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Review on: mucoadhesive medication delivery methods

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Article History	Abstract
Received on: 15-11-2022 Revised on: 22-11-2022 Accepted on: 27-12-2022 Keywords: Mucoadhesive, drug delivery systems, Mucoadhesive dosage forms and mucoadhesive polymers.	Mucoadhesive drug delivery systems interact with the mucus layer covering the mucosal epithelial surface, and mucin molecules and increase the residence time of the dosage form at the site of absorption. Over the past few decades, mucosal drug delivery has received a great deal of attention. 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 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. This review covers the areas of mechanisms and theories of mucoadhesion, factors influencing the mucoadhesive materials, mucoadhesive polymers, and also various mucoadhesive dosage forms.
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Introduction

Adhesion can be defined as the bond produced by contact between a pressure sensitive adhesive and a surface. During the 1980s, this concept began to be applied to drug delivery systems. The concept of mucoadhesion has multiplied considerable interest in pharmaceutical technology [1]. 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. 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. Thereby increasing its bioavailability and promoting local or systemic effects [3, 4]. An extensive review on mucoadhesive systems was compiled by Andrews, Lavery and Jones (2008).

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 [2].

Bioadhesion can be defined as the state in which two materials, at least one of which is biological in nature, are maintained together for a prolonged time period by means of interfacial forces (Smart, 2005). During the 1980s, this concept began to be applied to drug delivery systems. It consists of the incorporation of adhesive molecules into some kind of pharmaceutical formulation

intended to stay in close contact with the absorption tissue, releasing the drug near to the action site, thereby increasing its bioavailability and promoting local or systemic effects (4; 3, 2001). An extensive review on mucoadhesive systems was compiled by Andrews, Laverty and Jones (2008).

The potential use for mucoadhesive systems as drug carriers lies in its continuation of the residence time at the absorption site, allowing intensified contact with the epithelial barrier [4]. On the other hand, adhesion of preparations onto mucous membrane can be impaired by the mucociliary clearance system. This clearance, a natural defense mechanism of the body against the deposition of impurities onto the mucous membrane, can also remove the preparation. Thus, by using bioadhesive molecules, it is possible to retain the preparation at the action site and to direct the drug to a specific site or tissue. Other features associated with the development of controlled drug delivery systems using bioadhesive molecules include a decrease in drug administration frequency and an increase in patient compliance to the therapy (3, 2001). Therefore, a bioadhesive system controlling drug release could improve the treatment of diseases, helping to maintain an effective concentration of the drug at the action site [5].

Adhesive systems applied to mucous membrane are frequently defined as mucoadhesive, but the terms are interchangeable (Leung, Robinson, 1990). It is feasible to design a bio (muco) adhesive system in different dosage forms, since the properties of adhesion largely depend on the features of the material used in its preparation [8]. Therefore, several conventional drug delivery systems already in use can become bioadhesive after redesign by including bioadhesive substances in their formulation. This approach to confer Bioadhesion properties has been widely applied in the development of a number of drug delivery systems.

Although studies on the mechanisms involved in mucoadhesion and the development of novel mucoadhesive systems and polymers have evolved over the last twenty years, mucoadhesion is not yet fully understood. Quantitative and qualitative techniques are still treated separately. The aim of this study was to systematically review the mechanisms and theories involving mucoadhesion, as well as to describe the methods and polymers most used in mucoadhesive systems for drug delivery.

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.

Mechanisms of Mucoadhesion

The mechanism of adhesion of certain macromolecules to the surface of a mucous tissue is not well understood yet. The mucoadhesive must spread over the substrate to initiate close contact and increase surface contact, promoting the diffusion of its chains within the mucus. Attraction and repulsion forces arise and, for a mucoadhesive to be successful, the attraction forces must dominate. The mechanism of mucoadhesion is generally divided into two steps: the contact stage and the consolidation stage.

The 1st stage is characterized by the contact between the mucoadhesive and the mucus membrane, with spreading and swelling of the formulation, initiating its deep contact with the mucus layer. Beginning its deep contact with the mucus layer [5]. In some cases, such as for ocular or vaginal formulations, the delivery system is mechanically attached over the membrane. In other cases, the deposition is promoted by the aerodynamics of the organ to which the system is administered, such as for the nasal route. If the particle approaches the mucous surface, it will come into contact with repulsive forces (osmotic pressure, electrostatic repulsion, etc.) and attractive forces (van der Waals forces and electrostatic attraction). Therefore, the particle must overcome this repulsive barrier [6].

