

MUCOADHESIVE DRUG DELIVERY: ADVANCES IN POLYMERS AND NOVEL DOASGE FORM

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ABSTRACT:

Mucoadhesive drug delivery systems have emerged as an advanced strategy to enhance drug residence time, bioavailability, and controlled release through various mucosal routes. These systems utilize natural and synthetic polymers capable of adhering to mucosal surfaces, thereby improving drug absorption and therapeutic efficiency. Buccal drug delivery is considered the most promising route due to its accessibility, high vascularization, and avoidance of first-pass metabolism. This review highlights the principles of mucoadhesion, mechanisms of adhesion, influencing factors, and various theories governing polymer-mucus interactions. It also discusses buccal drug delivery systems, formulation components, dosage forms, and evaluation techniques used to assess mucoadhesive performance. The challenges and future perspectives of mucoadhesive systems in pharmaceutical applications are also emphasized. Overall, mucoadhesive drug delivery systems offer a reliable approach for improving drug efficacy, especially for drugs with poor oral bioavailability.

KEYWORDS: Mucoadhesion, Buccal drug delivery, Bioadhesive polymers, Controlled release, Mucosal delivery, Drug absorption, First-pass metabolism.

1. INTRODUCTION

Since from the last 40 years, the concept of mucoadhesion has provided the great application in prolonging the residence time as well as controlled release effect of various bio adhesive dosage forms through different mucosal routes. The formulations based on the mucoadhesive drug delivery system have shown the enhanced bioavailability of many drugs. The use of various mucoadhesive polymers have achieved significant interest in formulating the sustained release, extended release as well as prolonged release dosage forms. The mucoadhesive drug delivery provides greater absorption and enhanced bioavailability of dosage forms due to the large surface area and higher blood flow in the mucosal cavities. The delivery across the mucus membrane provides various advantages over other drug delivery routes i.e., overcome the hepatic first pass metabolism as well as the degradation of drugs by various gastrointestinal enzymes as well as intestinal flora. For the desired mucoadhesive strength of the mucoadhesive dosage forms, there are various mucoadhesive polymers that can be used. These polymers are either natural or synthetic macromolecules which are capable of adhering to the mucosal surfaces. From last three decades, the use of various mucoadhesive polymers has achieved a great interest in the field of pharmaceutical technology. Nowadays, the use of mucoadhesive polymers has been accepted as an important strategy to prolong the residence time and to improve the localized effects of drug delivery systems on various mucus membranes of a biological system.

The potential candidates for drug delivery by mucoadhesive dosage form to different sites includes oral, gastrointestinal, nasal, ocular, vaginal, and rectal. A brief comparison was discussed about these sites for drug delivery. Buccal route found to be more suitable for the delivery of pharmaceutical agents using mucoadhesive polymers due to presence of relatively static and smooth surface on which various mucoadhesive dosage forms can be placed. Different dosage forms like films, tablets, gels, ointments and patches can be used for delivery of drug across the buccal mucosa. The drugs may be suitable candidates to be delivered via the oral cavity which are having short biological half-life, poor solubility and permeability, susceptible to enzymatic degradation and for achieving sustain release effect. The other important site is nasal route for mucoadhesive formulations. It has a large surface area of about 150-200 cm². The activity of muco-ciliary layer enhanced by presence of any foreign particle matter, therefore the residence time of particles in nasal mucosa varies between 15-30 min. Thus by employing various mucoadhesive formulations the residence time of the drug can be enhanced. Topical delivery of drugs to the eyes most important route

for the treatment of various eye related disorders. For achieving the effective delivery of therapeutic agents to the eye, various dosage forms such as eye-drops, ointments, gels and ocular inserts can be utilized. Due to effective protective mechanism of the eye, the bioavailability of many drugs is very poor. Reflex lachrymation, drainage and blinking of eyes remove drugs from the eye's surface rapidly. This problem can be overcome by employing mucoadhesive polymers like poloxamer, methyl cellulose, PVP, CAP, PAMAM and thiolated PAA. Mucoadhesive dosage form have also employed for delivery of drugs through rectal and vaginal routes. These routes have several advantages like pain avoidance, tissue damage avoidance, first pass metabolism avoidance, and decrease in hepatic side effects which are found very common during parenteral route of administration. The polymers used for delivery of drugs through rectal and vaginal routes are gelatin, mucin, poloxamer and polycarbophil. Various rectal and vaginal formulations include creams, ointments, in-situ gels, emulgels, tablets.

