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RECENT ADVANCES ON MUCOADHESIVE DRUG DELIVERY SYSTEM FOR ANTI ULCER DRUG

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ABSTRACT: Over the past few decades, mucosal drug delivery has received a great deal of attention. The drug adopted mucoadhesive delivery systems interact with the mucus layer which is covered by mucosal epithelial surface, mucin molecules and increase the residence time of the dosage form at the site of absorption. Mucoadhesive dosage forms may be designed to enable prolonged retention at the site of application, providing a controlled rate of drug release for improved therapeutic outcome. The drugs which have local action or those which have maximum absorption in gastrointestinal tract (GIT) require increased duration of stay in GIT. Thus, mucoadhesive dosage forms are advantageous in increasing the drug plasma concentrations and also therapeutic activity. The mucoadhesive ability of a dosage form is dependent upon a variety of factors, including the nature of the mucosal tissue and the physicochemical properties of the polymeric formulation. In this regard, this review covers the areas of mechanisms and theories of mucoadhesion, factors influencing the mucoadhesive devices and also various mucoadhesive dosage forms (buccal, nasal, ocular, gastro, vaginal, and rectal).

Introduction:

In the last two decades, mucoadhesion has shown renewed interest for prolonging the residence time of mucoadhesive dosage forms through various mucosal routes in drug delivery applications. Mucoadhesive based topical and local systems have shown enhanced bioavailability. Mucoadhesive drug delivery gives rapid absorption and good bioavailability due to its considerable surface area and high blood flow. Drug delivery across the mucosa bypasses the first-pass hepatic metabolism and avoiding the degradation of gastrointestinal enzymes. Thus mucosal drug delivery system could be of value in delivering a growing number of high-molecular-weight sensitive molecules such as peptide and oligonucleotides. In this review, the aim is to provide detailed understanding of mucoadhesion, bioadhesion of polymer, and techniques for the determination of mucoadhesion;

finally most common routes of mucoadhesive administration will be presented along with examples of formulation studied.

Since the early 1980s, the concept of mucoadhesion has gained considerable interest in pharmaceutical technology. Adhesion can be defined as the bond produced by contact between a pressure sensitive adhesive and a surface. Mucoadhesive drug delivery systems prolong the residence time of the dosage form at the site of application or absorption. They facilitate an intimate contact of the dosage form with the underlying absorption surface and thus improve the therapeutic performance of the drug. In recent years, many such mucoadhesive drug delivery systems have been developed for oral, buccal, nasal, rectal and vaginal routes for both systemic and local effects.

Dosage forms designed for mucoadhesive drug delivery should be small and flexible enough to be acceptable for patients and should not cause irritation. Other desired characteristics of a mucoadhesive dosage form include high drug loading capacity, controlled drug release (preferably unidirectional release), good mucoadhesive properties, smooth surface, tastelessness, and convenient application. Erodible formulations can be beneficial because they do not require system retrieval at the end of desired dosing interval. A number of relevant mucoadhesive dosage forms have been developed for a variety of drugs. Several peptides, including thyrotropin-releasing hormone (TRH), insulin, octreotide, leuprolide, and oxytocin, have been delivered via the mucosal route, albeit with relatively low bioavailability (0.1–5%), owing to their hydrophilicity and large molecular weight, as well as the inherent permeation and enzymatic barriers of the mucosa.

The development of sustain release dosage form can achieve the aim of releasing the drug slowly for a long period but this is not sufficient to get sustained therapeutic effect. They may be cleared from the site of absorption before emptying the drug content. Instead, the mucoadhesive dosage form will serve both the purposes of sustain release and presence of dosage form at the site of absorption. Mucoadhesive drug delivery systems includes the following

Buccal delivery system

- Oral delivery system
- Vaginal delivery system
- Rectal delivery system
- Nasal delivery system
- Ocular delivery system