In the 2nd stage consolidation step, 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 [6]. Essentially, there are two theories explaining the consolidation step: the diffusion theory and the dehydration theory. According to diffusion theory, the mucoadhesive molecules and the glycoproteins of the mucus mutually interact by means of interpenetration of their chains and the building of secondary bonds [6]. For this to take place the mucoadhesive device has features favouring both chemical and mechanical interactions.

Mucoadhesion Theories

The chemical and physical basis of mucoadhesion are not yet well understood, and it is a complex process and numerous theories have been proposed to explain the mechanisms involved. There are six classical theories revised from studies on the performance of several materials and polymer- polymer adhesion which explain the phenomenon.

Wetting theory

The wetting theory applies to liquid systems which present affinity to the surface in order to spread over it. This affinity can be found by using measuring techniques such as the contact angle. The general rule states that the lower the contact angle, the greater is the affinity (Figure 1). The contact angle should be equal or close to zero to provide adequate spread ability. The spread ability coefficient, SAB, can be calculated from the difference between the surface energies γ_B and γ_A and the interfacial energy γ_{AB} , as indicated in the equation given below [5]. This theory explains the importance of contact angle and reduction of surface and interfacial energies to achieve good amount of mucoadhesion.

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

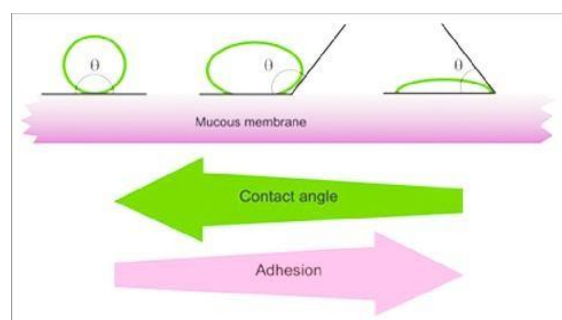


Fig no 1: Influence of contact angle on mucoadhesion

Diffusion theory

Diffusion theory describes the interpenetration of both polymer and mucin chains to a sufficient depth to create a semi-permanent adhesive bond (figure 2) it is believed that the adhesion force increases with the degree of penetration of the polymer chains [19]. This penetration rate depends on the diffusion coefficient, flexibility and nature of the mucoadhesive chains, mobility and contact time. According to the literature, the depth of interpenetration required to produce an efficient bio adhesive bond lies in the range 0.2-0.5 μm . This interpenetration depth of polymer and mucin chains can be estimated by following equation.

$$l = (tD_b)^{1/2} \text{ Where}$$

t is the contact time and D_b is the diffusion coefficient of the mucoadhesive material in the mucus. The greater the structural similarity, the better is the mucoadhesive bond.

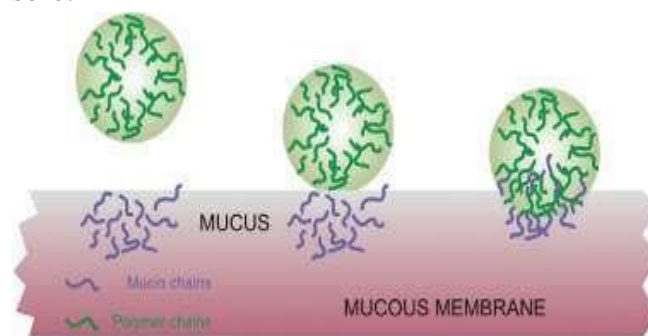


Fig. No: 2 Secondary interaction between mucoadhesive device and of mucus

Fracture theory

This is perhaps the most used theory in studies on the mechanical measurement of mucoadhesion. It analyses the force required to separate two surfaces after adhesion is Established. This force, s_m , is frequently calculated in tests of resistance to rupture by the ratio of the maximal detachment force, F_m , and the total surface area, A_0 , involved in the adhesive interaction.