1.1 Advantages of Mucoadhesive Drug Delivery System

- The buccal drug delivery provides a relatively rapid onset of action as compared to the other non-oral routes, hence, has a high patient acceptability.
- Improved patient compliance due to the easy application of dosage forms in comparison to the injections and don't provide any painful sensation.
- The mucosal membranes are highly vascularized so that the administration as well as removal of a dosage form is easy.
- The sustained drug delivery can be achieved by using the mucoadhesive polymers of 'SR' grades.
- Due to the high extent of perfusion the rate of drug absorption is faster.
- The side effect that can arise due to oral administration, such as, nausea and vomiting, they can be avoided completely.
- The mucoadhesive drug delivery can be easily used in case of unconscious and less Co-operative patients.
- The drugs, which show poor bioavailability via the oral route, can their bioavailability can be enhanced by formulating their mucoadhesive delivery systems .

1.2 Mechanism Of Mucoadhesion

The mucoadhesion can be defined as an interfacial phenomenon in which the two materials, in which one may be artificial such as mucoadhesive polymer and other may be the mucin layer of the mucosal tissue, are held together by means of interfacial forces of attraction. "Mucoadhesive" is defined as an artificial substance that is capable of interacting with mucus membrane and being retained on them or holding them together for extended or prolonged period of time. During the process of adhesion, generally the two stages have been identified are given below.

Contact Stage: During this stage, when the mucoadhesive material comes in contact with mucus membrane, an intimate wetting occurs between the mucoadhesive and mucous membrane. This wetting of the mucoadhesive is done by the mucus present in the mucosal membrane.

Consolidation Stage: By means of different physicochemical forces of attraction the mucoadhesive material gets joined to the mucus membrane and resulting in a long lasting mucoadhesion. This is called as the consolidation stage. After these two stages the process of mucoadhesion completes.

1.3 Theories Of Mucoadhesion

The process of mucoadhesion is mainly based on formation of two types of bond between bio adhesive system and mucus membrane and they are:

Chemical Bond: It may include covalent bonds, Weak secondary bonds, ionic bond and hydrogen bond etc.

Mechanical Bond: This bond can be arising from the physical connection between two surfaces. It is similar to that of the interlocking system. On the basis of nature and strength of these two kinds of bonds, there are following five theories of mucoadhesion that are been postulated.

Electronic Theory: According to the electronic theory, there is difference in the electronic structure of mucin surfaces and bio adhesive system which results in attaining a electronic gradient. Due to presence this electronic structure difference, the transfer of electrons occurs in these two systems (mucin surface and bioadhesive system) when they come in contact with each. As a result of this electron transfer there is the formation of an electronic bi-layer at the

interface of the two surfaces. This interfacial bi-layer exerts an attractive force in the interface of two surfaces that may produce an effective mucoadhesion .

Adsorption Theory: This theory describes the involvement of both type of chemical bond, that is, primary and secondary bond in the bio adhesion mechanism. Both the surface that is mucin and drug delivery system has their own surface energy. When they come in contact, the adhesion occurs due to the surface energy and results in the formation of two types of chemical bond. Primary chemical bond such as covalent bond, which is strong in nature, thus produces a permanent bonding, whereas secondary chemical bond involves Vander-Waals forces, hydrophobic interaction and hydrogen bonding, which are weak in nature, thus produces a semi-permanent bond.

Wetting Theory: This theory is based on the mechanism of spreadability of drug dosage form across the biological layer. This theory is mainly applicable to liquids or low viscous mucoadhesive system. According to this theory, the active components penetrate in to the surface irregularities and gets harden it that finally results in mucoadhesion

Diffusion Interlocking Theory: This theory describes the involvement of a mechanical bond between the polymeric chain of drug delivery system and polymeric chain of mucus membrane, that is, glycol proteins. When two surfaces are in intimate contact, the polymeric chain of drug delivery system penetrates in to the glycoprotein network. According to this theory, the bioadhesion basically depends on the diffusion coefficient of both polymeric chains. The other factors that may influence the inter movement of polymeric chain are molecular weight, cross linking density, chain flexibility, and temperature in order to achieve a good bio adhesion, the bio adhesive medium should have a similar solubility with glycoprotein resulting in effective mucoadhesion .