Advantages of mucoadhesive drug delivery system

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

- Targeting and localization of the dosage form at a specific site.
- Also, the mucoadhesive systems are known to provide intimate contact between dosage form and the absorptive mucosa, resulting in high drug flux at the absorbing tissue.
- Prolongs the residence time of the dosage form at the site of absorption, hence increases the bioavailability.
- Excellent accessibility, rapid onset of action.
- Rapid absorption because of enormous blood supply and good blood flow rates
- Drug is protected from degradation in the acidic environment in the git
- Improved patient compliance

Disadvantages of mucoadhesive drug delivery system

- Occurrence of local ulcerous effects due to prolonged contact of the drug possessing ulcerogenic property
- One of the major limitations in the development of oral mucosal delivery is the lack of a good model for in vitro screening to identify drugs suitable for such administration.
- Patient acceptability in terms to taste, irritancy and mouth feel is to be checked

Mucus Membranes

Mucus membranes (mucosae) 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 intestines and bronchi) or multilayered/stratified (e.g. in the esophagus, 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 either as 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 their weight, making them a highly hydrated system. The major functions of mucus are that of protection and lubrication.

Bioadhesion and mucoadhesion

The term bioadhesion can be defined 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. In biological systems, bioadhesion can be classified into 3 types:

1. Type 1, adhesion between two biological phases, for example, platelet aggregation and wound healing.
2. Type 2, adhesion of a biological phase to an artificial substrate, for example, cell adhesion to culture dishes and biofilm formation on prosthetic devices and inserts.
3. Type 3, adhesion of an artificial material to a biological substrate, for example, adhesion of synthetic hydrogels to soft tissues and adhesion of sealants to dental enamel.

For drug delivery purposes, the term bioadhesion implies attachment of a drug carrier system to a specified biological location. The biological surface can be epithelial tissue or the mucus coat on the surface of a tissue. If adhesive attachment is to a mucus coat, the phenomenon is referred to as mucoadhesion.

Theories of Mucoadhesion

Various theories exist to explain at least some of the experimental observations made during the bioadhesion process. Unfortunately, each theoretical model can only explain a limited number of the diverse range of interactions that constitute the bioadhesive bond. However, four main theories can be distinguished.

Wetting Theory of Mucoadhesion

The wetting theory is perhaps the oldest established theory of adhesion. It is best applied to liquid or low-viscosity bioadhesives. It explains adhesion as an embedding process, whereby adhesive agents penetrate into surface irregularities of the substrate and ultimately harden, producing many adhesive anchors. Free movement of the adhesive on the surface of the substrate means that it must overcome any surface tension effects present at the interface. The wetting theory calculates the contact angle and the thermodynamic work of adhesion.

Electrostatic Theory of Mucoadhesion

According to electrostatic theory, transfer of electrons occurs across the adhesive interface and adhering surface. This results in the establishment of the electrical double layer at the interface and a series of attractive forces responsible for maintaining contact between the two layers.

Diffusion Theory of Mucoadhesion

Diffusion theory describes that polymeric chains from the bioadhesive interpenetrate into glycoprotein mucin chains and reach a sufficient depth within the opposite matrix to allow formation of a semipermanent bond. The process can be visualized from the point of initial contact.

(a) Schematic representation of the diffusion theory of bioadhesion. Blue polymer layer and red mucus layer before contact; (b) upon contact; (c) The interface becomes diffuse after contact for a period of time

Adsorption Theory of Mucoadhesion

According to the adsorption theory, after an initial contact between two surfaces, the materials adhere because of surface forces acting between the chemical structures at the two surfaces. When polar molecules or groups are present, they reorientate at the interface. Chemisorption can occur when adhesion is particularly strong. The theory maintains that adherence to tissue is due to the net result of one or more secondary forces (van der Waal's forces, hydrogen bonding, and hydrophobic bonding).

Fracture Theory of Adhesion

This theory describes the force required for the separation of two surfaces after adhesion. The fracture strength is equivalent adhesive strength through the following equation. This theory is useful for the study of bioadhesion by tensile apparatus.

