World Journal of Advanced Research and Reviews
eISSN: 2581-9615 CODEN (USA): WJARAI
Cross Ref DOI: 10.30574/wjarr
Journal homepage: https://wjarr.com/

(REVIEW ARTICLE)

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Oral mucoadhesive drug delivery system: Formulation strategies and evaluation techniques

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World Journal of Advanced Research and Reviews, 2024, 24(01), 1706–1719

Publication history: Received on 05 September 2024; revised on 17 October 2024; accepted on 19 October 2024

Article DOI: https://doi.org/10.30574/wjarr.2024.24.1.3199

Abstract

Mucoadhesive drug delivery systems (MDDS) represent an innovative method for administering drugs through oral routes such as the buccal, sublingual, and gingival areas. These systems leverage natural or synthetic polymers to ensure prolonged adherence to mucosal surfaces, enabling extended and controlled release of medication. Several factors influence the effectiveness of mucoadhesion, including the hydrophilicity of polymers, molecular weight, and environmental factors like pH and moisture levels. MDDS can take various forms, including tablets, films, patches, lozenges, and gels, each offering different drug release profiles such as immediate, sustained, or controlled. These systems enhance drug bioavailability by avoiding first-pass metabolism, making them particularly beneficial for medications with low oral bioavailability or those requiring targeted delivery. Although MDDS offer improved patient compliance and therapeutic effectiveness, they still face challenges like irritation, taste concerns, and the diluting effect of saliva, which can impact drug stability. Despite these challenges, MDDS hold significant promise for advancing drug delivery technologies across various medical applications. This review thoroughly examines the mechanisms, advantages, limitations, and future prospects of mucoadhesive drug delivery systems.

Keywords: Mucoadhesive Drug Delivery Systems; Oral Mucosal Delivery; Buccal Patches; Drug Bioavailability; Controlled Release; Polymer-Based Drug Delivery.

1 Introduction

The buccal area of the mouth is a desirable location to administer the drug of choice [[1]]. Bio adhesive was first defined by Longer and Robinson in 1986 as a synthetic or natural macromolecule that adheres to mucus or an epithelial surface. All polymeric materials still cling to biological surfaces (bio adhesives) or mucosal tissue (mucoadhesive), according to the general definition.[0] Mucoadhesive preparations are designed to adhere to the mucosal epithelium in the oral cavity in order to stay there and allow for systemic drug absorption [[2]]. A substance needs to interact with mucus, a highly hydrated, viscous anionic hydrogel layer that shields the mucosa, in order for it to be considered bio adhesive [[3]]. Recent advancements have led to the development of numerous mucoadhesive drug delivery systems for oral, buccal, nasal, rectal, and vaginal routes, targeting both systemic and local effects [[5]]. Bio adhesion can be described simply as a process of "fixing" of two surfaces to one another [[6]].