Fracture Theory: The fracture theory is mainly based on the fact that, the force required to detach the polymeric chain from the mucin layer is the strength of their adhesive forces. This strength may be also called as fracture strength. The fracture strength can be determined by using the formula given below

$$G=(E \cdot e/L)^{1/2}$$

- G-Fracture strength,
- E-Young's modules of electricity,
- e-Fracture energy,
- L-Critical crack length.

1.4 Factors Affecting Mucoadhesion

Molecular Weight: The mucoadhesion strength of a mucoadhesive polymer mainly depends upon its molecular weight and polymeric linearity. Generally, for the linear polymers (e.g., Polyethylene glycol), the bioadhesive property is directly proportional to the molecular weight i.e., PEG-200000 having greater mucoadhesive strength than that of PEG-20000. But in case of nonlinear polymer, the mucoadhesive strength of polymer may or may not be dependent of its molecular weight. This is mainly because the helical or coiled structures of such polymer may shield some of the adhesive group, which are mainly responsible for the adhesive property.

Concentration Of Polymer: The concentration of a mucoadhesive polymer is a significant factor of determining its mucoadhesive strength. There is an optimum concentration for a mucoadhesive polymer where it produces the maximum mucoadhesion. For some highly concentrated polymeric systems, beyond the optimum level of polymer, the mucoadhesive strength of polymer starts to fall down significantly because the concentration of polymer molecules starts rising over the molecular concentration of the liquid medium so that there is no further chain formation between liquid medium and polymer. As a result of this, the polymer particles remain separated from liquid medium, due to this the mucoadhesive strength of that polymer starts fallen down. On the other hand, when the concentration of the polymer is too low as compare to the concentration of liquid medium, the number of polymer chains per unit volume of liquid medium is less, the mucoadhesive strength of polymer at that concentration is also very less.

Flexibility Of Polymer Chains: Greater the flexibility of the mucoadhesive chain causes the greater diffusion into the mucus network of buccal cavity. This results in increased mucoadhesion. The flexibility of polymer chain decreases with increase in the concentration of polymer. For an effective bioadhesion, the polymer chain should effectively diffuse into the mucus layer. The flexibility of polymer chain depends on the viscosity and diffusion coefficient of that chain.

Spatial Confirmation: The mucoadhesive strength of a polymer is also dependent on the conformation or spatial arrangement of polymers i.e., helical or linear. The polymers showing linear conformation having the greater mucoadhesive strength as compare to the polymers showing helical conformation. Because, the helical conformation of polymer may shield various active groups, that are primarily responsible for mucoadhesion, thus reducing the mucoadhesive strength of the polymer.

Swelling Or Hydration: The proper hydration of mucoadhesive polymer is essential for the desired mucoadhesive strength. With increase in hydration the pore size of polymer increases which results induced mobility and enhanced interpenetration.

Hydrogen Bonding Capacity: Hydrogen bonding is another important factor for mucoadhesion of a polymer. For mucoadhesion to occur, desired polymers must have functional groups that are able to form hydrogen bonds. Ability to form hydrogen bonds is due to the presence of (COOH, OH etc.,). Flexibility of the polymer is important to improve its hydrogen bonding potential. Polymers such as polyvinyl alcohol, hydroxylated methacrylate and poly (methacrylic acid) as well as all their co-polymers are having good hydrogen bonding capacity.

Cross Linking Density: The cross linking density of the polymer determines its higher molecular weight. The cross linking density indicates the number of average molecular weight of the cross linked polymer, which determines the average pore size. When the cross linking density of polymer is higher, it reduces the pore size of polymer chain which results in reduced diffusion of water into the polymer network. The reduced diffusion results in the decreased penetration of polymer into the mucin and finally decreases the mucoadhesive strength.

Charge: The bioadhesive property of ionic polymer is always higher than that of non-ionic polymer. In neutral or slightly alkaline medium, the cationic polymer shows superior mucoadhesive property. It has been proven that, cationic high molecular weight polymer such as chitosan possess good bioadhesive property.

1.5 Environment Related Factors

pH of Polymer-Substrate Interface: The pH of polymer-mucin interface should be same as it is possible, because, the difference in pH amongst the two systems may results in the transfer of charge due to the higher pH gradient. This may affect the mucoadhesion.

Applied Strength: While placing a buccal mucoadhesive drug delivery system, sufficient strength should be applied in order to provide a good bioadhesive property. Even though there is no attractive forces between polymer and mucus, then application of high pressure for sufficient long time make the polymer become bioadhesive with mucus.

