AN OVERVIEW OF "MUCOADHESIVE DRUG DELIVERY SYSTEMS: CHALLENGES & APPROACHES"

Dr. M. Sabareesh*, Vasavi K, Reddy Jyothi K, Priyanka N, Yagnasri P, Harsha M, Sachith M, Dr. Anna Balaji

Department of Pharmaceutics, SreeVidyanikethan College of Pharmacy, Sree Sainath Nagar, A.Rangampeta, Chittoor District, Andhra Pradesh-517102.

Corresponding Author

Dr. M. Sabareesh,

M.Pharm., PhD.

Associate Professor

Department of Pharmaceutics

Email.sabareesh.m@vidyanikethan.edu

Mobile no : 7989196222

SreeVidyanikethan College of Pharmacy, Tirupati.

REVIEWERS:

1) **Dr P.Dharani Prasad,**

Professor & HOD

Dept. of Pharmacy Practice

Email id dharniprasad.p@vidyanikethan.edu

Mobile no: 6302745529

SreeVidyanikethan College of Pharmacy

Tirupati.

2) **Dr G.Dharmamoorthy**

Associate professor & HOD

Dept. of Pharmaceutical Analysis

Email id dharmamoorthy.g@vidyanikethan.edu

Mobile no 9603774847

SreeVidyanikethan College of Pharmacy

Tirupati.

ABSTRACT:

The word mucoadhesion is the adhesion between the mucosal membrane and a drug formulation. A mucoadhesive delivery system is preferred these days as it could provide better bioavailability. For the past twenty years, MDDS was most preferred due to the longer duration of action at the site of application that provides a controlled release of drug for an effective therapeutic outcome. As the mucous membrane is in close contact with the absorption site, the drug release through the mucus membrane increases the local and systemic availability of the drug which enhances its therapeutic nature. Application of drug molecules over a mucosal surface is beneficial to the certain drug which is inactive orally, acid-degradable drugs and drugs with high bypass metabolism. A mucoadhesive drug delivery system increases the retention time of drug molecules at the target site. Polymer is used as an adhesive material in mucoadhesive drug delivery systems. The adhesion capability of the drug to the mucus membrane depends on various factors that include the nature of the mucosal membrane and the physical-chemical properties of Polymer-based formulations. The mucoadhesive drug delivery system provides extensive contact between the active drug molecules and the mucosal membrane at the absorption site, which results in a high influx of drug molecules through the absorption site. The above article provides a brief note on various aspects of mucoadhesive polymers, factors influencing mucoadhesion, theories of mucoadhesion, evaluation parameters and about various mucoadhesive drug delivery systems.

KEYWORDS: Mucous Membrane, Sustainability, First Pass Metabolism, Biodegradable Polymers, Swelling Index

INTRODUCTION

Mucoadhesive drug delivery system longer the duration of action of the dosage form at the site of application. In 1986, Longer and Robinson interpret the term bioadhesion as the attachment of natural or synthetic macromolecules to biological membrane[1] and mucoadhesion defines the adhesion of polymer with the mucus layer[2].

The human mucus membrane is relatively permeable and enhances drug absorption. The mucosal site mostly preferred in MDDS is the gastrointestinal mucus membrane and the other routes include buccal, vaginal, rectal, ocular, nasal and periodontal[3].

The Site-specific action of drug molecules in the body provides a controlled release of the drug. The amount of drug release is predictable from dosage form which is a potential candidate for drug release. The formulation of a mucoadhesive drug delivery system should be small, flexible and accepted by patients without causing any irritation.

POTENTIAL MERITS OF MDDS

- Drugs which are unstable in acid and degradable in the stomach or drugs unstable to alkaline Ph of the intestine can be administered through MDDS.
- Avoids acid hydrolysis in the gastrointestinal(GI) tract.
- The first-pass metabolism is avoided and shows local effects for an extended period.
- Improve Patient Compliance.
- Decreased dose frequency.

