MUCOADHESIVE DRUG DELIVERY SYSTEM

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Abstract - Drug actions can be improved by developing new drug delivery systems, such as the mucoadhesive system. 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. The drugs which have local action or those which have maximum absorption in gastrointestinal tract (GIT) require increased duration of stay in GIT. Thus, mucoadhesive dosage forms are advantageous in increasing the drug plasma concentrations and also 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. As such, mucoadhesive systems have found wide use throughout many mucosal covered organelles for active ingredients delivery for local or systemic effect. The administration of drugs by the buccal route has several advantages over per oral administration such as quick action, improved patient compliance particularly with paediatric & geriatric patient. This review article aims to provide an overview of the various aspects of mucoadhesion, ideal drug candidates for mucoadhesive drug delivery system , mucoadhesive dosage forms. mucoadhesive materials, and finally various mucoadhesive drug delivery systems.

Keywords - Mucoadhesion, theories, Mucoadhesive Polymers, mucoadhesive dosage forms, Mucoadhesive Drugs.

I. INTRODUCTION

Since the early 1980s, the concept of mucoadhesion has gained considerable interest in pharmaceutical technology. Adhesion can be defined as the bond produced by contact between a pressure sensitive adhesive and a surface. 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. 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. The development of sustain release dosage form can achieve the aim of releasing the drug slowly for a long period but this is not sufficient to get sustained therapeutic effect. They may be cleared from the site of absorption before emptying the drug content. Instead, the mucoadhesive dosage form will serve both the purposes of sustain release and presence of dosage form at the site of absorption. In this regard, our review is high lighting few aspects of mucoadhesive drug delivery systems.

II. MECHANISMS OF MUCOADHESION

2.1 Mucus Membranes: [4]

Mucus membranes (mucosae) [Figure 1] 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 (the lamina propria) above which is an epithelial layer, the surface of which is made moist usually by the presence of a mucus layer. The epithelia may be either single layered (e.g. the stomach, small and large intestines and bronchi) or multilayered/stratified (e.g. in the esophagus, vagina and cornea). The former contain goblet cells which secrete mucus directly onto the epithelial surfaces; the latter contain, or are adjacent to tissues containing, specialized glands such as salivary glands that secrete mucus onto the epithelial surface. Mucus is present either as a gel layer adherent to the mucosal surface or as a luminal soluble or suspended form. The major components of all mucus gels are mucin glycoproteins, lipids, inorganic salts and water, the later accounting for more than 95% of their weight, making them a highly hydrated system. The major functions of mucus are that of protection and lubrication.

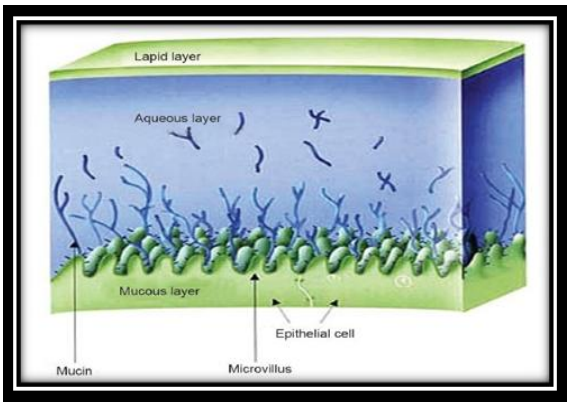


Figure 1: Mucus membrane structure

2.2 Mechanisms of Mucoadhesion: [5]

The mechanism of mucoadhesion is generally divided into two steps: the contact stage and the consolidation stage [Figure 2]. The first 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

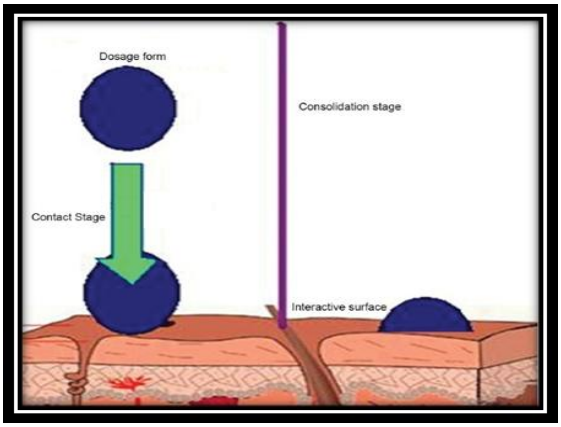


Figure 2: The process of contact and consolidation

In the consolidation step [Figure 2], 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 the 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. For this to take place, the mucoadhesive device has features favoring both chemical and mechanical interactions.

III. MUCOADHESION THEORIES

Mucoadhesion is a complex process and numerous theories have been proposed to explain the mechanisms involved. These theories include mechanical interlocking, electrostatic, diffusion interpenetration, adsorption and fracture processes. [4]

3.1 Wetting theory [4]

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 3]. The contact angle should be equal or close to zero to provide adequate spreadability. The spreadability coefficient, SAB, can be calculated from the difference between the surface energies γB and γA and the interfacial energy γAB, as indicated in the equation given below. This theory explains the importance of contact angle and reduction of surface and interfacial energies to achieve good amount of mucoadhesion.