Mucoadhesive Materials

Mucoadhesive polymers have numerous hydrophilic groups, such as hydroxyl, carboxyl, amide, and sulfate. These groups attach to mucus or the cell membrane by various interactions such as hydrogen bonding and hydrophobic or electrostatic interactions. These hydrophilic groups also cause polymers to swell in water and, thus, expose the maximum number of adhesive sites.

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

1. The polymer and its degradation products should be nontoxic and nonabsorbable.
2. It should be nonirritant.
3. It should preferably form a strong noncovalent bond with the mucus or epithelial cell surface.
4. It should adhere quickly to moist tissue and possess some site specificity.
5. It should allow easy incorporation of the drug and offer no hindrance to its release.
6. The polymer must not decompose on storage or during the shelf life of the dosage form.
7. The cost of the polymer should not be high so that the prepared dosage form remains competitive.

Polymers that adhere to biological surfaces can be divided into three broad categories:

1. Polymers that adhere through nonspecific, noncovalent interactions which are primarily electrostatic in nature
2. Polymers possessing hydrophilic functional groups that hydrogen bond with similar groups on biological substrates
3. Polymers that bind to specific receptor sites on the cell or mucus surface

Polymers Used For Mucoadhesive Drug Delivery

These polymers are classified as Hydrophillic polymers Contains carboxylic group and possess excellent mucoadhesive properties. These are,

- PVP (Poly vinyl pyrrolidine)
- MC (Methyl cellulose)
- SCMC (Sodium carboxy metyhyl cellulose)
- HPC (Hydroxyl propyl cellulose)

Hydrogels

These swell when in contact with water and adhere to the mucus membrane. These are further classified according to their charge

- Anionic polymers- carbopol, polyacrylates
- Cationic polymers- chitosan
- Neural/ non ionic polymers- eudragit analogues

Factors Affecting Mucoadhesion

Mucoadhesion may be affected by a number of factors, including hydrophilicity, molecular weight, cross-linking, swelling, pH, and the concentration of the active polymer.

Hydrophilicity

Bioadhesive polymers possess numerous hydrophilic functional groups, such as hydroxyl and carboxyl. These groups allow hydrogen bonding with the substrate, swelling in aqueous media, thereby allowing maximal exposure of potential anchor sites. In addition, swollen polymers have the maximum distance between their chains leading to increased chain flexibility and efficient penetration of the substrate.

Molecular Weight

The interpenetration of polymer molecules is favored by low-molecular-weight polymers, whereas entanglements are favored at higher molecular weights. The optimum molecular weight for the maximum mucoadhesion depends on the type of polymer, with bioadhesive forces increasing with the molecular weight of the polymer up to 100,000. Beyond this level, there is no further gain.

Cross-linking and Swelling

Cross-link density is inversely proportional to the degree of swelling. The lower the cross-link density, the higher the flexibility and hydration rate; the larger the surface area of the polymer, the better the mucoadhesion. To achieve a high degree of swelling, a lightly cross-linked polymer is favored. However, if too much moisture is present and the degree of swelling is too great, a slippy mucilage results and this can be easily removed from the substrate. The mucoadhesion of cross-linked polymers can be enhanced by the inclusion in the formulation of adhesion promoters, such as free polymer chains and polymers grafted onto the preformed network.

Spatial Conformation

Besides molecular weight or chain length, spatial conformation of a polymer is also important. Despite

a high molecular weight of 19,500,000 for dextrans, they have adhesive strength similar to that of polyethylene glycol (PEG), with a molecular weight of 200,000. The helical conformation of dextran may shield many adhesively active groups, primarily responsible for adhesion, unlike PEG polymers, which have a linear conformation.

pH

The pH at the bioadhesive to substrate interface can influence the adhesion of bioadhesives possessing ionizable groups. Many bioadhesives used in drug delivery are polyanions possessing carboxylic acid functionalities. If the local pH is above the pK of the polymer, it will be largely ionized; if the pH is below the pK of the polymer, it will be largely unionized. The approximate pKa for the poly(acrylic acid) family of polymers is between 4 and 5. The maximum adhesive strength of these polymers is observed around pH 4–5 and decreases gradually above a pH of 6. A systematic investigation of the mechanisms of mucoadhesion clearly showed that the protonated carboxyl groups, rather than the ionized carboxyl groups, react with mucin molecules, presumably by the simultaneous formation of numerous hydrogen bonds.