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1.1 Oral mucosa

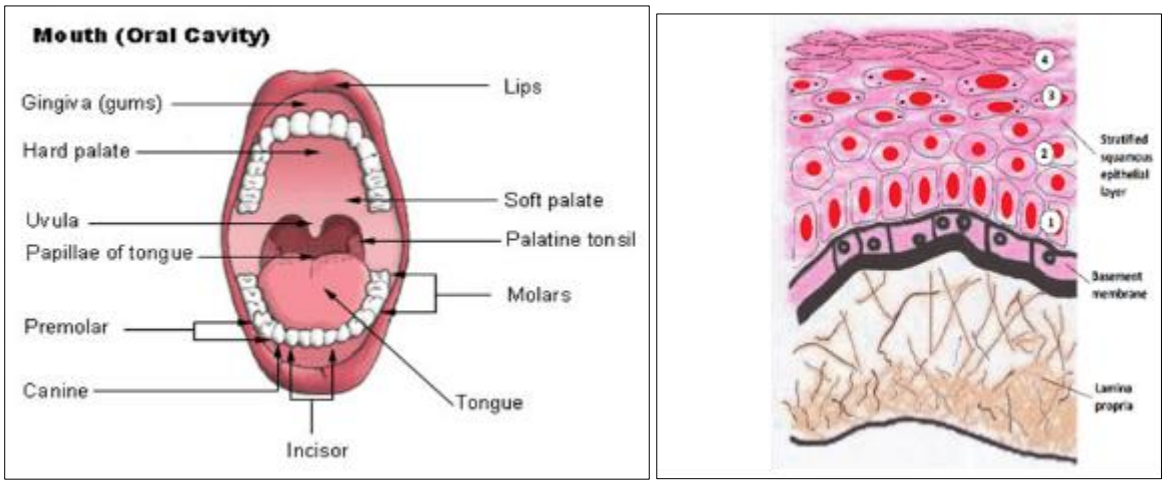

Figure 1 Oral cavity/ mucosa

A comparatively thick, dense, multilayered, and highly vascularized mucous membrane lines the oral cavity. There are four sites in oral mucosa which are as follows:

1) Buccal cavity 2) The sublingual area 3) The palate 4) Gingival region

The mucous-covered stratified squamous epithelium that comprises the oral mucosa is composed of four layers: the stratum distendum, stratum filamentosum, stratum suprabasale,

and stratum basale. As the lamina propria provides mechanical support and transports blood vessels and nerves, the epithelium serves as a mechanical barrier protecting the underlying tissues [[24]]. Saliva continuously washes the sublingual region, which could prevent adherence. It has been noted that increased salivation and involuntary swallowing can reduce the amount of drug absorbed [[45]].

1.2 Mechanism of mucoadhesion

For bioadhesion to occur, three steps take place:

- A close bond between a bio adhesive and a membrane that results from the bioadhesive swelling or from a proper wetting of the bioadhesive and membrane.
- Penetration of the bioadhesive into the tissue takes place.
- There is interpenetration of mucous into the bio adhesive chain. After that, low chemical bonds may settle [28].

During the process of adhesion there are two stages identified are given below.

- Contact Stage
- Consolidation Stage

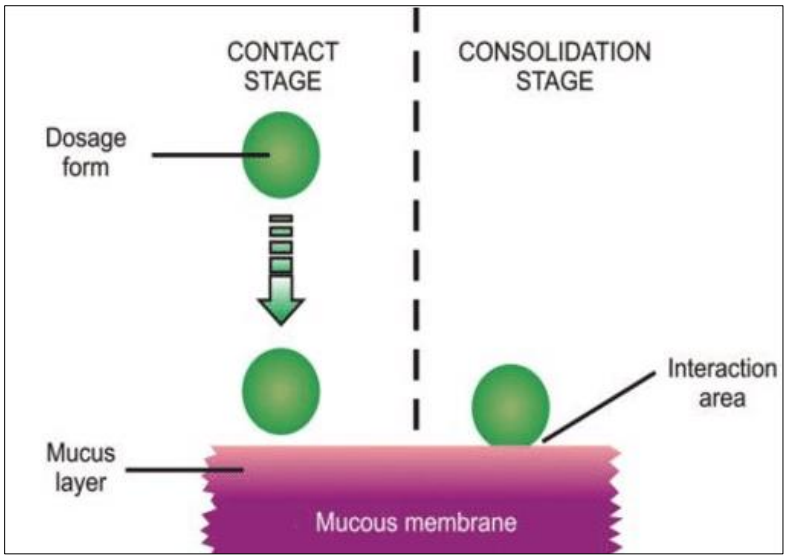

Figure 2 Mechanism of mucoadhesion

- Contact Stage

Initially, an intimate contact is formed between the mucosal membrane and mucoadhesive [[50]]. The mucus found in the mucosal membrane causes the mucoadhesive to become moist [[6]].

- Consolidation Stage

The mucoadhesive materials are activated by the presence of moisture [[5]]. Employing various physiochemical forces of attraction, including hydrogen bonds, electrostatic forces, and Vander Waals forces, this stage produces a sustained adhesion by strengthening and consolidating the adhesive junction through a variety of physicochemical interactions[[6]].

1.3 Factors affecting muco-adhesion

The muco-adhesion of a drug carrier system to the mucous membrane depends on the following factors:

- Polymer factors
- Physical factors
- Physiological factors

1.3.1 Polymer Factors:

Hydrophilicity: Mucoadhesive polymers include hydroxyl and carboxyl groups, among other hydrophilic functional groups. These groups permit the substrate to form hydrogen bonds with them, causing swelling in aqueous environments and maximum exposure of possible anchor sites [[7]].