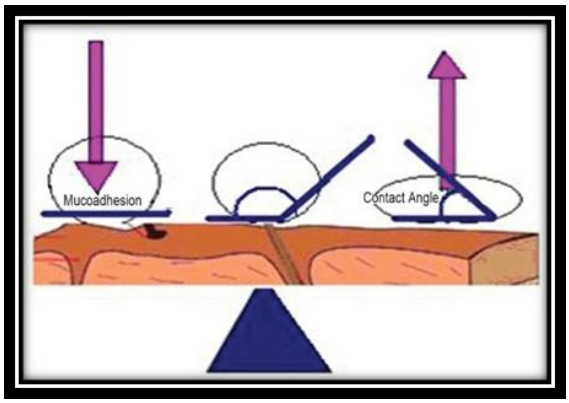


Figure 3: Influence of contact angle on mucoadhesion

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

3.2 Diffusion theory [5]

Diffusion theory describes the interpenetration of both polymer and mucin chains to a sufficient depth to create a semi-permanent adhesive bond [Figure 4]. It is believed that the adhesion force increases with the degree of penetration of the polymer chains. 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 bioadhesive bond lies in the range 0.2–0.5 μm. This interpenetration depth of polymer and mucin chains can be estimated by the following equation:

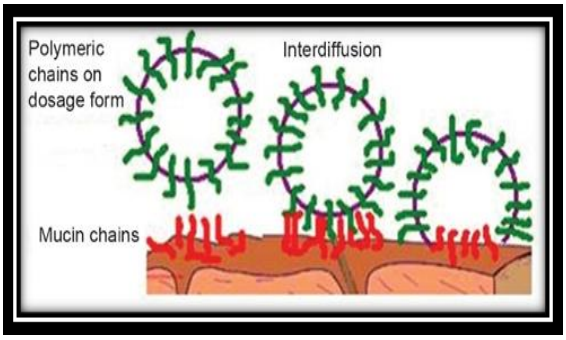


Figure 4: Secondary interaction between mucoadhesive device and of mucus

$l = (tDb)^{½}$ where t is the contact time and Db is the diffusion coefficient of the mucoadhesive material in the mucus. The adhesion strength for a polymer is reached when the depth of penetration is approximately equivalent to the polymer chain size. In order for diffusion to occur, it is important that the components involved have good mutual solubility, that is, both the bioadhesive and the mucus have similar chemical structures. The greater the structural similarity, the better is the mucoadhesive bond.

3.3 Fracture theory [4,5]

This is perhaps the most used theory in studies on the mechanical measurement of mucoadhesion. It analyzes the force required to separate two surfaces after adhesion is established. This force, sm, is frequently calculated in tests of resistance to rupture by the ratio of the maximal detachment force, Fm, and the total surface area, A0, involved in the adhesive interaction Sm=Fm/A0

Since the fracture theory [Figure 5] is concerned only with the force required to separate the parts, it does not take into account the interpenetration or diffusion of polymer chains. Consequently, it is appropriate for use in the calculations for rigid or semi-rigid bio adhesive materials, in which the polymer chains do not penetrate into the mucus layer

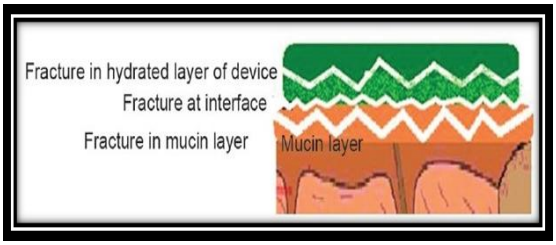


Figure 5: Fractures occurring for mucoadhesion

3.4 The electronic theory [6]

This theory describes adhesion occurring by means of electron transfer between the mucus and the mucoadhesive system, arising through differences in their electronic structures. The electron transfer between the mucus and the mucoadhesive results in the formation of double layer of electrical charges at the mucus and mucoadhesive interface. The net result of such a process is the formation of attractive forces within this double layer.

3.5 The adsorption theory [7,8]

In this instance, adhesion is the result of various surface interactions (primary and secondary bonding) between the adhesive polymer and mucus substrate. Primary bonds due to chemisorptions 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.

All these numerous theories should be considered as supplementary processes involved in the different stages of the mucus/substrate interaction, rather than individual and alternative theories. Each and every theory is equally important to describe the mucoadhesion process.

IV. IDEAL DRUG CANDIDATES FOR MUCOADHESIVE DRUG DELIVERY SYSTEM

4.1 Cardio vascular disease [9,10]

Hypertension, one of the major cardiovascular diseases, needs a lifelong therapy to remain under control. Most of the antihypertensive drugs like carvedilol, metoprolol, propranolol, isosorbide mononitrate etc. have low oral bioavailability and smaller half-life. Two main reasons for low bioavailability are poor aqueous solubility and high first pass metabolism. The buccal mucoadhesive route of drug delivery provides direct access to the systemic circulation through the internal jugular vein by bypassing the first pass metabolism, leading to high bioavailability. The dose of carvedilol, a model antihypertensive drug, is 25 mg twice a day; however, a lower effective dose is reported to be approximately 3.125 mg. Thus, by increasing the contact time and avoiding the first pass metabolism, a lower amount of drug can effectively produce the normal dose effect. Again, by sustaining the drug release, the frequent administration of drug can be avoided, thereby increasing the patient compliance.

