EMERGING TECHNOLOGIES AND ADVANCES OF MUCO ADHESIVE DRUG DELIVERY SYSTEMS: AN REVIEW

Ch. Tarakaramarao*

Assistant. Professor, Department of Pharmaceutical Technology, Sri Venkateswara College of Pharmacy, Etchrela, Srikakulam, Andhra Pradesh- 532402.

ABSTRACT

The aim of this study was to review the mechanisms and theories involved in mucoadhesion. However this route could become a significant means for the delivery of a range of active agents in the coming years, if the barriers to buccal drug delivery are overcome. Mucoadhesion can be defined as a state in which two components, of which one is of biological origin are held together for extended periods of time by the help of interfacial forces. 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. Mucoadhesive drug delivery system prolong the residence time of the dosage form at the site of application or absorption and facilitate an intimate contact of the dosage form with the underline absorption surface and thus contribute to improved better therapeutic performance of the drug. Mucoadhesion is a complex phenomenon which involves wetting, adsorption and interpenetration of polymer chains. The current review provides a good insight on mucoadhesive polymers, the phenomenon of mucoadhesion and the factors which have the ability to affect the mucoadhesive properties of a polymer. This paper describes some effort to increase the residence time of drug dosage forms in GI tract, by gastroretentive units and bioadhesive gastrointestinal patches. Several gastrointestinal patch systems provide bioadhesion, drug protection and unidirectional release, This combination of function could improve the overall oral bioavailability.

KEYWORDS: Mucoadhesive, Bioadhession, Gastrointestinal, residence time, oral mucosa, Mucin.
INTRODUCTION

The present topic deals with bioadhesion mediate improving drug therapy using man made materials as bioadhesives focusing on oral drug administration. Oral drug delivery is the most convenient means of any drug delivery to the systematic circulation. The oral controlled release drug delivery have been recently of increasing interest in pharmaceutical field to achieve improved therapeutic, such as easy of dosing administration, flexibility in formulation and patient compliance. Local therapy of diseases can be unsatisfactory because the drug may not stay at the site of action long enough for the desired effect. Similarly systemic treatment via the oral route can be hampered because the drug may not stay at the site of absorption long enough.

Controlled release technologies allow for more effective use of existing drugs and successful development of new drug candidates. Adhesion as a process is simply defined as the “fixing” of two surfaces to one another.[1] There are many different terminological subsets of adhesion depending upon the environment in which the process occurs. When adhesion occurs in a biological setting it is often termed “bioadhesion”, furthermore if this adhesion occurs on mucosal membranes it is termed “mucoadhesion”. Bioadhesion can be defined as the binding of a natural or synthetic polymer to a biological substrate. When this substrate is a mucous layer, the term mucoadhesion is often used.[2] Gastro retentive systems can remain in the gastric region for several hours and hence significantly prolong the gastric residence time of drugs. Prolonged gastric retention improves bioavailability, reduces drug waste and improves solubility of drugs that are less soluble in a high pH environment. It has applications also for local drug delivery to the stomach and proximal small intestines. Gastro retention helps to provide better availability of new products with new therapeutic possibilities and substantial benefits for patients.[3]

In the early 1980s; academic research groups working in the ophthalmic field pioneered the concept of mucoadhesion as a new strategy to improve the efficacy of various drug delivery systems. Since then, the potential of mucoadhesive polymers was shown in ocular, nasal, vagina and buccal drug delivery systems, leading to a significantly prolonged residence time of sustained release delivery systems on this mucosal membrane.[4-7]

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. When the adhesion involves mucus or mucus membrane it is
termed as mucoadhesion\textsuperscript{7} 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.\textsuperscript{8}

Mucoadhesive drug delivery system prolongs the residence time of the dosage form at the site of application or 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 mucoadhesive drug delivery system may include the following vocal delivery system, Sublingual Delivery system, Vaginal delivery system, Rectal delivery system, Nasal delivery system, Ocular delivery system, Gastro Intestinal delivery system.\textsuperscript{9}

The use of mucoadhesive polymers for the development of pharmaceutical formulations dates back to 1947, when attempts were made to formulate a penicillin drug delivery system for delivering the bioactive agent to the oral mucosa using gum tragacanth and dental adhesive powders.\textsuperscript{10} Subsequent research resulted in the development of a mucoadhesive delivery vehicle which consisted of finely ground sodium CMC, pectin, and gelatin. Various other polymers Carbapol, sodium alginate, HPMC, Guar gum, Hydroxy ethylcellulose, Karya gum, Methyl cellulose, polyethylene glycol have been found to exhibit muco adhesive properties. The mucoadhesive drug delivery systems provide a means of enhancing retention at defined sites, if systemic uptake occurs the use of mucoadhesive polymers will not prevent a wider distribution of the active ingredient. There are several advantages in using mucoadhesive drug delivery systems including