LIMITATIONS OF MDDS

- One of the major limitations in oral mucosal drug development is the lack of a better i*n-vitro* screening method to identify suitable drugs for oral administration.
- The lack of physical flexibility of mucoadhesive tablets is one of the drawbacks as it leads to poor patient compliance for repeated use.
- The use of chitosan polymer is limited due to limited mucoadhesive strength and water solubility at neutral and basic pH.

DRUG CANDIDATE APPROPRIATE FOR MDDS

Molecular size 75-100 daltons, Molecular weight 200-500 daltons.

Drugs with poor bioavailability through oral route.

Drugs that are having short biological half-lives.

MUCOADHESIVE POLYMERS

Mucoadhesive drug delivery systems are being of active agents to a particular site[4]. Polymers play an important role in this type of system by increasing the residence time of active agents at the desired site[4.]

Ideal Properties

- To promote the adhesiveness between the polymer and mucus the polymers must have a high molecular weight of up to 10,000 or more.

- The length of polymer chains must be long enough to promote interpenetration and if it is too long then the problem of diffusion arises.
- Optimum hydration, pH and concentration must be maintained.
- High viscosity and spatial confirmation.

Table 1. List of biodegradable mucoadhesive polymers

Natural Polymers	Semi-Synthetic Polymers	Synthetic Polymers
Tragacanth	Microcrystalline Cellulose	Polyhydroxyethylmethacrylate
Alginate (Na)	Hydroxypropyl Methylcellulose	Polyethene oxide
Guar gum	Hydroxypropyl Cellulose	Polyvinyl pyrrolidine
Xanthum gum	Carboxy Methylcellulose (Na)	Polyvinyl alcohol[5]
Soluble starch	Hydroxyethyl Cellulose	
Gelatin		
Chitosan		

APPROACHES TO MDDS/TYPES OF MDDS

1. Vaginal mucoadhesive drug delivery system

The vaginal mucosa is favourable for drug administration as it avoids first-pass metabolism. Vagina mucosa has low enzymatic activity, is highly vascularized and intensively permeable. Vaginal cavity has the capability of controlled delivery of active ingredients through the transmucosal membrane for the local and systemic activity of drugs. Proteins and peptides are the compounds that are given through vaginal mucosa for systemic delivery.

The vaginal mucosa consists of microflora. Factors such asvaginalpH, and cyclic changes have to be considered while developing and evaluating avaginal mucosal drug delivery system. Lactobacilli bacteria maintain the vaginal pH. It secretes lactic acid and provides a PH range of 3.5-4.5 which changes with age due to menstrual cycle changes. The vaginal dosage forms that are commercially available in the market are mucoadhesive tablets, mucoadhesive gels, mucoadhesive films, pessaries or suppositories and emulsions-type mucoadhesive systems.

2. Ocular drug delivery system

Site specificity and localization of drug molecules within the eye is a challenging part of the ocular drug delivery system. The limitations in ocular drug delivery systems can be avoided by increasing the retention time and obtaining the site specificity of a drug molecule within the eye. The duration and the amount of drug administration through the ocular drug delivery system depend on the severity of the eye disease. Among various ocular delivery formulations, eye drops have the least bioavailability at the site of application as it is applied topically on the eye and the eye has various complex mechanisms and membranes.

Important factors to be considered

- The localization of drug molecules is important for pharmacodynamic activity in eye tissue and to avoid movement in other tissues.

- The retention time of the drug molecule should be increased to avoid repeated administration of the drug molecule.
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3. Rectal drug delivery system

Rectal drug delivery system refers to the administration of medications through the rectum for local and systemic effects. These systems provide mucoadhesion, i.e. the drug's attachment to the mucous membrane along with an effective carrier[12].

Standards for drug selection

Elevated therapeutic doses of drugs are required.

Medications with swallowing difficulties. Drugs such as proteins and peptides are substrates for proteolytic activity in the upper gastrointestinal tract.