4.2 Fungal/microbial infections [11,12]

Oral candidiasis is an opportunistic fungal infection caused by Candida albicans. These yeast infections are usually treated locally by application of gels or suspensions. Release of drugs from these preparations involves an initial burst of activity whose level rapidly declines to subtherapeutic concentrations. Thus, systemic antifungals such as fluconazole are usually preferred for treating oral candidiasis. The oral dose of fluconazole for the treatment of oral candidiasis (100 mg/day for 1 or 2 weeks) results in notable side effects varying from headache, nausea to liver dysfunction, and hepatic failure. Furthermore, oral fluconazole is reported to interact with a number of medications, including oral hypoglycemics, coumarin-type anticoagulants, cyclosporins, terfenadine, theophylline, phenytoin, rifampin, and astemizole. The pathogenic yeasts in oral candidiasis are usually detected in the superficial layers of the oral mucosa. Thus, the effectiveness of the systemic fluconazole may be partially topical through its concentration in oral fluids. The reported topical efficacy of fluconazole together with the adverse effects and drug interaction of systemic fluconazole justifies the design of MBDDS containing a small dose of fluconazole to increase the contact between the drug and the pathogenic yeast for a long time.

4.3 Migraine

Migraines are thought to occur when certain blood vessels in the brain become swollen (dilated). Drugs used for the treatment include the "triptan" group, comprising of sumatriptan, zolmitriptan, and

rizatriptan. These drugs work by helping blood vessels in the brain to return to normal size. It may also block pain signals in the brain. The model drug, sumatriptan is administered orally, in doses of 25, 50 or 100 mg as a single dose, nasally in doses of 10 mg or 20 mg and also subcutaneously as two 6-mg doses over 24 hours. However, a substantial proportion of patients suffer from severe nausea or vomiting during their migraine attack, and also low oral bioavailability (15%) due to high first-pass metabolism may make oral treatment unsatisfactory. Nasal route and subcutaneous route have their own limitations, like lower retention time for nasal solution and inability of self- administration for injectables, respectively. This justifies a need to develop an effective formulation, which allows the drug to directly enter the systemic circulation, bypassing the first-pass metabolism, thereby increasing bioavailability of sumatriptan succinate. Buccal mucosal route is one such alternative.

4.4 Nausea and vomiting

Ondansetron HCl, chosen as a model drug for treating postoperative nausea and vomiting associated with emetogenic cancer chemotherapy, possesses certain characteristics that a drug should have to get absorbed through buccal mucosa viz., biphasic solubility and low molecular weight. Moreover, the primary route of ondansetron clearance is by hepatic phase I metabolism, so its bioavailability may be improved when delivered through the buccal mucosal route. Patients may have frequent vomiting following chemotherapy and they may be unable to swallow a tablet to prevent vomiting. It justifies the need to develop a buccal patch/film of ondansetron hydrochloride, which increases patient compliance. Its bioavailability when administered by oral route is only 50% to 60% and its dose is low i.e., 4-8 mg; hence, it can be conveniently loaded onto a patch.

V. ADVANTAGES OF MUCOADHESIVE DRUG DELIVERY SYSTEMS:- [5,7,2]

- 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.
- Mucoadhesive-based topical and local systems have shown enhanced bioavailability.
- Mucoadhesive drug delivery gives rapid absorption and good bioavailability due to its considerable surface area and high blood flow.
- Drug delivery across the mucosa bypasses the first-pass hepatic metabolism and avoiding the degradation of gastrointestinal enzymes.
- Mucosal drug delivery system could be of value in delivering a growing number of high-molecular-weight sensitive molecules such as peptide and oligonucleotides.
- Drug delivery through the oral mucosa has gained significant attention due to its convenient accessibility. The buccal and sublingual routes are considered as the most commonly used rotes.
- Unlike conventional tablets, buccal tablets allow drinking, eating, and speaking without any major discomfort.
- MDDS offer several advantages over other controlled oral controlled release systems by virtue of prolongation of residence of drug in GIT.
- Targeting & localization of the dosage form at a specific site.
- High drug flux at the absorbing tissue.
- MDDS will serve both the purposes of sustain release & presence of dosage form at the site of absorption.
- Excellent accessibility.
- Painless administration.
- Low enzymatic activity & avoid of first pass metabolism.
- Prolongs the residence time of the dosage form at the site of absorption, hence increases the bioavailability.
- Excellent accessibility, rapid onset of action.
- Rapid absorption because of enormous blood supply and good blood flow rates.
- Drug is protected from degradation in the acidic environment in the git.
- Improved patient compliance.

VI. DISADVANTAGES OF MUCOADHESIVE DRUG DELIVERY SYSTEMS:- [5,7,8]

- Costly drug delivery system
- Medication administered orally do not enter the blood stream immediately after passage through buccal mucosa
- Mucoadhesive drugs adheres too tightly because it is undesirable to exert too much force to remove the formulation after use, otherwise the mucosa could be injured.
- Some patient suffers unpleasant feeling.
- Oral ingestions results in more exposure of a drug to the GI tract. One of the side effects of many antibiotics is the destruction of normal GI flora resulting in diarrhea and overgrowth with dangerous organisms such as C. difficile.
- The absorption of mucoadhesive drugs is adversely affected by the presence of food. Tetracyclines, in particular complicates the

administration of this class of antibiotics via the oral route
- Occurrence of local ulcerous effects due to prolonged contact of the drug possessing ulcerogenic property.
- One of the major limitations in the development of oral mucosal delivery is the lack of a good model for in vitro screening to identify drugs suitable for such administration.
- Patient acceptability in terms to taste and irritancy.
- Eating and Drinking is prohibited.

