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MUCOADHESIVE DRUG DELIVERY SYSTEM: A REVIEW

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ABSTRACT

Drug actions can be improved by developing new drug delivery systems, such as the mucoadhesive system. Mucoadhesion is a field of current interest in the design of drug delivery systems. These systems remain in close contact with the absorption tissue, the mucous membrane, releasing the drug at the action site leading to a bioavailability increase and both local and systemic effects. 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. Mucoadhesion is currently explained by six theories: electronic, adsorption, wettability, diffusion, fracture and mechanical. The aim of this study was to review the mechanisms and theories involved in mucoadhesion, as well as to describe the most-used methodologies and polymers in mucoadhesive drug delivery systems. Several in vitro and in vivo methodologies are proposed for studying its mechanisms and factors affecting mucoadhesion, Therefore It is a growth area whose goal is the development of new devices and more "intelligent" polymers, as well as the creation of new methodologies that can better elucidate the mucoadhesion phenomenon.

KEYWORDS: Mucoadhesive drug delivery system, Mechanism, six theories, factors affecting.

INTRODUCTION

Mucoadhesive is a topic of current interest in the design of drug delivery systems to prolong the residence time of the dosage form at the site of application or absorption and to facilitate intimate contact of the dosage form with the underlying absorption surface to improve and enhance the bioavailability of drug.

Defination

Adhesion can be defined as the bond produced by contact between a pressure - sensitive adhesive and a surface.[3] 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. Bioadhesive systems applied to mucous membrane are frequently defined as mucoadhesive, but the terms are interchangeable.

Mechanism of Bioadhesion

For Bioadhesion to occur, three stages are involved.

Stage-1: Thus, the mechanism of mucoadhesion is generally divided in two steps:
The contact stage and consolidation stage (Figure 1).
The contact stage: The first 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 the consolidation step (Figure 1): 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. 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.

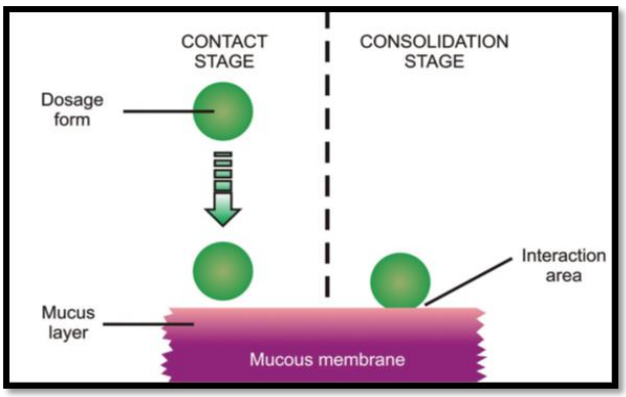

Figure 1: The two steps of the mucoadhesion process.

According to dehydration theory, materials that are able to readily gelify in an aqueous environment, when placed in contact with the mucus can cause its dehydration due to the difference of osmotic pressure. The difference in concentration gradient draws the water into the formulation until the osmotic balance is reached. This process leads to the mixture of formulation and mucus and can thus increase contact time with the mucous membrane.

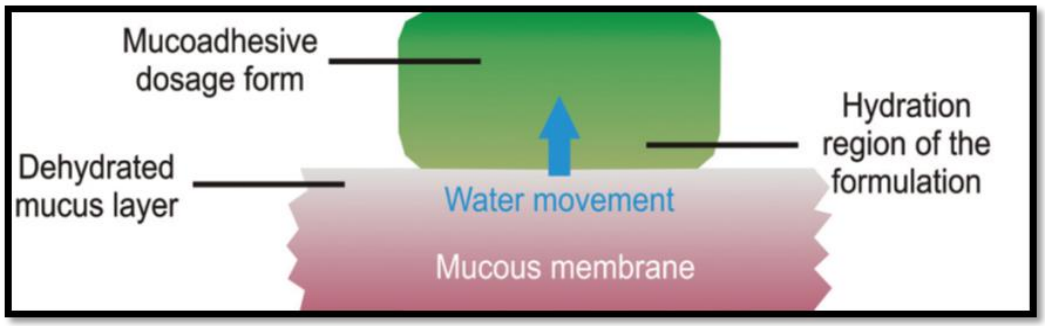

Figure 2: Dehydration theory of mucoadhesion.

