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A Detailed Discussion on Mucoadhesive Drug Delivery System

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Abstract: *Two surfaces that cling to one another—a mucous membrane being one of them—are said to exhibit mucoadhesion. In the pharmaceutical sciences, this has been of interest to improve the distribution of drugs locally or to introduce challenging molecules (such as proteins and oligonucleotides) into the bloodstream. The carbomers and chitosans are two well-known examples of mucoadhesive materials, which are hydrophilic macromolecules with several hydrogen bond-forming groups. It has been suggested that there are two steps to the mechanism underlying mucoadhesion: the contact (wetting) stage and the consolidation stage (the formation of sticky contacts). Every application is different when it comes to the proportional relevance of each step. Adsorption, for instance, is a crucial step if the dosage form cannot be applied directly to the target mucosa, and consolidation is a crucial step if the formulation is subjected to high dislodging forces. Overhydration of a dose form, mucus turnover, or epithelia will all eventually lead to adhesive joint failure. Present research is yielding new mucoadhesive materials with ideal adhesive qualities, which should expand the technology's possible uses. The mucosal membrane, mucoadhesion mechanism, hypotheses, factors influencing mucoadhesion, dosage forms for mucoadhesive, evaluation techniques, and their application are all covered in this review.*

Key words*: mucoadhesion, mucus layer, mechanism, theories, mucoadhesive dosage forms*

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I. Introduction:

The oral drug delivery system is the most widely used route of administration because ofease of administration of drugs and higher patients'compliance. The bioavailability of orallyadministered drugs is subjective by various factors. One of the most significant parameters is residence time (RT) of the dosage as most of the conventional dosage forms have limits relating to fast gastric emptying time. Mucoadhesive dosage form is a type of novel drug delivery system which can stay in contact of the mucosal lining for a prolong period of time due to its bio adhesive property and improve the residence time of the drugs. Mucoadhesive drug delivery system helps to improve the bioavailability of drugs at the site of action for prolongperiod of time at a controlled manner of drug releases(Boddupalli et al. 2010).

To maintain drug concentration in the therapeutically effective range at the site of action by conventional drug delivery system, the drugs need to be administered numerous times a day, which is incompatible to patients and may lead to appearance of drug toxicity. To overcome the above limitation of conventional drug delivery system, mucoadhesive drug delivery system is an emerging tool in the field of novel drug delivery system.

Many problems are arising during the preparation of controlled drug delivery system for better absorption and enhanced bioavailability. The process of drug absorption from GIT is complex and is subjected to several factors. It is recognized that the extent of GIT drug absorption is correlated to residence time at the intestinal mucosa region(Pant, Badola, and Division 2016). Mucoadhesive drug delivery system can persist in the GI region for many hours and therefore significantly improved the residence time of the drugs at mucosal region(Ugwoke et al. 2005).Extended gastric retention increases bioavailability, decrease drug waste and increases the solubility of drugs which are less soluble in high pH environment.

Many techniques, such as the hydrodynamically balanced system (HBS), floating drug delivery system, low density system, raft system with alginate gels, mucoadhesive or bio-adhesive system, high density system, super porous hydrogel, and magnetic system, are currently used to prepare a successful specific drug delivery system(Tripathi et al. 2019).Modern technological advancements have made it possible to create dosage forms

that can be administered orally, topically, parenterally, rectally, nasally, ocularly, vaginally, etc. Out of all these routes, oral route is considered as the best preferred and practiced way of drug delivery due to

- Ease of administration
- Ease of production
- More flexibility in designing
- Low cost

Drugs taken orally are absorbed mostly through the gastrointestinal tract (GIT), primarily from the stomach and intestine. Medications that enter the stomach and have a localized effect ought to remain there for an extended period of time(Kharia et al. 2011), which is hard to happen in case of available conventional dosage forms like tablets, capsules etc due to gastric emptying(Sarawade, Ratnaparkhi, and Chaudhari 2014).Many factors, such as temperature, meal viscosity, volume, and composition, emotional state, pH of the stomach area, posture, and so on, affect how quickly dosage forms are gastric emptied. (Bhardwaj, Kumar Sharma, and Malviya 2011).

The distribution of medication to moist cavities, such as the bladder, vagina, and mouth lining, is known as mucosal drug delivery. This makes it possible to treat diseases locally with high medication concentrations and fewer systemic negative effects.(Davis et al. 2005).These are the systems in which formulation interact with mucosal layer and increase the residential time of formulation at the site of administration for better absorption(Smart 2005). These systems are designed to provide Controlled/Sustained Release of drug at the site of administration.