Eliminate medications that have a lesser half-life and drugs which have low bioavailability.

4. Nasal mucoadhesive drug delivery

A nasal drug delivery system is preferred as another route for the parenteral administration of an active drug molecule because of its vast permeability through the nasal epithelial membrane. The nasal mucous membrane allows the molecules higher molecular weights of up to 1000 Daltons and shows an improved drug absorption rate. The drug and plasma profile concentrations of the nasal drug delivery system are similar to that of intravenous administration. To treat diseases within the nasal cavity, nasal mucosal drug delivery is preferred. The best examples of nasal mucosal drug delivery systems are nasal decongestants and anti-allergic drugs.

The rationale for nasal drug delivery

A relatively large surface area is available for drug absorption which is epithelium covered with microvilli.

Nasal and buccal mucoadhesive systems decrease enzymatic activity.

Site-specific actions of the drugs can be achieved by mucoadhesive drug delivery systems.

5. Sublingual drug delivery system

The sublingual route provides effective absorption of drug molecules and rapid onset of action for a systemically active drug. Sublingual glands secrete saliva which shows the lubricating and binding actions that help in swallowing food.

Drugs for sublingual administration

Drugs acting on the cardiovascular system, steroids, enzymes and barbiturates are given through a sublingual drug delivery system. Compounds such as vitamins and minerals are mostly administered through the sublingual route as it provides immediate absorption.

Examples

- ❖ Antianginal drugs- Nitrites and Nitrates
- ❖ Antihypertensive drugs- Nifedipine

- Analgesics- Morphine
- Bronchodilators- Fenoterol

Method of preparation - Sublingual formulation

Sublingual tablets- Sublingual tablets are formulated by using a direct compression method in which a super-disintegrating material is necessary for the formulation. A highly water-soluble substance can also be used as an excipient for fat disintegration.
Films- films are prepared by using the solvent casting method. Another alternative other than the solvent casting method in sublingual film preparation is the solvent evaporation technique. Among all the sublingual formulations, sublingual sprays provide the highest plasma drug concentration.

6. Buccal drug delivery system

The Administration of the drug through a buccal drug delivery system is easy than the other routes. For the drugs that are given through the buccal drug delivery system, the formulation is placed on the buccal mucosal membrane within the oral cavity. Both the mucosal and transmucosal active drugs can be administered. Localization of the drug can be achieved which also provides the systemic circulation of the drug passing through the buccal mucous membrane.

Advantages

Excellent accessibility
The buccal mucosa is the most suitable for drug delivery as the mucous membrane in the buccal cavity has smooth muscle and is immobile which increases the retention time.
It avoids first-pass metabolism by the direct systemic circulation of the drug.
Low enzymatic activity
Permeation enhancers, enzyme inhibitors and pH modifiers can be used in the development of formulation.

THEORIES OF MUCOADHESION:

Mucoadhesion theories explain the adhesion phenomena between polymer and mucous membranes.

- ✓ **Electronic Theory**

The electronic theory is based on the principle of opposite electric charges on mucous membranes and polymers. when a polymer comes in contact with a mucous membrane there is an exchange of electrons which leads to forming of an electronic double layer at the interface. Mucoadhesive strength is determined by the attractive forces in the electronic double layer.

- ✓ **Adsorption Theory**

The mucoadhesive material binds to the mucous membrane by secondary chemical interactions which are van der Waals forces and hydrogen bonds, electrostatic attractions or

hydrophobic bonds. Hydrophobic bonds are prominent interfacial forces in the adhesion of carboxyl groups. These forces are important in adhesion. Although the individual bonds are weak, a group of interactions results in great adhesion.

- ✓ **Wetting Theory**

The wetting theory is for liquids which have the greatest affinity for the solid surface to spread over the surface. The contact angle is used to measure the affinity of the solid and liquid surfaces. If the contact angle is low then the affinity is high. To achieve good spreading nature the contact angle must be zero or equal to zero.