VII. MUCOADHESIVE POLYMERS:- [9]

Mucoadhesive polymers are water-soluble and water insoluble polymers, which are swellable networks, jointed by cross-linking agents. Mucoadhesive polymers that adhere to the musin epithelial surface can be conveniently divided into three broad classes:

1. Polymers that become sticky when placed in water and owe their mucoadhesion to stickiness.
2. Polymers that adhere through nonspecific, non covalent interactions that is primarily electrostatic in nature (although hydrogen and hydrophobic bonding may be significant)
3. Polymers that bind to specific receptor site on tile self-surface. All three polymer types can be used for drug delivery.

- **An ideal mucoadhesive polymer has the following characteristics: [8,6,]**

A mucoadhesion promoting agent or the polymer is added to the formulation which helps to promote the adhering of the active pharmaceutical ingredient to the oral mucosa.

- Polymer must have a high molecular weight up to 100.00 or more. This is necessary to promote the adhesiveness between the polymer and mucus.
- Long chain polymers-chain length must be long enough to promote the interpenetration and it should not be too long that diffusion becomes a problem.
- High viscosity.
- Degree of cross linking- it influences chain mobility and resistance to dissolution. Highly cross linked polymers swell in presence of water and retain their structure. Swelling favours controlled release of the drug and increases the polymer/mucus interpenetration
- Spatial conformation.
- Flexibility of polymer chain- this promotes the interpenetration of the polymer within the mucus network.
- Concentration of the polymer- an optimum concentration is required to promote the mucoadhesive strength. It depends however, on the dosage form.
- Optimum hydration- excessive hydration leads to decreased mucoadhesive strength due to formation of a slippery mucilage.
- The polymer and its degradation products should be nontoxic and should be non-absorbable from 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

- **Various mucoadhesive polymers can broadly be categorized as follow:**

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 methylacrylate.
4. Poly ethylene oxide.
5. Poly vinyl pyrrolidone.
6. Poly vinyl alcohol.

Natural polymers:

Tragacanth, Sodium alginate, Guar gum, Xanthum gum, soluble starch, Gelatin, Chitosan Mucoadhesive polymers can also classify into following categories: [8,4]

- Traditional non-specific first-generation mucoadhesive polymers:
- First-generation mucoadhesive polymers may be divided into three main subsets, namely:

1) Anionic polymers,
2) Cationic polymers,
3) Non-ionic polymers.

- Of these, anionic and cationic polymers have been shown to exhibit the greatest mucoadhesive strength. Consequently, such charged polymeric systems will now be examined in more depth.

Anionic polymers:

are the most widely employed mucoadhesive polymers within pharmaceutical formulation due to their high mucoadhesive functionality and low toxicity. Typical examples include poly (acrylic acid) (PAA) and its

weakly cross-linked derivatives and sodium carboxymethylcellulose (NaCMC). PAA and NaCMC possess excellent mucoadhesive characteristics due to the formation of strong hydrogen bonding interactions with mucin.
Polycarbophil (Noveon) and Carbomers (Carbopol), PAA derivatives have been studied extensively as mucoadhesive platforms for drug delivery to the GI tract.

Cationic Polymers:
Of the cationic polymer systems, undoubtedly chitosan is the most extensively investigated within the current scientific literature. Chitosan is a cationic polysaccharide, produced by the deacetylation of chitin, the most abundant polysaccharide in the world, next to cellulose. The intriguing properties of chitosan have been known for many years with many medicine.

Novel second-generation mucoadhesive:
The major disadvantage in using traditional nonspecific mucoadhesive systems (first generation) is that adhesion may occur at sites other than those intended. Unlike first-generation non-specific platforms, certain second-generation polymer platforms are less susceptible to mucus turnover rates, with some species binding directly to mucosal surfaces; more accurately termed ‘‘Cytoadhesives”.

Lectins:
The most widely investigated of such systems in this respect are lectins. Lectins belong to a group of structurally diverse proteins and glycoproteins that can bind reversibly to specific carbohydrate residues. After initial mucosal cell-binding, lectins can either remain on the cell surface or in the case of receptor mediated adhesion possibly become internalised via a process of endocytosis.

Thiolated polymers:
The presence of free thiol groups in the polymeric skeleton helps in the formation of disulphide bonds with that of the cysteine-rich sub-domains present in mucin which can substantially improve the mucoadhesive properties of the polymers (e.g. poly (acrylic acid) and chitosan).Various thiolated polymers include chitosan–iminothiolane, poly(acrylic acid)– cysteine, poly (acrylic acid)–homocysteine, chitosan–thioglycolic acid, chitosan–thioethylamidine, alginate–cysteine, poly (methacrylic acid)–cysteine and sodium carboxymethyl cellulose–cysteine.

Polyox WSR:
A class of high molecular weight polyethylene molecular weight polyethylene oxide homopolymers having the following properties,

- Water soluble hydrophilic nature
- Functional group for hydrogen bonding
- Biocompatible and non toxic
- High molecular weight

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. [2,4]

VIII. DOSAGE FORMS:- [5,6,7]

Depending on the dosage form and route, mucoadhesives may be used for either local or systemic administration of pharmaceuticals. An overview on the mucoadhesive properties ofmucoadhesives is provided by Vjera Grabovac and Andreas Bernkop Schnürch. The bioavailability of such drugs is affected by many factors unique to each route of application.