Initial Contact Time: Greater the initial contact time between the mucoadhesive polymer and the mucus layer results in the increased swelling as well as interpenetration of the mucoadhesive polymer chain. Hence, increases the mucoadhesion strength of the polymer chain.

Moistening: Moistening is required to allow the mucoadhesive polymer to spread over the surface. It creates a network of polymer chains of sufficient pore size. Through these pores, the interpenetration of polymer and mucin molecules takes place that results in increasing the mobility of polymer chains for the proper diffusion of mucoadhesive polymer in mucin layer.

Mucin turnover: High mucin turnover is not beneficial for the mucoadhesive property because of following reasons: The high mucin turn over limits the residence time of bioadhesive polymer as it detaches from the mucin layer, even though it has a good bioadhesive property. High mucin turn over may produce soluble mucin molecule, thus molecule interact with the polymer before they interact with mucin hence there will not be sufficient mucoadhesion.

Disease State: In some disease states, the secretion of mucus from the mucus membrane gets decreased (e.g., in Dry Mouth Syndrome and in old age). So that there is not sufficient amount of mucus present at the site of attachment of mucoadhesive dosage form. This may leads to improper moistening and swelling of polymer. Due to which there is decreased mucoadhesive strength of mucoadhesive dosage form.

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.

Concomitant Diseases: Concomitant diseases can alter the physicochemical properties of mucous or its quantity (for example, hypo and hyper secretion of gastric juice), increases in body temperature, ulcer disease, colitis, tissue fibrosis, allergic rhinitis, bacterial or fungal infection and inflammation.

Tissue Movement: Tissue movement occurs on consumption of liquid and food, speaking, peristalsis in the GIT and it affects the mucoadhesive system especially in case of gastro retentive dosage forms.

2. BUCCAL MUCOADHESIVE DRUG DELIVERY SYSTEM:

The mucoadhesive drug delivery system in the mucus membrane of oral cavity can be categorized into three delivery systems:

- Sublingual delivery
- Buccal delivery
- Local delivery

These oral sites provide the high blood supply for the greater absorption of drug with sufficient permeability. From these three sites of oral mucoadhesive drug delivery system, the buccal delivery is the most convenient site. There are many advantages of buccal mucoadhesive drug delivery system over other drug delivery systems are given as follow:

The buccal mucoadhesive drug delivery system can be used for both local as well as systemic delivery of many drugs. Buccal mucoadhesive dosage forms are easy to applicate as compare to other adhesive dosage forms. Increased patient compliance over the injectables. It is the most preferred delivery system for the local treatment of drugs. So that there are wide range of mucoadhesive formulations has been.

2.1 Limitations:

- The drugs having bitter taste cannot be formulated.
- The drugs which irritate oral mucosa, cause allergic reactions and discoloration of teeth cannot be formulated.

- If formulation contains antimicrobial agents, affects the natural microbes in the buccal cavity.
- The patient feels discomfort in eating, drinking and speaking.
- Only the drugs which are absorbed by means of passive diffusion can be administered by buccal route.
- Drugs which are unstable at buccal pH cannot be administered by this route.
- Sometimes, the degradation of moisture sensitive drugs may take place by saliva.

2.2 Disadvantages of Buccal Drug Delivery System:

- Low permeability of the buccal membrane, specifically when compared to the sublingual membrane.
- Smaller surface area. The total surface area of membranes of the oral cavity available for drug absorption is 170 cm² of which ~50 cm represents non-keratinized tissues, including the buccal membrane.
- The continuous secretion of saliva (0.5-2 l/day) leads to subsequent dilution of the drug.
- Swallowing of saliva can also potentially lead to the loss of dissolved or suspended drug and, ultimately, the involuntary removal of the dosage form .
- These are some of the problems that are associated with current buccal drug delivery system.

3. OVERVIEW OF ORAL MUCOSA:

The oral mucosa acts as the one of most important route for the delivery of drugs. It provides the delivery of drugs by both systemic as well as local pathways. The oral cavity contains a large surface area of mucus membranes for the complete absorption of various drugs. The total surface area of oral cavity i.e., lined by mucus membranes is near about 100 cm² .

Following are the several parts of the oral cavity:

- The floor of mouth (sublingual)
- The buccal mucosa (cheeks)
- The gums (gingiva)
- The palatal mucosa and
- The lining of lips.