Theories of Bioadhesion/Mucoadhesion[1, 2, 3]

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

Wetting

Wetting theory is predominantly applicable to liquid bioadhesive systems and analyzes adhesive and contact behavior in terms of a liquid or a paste to spread over a biological system This affinity can be found by using measuring techniques such as the contact angle. The general rule states that the lower the contact angle then the greater the affinity (Figure 3). The contact angle should be equal or close to zero to provide adequate spreadability.

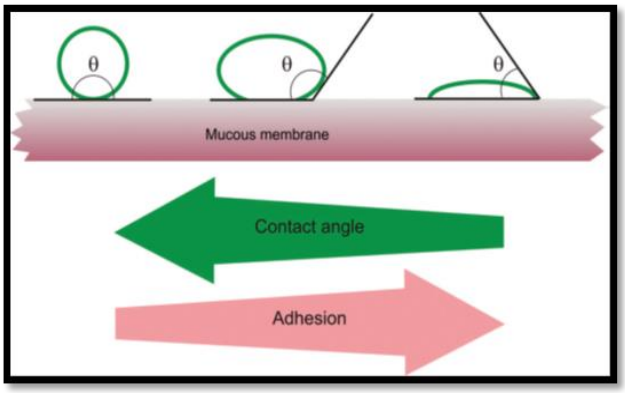

Figure 3: Schematic diagram showing influence of contact angle between device and mucous membrane on bioadhesion.

Diffusion

According to this theory the polymer chains and the mucus mix to a sufficient depth to create a semi permanent adhesive bond. The polymer chains penetrate the mucous; the exact depth of penetration depends, on the diffusion co- efficient, time of contact, molecular weights and decreases rapidly as the cross linking density as shown by Peppas.

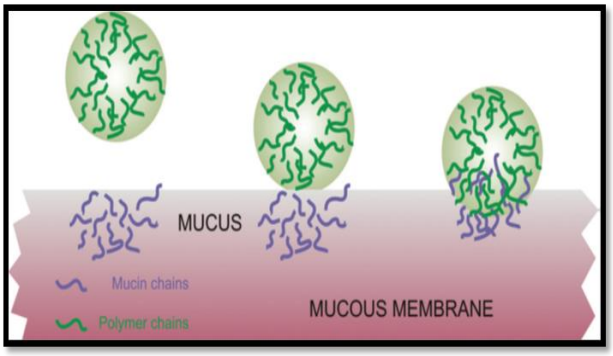

Figure 4: Secondary interactions resulting from interdiffusion of polymer chains of bioadhesive device and of mucus.

Electronic

According to this theory, electronic transfer occurs upon contact of an adhesive polymer and the mucous glycoprotein network because of differences in their electronic structure. This result in the formulation of an electronic double layer at the interface adhesion occurs due to attractive forces across the double layers.

Fracture

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

$$G = (E\varepsilon. /L)\ ½$$

Where: E- Young's modules of elasticity

ε- Fracture energy

L- Critical crack length when two surfaces are separated

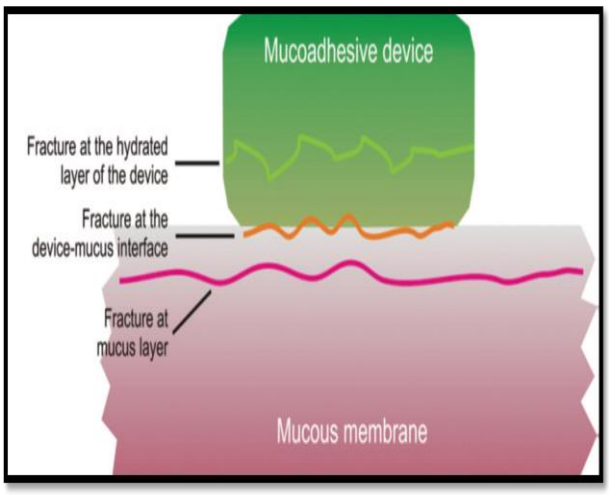

Figure 5: Regions where the mucoadhesive bond rupture can occur.

Absorption

According to this theory, after an initial contact between two surfaces, the materials adhere because of surface forces acting between the atoms in the two surfaces.

Two types of chemical bonds such as Primary covalent (permanent) and secondary chemical bonds (including electrostatic forces, Vander Waals forces and hydrogen and hydrophobic bonds).

Factors affecting muco/bioadhesion

Structural and physicochemical properties of a potential bioadhesion material influence bioadhesion.

a) Polymer related factors:

1. Molecular weight

The bioadhesive force increases with molecular weight of polymer, up to 1, 0000 and beyond this level there is no much effect.

