depression slows it down[8].

The resting volume of the stomach is 25 to 50 mL. Volume of liquids administered affects the gastric emptying time. When volume is large, the emptying is faster. Fluids taken at body temperature leave the stomach faster than colder or warmer fluids. Studies have revealed gastric emptying of a dosage form in the fed state can also be influenced by its size. Small-size tablets leave the stomach during the digestive

phase while the large-size tablets are emptied during the housekeeping waves.

Important factors affecting mucoadhesion:

1) Polymer Related Factors:

a) 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.

b) Concentration of active polymer: For solid dosage forms such as tablets, the higher the concentration of polymer, the stronger the bioadhesion force.

c) 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.

d) 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[15].

e) Degree of Hydration:

Another important factor affecting the mucoadhesive strength of polymeric components is the degree of hydration. In this respect many polymers will exhibit adhesive properties under conditions where the amount of water is limited. However in such a situation, adhesion is thought to be a result of a combination of capillary attraction and osmotic forces between the dry polymer and the wet mucosal surface which act to dehydrate and strengthen the mucus layer. Although this kind of "sticking" has been referred to as mucoadhesion it is important to clearly distinguish such processes from "wet-on-wet" adhesion in which swollen mucoadhesive polymers attach to mucosal surfaces. Whilst hydration is essential for the relaxation and interpenetration of polymer chains, excess hydration could lead to decreased mucoadhesion and/or retention due to the formation of a slippery mucilage In this situation cross linked polymers that only permit a certain degree of hydration may be advantageous for providing a prolonged mucoadhesive effect[16].

f) Functional Group Contribution:

The attachment and bonding of bioadhesive polymers to biological substrates occurs mainly through interpenetration followed by secondary non-covalent bonding between substrates. Given that secondary bonding mainly arises due to hydrogen bond formation, it is well accepted that mucoadhesive polymers possessing hydrophilic functional such as, carboxyl (COOH), hydroxyl (OH), amide (NH2) and sulphate groups (SO4H) may be more favorable in formulating targeted drug delivery platforms. Typically, physical entanglements and secondary interactions (hydrogen bonds) contribute to the formation of a strengthened network; therefore polymers that exhibit a high density of available hydrogen bonding groups would be able to interact more strongly with mucin glycoproteins[21].

2) Environmental – Related Factors: [21-25]

a) 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.

b) 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.

c) 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.

d) 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.

3) 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. More the swelling of polymeric matrix higher the adhesion time of polymers.

4) Physiological variables:

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

MUCOADHESIVE POLYMERS:

1. Introduction to 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[26].

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. Polymers that adhere to the mucin-epithelial surface can be divided into three broad categories[27]:

1. Polymers that become sticky when placed in water and owe their mucoadhesion to stickiness.
2. Polymers that adhere through nonspecific, noncovalent interactions those are primarily electrostatic in nature (although hydrogen and hydrophobic bonding may be significant).
3. 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 carboxymethyl cellulose (Sodium CMC).30-32 Also different blends of two or more adhesive polymers may be used as mucoadhesive systems[16, 28, 29].

Characteristics of ideal mucoadhesive polymer to be used in drug delivery system: [27, 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.

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.[30]

To Summarize Key attributes of polymers for contribution to bioadhesion are

- Sufficient quantity of hydrogen bonding functional groups (−OH and −COOH)
- High molecular weight and chain flexibility.
- Anionic surface charges.
- Adequate surface tension to promote spreading into the mucus layer.
- Surface anchored groups with affinity to form bridges between polymer and Mucin.

Conclusion

There is no doubt that the oral route is the most favored and probably most complex route of drug delivery. Critical barriers such as mucus covering the GI epithelia, high turnover rate of mucus, variable range of pH, transit time with broad spectrum, absorption barrier, degradation during absorption, hepatic first pass metabolism, rapid luminal enzymatic degradation ,longer time to achieve therapeutic blood levels, and intrasubject variability, are all possible issues with oral route. The idea of bioadhesive began with the clear need to localize a drug at a certain site in the GI tract. Therefore a primary objective of using bioadhesive systems orally would be achieved by obtaining a substantial increase in residence time of the drug for local drug effect and to permit once daily dosing.

Examples of different of bioadhesive polymers:

CATIONIC POLYMERS	Chitosan (Hydrogel polymers)
ANIONIC POLYMERS	Polyacrylic acid (Hydrophilic soluble polymer) Carbopol 934P, 971P, 980 (Hydrogel polymers) Polycarbophil (Hydrogel polymers) Poly(methacrylic acid) Sodium alginate
NON-IONIC POLYMERS	Methocel (HPMC) K100M, K15M, K4M Hydroxyethylcelullose (HEC) Hydroxypropylcelullose(HPC) Polyoxyethylene (POE)
ION EXCHANGE RESINS	Cholestyramine (Duolite AP-143)
MISCELLANEOUS	Sucralfate, Gliadin

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