Molecular Weight: Low molecular weight polymers promote interpenetration between molecules, while higher molecular weight polymers encourage entanglements [[8]].

Concentration of active polymer: The ideal concentration of the bio adhesive polymer is necessary for maximum bio adhesion. In highly concentrated solutions, the adhesive strength significantly declines beyond the ideal concentration. In concentrated solutions, the coiled molecules become less solvent-rich and have fewer chains accessible for interpenetration. In this result, only formulations that are essentially liquid mucoadhesive seem to be of interest [[33]].

Flexibility of polymer chains: • The flexibility of polymer chains facilitates the polymer's interpenetration into the mucus network [[23]].

Swelling: Hydration is necessary for a mucoadhesive polymer to expand and form an appropriate "macromolecular mesh" of the right size. Additionally, hydration makes the polymer chains flexible, which enhances the polymer and mucin interpenetration process [[7]]. Swelling depends on both polymers' concentration and on the presence of water.

Charge: This is an essential part of the bio adhesion process. Comparing non-ionic polymers to anionic polymers, the former has a lower degree of adhesion. An important requirement for mucoadhesion is a large anionic charge on the polymer. It has been discovered that a number of cationic high-molecular-weight polymers exhibit good adhesion properties in neutral or slightly alkaline conditions, such as chitosan [[36]].

Spatial conformation:- Spatial confirmation is just as significant as molecular weight or chain length. For example, dextran has a large molecular weight of 19,500,000, but its adhesive strength is comparable to that of poly ethylene glycolate, which has a molecular weight of 2,00,000 [[10]].

1.3.2 Physical Factors

pH: Both the pH of the saliva used as a dissolving medium and the pH of the polymer-substrate interaction affect the polymer's behavior. Based on saliva flow rate and measurement method, the pH range for this medium has been determined to be between 6.5 and 7.5. The degree of hydration of cross-linked polyacrylic acid polymers is influenced by the medium's pH, according to certain studies, which consistently demonstrate increasing hydration from pH 4 through pH 7 and a decrease at alkaline pH levels [[51]].

Applied strength: The pressure exerted on the adhesive system has an impact on the diffusion depth of chains [[52]]. Regardless of the polymer—poly[acrylic acid/divinyl benzene poly(HEMA)] or Carbopol 934—the adhesion strength rises with the strength applied or with the application's time, reaching an optimal level [[11]].

Initial contact time: The degree to which the polymers expand and penetrate is determined by the first contact time. The Bio-adhesive systems do not allow for the adjustment of this parameter [[6]].

1.3.3 Physiological Factors

Mucin turnover rate

There are two main reasons why the natural turnover of mucin molecules is significant. Initially, it is anticipated that the mucin turnover will shorten the mucoadhesive residence period on the mucus layer [[53]]. Mucoadhesive separate from the surface when the adhesive strength is high because mucin turns over. Second, significant numbers of soluble mucin molecules are produced as a result of mucin turnover [[25]]. A mucoadhesive formulation has therefore been proposed in order to prolong the residence time in the oral cavity.

Disease state:

The physical and chemical characteristics of mucus, as well as its quantity (e.g., hypo- and hyper-secretion of gastric juice), can be affected by concomitant diseases. Other symptoms include elevated body temperature, ulcer disease, colitis, tissue fibrosis, allergic rhinitis, bacterial or fungal infection, and inflammation [[10]].

Rate of renewal of mucosal cells

The pace at which mucosal cells renew varies greatly throughout mucosa types. It restricts the bio adhesive systems' ability to remain on mucosal surfaces [[9]].

Tissue movement

The mucoadhesive system is impacted by tissue movement, which happens during speaking, eating, and peristalsis in the gastrointestinal tract, particularly when it comes to gastro-retentive dosage forms [[68]].

1.4 Classification of oral mucoadhesive drug delivery system

According to the location of drug action, oral drug delivery is divided into three categories:

- Sublingual drug delivery: The drug is delivered to the systemic circulation through the mucus membrane covering the oral cavity floor.