1.1 Mucosal membrane:

Mucus membranes are moist surface lining of the wall of most of the body cavities such as gastrointestinal tract and respiratory tract. They consist of connective tissue layer (the lamina propria), an epithelial layer, and mucus layer. The epithelial layer may be singled layer (stomach, small and large intestine, bronchi) or multi layered /stratified (oesophagus cornea, vagina,). It also contains goblets cell which secretes mucus directly onto the surface of epithelial tissue layer. Mucus layer contains specialised secretory glands such as salivary glands which secretes mucus directly onto the epithelial layer(Hooda, Tripathi, and Kapoor 2012). Mucus is a translucent and viscid secretion which forms a thin, continuous gel blanket adherent to the mucosal epithelial surface. The average thickness of this layer varies from about 50 to 450 µm in human(Ahuja, Khar, and Ali 1997). Mucus is present as either gel layer adherent to mucosal surface or luminal soluble or suspended form(Khanvilkar, Donovan, and Flanagan 2001). Mucus is usually consisting of following components

- Water (95%)
- Mucin glycoproteins and lipid (0.5-5%)
- Mineral salts (1%)
- Free proteins (0.5-1%) (12)

Mucus glycoproteins are high molecular proteins and is attached with oligosaccharides units (8 to 10 monosaccharides residues)(Strous and Dekker 1992).

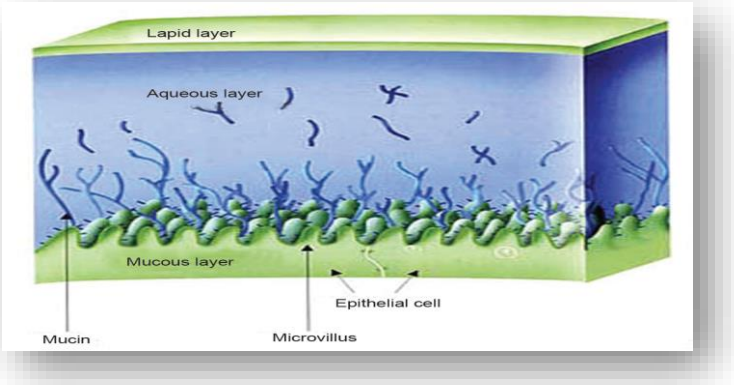

Figure1: Structure of mucus layer

Mucosal drug delivery system can be delivered via different routes:

- Oral route
- Buccal route
- Nasal route

- Vaginal route
- Rectal route

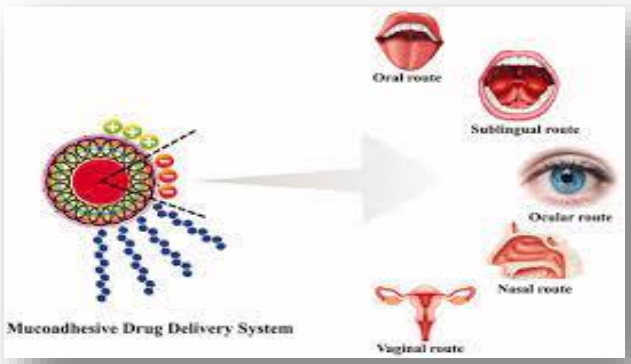

Figure 2 : Routes of administration

1.2 Advantages: Mucoadhesive drug delivery system provides several advantages over other controlled drug delivery system

- Enhances the residential time of the drug at the site of drug absorption and improve the drugs absorption
- Painless and ease of drug administration
- Enhance the bioavailability of the drug
- Lowers the frequency of drug administration
- Provides site specific drug delivery and reduces the side effect
- Protect the drug from degradation due to pH sensitive environment
- Improve the therapeutic performance of drug
- Low enzymatic activity and first pass metabolism was avoided
- Non-invasive method of drug administration

1.3 Disadvantages:

- If MDDS are adhere too tightly then it will be difficult to remove and injury of mucosal lining may happen
- Patient may suffer from unpleasant feeling
- Eating and drinking may be restricted
- Expensive as compared to other formulation

1.4 Ideal characteristics of mucoadhesive polymers:

• The polymer and its degradation products should be nontoxic and should be non-absorbable from the GI tract.

- It should be non-irritant to the mucus 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 easy incorporation of the drug and should offer no hindrance to its release.
- The polymers must not decompose on storage or during the shelf life of the dosage 0form.
- The cost of polymer should not be high so that the prepared dosage form remains competitive.
- 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 weigh

II. Mechanism of mucoadhesion:

The process by which specific macromolecules adhere to the mucous layer surface is still poorly understood. To enhance surface contact and create intimate contact, mucoadhesive must spread throughout the substrate, which will aid in the mucus's chain's diffusion. A strong mucoadhesion requires the dominance of the attractive force over the repulsive force.(Carvalho et al. 2010). The mechanism of mucoadhesion is generally divided into two steps:

