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"A Review on Mucoadhesive Drug Delivery System"

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ABSTRACT: Mucoadhesive Drug Delivery System(MDDS) blazing these days asit has myraid advantages among these utmost is it prolong the residence time of dosage form with the underlying absorption surface to improve and enhance the bioavailability of the drugs. Faster onset of these dosage forms is a result of highly perfused mucosal membrane. When the biological substrate is attached to a mucosal layer then this phenomenon is known as mucoadhesion. Numerous polymers are responsible for forming complex with mucin protein and thus are used to improve drug delivery by enhancing the dosage form, contact time and residence time. Various natural and synthetic mucoadhesive polymers are used for designing of mucoadhesive drug delivery system such as tablets ,patches, gels, tapes, films, semisolids and powders. Most widely used polymers are euderagits, carbapol, polyacerlyic acid. Common sites where mucoadhesive polymers have the ability to deliver pharmacological active agents include oral cavity, eye conjunctiva, rectal lumen, vagina, nasal and entire gastrointenstinal tract. Mucoadhesive system remains close contact with absorption tissue the mucus membrane releasing the drug at site of action leading to both local and systemic effects. Preferred drug candidates for the drug delivery system should have high permeability and solubility. Many antibiotic, antiulcer, antidiabetic, antifungal and NSAID's are incorporated in mucoadhesive drug delivery system. Current review emphasis on current scenario and status of mucoadhesive drug delivery system.

I. INTRODUCTION:

The oral mucosa has many properties which make it an attractive sitefor drug delivery but simultaneously provide several problems for researchers for effective and efficient delivery of active drugs. However, with the development of novel delivery techniques overcomes several challenges. Different formulations including sprays, tablets, mouthwashes, gels, pastes and patches are presently used for delivery into and/ or across the oral mucosa (Hearnde et al., 2011; Mathiowitz, 2000). The term bioadhesion refers to any bond formed between two biological surfaces or a bond between a biological and a synthetic surface. In case of bioadhesive drug delivery, the term bioadhesion is used to describe the adhesion between polymers, either synthetic or natural and soft tissues or the gastrointestinal mucosa. In cases where the bond is formed with the mucus the term mucoadhesion may be used synonymously with bioadhesion. 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.[1]. Mucoadhesive drug delivery system interact with the mucosa layer covering the mucosal epithelial surface & mucin thus increase the residence time of the dosage form at the site of absorption. In pharmaceutical science, when the adhesive attachment is to mucous or a mucous membrane, the phenomenon is referred to as mucoadheshion. In the early1980s ,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 system. Sincethen , the potential of mucoadhesive polymers was shown in oral, nasal, ocular, buccal and vaginal drug delivery system leading to significantly prolonged residence time of sustained release delivery system on the mucosal membrane**.** The need to deliver 'challenging' moleculessuch as biopharmaceuticals (proteins and oligonucleotides) has increased interest in this area. Mucoadhesive materials could also be used as therapeutic agents in their own right, to coat and protect damaged tissues (gastric ulcers or lesions of the oral mucosa) or to act as lubricating agents (in the oral cavity, eye and vagina)[2].

NEED OF MDDS:

- Prolongs the residence time of the dosage form at the site of absorption.
- Due to an increased residence time it

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enhances absorption and hence the therapeuticefficacy of the drug.

- Excellent accessibility.
- Rapid absorption because of enormous blood supply and good blood flow rates.
- Increase in drug bioavailability due to first pass metabolism avoidance.
- Drug is protected from degradation in the acidic environment in the gastrointestinal tract.
- Improved patient compliance- ease of drug administration.
- Faster onset of action is achieved due to mucosal surface [3].

Composition of Mucus Layer:
Mucus is a translucent and viscid secretion which forms a thin, contentious gel, mean thicknessof this layer varies from about 50-450 µm in humans secreted by the globet cells lining the epithelia. It has the following general **composition**.

- Water -95%
- Glycoprotein and lipids – 0.5-3.00%
- Mineral salts – 1%
- Free proteins – 0.5-1.0% [1]

Functions of Mucus Layer:

1. Protective: resulting particularly from its hydrophobicity.
2. Adhesion: Mucus has strong adhesion properties.
3. Lubrication: It is to keep the mucus from the goblet cell is necessary to compensate for the removal of the mucus layer due to digestion, bacterial degradation and solubilisation of mucin molecules.

SITES FOR MUCOADHESIVE DRUG DELIVERY SYSTEM
The common sites for mucoadhesive drug delivery systems include oral cavity, eye conjunctiva, vagina, nasal cavity and gastrointestinal tract.