The oral mucosal cavity consists of the multi-layered epithelial tissues that are further covered by mucus. There is a basal membrane present inner to the epithelial tissues. Inside the basement membrane there is a layer of connective tissues called as lamina propria. The

lamina propria functions as providing the mechanical support. After this, the sub-mucosal part starts. It contains the various blood vessels as well as nerves from central nervous system. The sub-mucosal part provides the highest vascularity for the complete absorption of the drugs. The human oral mucosa contains both keratinized epithelium (found in the gingiva and part of the hard palate) and the nonkeratinized epithelium (found in the surface of the distensible lining mucosa of the soft palate, floor of mouth, lips and cheek). The oral mucosa mainly composed of three layers.

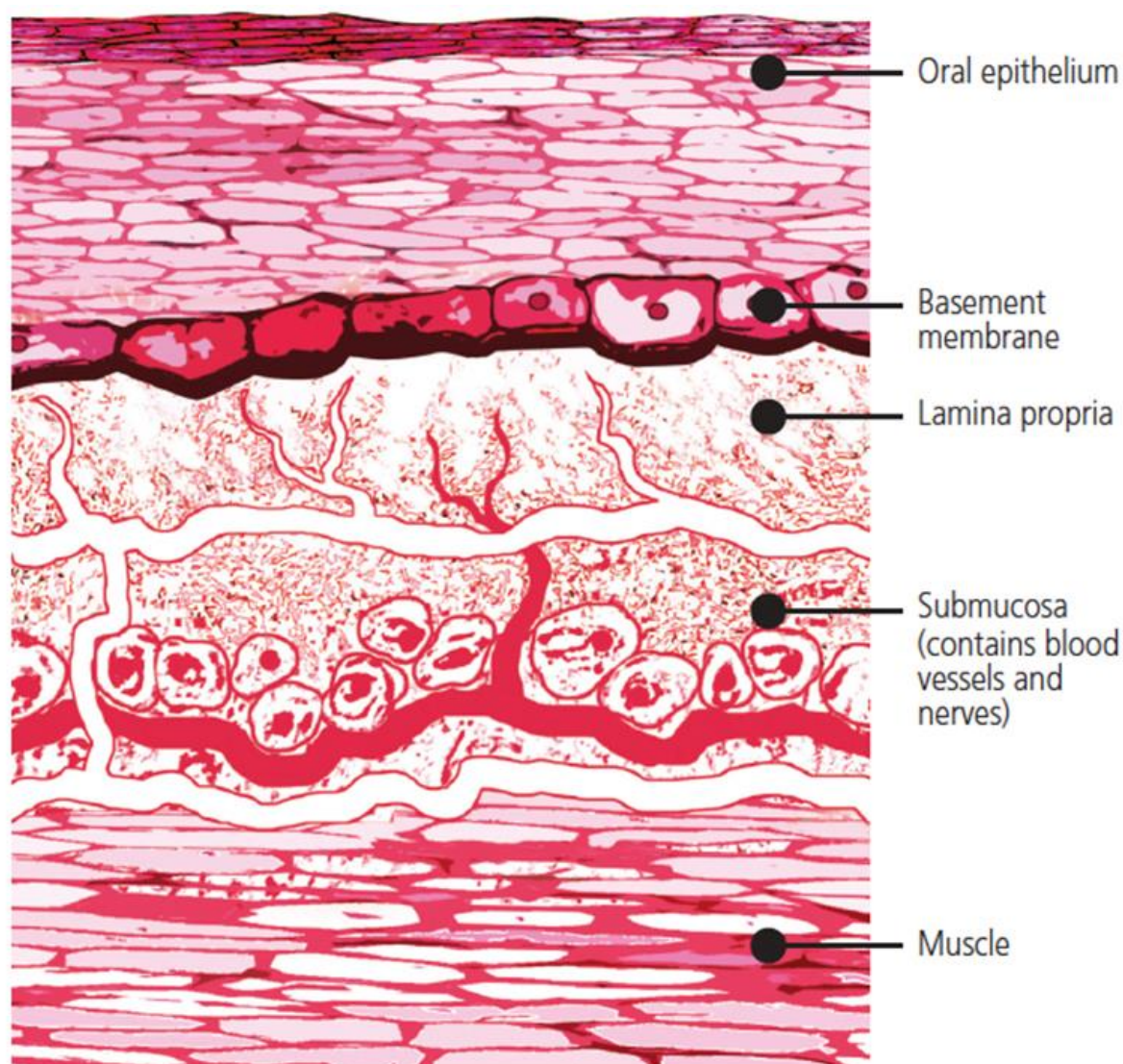


Fig. 1: Buccal Mucoadhesive.