- The contact stages
- The Consolidation stages

During the contact stage, the mucoadhesive and mucus membrane come into contact, and the formulation begins to spread and swell to make contact with the mucus layer. Mucoadhesive compounds are activated by moisture during the consolidation stage.(Boddupalli et al. 2010). The system becomes more malleable when there is moisture present, which enables the mucoadhesive molecules to separate and form weak hydrogen and van der Waals bonds. The mucoadhesive molecules and the mucus's glycoproteins interact with one another through chain penetration and the formation of secondary bonds, according to the diffusion theory. The mucoadhesive device contains properties that promote both chemical and mechanical interactions in order for this to happen. For instance, molecules with high molecular weight, flexible chains, anionic surface charge, hydrogen bond building groups (-OH, -COOH), and surface-active characteristics that aid in spreading throughout the mucus layer(Carvalho et al. 2010), can present mucoadhesive properties. Essentially there are theories to explain the mucoadhesion mechanism

1. Contact stages
2. Consolidation stages

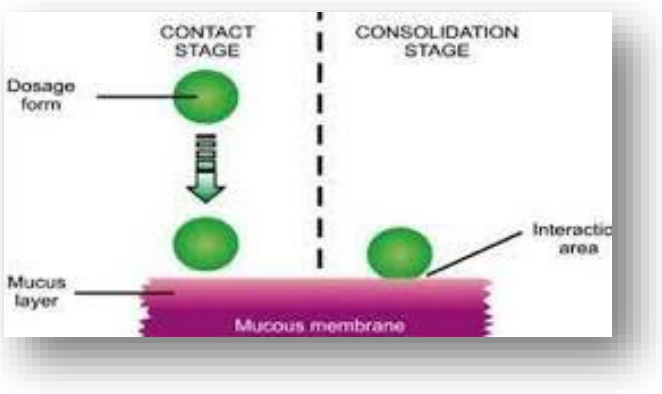

Figure 3: Mechanism of mucoadhasion

III. Theories of mucoadhesion:

Since mucoadhesive drug delivery is being studied for a long period of time since the 1980s, an overall knowledge has been procured. Till date a various number of mechanisms taking place at drug delivery system – mucus interface and the factors affecting the mechanistic pathways have been investigated by scientist. The different theories involved in mucoadhesion have been explained below-

3.1Wettability theory: The wetting theory is primarily involved in liquid or low viscous mucoadhesive system. It describes the ability of any mucoadhesive system to spread over the biological surface thus it gives an accountability of "spreadability" of the drug delivery system. The spread ability over the surface can be found by measuring the contact angle. This states that, lower the contact angle, greater the ability to spread over the surface. The contact angle should be zero or close to zero for adequate spreading over the surface(Boddupalli et al. 2010). The spreadability coefficient, *SAB*, can be calculated from the difference between thesurface energies γB and γA the interfacial energy γAB, as indicated in the equation given below(Eq-1)

$SAB = \gamma B - \gamma A - \gamma AB$ ----------1

3.2Adsorption theory: Adhesion is the result of interactions (primary and secondary bonding) between the adhesive polymer and mucus substrate. Primary bonds due to chemisorption's result in adhesion due to ionic, covalent and metallic bonding(Andrews, Laverty, and Jones 2009), which is generally undesirable due to their permanency. Secondary bonds are generally formed due to van der Waals forces, hydrophobic interactions and hydrogen bonding.

3.3. Diffusion theory: This theory describes the interpenetration of both the mucoadhesive polymer and mucin chain to a sufficient depth to form a semi-permanent adhesive bond. It is believed that the adhesive force is directly proportional to degree of penetration of polymer chain. This penetration rate depends on the diffusion coefficient, flexibility and nature

of the mucoadhesive chains, mobility and contact time(Sedley 2009). According to the literature, the depth of interpenetration required to produce an efficient bioadhesive bond lies in the range 0.2–0.5 μm. The required time (t) for the highest degree of adhesion during interpenetration among two substrates can be calculated using L (interpenetration depth) and Db (the coefficient of diffusion). (Eq: 2)
t=L2/Db …….2

3.4 Fracture theory: Fracture theory attempts to relate the difficulty of separation of two surfaces after adhesion. Fracture theory equivalent to adhesive strength is given by: (Eq: 3)

G = (E€/L) ½ ……3

where E is the Young's modulus of elasticity, € is the fracture energy, and L is the critical crack length when two surfaces are separated(Ahuja, Khar, and Ali 1997) .

3.5 Electronic theory: This theory suggests that electron transfer occurs upon contact of mucoadhesive surfaces due to differences in their electronic structure. This is proposed to result in the formation of an electrical double layer at the interface, with subsequent adhesion due to attractive forces(Smart 2005).