The buccal cavity has a very limited surface area of around 50 cm^2 but the accessibility of thesite makes it a preferred location for delivering therapeutic agents. Delivery through this site avoids hepatic first-pass metabolism in addition to the local treatment of the oral infections. The sublingual mucosa is relatively more permeable than the buccal mucosa; hence formulations for sublingual delivery are formulated to release the active agent immediately. The mucoadhesive formulation is of importance for the delivery of active agents to the buccal mucosa where the active agent has to be released in a controlled manner. Hence, the buccal cavity is more suitable for mucoadhesive drug delivery.

- **Nasal cavity** also offers a potential site for the designing of formulations using mucoadhesive polymers. The nasal mucosa has a surface area of about 150-200 cm^2 but the residence time of a particulate matter in the nasal mucosa varies between 15 and 30 min. This short time is due to the increased activity of the mucociliary layer due to stimulation by foreign particles.

- **Ophthalmic mucoadhesive drug delivery** is also of great 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 which canbe reduced by delivering the drugs using ocular inserts or patches.

- **The vaginal and the rectal lumen** have also been explored for the delivery of the active agents both systemically and locally. The active agents meant for the systemic delivery by this route of administration bypasses the hepatic first-pass metabolism. Quite often the delivery systems suffer from migration within the vaginal/rectal lumen which might affect the delivery of the active agent to the specific location. This can be overcome by applying the principles ofmucoadhesion.

- **Gastrointestinal tract** is also a potential site which has been explored since long for the development of mucoadhesive based formulations. The manipulation of the transit time of thedelivery systems in a particular area of the gastrointestinal system by using mucoadhesive polymers has evinced a great interest among researchers around the world[4].

Mechanism of mucoadhesion:
Mucoadhesion is the fixing of the drug to the mucous membrane by using a suitable carrier. It's a complex phenomenon which include wetting, adsorption and interpenetration of polymer chains. Following mechanism involve in mucoadhesion process such as:

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- Wetting or swelling phenomenon (intimate contact of mucoadhesive to the mucous membrane.
- Interpenetration (Penetration of the bioadhesive into the mucous membrane)

Contact time for all most mucosal routes is hardly an hour, it can be improve by the addition of an adhesive polymers in the delivery system which is useful to localize the delivery system and increases the residence time at the absorption site. The right mechanism of mucoadhesion is still have to establish but an accepted theory explain that an intimate contact between the mucoadhesive polymer and mucin takes place which is followed by the interpenetration of polymer and mucin. Due to the formation of van der vaals forces, electrostatic bonds and hydrogen bonds increases the adhesion process. The mucoadhesion mechanism is generally involves two steps

- Contact stage
- Consolidation step.

Contact stage: It is a stage at which contact of mucoadhesive polymer to the mucus membrane, by wetting, spreading and swelling of the delivery system.

Consolidation step: It involves the activation and bonding of Mucoadhesive agent. The mucoadhesive materials are activation is due to the presence of moisture. Moisture increase the plasticity of the system, allowing the mucoadhesive molecules to break free and to link up by hydrogen bonds and weak Vander Waals force.[5].

The mucoadhesive / mucosa interaction

A. Chemical bonds-- For adhesion to occur, molecules must bond across the interface. These bonds can arise in the following way.
B. Ionic bonds—where two oppositely charged ions attract each other via electrostatic interactions to form a strong bond (e.g. in a salt crystal).
C. Covalent bonds—where electrons are shared, in pairs, between the bonded atoms in order to 'fill' the orbitals in both. These are also strong bonds.
D. Hydrogen bonds—here a hydrogen atom, when covalently bonded to electronegtivity 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 than covalent bonds.
E. 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.
F. 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 present in an aqueous solution. Water molecules adjacent to non 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.[6].

Theories of MDDS

Mucoadhesion is a complex process and numerous theories have been proposed to explain the mechanisms involved.

These theories include.

- Electronic theory: Attractive electrostatic forces between glycoprotein mucin network and the bioadhesive material. Electrons transfer occurs between the two forming a double layer of electric charge at the surface.
- Wetting theory: Ability of bioadhesive polymer to spread and develop intimate contact with the mucous membrane. Spreading coefficient of polymers must be positive. Contact angle between polymer and cells must be near to zero.
- Adsorption theory:- Surface force resulting in chemical bonding. Strong primary force: covalent bonds. Weak secondary forces: hydrogen bonds and van der Waal's forces
- Diffusion theory:- Physical entanglement of mucin strands and flexible polymer chains. For maximum diffusion and best adhesive strength, solubility parameters of the bioadhesive polymer and the mucus glycoproteins must be similar
- Mechanical theory:- Adhesion arises from an interlocking of liquid adhesive into irregularities on the rough surface. Rough surfaces provide an increased surface area available for interaction along with an enhanced viscoelastic and plastic dissipation of energy during joint failure, which are more important in the adhesion process than a

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mechanical effect.