3.1 Mucus Composition:

The oral mucus is generally secreted by various glands of oral cavity that are sublingual gland, parotid gland, and other salivary glands. The mucus is a translucent gel secreted by goblet cell or by special exocrine glands with the mucus cells. Mucus glycoproteins are the

high molecular proteins that contain attached oligo-polysaccharide units. The mucus contains following oligosaccharide units.

- L-fructose
- D-galactose
- N-acetyl-D-glucosamine
- N-acetyl-D-galactosamine
- Sialic acid

3.2 Functions Of Mucus:

- Cell-cell adhesion
- Lubrication
- Bioadhesion
- Protective
- Barrier

3.3 Buccal Mucoadhesive Dosage Forms:

An ideal drug delivery system should possess the two main properties that are given below:

- a) Spatial placement (for targeting drug to specific organs/tissues)
- b) Temporal delivery (for controlling the rate of drug delivery)

Today, it is very difficult to formulate an ideal drug delivery. This led to development of sustained/controlled release delivery systems. Still, sustained or controlled delivery system lacks in preventing drug loss by either hepatic first pass metabolism or pre-systemic elimination like gastric, intestinal, or colonic degradation. So, several approaches have been tried to form a suitable dosage form for the above said conditions. Oral mucosal drug delivery, one of the physiological approaches, was reported to be a method to formulate these drugs into suitable dosage form with good therapeutics effects. Oral mucosal drug delivery of different drugs can be achieved by bioadhesive polymer systems.

3.4 General Considerations In Designing Dosage Forms:

Physiological Aspects: Due to the constant flow of saliva and regular movement of tissues present in the oral cavity the local delivery of the drugs in oral cavity is the most challenging aspect. Due to this, the residence time of the drugs for this route is very short. The buccal mucoadhesive formulations are being used to overcome this problem. The bioadhesive

polymers are been use for improving the residence time in the buccal mucosa, and hence increase the absorption of drugs delivered by this route. Due to the local absorption of drugs, side effects are also being reduced as compared to in case of systemic delivery. Generally, a buccal delivery device should have the size of about 1-3 cm² and the daily drug dose should be not more than 25 mg. An ellipsoid or circular shapes are being the most acceptable shapes for buccal delivery device.

Pathological Aspects: The barrier property of buccal mucosa is mainly due to the presence of epithelial tissue. The thickness of epithelial tissue can be affected by many diseases that may change the barrier property of epithelial tissue. Some diseases or treatments may cause the alteration in rate of mucus secretion. These changes at the mucosal surface due to various pathological conditions may affect the residence time buccal delivery device.

Pharmacological Aspects: The design and formulation of a buccal delivery dosage form depends upon the nature of delivery (local or systemic), drug targeting site and mucosal site to be treated. The buccal delivery is generally preferred for systemic delivery as compared to the local delivery of drugs.

Pharmaceutical Aspects: The buccal drug delivery system is generally used for desired absorption of poorly water soluble drugs. For this purpose, firstly, the water solubility of the drug is enhanced by using specific solubility enhancement method e.g., by forming complex with cyclodextrin. Hence by improving solubility, the absorption of drug also get increased in buccal mucosa. There are many other factors that affect the release and penetration of drug, must be optimized during formulation design. In addition to this required physicochemical characteristics required for desired release of and absorption of drug, organoleptic properties of the drug as well as buccal dosage form should also be considered during its formulation design. Some excipients such as plasticizers and penetration enhancers can be used in the formulations to enhance their effectiveness and acceptability. As the buccal mucosa is less permeable, so in order to enhance the permeability, various penetration enhancers can be used. Some commonly used penetration enhancers are bile salts, fatty acids, and sodium lauryl sulphate. Some enzyme inhibitors may be used to inhibiting the degradation of drug by various enzymes present in the saliva due to which the bioavailability of drug can be improved. There are some polymers such as carbopol, polycarbophil that can inhibit certain proteolytic enzymes (trypsin, carbo-peptidases etc.,). pH of delivery device is another pharmaceutical factor that should be considered during formulation of buccal delivery

devices containing ionisable drugs. The pH of buccal device should be near to neutral as the pH of saliva is from 6.6 to 7.4. The large differences in pH may cause irritation on the mucosal site.