- Buccal drug delivery: In this system dosage form is administered through the mucosal linings of the cheeks.
- Local drug delivery: This involves drug transfer locally to the affected tissues (local effect) [[13]].
- The classification of mucoadhesive systems is generally based on different criteria such as the form of the delivery system, the type of mucoadhesive polymers used, and the mechanism of drug release:

1.4.1 Based on Dosage Form

Tablets: The dosage type is generally small, flat and oval, with a diameter of probably 5–8 mm [[49]]. They become softer, adhere to the mucous membrane, and stay there until the release or dissolution process is finished [[13]]. Tablet drawbacks include fluctuation brought on by variations in salivary flow and intensity of sucking, unintentional swallowing, and brief exposure times usually no longer than 30 minutes [[27]].

Buccal Patches: When compared to tablets, patch systems have higher patient compliance because of their physical flexibility, which only slightly irritates the patient [[34]]. A bio adhesive surface for mucosal attachment, an impermeable backing layer, and a drug-containing reservoir layer from which the medication is released under regulated conditions make up patches [[54]]. Despite lengthy manufacturing period and expensive costs, oral patches properties make them a good dosage form for the direct treatment of localized and moderately distributed oral disease [[69]]. Two structures of patches:

- **Matrix type:** The drug, the adhesive, and other components are combined in a matrix structure to create the buccal patch design.
- **Reservoir type:** The reservoir system design incorporates a chamber for drugs and components apart from the adhesive [[12]].

Buccal Films: When it comes to patient acceptance and flexibility, mucosal adhesive films are preferred over adhesive discs and tablets. They also offer more accurate dosing and a longer residence time than gels and ointments. A good film should be strong enough to withstand the tension created by mouth motions while yet having adequate elasticity, flexibility, and softness [[13]].

Gels and Ointments: Gels and ointments are examples of semisolid dose forms that have the benefit of easily dispersing throughout the oral mucosa. It has been possible to overcome poor gel retention at the application site by utilizing bio-adhesive compositions [[39]]. Using gel-forming polymers such as PAAc derivatives allows sustained release and improved bioavailability compared with solutions [[48]].

Powder Dosage Forms: Drugs can be sprayed into the buccal mucosa to treat buccal diseases. The powder forms are composed of a physical mixture of an active agent with a bio adhesive polymer [[14]].

Bio adhesive Lozenges: Lozenges are an alternative form of bioadhesive that has good potential for patient compliance and sustained release [[32]]. They can deliver drugs multidirectional into the oral cavity or to the mucosal surface. Lozenges are used as antimicrobials, antifungals, local anesthetics, and antibiotics for the oral cavity [[14]].

1.4.2 Based on the Type of Mucoadhesive Polymers:

Mucoadhesive polymers should present some characteristics that facilitate the interactions with mucins [[57]]. A few examples of the latest polymers categorized in the following categories are shown in the figure:

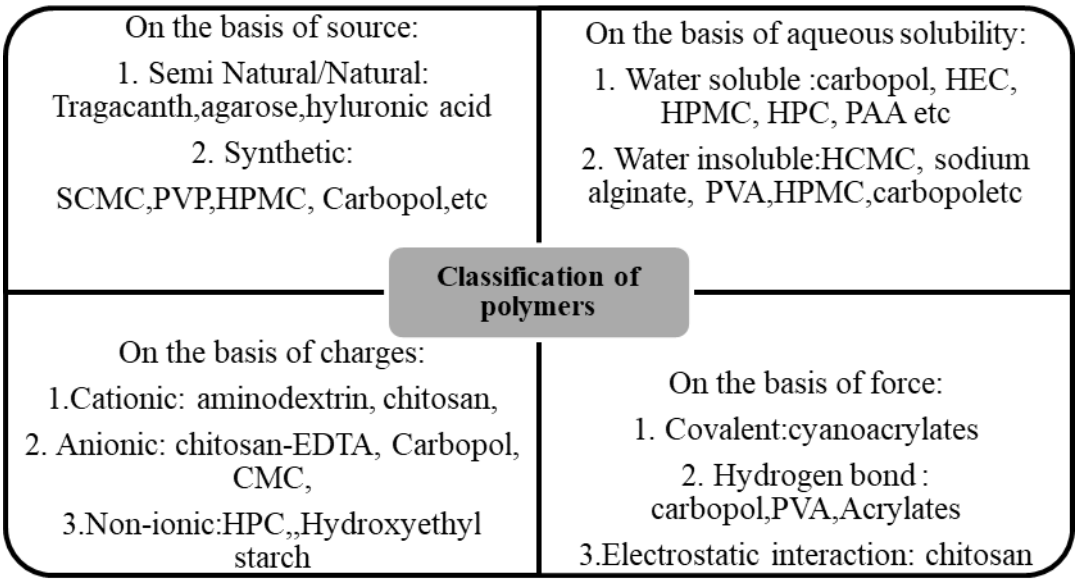

Figure 3 Classification of polymers

1.4.3 Based on the Mechanism of Mucoadhesion

Covalent Bonding: Some polymers may form covalent bonds with mucin or other components of the mucosal layer.

Non-covalent Interactions: These include hydrogen bonding, electrostatic interactions, van der Waals forces, and hydrophobic interactions [[58]].

Swelling/Interpenetration: Certain polymers absorb water and swell, allowing them to interpenetrate the mucosal layer, enhancing adhesion.

1.5 Advantages of oral mucoadhesive drug delivery systems:

Oral drug administration is a potentially effective technique to apply a wide range of therapeutic substances to the oral mucosal surface, according to several publications in the literature on clinical trials and registered patents of oral mucoadhesive medicines.

- Using this approach was also demonstrated to improve Cmax, AUC, and Tmax when compared to commercial drug formulations.
- Increases the dosage form's duration of residence at the absorption site, hence extending its bioavailability.
- Excellent accessibility and rapid onset of action
- Quick absorption due to high blood flow rates and a large blood supply
- Enhanced adherence from patients
- Drug absorption occurs by passive diffusion [[12]]
- In unconscious and trauma patients drugs can be administered [[31]]
- Drug has high bioavailability because it bypasses first pass metabolism [[12]]
- Drug is effortlessly administered and extinction of therapy in emergency may be facilitated.
- The presence of saliva ensures relatively large amount of water for drug dissolution unlike in case of rectal or transdermal routes.

1.6 Disadvantages of oral mucoadhesive drug delivery systems:

- High saliva turnover, Mastication [[59]]
- Patient acceptability in terms of taste, irritancy and mouth feel is to be checked
- Drugs that are unstable at buccal pH cannot be administered [[12]]
- Drugs having unpleasant and bitter taste cannot be given by oral route [[15]]
- A drug having small quantity or dose can only be given by this route [[12]]
- Drugs that are required to be absorbed by passive diffusion only can be given by this route.
- Drinking and eating may be avoided.

- Barrier properties of the mucosa.
- The continuous secretion of the saliva (0.5-2 l/day) leads to subsequent dilution of the drug.
- The hazard of choking by involuntarily swallowing the delivery system is a concern.

1.7 Basic components of mucoadhesives

Drug Substance: Before developing mucoadhesive drug delivery systems, it is critical to determine whether the intended action is for a localized or broad impact, as well as whether the drug will discharge quickly or slowly. This is why selecting the right drug is so important [[40]].

Bioadhesive Polymer: Bioadhesive polymers serve an important role in medication delivery systems based on Buccoadhesion [[55]]. Mucoadhesive drug delivery techniques rely heavily on bio adhesive polymers. Polymers are also utilized in matrix devices, which enclose a drug within a polymer matrix to regulate the drug's release time [[12]]. Apart from thiolate polymers, a new generation of mucoadhesive polymers can stick to the cell surface directly instead of the mucus [[16]].

Backing Membrane*:* The adhesion of bioadhesive devices to the mucous membrane is significantly influenced by the backing membrane. The backing membrane's elements ought to be immune to the medication and penetration booster [[12]].

Permeation Enhancers: Permeation enhancers are substances that make the buccal mucosa easier to penetrate. Enhancers that increase medication penetration in buccal mucosa also increase drug permeation in another absorptive mucosa [[35]].

Plasticizers: The plasticizers are used to improve the folding durability of the delivery mechanism. The plasticizer used should provide the film formulation with permanent flexibility; this depends on the plasticizer's volatile nature and the manner in which it interacts with the polymer [[56]]. They give the dosage form just enough flexibility to increase patient compliance and acceptance. A few examples are propylene glycol, dibutyl phthalate, PEG-400, and PEG-600 [[9]].