$$S_m = \frac{F_m}{A_0}$$

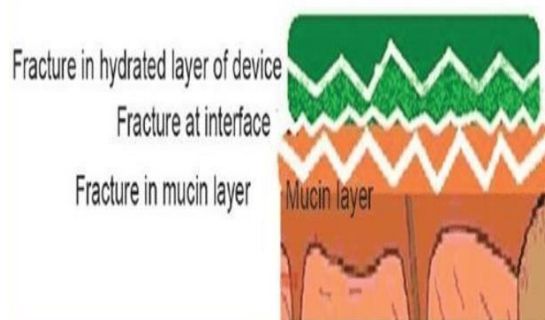


Fig No 2: Fractures occurring for mucoadhesion

Adsorption theory

According to the adsorption theory, adhesion is the result of various surface interactions (primary and secondary bonding) between the adhesive polymer and mucus substrate. 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. Primary bonds due to chemisorptions result in adhesion due to ionic, covalent and metallic bonding, which is generally undesirable due to their permanency. 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 such as van der Waal's forces, hydrogen bonding, and hydrophobic bonding. [9].

Electronic theory

In this theory describes based on the premise that both mucoadhesive and biological materials possess opposing electrical charges. Thus, when both materials come into contact, they transfer electrons leading to the building of a double electronic layer at the interface. The net result of such a process is the formation of attractive forces within this double layer [19].

Mucoadhesive Materials

Mucoadhesive polymers have numerous hydrophilic groups, such as hydroxyl, carboxyl, amide, and sulphate. 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 bio adhesive drug delivery system should have the following characteristics (Jimenez- Castellanos MR et al., 1993)

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 [11]

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

The latter polymer category includes lectins and thiolated polymers. Lectins are generally defined as

proteins or glycoprotein complexes of nonimmune origin that are able to bind sugars selectively in a noncovalent manner [5]. Lectins are capable of attaching themselves to carbohydrates on the mucus or epithelial cell surface and have been extensively studied, notably for drug-targeting applications [15].

These second-generation bioadhesives not only provide for cellular binding, but also for subsequent endo- and transcytosis.

Thiolated polymers, also designated thiomers, are hydrophilic macromolecules exhibiting free thiol groups on the polymeric backbone. Due to these functional groups, various features of polyacrylates and cellulose derivatives were strongly improved [17]. The presence of thiol groups in the polymer allows the formation of stable covalent bonds with cysteine-rich subdomains of mucus glycoproteins leading to increased residence time and improved bioavailability [18]. Other advantageous mucoadhesive properties of thiolated polymers include improved tensile strength, rapid swelling, and water uptake behavior.

Synthetic polymers

1. Cellulose derivatives
(Methylcellulose, Ethyl cellulose, Hydroxyl ethyl cellulose, Hydroxyl propyl cellulose, Hydroxy propyl methylcellulose, Sodium carboxy methylcellulose).
2. Poly (Acrylic acid) polymers
(Carbomers, Polycarbophil).
3. Poly hydroxyl ethyl methacrylate
4. Poly ethylene oxide.
5. Poly vinyl pyrrolidone

Natural polymers

Tragacanth, Sodium alginate, Guar gum, Xanthum gum, soluble starch, Gelatin, Chitosan Mucoadhesive polymers can also classify into following categories

Novel polymers:

Tomato lectin showed that it has binding selectivity to the small intestine epithelium.

A new class of hydrophilic pressure sensitive adhesives (PSA) have been developed by corium technologies. Complex have been prepared by non-covalent hydrogen bonding crosslinking of a film forming hydrophilic polymer with a short chain plasticizer having reactive OH groups at chain ends [12].

Recent Advances in Mucoadhesive Drug Delivery System Mucoadhesive Polymers

Diverse classes of polymers have been investigated for potential use as mucoadhesive. PAA has been considered as a good mucoadhesive. PAA is

copolymerised with polyethylene glycol (PEG) or poly (vinyl pyrrolidone) (PVP) to improve these properties.

Devices

Several laminated devices have been developed to achieve sustained drug release. It can be classified as:

Monolithic (or matrix) systems where the drug is dissolved or dispersed in the polymer system – diffusion of drug from the drug/polymer matrix controls the overall rate of its release from the device.

Reservoir (or membrane) systems where diffusional resistance across a polymeric membrane controls the overall drug release rate [13].

Conclusion

This overview about the mucoadhesive dosage forms might be a useful tool for the efficient design of novel mucoadhesive drug delivery systems. Mucoadhesive drug delivery systems have applications from different angles, including development of novel mucoadhesives, design of the device, mechanisms of mucoadhesion and permeation enhancement. Novel mucoadhesive formulations require much more work, to deliver clinically for the treatment of both topical and systemic diseases. So finally concluded that mucoadhesive systems may play an increasing the role in the development of new pharmaceuticals.

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