3.5 Basic Components Of Buccal Drug Delivery System:

Drug Substance: The suitable active pharmaceutical ingredient or drug substance should be selected on the basis of its pharmacokinetic properties. The drug should be of following characteristics:

- The one time dose of drug should be small (dose \leq 25 mg).
- The drug should be having short biological half life ranging from 2 to 8 hrs.
- The drugs showing first pass metabolism can be used for buccal drug delivery for avoiding the first pass metabolism.

Bioadhesive Polymer: The use of bio adhesive polymer determines the various parameters such as mucoadhesive strength, thickness, in-vitro release and the residence time of the drug delivery device. Generally the polymers with high molecular weight are preferred because; they show effective release rate controlling properties. An ideal polymer should have following characteristics for achieving the optimized results:

- It should be inert.
- It should be compatible with the environment and drug.
- It should be adhere quickly with the mucus membrane and adherence should be long lasting for required time.

Backing Membrane: Backing membrane used for the formulations should be impermeable to drug as well as mucus in order to prevent the unnecessary drug loss from all sides of the device. The materials used for preparing backing membrane should be inert, insoluble or should have low water solubility. The commonly used materials in backing membrane include ethyl cellulose, carbopol, sodium alginate, HPMC, polycarbophil etc.,

Plasticizers: The plasticizers are used in order to improve the folding endurance of the delivery device. They provide enough flexibility to the dosage form for improving its patient acceptability and patient compliance. Few examples of commonly used plasticizers are PEG-400, PEG-600, dibutyl phthalate, propylene glycol etc.,

Permeation Enhancers: These are the chemicals or liquids used to improve the permeation of drug from device into the mucus membrane. The permeation enhancers work by following mechanisms.

Mechanisms Of Action Of Permeation

- By reducing the viscosity of mucus.
- By increasing the fluidity of lipid bilayer membrane.
- By countering the enzymatic barrier.
- By increasing the thermodynamic activity of drugs

3.6 Classification Of Buccal Adhesive Dosage Forms:

3.6.1 Solid Dosage Form:

Buccal Tablet: The bioadhesive tablets are most preferable mucoadhesive device in order to improve bioavailability of drugs. Mucoadhesive tablet can be prepared by methods such as wet granulation and direct compression. In case of buccal drug delivery, the tablets are placed in buccal pouch below the muscles of teeth. Mechanism of drug release is erosion.

Advantages: The buccal tablet can developed for verity of drug including insoluble to soluble, low dose to high dose, hydrophilic to lipophilic. As compared to conventional tablet, buccal tablet are flat, small and retained at site until release and/or dissolution is complete.

Disadvantages: They provide little bit of discomfort to the buccal cavity because of their solid nature.

Bioadhesive Microsphere: Microsphere is an important part in case of novel drug delivery system. This mucoadhesive microsphere is mainly used for purpose of targeting to specific body cavity.

Advantages: They provide high absorption and enhanced bioavailability of drug due to their surface-to-volume ratio that provide highest contact of microspheres with mucus membrane.

Bioadhesive Wafers: It is a newer dosage form for bioadhesive buccal delivery. It is used at the periodontal region for the treatment of infections related with periodontitis .

Bioadhesive Lozenges: Bioadhesive lozenges are generally used for delivery of drugs that are antimicrobials, corticosteroids, local anesthetics, antibiotics and anti-fungals and are used topically in the buccal cavity.

Advantages: Better patient compliance and easy to swallow.

Disadvantages: The lozenge produce a high release rate of drug at initial stage and rapidly reaches the sub-therapeutic level.

3.6.2 Semisolid Dosage Form:

Bioadhesive Patch/Film: Patches or film are preferred over tablet because of their comfort and flexibility. They are formulated such that it can provide contact between bioadhesive formulation and mucosa. Thickness of patch is a constraint which cannot provide control release of drug for longer period of time. In case of drug containing reservoir layer type; drug is released in controlled manner. Patches and film are mostly preferred for local action to treat oral diseases. There are many methods used for formulation of patch or films such as solvent casting method, hot melt extrusion technique, direct milling, semisolid casting, solid dispersion extrusion etc. Among that solvent casting is most popular method and widely used.

Buccal Gel and Ointment: As the advantage of dispersion gel and ointment has come in focus. They do not have accurate dosing as unit dosage form like tablet, patches or films, hence they are mostly preferred for local action where dose accuracy is less or not concern.