- To minimize first-pass metabolism.
- Low administration frequency and increase residence time
- Allow to possible specific site or tissues for targeting to GIT etc.
- The formulation stays longer time at the delivery site, improving bioavailability of the active ingredient
- Cost reduction and minimize side effect may be reduced.\textsuperscript{11}
ANATOMY AND PHYSIOLOGY: MUCUS

STRUCTURE OF STOMACH

Mucous membranes 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 above which is an epithelial layer, the surface of which is made moist usually by the presence of a mucus layer. 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 as a permeable gel layer allowing for the exchange of gases and nutrients to and from underlying epithelium.[12] The GIT consist of three main parts such as stomach, small intestine and large intestine shown in Fig.1. The mucin glycoproteins 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 theological properties. Mucus is composed mainly of water and mucins, which are glycoproteins of exceptionally high molecular weight. Also found within this “visco elastic soup” are proteins, lipids and muco polysaccharides, which are found in smaller proportions.[13-14] Mucus glycoprotiens are high molecular proteins possessing attached oligosaccharide units containing the composition of mucus is L-fucose, D-galactose, N-acetyl-D-Glucosamine, N-acetyl-D-galactosamine, Sialic acid. The common sites of application where mucoadhesive drug delivery systems have the ability to deliver pharmacologically active agents include oral cavity, eye conjunctiva, vagina, nasal cavity and gastrointestinal tract. The buccal cavity has
a very limited surface area, but the easy access to the site makes it a preferred location for delivering active agents. The site provides an opportunity to deliver pharmacologically active agents systemically by avoiding hepatic first-pass metabolism in addition to the local treatment of the oral lesions. The sublingual mucosa is relatively more permeable than the buccal mucosa, hence formulations for sublingual delivery are designed to release the active agent quickly while mucoadhesive formulation is of importance in the delivery of active agents to the buccal mucosa where the active agent has to be released in a controlled manner. This makes the buccal cavity more suitable for mucoadhesive drug delivery.\[15\] Ocular mucoadhesives has also been another area of interest. Due to the continuous formation of tears and blinking of eye lids there is a rapid removal of the active medicament from the ocular cavity, which results in the poor bioavailability of the active agents. This can be minimized by delivering the drugs using ocular insert or patches.\[16-18\]

**MODE OF ACTION MUCOADHESIVE SUBSTANCES**

The mechanism of mucoadhesion is generally divided in two steps, the contact stage and the consolidation stage shown in Fig.2. Initial stage is characterized by the contact between the mucoadhesive and the mucous membrane, with spreading and swelling of the formulation, initiating its deep contact with the mucus layer in some cases, such as for ocular and vaginal dosage forms, delivery system is mechanically attached over the membrane, the mucoadhesion can be explained by peristalsis, the motion of organic fluids in the organ cavity, or by Brownian motion. The mucoadhesive materials are activated by the presence of moisture. Moisture plasticizes the system, allowing the mucoadhesive molecules to break free and to link up by weak van der Waals and hydrogen bonds.

![Fig.2]
Theories of Mucoadhesion

Diffusion Theory
The essence of this theory is that chains of the adhesive and the substrate interpenetrate one another to a sufficient depth to create a semi permanent adhesive bond. The penetration rate depends on the diffusion coefficient of both interacting polymers, and the diffusion coefficient is known to depend on molecular weight and cross-linking density. In addition, segment mobility, flexibility of the bioadhesive polymer, mucus glycoprotein, and the expanded nature of both network are important parameters that need to be considered.

Adsorption theory
In this instance, adhesion is defined as being the result of various surface interactions (primary and secondary bonding) between the adhesive polymer and mucus substrate. Primary bonds due to chemisorption result in adhesion due to ionic, covalent and metallic bonding, which is generally undesirable due to their permanency. Secondary bonds arise mainly due to van der Waals forces, hydrophobic interactions and hydrogen bonding. Whilst these interactions require less energy to ‘break’ they are the most prominent form of surface interaction in mucoadhesion processes as they have the advantage of being semi-permanent bonds.

Fracture theory
Fracture theory of adhesion is related to separation of two surfaces after adhesion. The fracture strength is equivalent to adhesive strength as given by

\[ G = \left( \frac{E \varepsilon}{L} \right)^{1/2} \]

\( E \)- Young’s modules of elasticity
\( \varepsilon \)- Fracture energy
\( L \)- Critical crack length when two surfaces are separated

Wetting Theory
Primary application to liquid bioadhesive system, the wetting theory emphasizes the intimate contact between the adhesive and mucus. Thus, a wetting surface is controlled by structural similarity, degree of cross linking of the adhesive polymer, or use of a surfactant. The work of adhesion [expressed in terms of surface and interfacial tension (Y) being defined as energy per cm² released when an interface is formed.

According to Dupres equation work of adhesion is given by

\[ Wa = YA + YB - YAB \]
Where A & B refer to the biological membranes and the bioadhesive formulation respectively.

The work of cohesion is given by

\[ W_c = 2YA \text{ or } YB \]

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

\[ SB/A = YA - (YB + YAB) \]

SB/A should be positive for a bioadhesive material to adhere to a biological membrane.