2 Formulation strategies

Some Methods of preparation of oral mucoadhesive are as follows:

2.1 Solvent casting:

Using this technique, the medication and all patch excipients are co-dispersed in an organic solvent and coated on a release liner sheet [[17]].

Steps involved in Solvent Casting Method:

- Step 1: Preparation of casting solution
- Step 2: Deaeration of solution
- Step 3: Transfer of appropriate volume of solution into the mold
- Step 4: Drying the casting solution
- Step 5: Cutting the final dosage form to contain desired amount of drug [[18]].

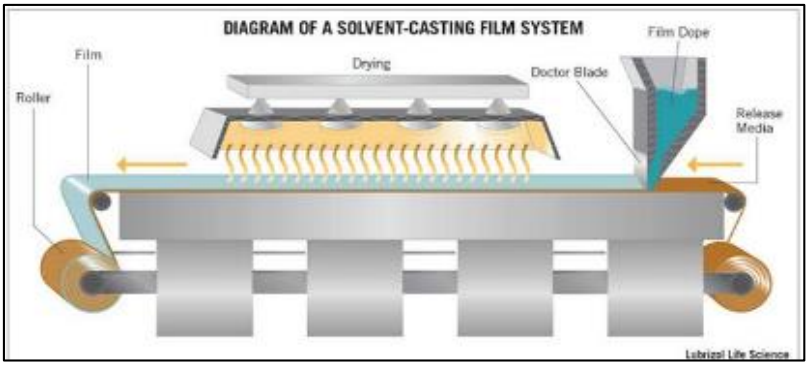

Figure 4 Solvent-casting method

2.2 Direct milling

Kneading is a method of mixing drugs and excipients, typically in the absence of liquids. The material is rolled on a release linear after the mixing process. until the thickness is reached that is desired [[30]].

2.3 Solid dispersion extrusion

Solid dispersions are created by extruding the medication into this immiscible component. Ultimately, dies are used to mold the solid dispersions into films [[37]].

2.4 Semisolid casting

A water-soluble film-forming polymer solution is first made for the semisolid casting process. The resultant mixture is mixed with an acid-insoluble polymer solution (cellulose acetate butyrate or phthalate) that was made using sodium or ammonium hydroxide. Ultimately, the gel mixture is heated-controlled drummed and molded into films or ribbons [[17]]. The film has a thickness of between 0.015 and 0.05 inches. The acid insoluble producing polymer should have a ratio of 1:4 [[17]].

2.5 Rolling Method

A drug-containing solution or suspension is rolled on a carrier in the rolling method. The primary solvents are alcohol and water mixtures. The wet film is then dried using controlled bottom drying [[63]]. The film is cut into the appropriate shapes and sizes after being dried on rollers [[17]].

2.6 Hot melt extrusion

Using the hot melt extrusion process, the medication is first combined with solid carriers. The mixture is then melted by the extruder, which has heaters [[17]]. To produce evenly thick films, a 1.5 mm die opening was connected [[64]]. Steps involved in Hot Melt Extrusion Method:

- Step 1: The drug is mixed with carriers in solid form.
- Step 2: Extruder having heaters melts the mixture.
- Step 3: Finally, the melted mixture is shaped in films by the dies [[18]].

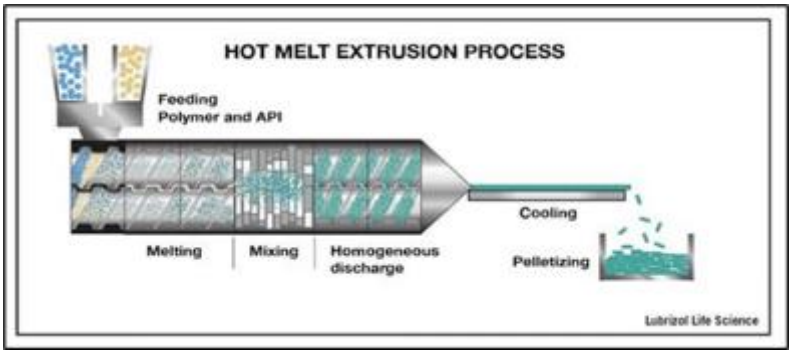

Figure 5 Hot melt extrusion method

2.7 Printing technology

The printing technique (also known as inkjet printing) is a non-contact method in which the components are sprayed to form 2D and 3D structures. Printing a mucoadhesive buccal film is a new platform for producing formulations tailored to individual needs and providing customized formulations and personalized medication at the point of treatment [[60]].