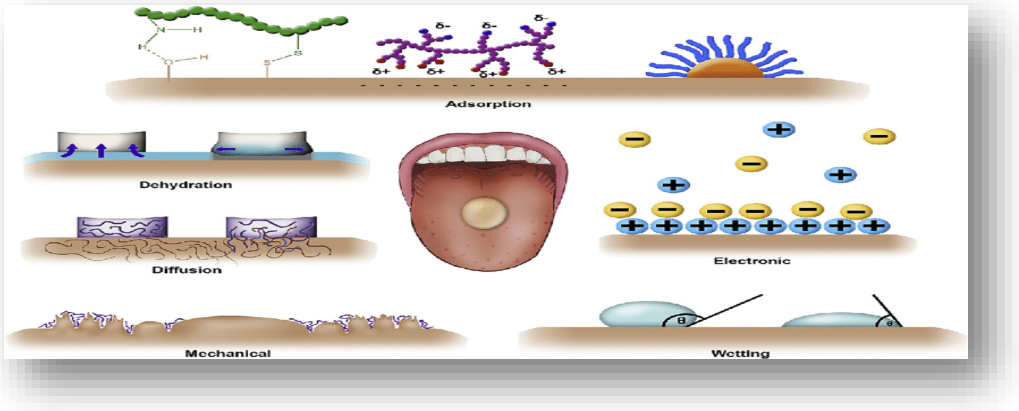

Figure 4 Theories of mucoadhesion

IV. Factors affecting mucoadhesive drug delivery system:

4.1 Polymers related factors:

a. **Molecular weight:**The mucoadhesive strength of a polymer increases with molecular weights above 100,000. Direct correlationbetween the mucoadhesive strength of polyoxymethylene polymers and their molecular weights lies in the range of 200,000–7,000,000(Mukhopadhyay et al. 2018). The interpenetration of polymer molecule is favourable for low molecular weight and polymer with lower molecular weight will form weak gels and readily dissolve whereas entanglement is favour for higher molecular weight polymers(Leitner, Marschütz, and Bernkop-Schnürch 2003).

b. **Flexibility of polymer chain:** Mucoadhesion starts with the diffusion of polymer chain in the interfacial region. To achieve desire entanglement with the mucus, polymer chain should contain a substantial degree of flexibility. this parameter is believed to be important for interpenetration and entanglement, allowing binding groups to come together as water soluble polymers become crosslinked and mobility of the chain get reduced.

c. **Concentration of polymer:** The importance of this factor lies in the formation of strong bond between bio adhesive polymer and the mucus. This can be explained by available polymer chain length for penetration into the mucus membrane. When the concentration of polymer is too low, then the number of penetrating polymers is less and the interaction between the polymer and mucus is unstable. In general, the number of penetrating polymer and strength of bio adhesion is directly proportional the concentration of polymer. However, for each polymer, there is a critical concentration, above which the polymer produces an "unperturbed" state due to a significantly coiled structure(Salamat-Miller, Chittchang, and Johnston 2005).

d. **Cross linking density:**The average pore size, the number and average molecular weight of the cross-linked polymers, and the density of cross-linking are three important and inter-related structural parameters of a polymer network. Therefore, it seems reasonable that with increasing density of crosslinking, diffusion of water into the polymer network occurs at a lower rate which, in turn, causes an insufficient swelling of the polymer and a decreased rate of interpenetration between polymer and mucin(Andrews, Laverty, and Jones 2009).

e. **Hydrogen bonding capacity:**Another crucial element for a polymer's mucoadhesion is hydrogen bonding. Desired polymers need to have functional groups that can create hydrogen bonds in order for mucoadhesion to happen. The existence of (COOH, OH etc.) is what allows for the formation of hydrogen bonds. To increase the polymer's capacity for hydrogen bonding, it must be flexible. Good hydrogen bonding ability is exhibited by polymers such polyvinyl alcohol, hydroxylated methacrylate, poly (methacrylic acid), and all of their co-polymers.

4.2 Physiological factors

a. **Mucin turnover:**High mucin turnover is not beneficial for mucoadhesive property because of following reason: the high mucin turnover limits theresidence time of mucoadhesive drug delivery system as it detaches from mucin layer, even though it has good bio adhesive property(Saraswathi, Balaji, and Umashankar 2013). High mucin turnover may produce soluble mucin molecule; thus, molecule interact with polymer before they interact with mucin layer. hence there will not besufficient mucoadhesion.

b. **Diseases state:** The physicochemical property of mucus may alter during some disease state, such as common cold, gastric ulcers, ulcerative colitis, bacterial and fungal infections etc. Thus, alteration in the physiological state may affect the bio adhesive property.

c. **Rate of renewal of mucosal cells:** Rate of renewal of mucosal cells varies extensively from different types of mucosa. It limits the persistence of bioadhesive systems on mucosal surfaces.

d. **Tissue movement:**When food and liquids are consumed, tissue moves around in the GIT during peristalsis, which impacts the mucoadhesive system, particularly when a gastro-retentive dosage form is used.