8.1 Tablets
Tablets are small, solid dosages suitable for the use of mucoadhesive coatings. The coating may be formulated to adhere to a specific mucosa, enabling both systemic and targeted local administration. Tablets are generally taken enterally, as the size and stiffness of the form results in poor patient compliance when administered through other routes.



Figure 6: Disk-shaped tablets.

8.2 Patches
In general patches consist of three separate layers that contribute and control the release of medicine. The outer impermeable backing layer controls the direction of release and reduces drug loss away from the site of contact. It also protects the other layers and acts as a mechanical support. The middle reservoir layer holds the drug and is tailored to provide the specified dosage. The final inner layer consists of the mucoadhesive, allowing the patch to adhere to the specified mucosa.



Figure 7: Common Patch System.

8.3 Gels

As a liquid or semisolid dosage, gels are typically used where a solid form would affect the patient's comfort. As a trade-off, conventional gels have poor retention rates. This results in unpredictable losses of the drug, as the non-solid dosage is unable to maintain its position at the site of administration. Mucoadhesives increase retention by dynamically increasing the viscosity of the gel after application. This allows the gel to effectively administer the drug at the local site while maintaining the comfort of the patient.

8.4 Solutions

These dosage forms are commonly used to deliver drugs to the eye and nasal cavity. They often include mucoadhesive polymers to improve retention on dynamic mucosal surfaces. Some advanced eye drop formulations may also turn from a liquid to a gel (so called in situ gelling systems) upon drug administration. For example, gel-forming solutions containing Pluronics could be used to improve the efficiency of eye drops and provide better retention on ocular surfaces.

IX. ROUTES OF ADMINISTRATION FOR MUCOADHESIVE DRUG DELIVERY SYSTEM [7,8,3]

Mucosa or the mucus membrane is the moist tissue that lines organs and body cavities such as mouth, gut, rectum, genital area, nose, and eye lid. Anatomical differences of the mucus membrane at varying body locations are given in .

OROMUCOSAL:

With a 0.1-0.7 mm thick mucus layer, the oral cavity serves as an important route of administration for mucoadhesive dosages. Permeation sites can be separated into two groups: sublingual and buccal, in which the former is much more permeable than the latter. However, the sublingual mucosa also produces more saliva, resulting in relatively low retention rates. Thus, sublingual mucosa is preferable for rapid onset and short duration treatments, while the buccal mucosa is more appropriate for longer dosage and onset times. Because of this dichotomy, the oral cavity is suitable for both local and systemic administration.

NASAL:

With an active surface area of 160 cm2, the nasal cavity is another noteworthy route of mucoadhesive administration. Due to the sweeping motion of the cilia that lines the mucosa, nasal mucus has a quick turnover of 10 to 15 minutes. Because of this, the nasal cavity is most suitable for rapid, local medicinal dosages. Additionally, its close proximity to the blood-brain barrier makes it a convenient route for administering specialized drugs to the central nervous system. Gels, solutions, and aerosols are common dosage forms in the nasal cavity. However, recent research into particles and microspheres have shown increased bioavailability over non-solid forms of medicine largely due to the use of mucoadhesives.

OCULAR :

Within the eye, it is difficult to achieve therapeutic concentrations through systemic administration. Often, other parts of the body will reach toxic levels of the medication before the eye reaches the treatment concentration. Consequently, direct administration through the fibrous tunic is common. This is made difficult due to the numerous defense mechanisms in place, such as blinking, tear production, and the tightness of the corneal epithelium. Estimates put tear turnover rates at 5 minutes, meaning most conventional drugs are not retained for long periods of time. Mucoadhesives increase retention rates, either by enhancing the viscosity or bonding directly to one of the mucosae surrounding the eye.

INTRAVESICAL :

Intravesical drug administration is the delivery of pharmaceuticals to the urinary bladder through a catheter. This route of administration is used for the therapy of bladder cancer and interstitial cystitis. The retention of dosage forms in the bladder is relatively poor, which is related to the need for a periodical urine voiding. Some mucoadhesive materials are able to stick to mucosal lining in the bladder, resist urine wash out effects and provide a sustained drug delivery.[15][16]

X. TECHNIQUES TO EVALUATE MUCOADHESION

The techniques used to evaluate mucoadhesive dosage forms include the followings:-

A. IN VITRO METHODS.
1. Tensile strength measurement.
2. Shear strength measurement.
3. Modified physical balance.
4. Detachment force method.

5. Micro balance method.
6. Ex – vivo mucoadhesion.
7. Falling film method.
8. Swelling index.
9. Wash off method.
10. Colloidal gold staining, And other methods.

B. IN VIVO METHODS
C. IN VITRO AS WELL AS IN VIVO METHOD

1. TENSILE STRENGTH MEASUREMENT

a. WILHELMY PLATE TECHNIQUE:

The Wilhelmy plate technique is traditionally used for the measurement of dynamic contact angles. The instrument measures the bioadhesive force between mucosal tissue and the dosage form

METHOD: - A small glass plate (2×5cm) was coated with 1% w/v of the mucoadhesive agent. The mucus gel was taken from goat intestine kept in a suitable container, where the above mentioned glass plate can be kept in contact with gel in a balanced condition and the temperature was maintain at30°C. Nylon thread was attached at one end of the glass plate. Provision was given to raise the weight at the other end. At specified intervals, weight was added to detach the coated glass plate from gel and the force required to pull the plate out of the gel was determined under experimental condition. Six plates were tested for each material and the average weights required were calculated.