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

The adherence of adhesive and substrate is given by Dupre's equation

$$W_A = \gamma_b + \gamma_t - \gamma_b$$

Where,

W_A =work of adhesion

γ_b= surface tension of polymer

γ_t= substrate

- ✓ **Diffusion theory**

Diffusion theory explains the interpenetration of polymer chains in mucoadhesion. To create a semi-permanent adhesive bond, both polymer and mucin chains penetrate to a sufficient depth.

The concentration gradient drives the polymer chains into the mucous network and mucin chains into the matrix until penetration depth reaches equilibrium.

The Range of depth needed for bioadhesive bonds is 0.2-0.5µm.

Diffusional depth of polymer S=$\sqrt{2}tD$

Where, D = diffusion coefficient

t= contact time

$$t=l^2/D_b$$

where, l = interpenetration depth

D_b = diffusion coefficient of mucoadhesive material in the mucus.

The diffusion coefficient is dependent on the molecular weight of the polymer strand and that is decreased by increasing cross-linking density.

- ✓ **Fracture Theory**

Fracture theory explains the force required for the detachment of two forces after adhesion. This theory helps to study bio-adhesion by using tensile strength apparatus. The adhesive strength is equal to that of the fracture strength.

$$\sigma=(E \times \mathcal{E}/L)½$$

Where, σ = fracture strength

E= young modulus of elasticity

Ɛ = fracture energy

L = critical crack length.

FACTORS AFFECTING THE MUCOADHESIVE DRUG DELIVERY SYSTEM

BIOPHARMACEUTIC CHARACTERISTICS

The molecular weight of the drug

The molecular size in pore transport should be 150 Daltons for a spherical molecule and 400 Daltons for a linear drug molecule. average molecular size should be 600 Daltons. the lower the molecular weight of the drug higher the absorption rate.

Aqueous solubility of the drug

Drug molecules with good solubility and which are pH Independent are excellent candidates for mucoadhesive drug delivery systems. the lowest limit of solubility of the drug to be formulated in controlled systems is 0.1mg/ml. absorption of poorly soluble drugs is very less in controlled delivery systems as dissolution is a rate-limiting step so the drugs with lower solubility are not prefered in mucoadhesive drug delivery systems.

Partition Coefficient

The drugs having higher partition coefficients have more lipophilicity and greater absorption. Higher lipophilic drugs have a maximum capacity to cross the biological membrane and selective barriers such as blood-brain barriers(BBB).

Drug PK_A and Ionisation of Physiological pH

The PKA range for optimum passive absorption of acidic drugs is 3-7.5 and for basic drugs 7-11. the drug should be non-ionised for at Least 1-5% at the absorption site. For better absorption, the drug should be in the non-ionised form as the ionised drug molecules are not absorbed through a biological membrane.

Drug Permeability

The three major drug characteristics of permeation across intestinal epithelium are

Lipophilicity of drug

polarity of drug

Molecular size

Drug Stability

Drugs which are unstable in the GI environment should be given through the oral route as they have less bioavailability. A drug which is unstable at gastric PH can be designed to release the drug formulation in intestinal pH in the sustained release dosage form. On the other hand, drugs which are unstable in the intestine can be designed as gastroretentive drugs.

Hydrophilicity

Hydrophilicity is because of hydrophilic groups in the mucoadhesive polymer. Polymers are hydroxyl and carboxyl groups. These polymer groups form hydrogen bonds with the mucus membrane. This results in the swelling of the polymer and anchors the sites. The swollen polymers have more distance between polymer chains and mucous membrane which has increased flexibility and efficient penetration.

Cross-linking and Swelling

Cross-linking density is inversely proportional to the degree of swelling. The higher the crosslinking density Lower is the degree of swelling, flexibility and hydration rate. Polymers having larger surface areas have extensive mucoadhesion. To have a high degree of swelling lightly cross-linked polymers are favoured. The presence of moisture increases the degree of swelling. The mucoadhesion can be increased by incorporating the adhesive enhancers which may be free polymer chains.