Gastrointestinal Mucoadhesive Drug Delivery Systems

Oral route is undoubtedly most favored route of administration, but hepatic first-pass metabolism, degradation of drug during absorption, mucus covering GI epithilia, and high turnover of mucus are serious concerns of oral route. In recent years, the gastrointestinal tract (GIT) delivery emerged as a most important route of administration. Bioadhesive retentive system involves the use of bioadhesive polymers, which can adhere to the epithelial surface in the GIT. Using bioadhesive would be achieved increase GI transit time and increase in bioavailability.

Methods of Evaluation:

Mucoadhesive polymers and drug delivery systems can be evaluated by testing their adhesion strength by both in vitro and in vivo tests.

In vitro tests / ex-vivo

- Methods determining tensile strength
- Methods determining shear stress
- Adhesion weight method
- Fluorescent probe method
- Flow channel method
- Mechanical spectroscopic method
- Falling liquid film method
- Colloidal gold staining method
- Viscometer method
- Thumb method
- Adhesion number
- Electrical conductance
- Swelling properties
- In vitro drug release studies
- Mucoretentability studies

In vivo methods

- Use of radioisotopes
- Use of gamma scintigraphy
- Use of pharmacoscintigraphy
- Use of electron paramagnetic Resonance (EPR) oximetry
- X ray studies
- Isolated loop technique

These techniques are less common due to high cost, time consuming and ethical factors. But these are important to assess the true mucoadhesive potential specially an the case of oral mucoadhesive drug delivery. The GI transit time can be measured by using one of the many radio opaque markers like barium sulphate which is coated to the bioadhesive dosage form so as to assess the GI transit by means of X-ray inspection. By means of gamma scintigraphy both the distribution and retention can be studied. In 1985 Chng et.al., studied the transit of various 51 cr radio labeled polyacrylic acid beads through the rat GI tract,. The beads were fed to the rats and at various tome intervals after which the rats were sacrificed. The rats intestine was then systemically dissected into 20 equal parts and the amount of radiation in each part measured thus allowing, the transit overtime to be realized.34 The development of a non invasive technique to determine the transit time of mucoadhesive polymers was done by Davis. The transit time could be imaged via labeling of the polymer with a gamma emitting nucleotide which was determined with the help of gamma scintigraphy. A recent technique by Albrecht et al. was to use magnetic resonance imaging to localize the point of release of thiolated polymers from dosage forms via the use of gadolinium. In vivo mucoadhesion was determined by ascertaining thre residence time of the fluorescently tagged thiomer on intestinal mucosa of rats after 3 hours.

Conclusion

The mucoadhesive dosage forms offer prolonged contact at the site of administration, low enzymatic activity, and patient compliance. The formulation of mucoadhesive drug delivery system depends on the selection of suitable polymer with excellent mucosal adhesive properties and biocompatibility.

The phenomenon of mucoadhesion is a novel controlled drug delivery approache. The various advantages of the oral mucoadhesive drug delivery systems like prolongation of the residence time of the drug which in turn increases the absorption of the drug are important factors in the oral bioavailability of many drugs. A number of both in-vitro and invivo techniques have been developed for the evaluation of the mucoadhesive drug delivery systems. Mucoadhesive dosage forms extend from the simple oral mucosal delivery to the nasal, vaginal, ocular and rectal drug delivery systems. The most widely studied and accepted polymers for mucoadhesion have been the hydrophilic, high molecular weight, anionic molecules like carbomers. Recently the focus has been on the novel second generation polymers like the thiolated polymers, lectins and lecithins.

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