4.3 Biological environment related factors:

a. **pH of polymer-substrate interface:**The charge on the surface of polymers and mucus is influenced by pH. Because of variations in the dissociation of functional groups on the carbohydrate moiety and the amino acids of the polypeptide backbone, mucus will have a varied charge density depending on pH, which may have an impact on adherence. The degree of hydration of cross-linked polycyclic acid is dependent on the medium's pH; it progressively increases from pH 4 to pH 7, then decreases as alkalinity or ionic strength rises. Nevertheless, the carboxylate anions' electrostatic repulsion causes the chain to fully expand at higher pH values.

b. **Applied strength:**To ensure a good bio adhesive property, the appropriate strength should be given while putting a buccal mucoadhesive drug delivery system. Pressure initially supplied to the mucoadhesive tissue contact site can impact the depth of interpenetration even when there are no attractive forces between the polymer and mucus. This is because strong pressure applied for a sufficient amount of time causes the polymer to become bioadhesive with mucus.

c. **Initial contact time:**The amount of swelling and interpenetration of the bioadhesive polymer chains is determined by the contact time between the mucus layer and the bioadhesive. Furthermore, the bioadhesive strength rises with an increase in the initial contact time. Even yet, the system's performance is severely impacted by the initial pressure and initial contact time.

d. **Moistening:**To enhance the mobility of polymer chains, the mucoadhesive polymer needs to be moistened in order for it to spread across the surface and form a large enough macromolecular network for the interpenetration of mucin molecules and polymer. But for mucoadhesive polymers, which exhibit optimal swelling and bioadhesion, there is a threshold hydration level..

V. Mucoadhesive dosage formulations

5.1. Tablet: Tablets have an oval shape, are flat, and have a diameter of about 5 to 8 mm. Mucoadhesive tablets, in contrast to traditional tablets, don't cause significant discomfort when speaking or drinking. They become softer, stick to the mucosa, and stay there until the release or disintegration process is finished. The coupling of mucoadhesive properties to tablets has additional benefits, such as efficient absorption and enhanced drug bioavailability due to a high surface to volume ratio and facilitated much more intimate contact with the mucus layer. Mucoadhesive tablets, in general, have the potential to be used for controlled release drug delivery. Because mucoadhesive tablets can be made to stick to any mucosal tissue, including the stomach mucosa, they provide the opportunity for both localized and systemic control drug release.Mucoadhesive tablets are applied to the gastric epithelium's mucosal tissues in order to administer medications with a localized effect. Because they extend the medicine's release, decrease the frequency of drug administration, and increase patient compliance, mucoadhesive tablets are frequently utilized. Mucoadhesive tablets' primary flaw is their lack of physical flexibility, which makes it difficult for patients to comply with repeated, long-term use.

5.2 Patches: Bio adhesive patches may range from simple erodible and nonerodable adhesive disks to laminated systems in the size range of 1-16cm2. These can be designed to provide either unidirectional or bidirectionalrelease of the drug. Adhesive patches are prepared using two techniques: solvent casting and direct

milling. Using the solvent casting process, the drug and polymer solution is cast onto a backing layer sheet, and the solvent(s) are then allowed to evaporate to create the intermediate sheet from which patches are punched. The direct milling method involves mixing formulation ingredients uniformly, compressing them to the required thickness, and then cutting or punching out patches of a predefined size and shape. To regulate the direction of medication release, stop drug loss, and reduce device deformation and disintegration throughout the application time, an impermeable backing layer may also be used.