2. Concentration of active polymers

There is an optimum concentration of polymer corresponding to the best bioadhesion infect, in concentrated solutions, the coiled molecules become solvent poor and the chains available for interpenetration are not numerous, for solid dosage forms such as tablets showed that the higher the polymer concentration the stronger the bioadhesion.

3. Flexibility of polymer chain

Flexibility is an important factor for interpenetration and enlargement. As watersoluble polymers become cross linked, the mobility of individual polymer chain decreases. As the cross linking density increases, the effective length of the chain which can penetrate into the mucous layer decreases further and mucoadhesive strength is reduced.

b) Environment related factors:

1. pH

pH influences the charge on the surface of both mucus and the polymers. Mucus will have a different charge density depending on pH because of difference in dissociation of functional groups on the carbohydrate moiety and amino acids of the polypeptideback bone.

2. Applied strength:

To place a solid bioadhesive system, it is necessary to apply a defined strength.

3. Initial contact time:

The mucoadhesive strength increases as the initial contact time increases.

4. Selection of the model substrate surface:

The viability of biological substrate should be confirmed by examining properties such as permeability, electrophysiology of histology.

5. Swelling:

Swelling depends on both polymers concentration and on presence of water. When swelling is too great a decrease in bioadhesion occurs.

c) Physiological Variables:

1. Mucin turnover

The natural turnover from the mucus layers is important for at least two reasons. (a) The mucin turnover is expected to limit the residence time of the mucoadhesive on the mucus layers. (b) Mucin turnover results in substantial amounts of soluble mucin molecules.

2. Diseased states

Physicochemical properties of mucus are known to change during diseased states, such as common cold, gastric ulcers, ulcerative colitis, cystic fibrosis, bacterial and fungal infections of the female reproductive tract and inflammatory conditions of the eye.

POLYMERS USED IN MUCOADHESION

Classification of mucoadhesive polymers

Property used for classification	Examples	
	Natural and modified natural polymers	**Synthetic**
Source	Agarose, Chitosan, Gelatin, Hyaluronic acid, Carrageenan, Pectin, Sodium alginate. **Cellulose derivatives** CMC, thiolated CMC, Na CMC, hydroxyethylcellulose, HPC, HPMC, methylcellulose, Methylhydroxyethylcellulose	**Polymers based on poly (meth) acrylic acid.** Carbopol, Polycarbophil, Polyacrylic acid, Polyacrylates, Copolymer of acrylic acid and PEG, Copolymer of methylvinyl ether and Methacrylic acid, Poly-2-hydroxyethylmethacrylate, Copolymer of acrylic acid and Ethylhexylacrylate, Polymethacrylate, Polyalkylcyanoacrylates:- Polyisobutylcyanoacrylate, Polyisohexylcyanoacrylate.
Solubility in water	**Water-soluble** **Cellulose derivatives** CMC, Thiolated CMC, Na CMC, Hydroxyethylcellulose, HPC, HPMC, Methylcellulose, Methylhydroxyethylcellulose.	**Polymers based on poly(meth)acrylic acid** Carbopol, Polycarbophil, Polyacrylic acid, Polyacrylates, Copolymer of acrylic acid and PEG, Copolymer of methylvinyl ether and Methacrylic acid, Poly-2-hydroxyethylmethacrylate, Copolymer of acrylic acid and Ethylhexylacrylate, Polymethacrylate,

METHOD USED TO STUDY BIOADHESION

Several test methods have been reported for studying bioadhesion. These tests are important during the design and development of bioadhesion controlled released system as they ensure compatibility, physical and mechanical stability, surface analysis and bioadhesion bond strength.

The tests can be broadly classified into 2 major categories

1. In-vitro / Ex-vivo methods
2. In-vivo methods

1. In-vitro / Ex-vivo methods:

1. Mucoadhesive Strength (Detachment strength,Shear Strength,Rupture tensile strength)
2. Rheological Study
3. In vitro Diffusion

2. In-vivo methods

Gamma scintigraphy

CONCLUSION

Studies on mucoadhesive systems have focused on a broad array of aspects. It is a growth area whose goal is the development of new devices and more "intelligent" polymers, as well as the creation of new methodologies that can better elucidate the mucoadhesion phenomenon. With the great influx of new molecules stemming from drug research, mucoadhesive systems may play an increasing role in the development of new pharmaceuticals.

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