2.8 Direct Compression

Except for the lubricant, all of the ingredients are thoroughly combined in a glass mortar and pestle for 15 minutes. The combination is compressed using a tablet compression machine. All tablets contain fillers, lubricants, diluents, and bioadhesive polymers such as sodium alginate and PVP [[61]].

2.9 Lyophilization (Freeze-Drying)

This technique produces oral disintegrating tablets and has been recently applied to produce a mucoadhesive matrix and wafers for buccal drug delivery [[62]].

3 Evaluation studies of mucoadhesive drug delivery system

3.1 In vitro/ex vivo tests

- Determination of tensile strength
- Falling liquid film method
- Fluorescent probe method
- Colloidal gold mucin conjugate method
- Adhesion number
- Detachment force measurement/ The Wilhelm plate method
- Flow channel method
- Thumb method
- Swelling index
- Electrical conductance
- Stability studies
- Moisture absorption studies for buccal patches
- Folding endurance

3.1.1 Determination of tensile strength

The maximum stress given to a strip specimen before it breaks is known as its tensile strength. [[65]]. Therefore, while peel strength measures the peeling force, tensile and shear measure the mechanical qualities of the system [[19]]. The measurement of mucoadhesive strength, aiming to determine the force required to break the bond between the mucoadhesive and model membrane. Tensile strengths can be broken as well as objectivity, shear, and other properties depending on which way the mucoadhesive is separated from the substrate molecule [[26]]. Cellulose and pectin work together to boost tensile strength [[43]]. The following formula can be used for determining the tensile strength of buccal mucoadhesive device.

Force of adhesion (N) =Mucoadhesive strength × 9.81/1000

Bond strength (N/m^2) = Force of adhesion (N)/Surface area of tablet [[20]].

3.1.2 Falling liquid film method

Teng and Ho reported the earliest flowing technique for the quantification of the interaction between material and mucosa [[66]]. This technique measures the proportion of particles that remain on a mucosal tissue after a suspension of microspheres is allowed to pass through the tissue and is spread out on an angled plastic slide. The Coulter current method can be used to help with the quantification [[20]].

3.1.3 Fluorescent probe method

This approach labels the membrane proteins and the membrane lipid bilayer with fluorescein isothiocyanate, respectively. After mixing the mucoadhesive agents with the cells, variations in the fluorescence spectrum are seen. This illustrates the function of polymer binding in polymer adhesion [[21]].

3.1.4 Colloidal gold mucin conjugate method

The process creates mucin–gold conjugates by adsorbing red colloidal gold particles on mucin molecules [[22]]. These conjugates take on a reddish hue when they come into contact with bio adhesive hydrogels [3]. This can be assessed by measuring the amount of red color on the hydrogel surface or by monitoring the decrease in conjugate concentration as shown by a change in absorbance at 525 nm.

3.1.5 Adhesion number

It is the proportion of the total amount of applied particles to the number of particles that are adhered to the substrate. It has a percentage as its expression [[20]].

3.1.6 Detachment force measurement

One of the established techniques for determining the force of adherence of different bio adhesive dose forms is the Wilhelmy plate method. The technique makes use of a micro tensiometer and a microbalance and measures the dynamic contact angles. The bio adhesive force between the polymer or dosage form hung inside the micro tensiometer on a metal wire and the mucosal tissue is measured using the Wilhelmy plate method [[20]].

3.1.7 Flow channel method

The membrane lipid bilayer and membrane proteins are labelled with pyrene and fluorescence isothiocyanate, respectively. The cells then mixed with candidate bio adhesives and the change in florescence spectra is monitored. This gives an indication of polymer binding and its influence on polymer adhesion [[20]].