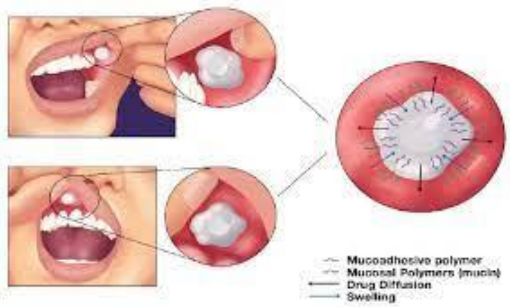

Figure 5: Mucoadhesive tablet

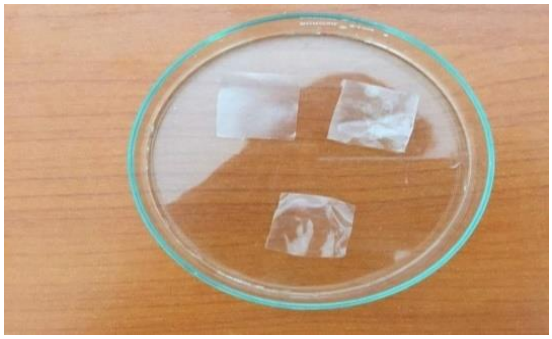

Figure 6: Mucoadhesive patch

5.3 Films: Due of their greater flexibility and comfort, mucoadhesive films are favored over mucoadhesive tablets. Additionally, they can avoid oral gels' brief duration of residence on the mucosa, as saliva readily washes and removes them. Additionally, films aid in wound protection during local drug delivery for oral disorders, hence lessening discomfort and improving disease treatment outcomes. In addition to being soft, elastic, and flexible, the perfect film should also be sturdy enough to resist breaking from the pressure of mouth movements. For the intended duration of action, it must also have strong mucoadhesive properties to stay in the mouth.

Figure 7: Mucoadhesive film

Figure 8: mucoadhesive gel

5.4 Gel and ointments: Ointments and gels, which are semi-solid dosage forms, have the advantage of being easily distributed throughout the mouth mucosa, vagina, or eye. Even while the accuracy of medication dosing with semi-solid dose forms may not match that of patches, tablets, or films, By employing particular mucoadhesive polymers, such as sodium carboxy-methyl-cellulose, Carbopol, and xanthan gum, low retention of the gels at the site of administration has been overcome. These polymers experience a phase shift from liquid to semi-solid. This alteration increases the viscosity, resulting in a steady and regulated release of the medication.

VI. Evaluation of mucoadhesive drug delivery system:

6.1Surface pH: The created mucoadhesive film is placed on a Petri plate that has previously held 4 mL of distilled water. It is then allowed to swell for one hour at room temperature (25 ± 1°C). Subsequently, the film's pH is determined by placing the pH meter's terminal electrode on its enlarged surface.

6.2 Flatness:A distinct-sized (1 cm2) sheet of mucoadhesive film is placed up against a plane surface, sliced into many vertical pieces (strips), and its length is then measured. The formula below is used to compute percent constriction. A zero-percentage restriction implies 100% flatness.

Constriction (%) = {(L1 −L2)/L1} * 100 …….4

Here, L1 represents the initial length of the film and L2 represents the final length of the strip.

Flatness (%) = 100−constriction (%).

6.3 Drug content: Using a magnetic stirrer, little bits of mucoadhesive films are dissolved in 100 mL of 0.1 N NaOH. At that stage, a 0.45 µm syringe filter is used to filter the mixture. A sample with a concentration of 10 µg/mL is obtained from the prepared stock solution, and it is scanned using an ultraviolet–vis spectrophotometer. Usually, placebo mucoadhesive films are employed as a blank control. The absorbance is used to calculate the drug's content(Tangri, Khurana, and Satheesh Madhav 2011).

6.4 Swelling properties: Buccal adhesive dose forms were weighed one at a time (w1) and arranged independently in Petri dishes with 4 millilitres of pH 6.6 phosphate buffer. The dose forms were taken out of the Petri plates at regular intervals of 5, 1, 2, 3, 4, 5, and 6 hours, and any extra surface water was wiped off using filter paper (W2). After reweighing the dose form, the swelling index (SI) was computed as follows, (Eq: 5)

$$SI= (W2-W1)/W1 \quad \ldots\ldots\ldots 5$$

6.5 Measuring the force of attachment:

One of the established techniques for determining the force of adherence of different bioadhesive dose forms is the Wilhelmy plate method. A micro tensiometer and a microbalance are used in the process, which measures the dynamic contact angles. For this, the CAHN dynamic contact angle analyser is employed.(Vasir, Tambwekar, and Garg 2003). The bioadhesive force between the polymer or dosage form suspended in a micro tensiometer and attached to a metal wire is measured using the Wilhelmy plate method. The tissue chamber, which is elevated to allow for contact between the tissue and the test substance, is filled with mucosal tissue, often rat jejunum. The stage is lowered and the force of adhesion is measured after a predetermined amount of time—seven minutes for microspheres.