**Evaluation Methods**

**In vitro and ex vivo tests**

In vitro/ex vivo tests are important in the development of a controlled release bioadhesive system because they contribute to studies of permeation, release, compatibility, mechanical and physical stability, superficial interaction between formulation and mucous membrane and strength of the bioadhesive bond. These tests can simulate a number of administration routes including oral, buccal, periodontal, nasal, gastrointestinal, vaginal and rectal.

**Force of attachment Measuring**

The most obvious method in which to assess a systems mucoadhesiveness is through the determination of the adhesive strength between polymer and the attached substrate. The adhesive strength at such a bonding interface can be measured by measuring the force required to detach one entity from the other through the application of an external force. As such the destruction of the adhesive bond is usually under the application of either a shearing, tensile or peeling force. Here the authors used a modified version of the Wilhelmy plate surface technique in order to determine mucoadhesion of a range of candidate polymers. The device itself basically consists of a glass plate suspended from a microbalance. The polymer-coated plate was then slowly dipped into a beaker of mucus. The work required to remove the various polymer-coated glass slides could then be related to one another and their adhesiveness could be ranked. This environmental conditions via simple modification of instrumental setup. technique had the advantage of allowing the analysis of mucoadhesion under different, Wilhemys’s plate technique shown in Fig.3, or the microforce balance technique, can also be modified in order to measure the specific adhesion force of microparticles. This involves the use of a microtensiometer and a microforce balance and is specific, yielding both contact angle and surface tension. The mucous membrane is placed in a small mobile chamber with both pH and physiological temperature controlled. A unique
microsphere is attached by a thread to the stationary microbalance. The chamber with the mucous membrane is raised until it comes into contact with the microsphere and, after contact time, is lowered back to the initial position.

![Fig.3 Wilhemy’s technique](image)

**In vivo tests**

There is scant information available on the *in vivo* behavior of mucoadhesive formulations, especially in humans. Gamma scintigraphy allows the immediate visualization of all the formulation transit, with low exposure of the subjects to radiation. The study emphasized the importance of *in vivo* studies, because although chitosan exhibits an outstanding mucoadhesion capacity *in vitro*, the retention time at the absorption site in the human gastrointestinal tract was relatively short and not sufficiently reproducible. The gastrointestinal transit time in animals can also be evaluated in a non-invasive way, in which the release systems can be formulated with opaque radioisotopes and signals can be followed by X-rays, without affecting normal gastrointestinal motility.[22,23]

**Sanning electron microscopy (SEM)**

The microspheres were previously mounted on a brass stub using double-sided adhesive tape and then coated under vacuum with a thin layer of gold (3~5nm) for 75 sec and at 40W to make them electrically conductive. Afterwards, the stub containing the sample was placed in the scanning electron microscope chamber. The surface morphology of blank microspheres, drug loaded microspheres before and after dissolution was studied by photomicrographs at an excited voltage of 20 KV, specific chamber pressure (in mm Hg) under different magnification.
Swelling study

The swelling properties of the mucoadhesive microcapsules were determined in SGF (pH 1.2). Samples of microcapsules of known weight (50mg) were placed in petri dish containing 10ml of 0.1 N HCl. At regular intervals of time, the swollen microcapsules were removed from Petridish; the excess water was removed with the help of a filter paper and weighed again (W2). The Swelling Index (SI) can be calculated using the formula.

\[ \%\text{swelling of microcapsules} = \frac{\text{weight of microcapsules at time } t - \text{initial weight of microcapsules}}{\text{Initial weight of microcapsules}} \]

**Percentage yield:** The total amount of dried microcapsules was weighed and the percentage yield was calculated by taking into consideration the total weight of the drug and polymer used for preparation of microcapsules.

\[ \text{Percentage yield} = \frac{\text{Practical mass (microcapsules)}}{\text{Theoretical mass (microcapsules)}} \times 100 \]

**Estimation of Drug content:** 100 mg of microcapsules was crushed in a glass mortar and suspended in 0.1N HCl for dissolving the coat shell of microcapsules. The suspension was suitably diluted with 0.1N HCl in 100 ml volumetric flask and volume was made up using 0.1N HCl. The solution was filtered to separate the shell fragments and from the filtrate 10 ml was taken. Drug content was analyzed after suitable dilution by UV-Spectrophotometer.

**Entrapment efficiency (EE):** The % EE of each formulation was calculated using the following equation:

\[ \%\text{EE} = \frac{\text{Actual drug content}}{\text{Theoretical drug content}} \times 100 \]

**CONCLUSION**

The phenomenon of mucoadhesion can be used as a model for the controlled drug delivery approaches for a number of drug candidates. The complex procedure of mucoadhesion can allow for the target-controlled delivery of a range of APIs. Certain polymer properties such as charge, hydrophilicity, molecular weight amongst other parameters can affect the success and strength of adhesive bond. 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.
REFERENCES