3.1.8 Swelling index

The dose form allows for the measurement of swelling in terms of percentage weight gain .The swelling index is calculated using following formula [[41]].

$$\text{Swelling Index (S.I.)} = (Wt - Wo)/Wo$$

Where, S.I = Swelling index

W t = Tablet weight at time t;

Wo = Tablet weight before being placed in the beaker

3.1.9 Thumb method

This is a fairly easy test that is used to determine the polymer's peel adhesive strength qualitatively. It is a helpful tool in the development of buccal adhesive delivery systems. The difficulty of removing the thumb from the adhesive as a function of pressure and contact time is used to determine the adhesiveness [[20]].

3.2 Electrical conductance

In order to measure the electrical conductance of different semi-solid mucoadhesive ointments, the rotating viscometer was modified. It was discovered that the electrical conductance was low when adhesive substance was present.

3.3 Stability study in human saliva:

With human saliva, the stability of ideal bi- and multi-layered patches can be examined. Saliva is extracted from individuals between the ages of 18 and 50. Five milliliters of human saliva are contained in buccal patches, which are placed in individual Petri plates and baked for six hours at 37°C 0.2°C in a temperature-controlled oven. A stability test is performed on every batch of films in accordance with ICH regulations [[29]].

3.3.1 Moisture absorption studies for buccal patches:

Evaluation of the drug absorption and drug release parameters requires knowledge of the moisture absorption by the buccal films or patches. Studies on moisture absorption can be carried out in distilled water with 5% w/v agar. After heating the mixture, pour it into petri dishes and let it set. Next, choose the six buccal patches and weigh each batch accurately. Place them on the agar plate's surface after the agar has solidified, then place the incubator at 37°C.

Weigh every patch once more, then use the following calculation to determine the percentage of absorbed moisture:

$$\% \text{ Moisture absorbed} = \frac{\text{Initial weight} - \text{Final weight}}{\text{Initial}} \times 100$$ [[9]].

3.3.2 Folding endurance

The manual method of measuring the folding endurance of patches involves folding a film repeatedly at the same location until it ruptures [[38]]. The value of folding endurance was determined by counting how many times the film could be folded in the same direction without breaking. Three observations are averaged and the mean value is computed.

3.4 Future prospectus

Drug administration has been completely transformed by mucoadhesive drug delivery systems (MDDS), which provide a non-invasive, patient-friendly method of delivering drugs directly to mucosal surfaces [[46]]. Pharmaceutical advancements such as Novel Drug Delivery Systems provide medical practitioners with an array of tools to treat diseases with unprecedented safety, efficacy, and accuracy. A disease could be treated more successfully with a smaller dosage and fewer doses of the medication [[47]]. The future of Mucosal Drug Delivery Systems holds significant promise and potential for development:

- Personalized Mucosal Therapies: Precision medicine developments will probably make it possible to create customized MDDS formulations that will allow for customized drug delivery to meet the demands of each patient.
- Vaccine Delivery: With potential applications in COVID-19 and other infectious illnesses, MDDS is expected to serve a critical role in vaccine delivery, enhancing patient compliance and immunity.
- Telemedicine and Remote Monitoring: Healthcare professionals may be able to administer and oversee treatments from a distance with the integration of MDDS with telemedicine and remote patient monitoring.
- Enhanced Drug Delivery Devices: Patients' adherence is expected to increase and real-time data will be provided by the development of smart and linked drug delivery systems.

4. Conclusion

Mucoadhesive drug delivery systems offer significant potential for improving the efficacy of pharmaceutical treatments, particularly for drugs that require localized or systemic delivery through the oral mucosa. By prolonging the residence time of the drug at the absorption site and bypassing first-pass metabolism, these systems enhance bioavailability, minimize dosing frequency, and improve patient compliance. Advances in polymer science, along with novel formulation strategies such as buccal patches, films, and lozenges, have opened new avenues for tailored drug delivery systems. However, challenges such as patient discomfort, irritation, and the need for drug compatibility with the mucosal environment remain areas for further research. Continued innovation in mucoadhesive technologies promises to expand the therapeutic applications of these systems, making them a crucial component of modern drug delivery strategies.

Compliance with ethical standards

Disclosure of conflict of interest

No conflict of interest to be disclosed.

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