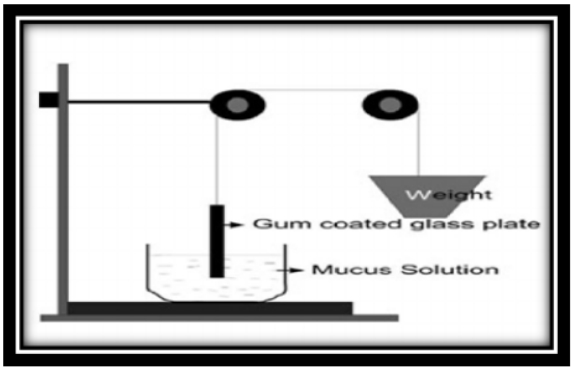


Figure. 8: Instrument of Wilhelmy Plate Technique.

b) TENSILE TESTER:

It is used to measure the adhesive force of the polymer complexes with a plastic (PolyVinylChloride) plate. Polymers and plastic plates were cut with the area 1 cm sq. (thickness: 0.8 mm). The polymer was prewetted with water and placed on the surface of the plastic plate. They were kept in contact with the plate under the force of "finger tip for 2 min before the measurement. The peak force required to detach the polymer from the plastic plate was measured.

C) ELECTROMAGNETIC FORCE TRANSDUCER (EMFT):

The electromagnetic force transducer (EMFT) is a remote sensing instrument that uses a calibrated electromagnet to detach a magnetic loaded polymer microsphere from a tissue sample. It has the unique ability to record simultaneously the tensile force information as well as high magnification video images of mucoadhesive interactions at near physiological conditions. The EMFT measures tissue adhesive forces by monitoring the magnetic force required to exactly oppose the mucoadhesive force.

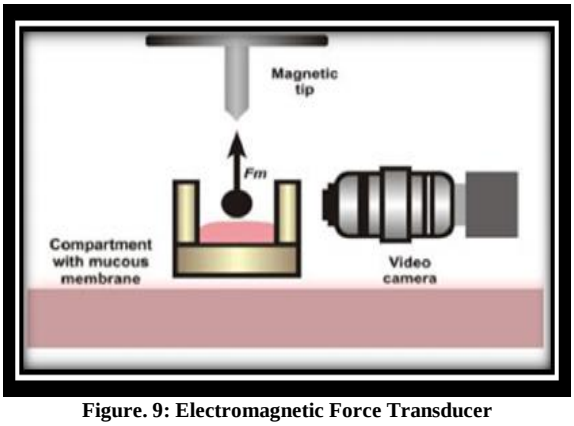


Figure. 9: Electromagnetic Force Transducer

2. SHEAR STRESS MEASUREMEN:

The shear stress measures the force that causes a mucoadhesive to slide with respect to the mucus layer in a direction parallel to their place of contact of adhesion.

PRINCIPLE:- Adhesion tests based on the shear stress measurement involve two glass slides coated with polymer and a film of mucous. Mucous forms a thin film between the two polymer coated slides, and the test measures the force required to separate the two surfaces.[42,44]

METHOD:- Two smooth, polished plexi glass box were selected; one block was fixed with adhesive araldite on a glass plate, which was fixed on levelled table. The level was adjusted with the spirit level. To the upper block, a thread was tied and the thread was passed down through a pulley. At the end of the thread a pan was attached into which the weights can be added.

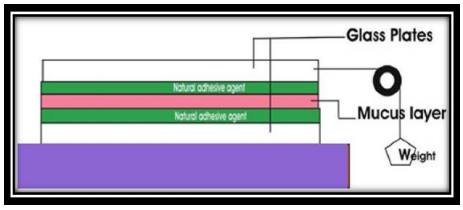


Figure. 10: Shear Stress Measurement.

3. MODIFIED PHYSICAL BALANCE

A modified balance method was used to determine the ex vivo mucoadhesive strength. Fresh sheep buccal mucosa or goat stomach mucosa or rat stomach mucosa or porcine gastric mucosa was obtained from a local slaughterhouse and used within 2 hours of slaughter. The mucosal membrane was separated by removing underlying fat and loose tissues. The membrane was washed with distilled water and then with proper medium at 37°C.The sheep buccal mucosa was cut into pieces and washed with proper medium. A piece of buccal mucosa was tied to the glas vial, which was filled with phosphate buffer. The glass vial was tightly fitted into a glass beaker (filled with proper medium, at 37°C ± 1°C) so that it just touched the mucosal surface. The buccal tablet was stuck to the lower side of a rubber stopper with adhesive. The two sides of the balance were made equal before the study, by keeping a 5-g weight on the right-hand pan. A weight of 5 g was removed from the right-hand pan, which lowered the pan along with the tablet over the mucosa. The balance was kept in this position for 5 minutes contact time. The water (equivalent to weight) was added slowly with an infusion set (100 drops/min) to the right-hand pan until the tablet detached from the mucosal surface. This detachment force give the mucoadhesive strength of the buccal tablet in grams. The weight of water required to detach mucoadhesive tablet from stomach mucosa was noted as mucoadhesive strength in grams. From the mucoadhesive strength following parameter was calculated.