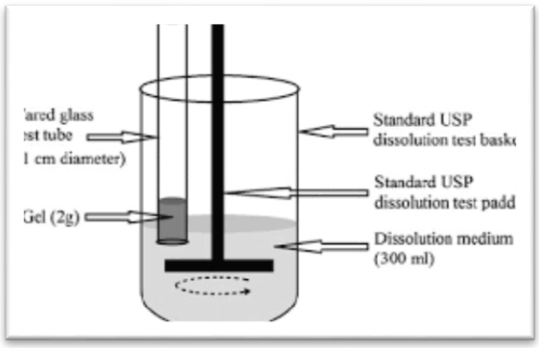

Figure 3 : USP apparatus

Figure 9: Wilhelmy plate

6.6 In vitro residence time determination*:* The duration of in vitro residence is estimated using a USP disintegration device. Eight hundred milliliters of isotonic phosphate buffer (IPB), maintained at 37°C and with a pH of 6.75, make up the disintegration medium. A segment of rabbit intestinal mucosa, measuring 3 cm in length, is adhered vertically to the glass section surface of the apparatus. The mucoadhesive film is hydrated using a pH of 6.75 and an IPB of 15 µl. The glass slab is placed vertically against the mechanical assembly and allowed to move simultaneously up and down to fully submerge the film in the buffer solution at the lowest position and remove it again at the highest point. The duration required for the film to fully separate from the mucosal surface is noted (average of three trials). Again, the in vitro residence duration is determined by regulating the substrate type, pH, temperature, and composition of the media. The in vitro residence time estimation provides information to improve the formulation, but it does not disclose the true strength of the mucoadhesive bond. The maximum force required to remove the film from the substrate is used to determine the strength of mucoadhesion.

6.7.Tensile strength: The aqueous dispersion sample of a mucoadhesive polymer was sandwiched between two polyoxymethylene discs. While the lower end disc is fixed and rests on a machine frame, the upper disc is adjustable. Tensile strength is the amount of force extracted from the buccal mucosa of a recently removed cow. In this test, the stress is evenly distributed across the mucoadhesive joint. Pig mucous membrane that connects the top moveable disc to the big intestine. Thus, it can be concluded that the tensile strength depends on both the type of polymer and concentration used after calculating the maximum force and work for detachment.
Tensile strength = (Force at failure/Cross-sectional area of the film)

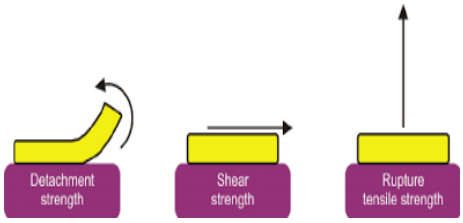

Figure 4 : Tensile strength determination

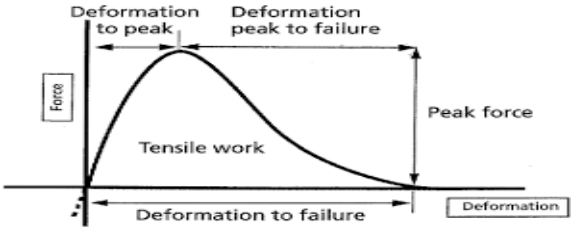

Figure 5: Graph of deformation of mucoadhesive dosage

VII. Application of mucoadhesive dosage formulations:

Mucoadhesive drug delivery system can be applied to deliver the drug via various routes of administration for the treatment of associated diseases. Routes and associated application of mucoadhesive dosage form are described below.

7.1. Nasal routes: This section examines specific applications of mucoadhesive compounds with respect to nasal administration of small organic molecules, antibiotics, vaccines, DNA, proteins and other macromolecules.

7.1.1Antibiotic: Parenteral administration is still the only way that many antibiotics are now given. Mucoadhesive polymers have been used in a few recent studies to investigate the nasal route's potential for systemic antibiotic administration. Lim et al. developed and assessed mucoadhesive microspheres of hyaluronic acid and chitosan for nasal administration of gentamicin and other medications in a preliminary investigation.(Ugwoke et al. 2005).

7.1.2 Small organic molecule: The preferred medication for treating Parkinson's disease patients with on/off phenomenon is apomorphine. After being administered via nasal delivery, the compound's aqueous solution has a relative bioavailability of 45% and is absorbed rather effectively. Other small molecular weight drugs that have been characterized for nasal administration with mucoadhesive agents, in addition to apomorphine, are budesonide, caffeine, ketorolac, metoprolol, midazolam, morphine-6-glucoronate, nicotine, oxprenolol, oxymetazoline, and pentazocine.(Ugwoke et al. 2005).

7.1.3Vaccine and DNA: Pathogens enter the body through mucosal contact, which leads to pathogenic infections in disease states as influenza, pertussis, meningitis, measles, etc. Since neutralizing antibodies and particular cellular responses might occur at these locations of pathogen entry, these diseases make excellent candidates for nasal vaccination. Given the remarkable efficiency of the live polio vaccine when administered at birth, mucosal immunization may be safer and more effective in young children when maternal antibodies are present.(Ugwoke et al. 2005).

7.1.4 Proteins: It has been proposed that mucoadhesive polymers can increase the uptake of big molecules across the nasal mucosa and prolong their residence duration. According to Garcia et al., cyanocobalamin's bioavailability in rabbits was significantly increased by incorporating it into microcrystalline cellulose, dextran microspheres, and crospovidone as opposed to only using basic nasal solutions.