Polymer Concentration

The optimum polymer concentration is preferred in mucoadhesion for better adhesion. In tablets higher, the polymer concentration higher will be the adhesion strength. In some cases highly concentrated systems, which are above optimum concentration results drop in adhesion significantly. The coiled molecules have the poor solvent capacity and chains for penetration will be less, so the adhesion will be decreased significantly for liquid mucoadhesion formulation.

- ✓ Mechanism and site of absorption
- ✓ Drugs which are absorbed by carrier-mediated transport processes Are poor candidates for mucoadhesive drug delivery systems.
- ✓ Biopharmaceutic aspects of the route of administration
- ✓ Oral and parental routes are major routes and the minor routes are sublingual, rectal, nasal, ocular, pulmonary, vaginal, and intranasal routes of administration.

PHARMACOKINETIC CHARACTERISTICS

- ✓ **Absorption Rate**

  Drugs containing lower absorption rates are less suitable for mucoadhesive drug delivery systems as the continuous release of the drug may result in stagnant nature and the drug remains unabsorbed. Drugs that are aqueous soluble and potent are poor candidates for controlled release that may precipitate potential toxicity.

- ✓ **Elimination Half-life**

  The optimum half-life for elimination should be 2-4 hours for a good mucoadhesive drug delivery system. A drug with a half-life of fewer than 2 hours requires a large amount of drug to obtain a better release rate.

- ✓ **Rate of Metabolism**

  A drug which is extensively metabolised is suitable for a mucoadhesive drug delivery system as long as metabolism is not too rapid. Metabolism parameters should be predictable and identical when the drug administration is by various routes.

- ✓ **Dosage Form Index**

  It is defined as Cssmax/Cssmin, ideally, the value should be close to 1.

- ✓ **Pharmacodynamic Characteristics**

- ✓ **Drug Dose**

  A dose strength of 1gram is considered the maximum for a mucoadhesive drug delivery system.

- ✓ **Therapeutic Index (TI)**
  To avoid toxicity the drug in plasma concentration should be within the minimum effective concentration. This is important because some drugs may attain toxicity within the therapeutic range.
- ✓ **Therapeutic Range**
  The therapeutic range should be wide enough for the drug in a mucoadhesive drug delivery system. The variations in release rate shouldn't result in concentration beyond this level.
- ✓ **Plasma Concentration-Response (PK/PD) Relationship**
  When the concentration of the drug molecule is independent of its pharmacological activity then it is a poor candidate for a mucoadhesive drug delivery system.

FUTURE CHALLENGES OF MDDS

The mucoadhesive drug delivery system provides numerous benefits in case of dosage administration, economy and great patient compliance. Research is mainly focussed on the traditional polymers usage for novel drug delivery systems.

In these recent years, research on mucoadhesive drug delivery systems has shown various methods of adhesion of drugs to enhance the bioavailability of orally inactive drugs. The second-generation mucoadhesive polymers have more potential to deliver the drug. The less bioavailable drugs can be formulated in microparticulate or nanoparticulate systems to show more satisfactory results when compared to conventional dosage forms.

SUMMARY AND CONCLUSION

From the literature, it is observed that mucoadhesive formulations provide various advantages which are beneficial for controlled drug delivery systems for long-term use and provide a favourable area for systemic delivery.

Complete information about the mucoadhesive dosage forms may be helpful for the development of a novel drug delivery system. Mucoadhesive drug delivery systems have an application from different angles that includes the novel mucoadhesives, design of the device, mechanisms of mucoadhesion and permeation enhancers with the influence of larger molecules due to drug delivery, which will play a more important role. mucoadhesive drug delivery system is an alternative for various dosage forms as it improves the bioavailability of insoluble drugs and also avoids first-pass metabolism and prevents gastric degradation.

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