Force of adhesion(N)=bioadhesive strength(gm)/1000x9.8

Bondstrength (N/m2)=force of adhesion(N)/surface area of tablet(m2)

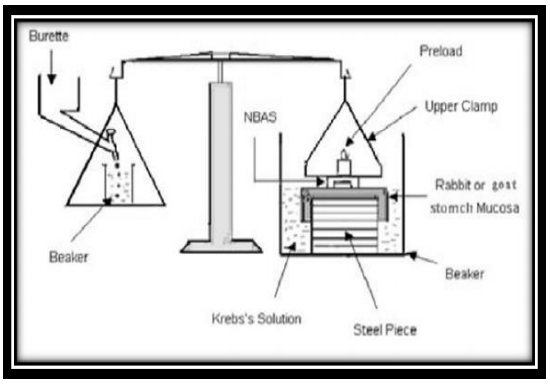


Figure. 11: Modified Physical Balance

4. DETACHMENT FORCE METHOD

This method is based on the evaluation of mucoadhesive strength, i.e. the force required to break the binding between the model membrane and the mucoadhesive. Depending on the direction in which the mucoadhesive is separated from the substrate, it is possible to obtain the detachment, shear, and rupture tensile strengths.

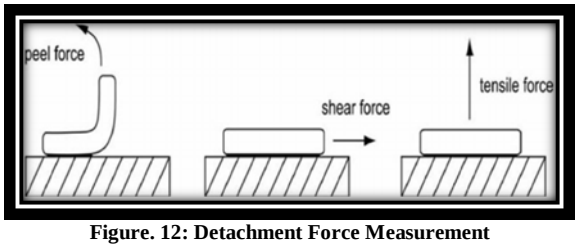


Figure. 12: Detachment Force Measurement

METHOD:- To characterize the mucoadhesive strength, the detachment force method was used. Mouth of a glass vial fixed with a fresh section of animal tissue from fundus portion of goat intestine, facing mucosal side out and kept in simulated gastric fluid (pH 1.2) without pepsin. Kept another portion of mucus side of exposed tissue over a rubber stopper and secured with an aluminum cap.The mucoadhesive tablet placed on the exposed mucous layer is kept in contact with the former tissue which is connected with a pan in which the weight can be raised. At specific intervals, applied weight and the force required to detach was measured to determine mucoadhesive strength

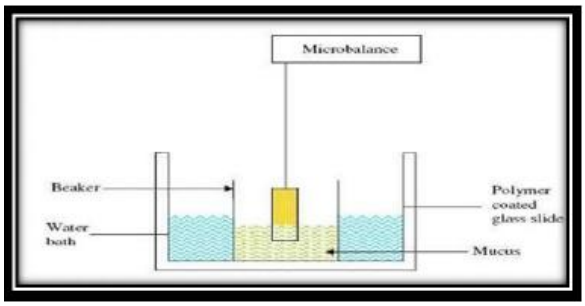


Figure. 13: Mucoadhesive testing system by the detachment force method

5. MICROBALANCE METHOD

The microforce balance technique, is used to measure the specific adhesion force of microparticles. This involves the use of a micro tensiometer and a microforce balance, 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.

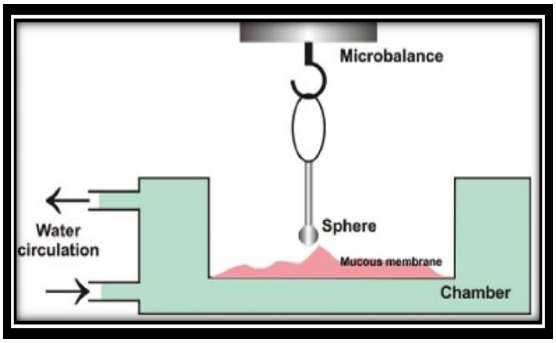


Figure. 14: Microbalance Method for measuring Mucoadhesion.

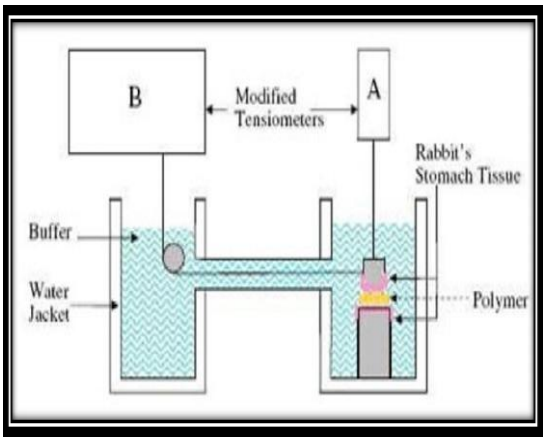


Figure. 15: Modified Dual Tensiometer, for measuring Mucoadhesion.

6. EX VIVO MUCOADHESIVE STRENGTH DETERMINATION

This technique is specific for microspheres and in this technique four number of Albino rats were fasted overnight and then 25 number of microspheres (N0) were ingested to these rats through an oral feeding needle. These were then sacrificed at an interval of 0, 4, 8, 12 hours respectively to isolate their stomach and intestine region. The stomach and intestine regions are cut and opened longitudinally to note the number of microspheres adhering to these regions (NS). This ultimately gives the adhesive strength of the formulation which is calculated using the formula given below

% adhesive strength = (Ns/No)*100.

Where:

No =Number of microspheres

Ns = Number of microspheres adhered.