7.2 Buccal route: Many medications that have poor bioavailability and are quickly broken down when taken orally can benefit from oral mucoadhesive drug delivery, which has the advantages of low enzymatic activity and high accessibility. In the past, periodontal disorders were treated using hydrophilic polymers such as SCMC, HPC, and polycarbophil; however, the current tendency is to effectively exploit these systems for the delivery of peptides, proteins, and polysaccharides. A first-generation mucoadhesive paste called Orabase has been utilized as a barrier for oral ulcers. This is typically how buccostem, an adhesive antiemetic pill containing prochlorperazine, is delivered.(Tangri, Khurana, and Satheesh Madhav 2011).

7.3 Ocular route: Natamycin can be delivered using mucoadhesive drug delivery system to treat fungal eye infection. Palmitoyl-ethanolamide (PEA) are now a days delivered via mucoadhesive system to treat glaucoma. Ciprofloxacin is administered as PEGylated nano lipid as mucoadhesive carrier to treat bacterial conjunctivitis(Dave et al. 2021).

7.4 . Vaginal mucoadhesive drug delivery: Choi et al. created temperature-sensitive, mucoadhesive liquid suppositories with acetaminophen utilizing the mucoadhesive qualities of carboxyvinyl polymer and poloxamer, which are utilized to improve drug absorption. It was shown that HPMC mucoadhesive tablets were an appropriate method of administering benzydamine and a good substitute for conventional dosage forms for topical vaginal therapy.(Perioli et al. 2011). Clotrimazole (CT) which is an imidazole derivative having antifungal activity was also developed for treatment of human mycotic infections and plays an important role in antifungal chemotherapy.

7.5 Rectal route: It was also demonstrated that the tuberculous medication rifampicin was better absorbed when administered rectal via a mucoadhesive gel as opposed to oral solution and solid suppositories.

Table 1: Different types of mucoadhesive dosage forms and associated routes of administration:

Delivery route	Dosage forms				
	Tablets	Ointments	Gel	Patch	Film
Buccal	Theophylline, multiple polymers	Benzyl nicotinate, multiple polymers	Benzydamine, chitosan derivative	Miconazole, PVA/PVP	Femtanyl, PVP
Nasal	N/A	Mupirocin, glycerine ester	Insulin, starch	Insulin, chitosan/PGE	Chlorpromazine, chitosan/pectin
Ocular	Diclofenac, poly(acrylic) acid	Sulphadicramide, multiple polymers	Puerarin, poloxamer/ Carbopol	Ciprofloxacin, PVA/CMC	Fluorescein, HPMC
Vaginal	Metronidazole, chitosan	Terameprocol, white petroleum	Amphotericin, pluronic	ALA, PMVE/MA	SDS, multiple polymers
Rectal	Ramosetron, carbopol	Zinc oxide, petroleum	Quinine, HPMC	N/A	Theophylline, pHEMA

8. **Conclusion and future trends:** Since mucosal locations are easily accessible and have minimal enzymatic activity, they make an appealing non-invasive alternative for quick, regulated drug administration for both local and systemic application. To achieve the best possible therapeutic result, it is crucial to choose the right therapeutic agent, polymer, and drug carrier based on the pathophysiological state of the mucosa. A molecular weight of less than 400 to 500D, aqueous solubility of 1 mg/ml, a logP value in the range of 1 to 2, and a daily dose not to exceed 10 mg are the characteristics of an ideal medication candidate. The chemical makeup, surface tension, charge on the surface, molecular weight, rate of hydration, and concentration of polymers are important factors that influence how long drug delivery systems stay at the application site.

Now a days cationic, thiolated and pre-activated thiomers polymers are widely used in mucosal drug delivery system. Recent the use of nanocarriers in the mucosal drug delivery system indicated higher retention at the mucosal site, tuneable drug release behaviour and enhanced permeability for higher therapeutic outcomes. **Nanofibers** has been chosen as a special drug carrier in mucoadhesive drug delivery system due to its "unique structural and functional features". Along with superior biophysical property, nanofibers have ability to enhance the solubility of poorly soluble drug. Further electrospinning and electrospraying appear to be a versatile and simple electrostatic spinning technique capable to impart the nanofiber matrices with many desirable properties suitable for mucoadhesive systems. Degree of keratinization, mucosal thickness, low absorptive surface area, mucosal microbiome and mucosal secretion are the key challenges must be addressed for determining the acceptability of a mucosal site for optimum therapeutic response.

The effective design of innovative mucoadhesive drug delivery systems may benefit from this overview of mucoadhesive dosage forms. Mucoadhesive drug delivery systems offer a variety of uses, such as the creation of new mucoadhesive, device design, mucoadhesion processes, and improved penetration. Mucoadhesive drug delivery will become even more crucial in the delivery of these molecules as a result of the flood of new drug molecules brought out by drug discovery.

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