- Fracture theory:- Analyses the maximum tensile stress developed during attachment of the transmucosal DDS from the mucosal surface Does not require physical entanglement of bioadhesive polymer chains and mucous strands, hence it is appropriate to study the bioadhesion of hard polymers which lack flexible chains[7].

Mucoadhesive Polymers:

Mucoadhesive polymers are water-soluble and water insoluble polymers, which are swellable networks, jointed by cross-linking agents. These polymers possess optimal polarity to make sure that they permit sufficient wetting by the mucus and optimal fluidity that permits the mutual adsorption and interpenetration of polymer and mucus to take place. Mucoadhesive polymers that adhere to the mucin-epithelial surface can be conveniently divided into three broad classes:

- Polymers that become sticky when placed in water and owe their mucoadhesion to stickiness.
- Polymers that adhere through nonspecific, non-covalent interactions that is primarily electrostatic in nature (although hydrogen and hydrophobic bonding may be significant).
- Polymers that bind to specific receptor site on tile self surface.

A. Characteristics of an ideal mucoadhesive polymers:

An ideal mucoadhesive polymer has the following characteristics:

- The polymer and its degradation products should be nontoxic and should be non-absorbablefrom the gastrointestinal tract.
- It should be nonirritant to the mucous membrane.
- It should preferably form a strong non-covalent bond with the mucin-epithelial cell surfaces.
- It should adhere quickly to most tissue and should possess some site-specificity.
- It should allow daily incorporation to the drug and offer no hindrance to its release.
- The polymer must not decompose on storage or during the shelf life of the dosage form.
- The cost of polymer should not be high so that the prepared dosage form remains competitive.

B. Molecular characteristics :

The properties exhibited by a good mucoadhesive may be summarized as follows

- Strong hydrogen bonding groups (-OH, -COOH).
- Strong anionic charges.
- Sufficient flexibility to penetrate the mucus network or tissue crevices.
- Surface tension characteristics suitable for wetting mucus/mucosal tissue surface.
- High molecular weight. Although an anionic nature is preferable for a good mucoadhesive, a range of nonionic molecules (e.g., cellulose derivatives) and some cationic (e.g., Chitosan) canbe successfully used.[8,9]

FACTOR AFFECTING MUCOADHESION

I. POLYMER RELATED FACTORS:

1) Molecular weight:

- There is certain molecular weight at which bioadhesion is at a maximum.
- The interpenetration of polymer molecules is favorable for low molecular weight polymers, whereas entanglements are favored for high molecular weight polymers.
- It seems that the bioadhesive forces increases with the molecular weight of the bioadhesive polymer up to 100000, and that beyond this level there is not much affect. Example: Polyethylene glycol (PEG) with a molecular weight of 20,000 has little adhesive character, whereas PEG with 200,000 molecular weight has improved, and a PEG with 400,000 has superior adhesive properties. The bioadhesive nature improves with increasing molecular weight for linear polymers.
- Adhesiveness of a nonlinear structure follows different trend [10].

2) Concentration of active polymer:-

- Bremecker relates that there is an optimum concentration of polymer corresponding to the best bioadhesion.
- In highly concentrated systems, the adhesive strength drops significantly. In fact, in concentrated solutions, the coiled molecules become solvent-poor, and the chains available for interpenetration are not numerous.
- This result seems to be of interest only for more or less liquid bioadhesive forms

3) Degree of hydration:

- Depending on the degree of hydration adhesive

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properties are different. It is maximum at a certain degree of hydration.

- When the degree of hydration is high, adhesiveness is lost probably due to formation of slippery, non-adhesive mucilage in an environment of large amount of water at or near the interface.

4) Charge on polymer:

Mucosal surface is negatively charged. So positively charged polymer might facilitate the mucoadhesive process. Perhaps the initial step of mucoadhesion of a positively charged polymer to the biologic surface is through electrostatic attraction, followed by mechanical interlinking of polymer chains, vanderwaal forces, H bonds and other forces. Chitosan have bioadhesion due to electrostatic attraction between positively charged D- glucosamine residue of chitosan and negatively charged sialic acid residues[6].Besides molecular weight or chain length, spatial conformation of a molecule is alsoimportant.

Example: High molecular weight of 19,500,000 for dextrans, they have similar adhesive strength to the polyethylene glycol 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 [11,12].

Recent Advancement In Mucoadhesive Drug Delivery System

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 devices
- **Reservoir**(or membrane) system where diffusional resistance across a polymeric membrane control the overall drug release rate.[13]

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