7. FALLING LIQUID FILM TECHNIQUE

In this technique male Albino rats (200-250g) were sacrificed and their intestine region was isolated. Then from the intestine region, jejunum part was separated and cut longitudinally. This separated portion was placed on the semi cylindrical Plexi glass support, with a temperature controlled at 37 ºC and is washed with saline solution for 30 minutes at the rate of 30ml /minute. Then 25 number (N0) of counted mucoadhesive microspheres are hydrated with little amount of water and are dispersed on the mucosal tissue and left on it for 20 minutes for interaction with mucosal surface. During this period, whole system was placed in a constant humidity chamber which was adjusted to 90% relative humidity. At the end the system was washed with phosphate buffer pH 7.2 for 20 minutes at the rate of 22ml / minute and the number of microspheres remaining on the mucosal surface (NS) are counted. The adhesive strength can be determined using the formula given below :-

% adhesive strength = (Ns/No)*100 No =Number of microspheres Ns = Number of microspheres adhered.

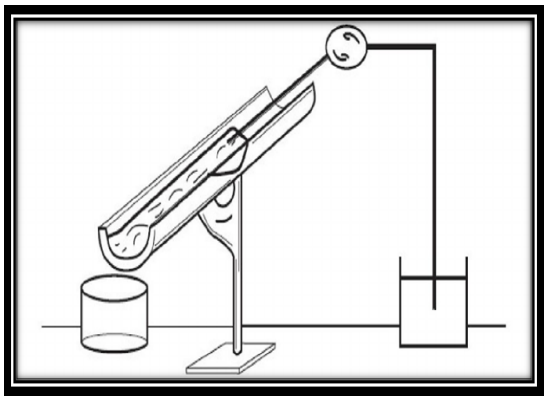


Figure.16: Falling Liquid Film Technique.

8. SWELLING INDEX;

Swelling of excipients of mucoadhesive dosage form involves the absorption of a liquid resulting in an increase in weight and volume. Liquid uptake by the particle may be due to saturation of capillary spaces within the particles or hydration of macromolecule. The liquid enters the particles through pores and bind to large molecule, breaking the hydrogen bond and resulting in the swelling of particle. The extent of swelling can be measured in terms of% weight gain by the mucoadhesive dosage form.

METHOD: One mucoadhesive dosage form is weighed and placed in a beaker containing 200 ml of buffer media. After each interval the dosage form is removed from beaker and weighed again up to 8 hours. The swelling index is calculated using following formula.

Swelling Index (S.I.) = (Wt-Wo)/Wo

Where, S.I. = Swelling index,

Wt = Weight of the dosage form at time t,

Wo = Weight of the dosage form before placing in the beaker .

9. WASH –OFF TEST

Wash-off test is used to determine the mucoadhesive property of dosage form. In this test, the mucosal tissue is attached onto a glass slide with the help of a double-sided cyanoacrylate tape. Thereafter, the dosage form is put on the surface of the tissue (exposed mucosal surface) with the subsequent vertical

attachment of the system into the USP tablet disintegrator apparatus, which contains 1 L of physiological solution maintained at 370C. The operation of the equipment gives an up-and-down movement to the tissue-delivery matrix system. In this study, the time for the complete detachment of the delivery system from the mucosal layer is determined.

% adhesive strength = (Ns/No)*100.

Where No = Initial number of the dosage form spread over the mucosal surface.

where: Ns = Number of the dosage form detaching from the mucosal surface.

10. COLLOIDAL GOLD STAINING METHOD

Colloidal gold staining was proposed in 1989 for bioadhesive hydrogels Interactions with mucin-gold conjugates resulted in the development of a red colour on the hydrogel surface. A direct-staining method to evaluate polymer adhesion to human buccal cells, following exposure to aqueous polymer dispersions The polymer in a form of strip is incubated with colloidal gold –mucin conjugate and after a rinsing procedure the absorbance of strips is measured.

METHOD:-

This technique employs red colloidal gold particles, which are stabilized by the adsorbed mucin molecule by forming mucin–gold conjugates. Upon interaction with mucin–gold conjugates, bioadhesive hydrogels develop a red colour on the surface. Thus, the interaction between them can easily be quantified, either by the measurement of the intensity of the red colour on the hydrogel surface or by the measurement of the decrease in the concentration of the conjugates from the absorbance changes.

XI. FUTURE PROSPECTS AND CHALLENGES:- [11]

Research in buccal drug delivery has revealed remarkable growth and advances in the past few decades. The buccal mucosa holds a great promise for systemic delivery of orally inefficient drugs as well as a feasible and attractive alternative for non-invasive delivery of potent peptide and protein drug molecules. Mucoadhesive drug delivery systems offer unique carrier system for many pharmaceuticals and can be modified to adhere to any mucosal tissue, including those found in oral cavity, gastrointestinal tract, vagina, eye etc. One of the areas of interest is the novel buccal adhesive delivery system, where the drug delivery is directed towards buccal mucosa by protecting the local environment. In spite of significant advances in the field of mucoadhesion, there is no consensus between scientists in relation to the mechanisms of the interaction between materials and components of mucosal tissue.

XII. CONCLUSION

In conclusion, the mucosal adhesive dosage forms are now on the starting line. The advantages are tremendous which make further study in this field extremely important. The formulation of these drug delivery systems depends on the development of suitable polymers with excellent mucosal adhesive properties, stability and biocompatibility. Many mucoadhesive drug delivery systems are already in the market as discuss above . Moreover research in this field is becoming very active. Therefore we hope that in the near future these dosage forms will be a reality for use and become an alternative to controlled release dosage for the treatment of both tropical as well as systematic diseases.

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