Advantages: local application of steroidal gel for treatment of mucosal ulceration in order to decrease the side effects of steroids.

Disadvantages: It has less patient acceptability than other mucoadhesive formulation.

Medicated Chewing Gum: Medicated chewing gum contains drug which after chewed, offer high amount of drug to prove local action in mouth. It can also shows absorption through systemic circulation. The medicated chewing gum for nicotine replacement therapy is available. Likewise caffeine chewing gums are also available.

3.6.3 Liquid Dosage Form:

These are available in form of solution or suspension of drug in suitable vehicle. There are many liquid dosage forms that are available in market such as mouthwashes, mouth freshener, and are generally used for local delivery of drugs. Wide varieties of polymers are used from that chitosan has greatest binding capacity than other. Viscous liquid formulations are preferred to coat buccal cavity either as vehicle or as protectant .

4. EVALUATION OF BUCCAL MUCOADHESIVE DOSAGE FORMS:

4.1 Experimental Methodologies For Buccal Absorption/ Permeability Study:

In-Vitro And Ex-Vivo Methods Of Evaluation: The in-vitro studies are used to determine the release, solubility and dissolution of dosage forms. The ex-vivo studies conducted on the animal tissues and membranes by preparing animal models. The tissues are taken from the freshly died animals and are been used within 2 hrs after their separation. The membranes are then placed and stored in ice-cold (4°C) Krebs's buffer upto the time before they are mounted between diffusion cell for the ex-vivo permeation experiments.

In-Vivo Methods: It is also called as buccal absorption test. For kinetic drug absorption measurement this method can be used. The procedure involves the swirling of a 25 ml sample of the test solution for up to 15 min by human volunteers in their buccal cavity. After 15 min the solution expelled out. In order to calculate the amount of drug absorbed, the amount of drug present in expelled volume can be calculated. The main disadvantages including salivary dilution of drug and accidental swallowing of sample solution may arise.

Experimental Animal Species: Choice of animal for the experimental study is very important factor. To perform in-vivo study researchers can prefer the animals depending on test to be performed. Most of animals having the keratinized buccal mucosa, but the rabbit and pig are the only animals which having non-keratinized mucosa as like humans. To study permeation of drug monkey, dog, pig animals are mostly used.

In-Vitro Release Study: For simulating in-vivo conditions, researchers have developed different apparatus like:

- Beaker method
- Dissolution apparatus
- Interface diffusion system
- Modified Keshary Chien cell

4.2 Methods To Study Mucoadhesive Strength:

Polymer characterization can be done by evaluating their mucoadhesive strength both in-vivo and in-vitro technique.

In-Vitro Evaluation Techniques:

Measurement Of Tensile Strength: In this method, the force required for breaking the bioadhesive bond between mucus membrane and bioadhesive polymer is calculated. The following formula can be used for determining the tensile strength of buccal mucoadhesive device.

$$\text{Force of adhesion (N)} = \text{Mucoadhesive strength} \times 9.81/1000$$

$$\text{Bond strength (N/m}^2\text{)} = \text{Force of adhesion (N)} / \text{Surface area of tablet (m}^2\text{)}$$

Measurement Of Shear Strength: In this technique the mucoadhesive strength is determined means of measurement of shear stress applied to the adhesive device. In this technique, firstly select two smooth polished glass box, and fix one box on a glass plate with adhesive, on a leveled table. To the upper block, tied a thread and then pass down the block through a pulley. The length of the thread from the pulley should be 12 cm. At the bottom side of the thread, attach a 17 g pan along with weights. And hence the shear strength was determined using an appropriate method by correlating the weight required to break the adhesion.

4.3 Other In-Vitro Methods

Rheological Study: The rheological information of polymer–mucus mixtures can offer an acceptable in-vitro model which can correlate with in-vivo performance of a mucoadhesive polymer. It is best method for determination of mucoadhesive potential of polymer by comparing binary mucus/polymer blends to the equally concentrated monocomponent mucus/polymer system. The rheological behaviour of two macromolecular species can be changed by techniques such as chain interlocking, and chemical interaction that occur between the bioadhesive polymer and mucin chains.

Colloidal Gold Staining Method: This is a new in-vitro method which was described for comparison of mucoadhesive property of various hydrogels. In this technique, there is a use of red colloidal gold particles which are stabilized by the partially or fully adsorbed mucin gold. Because of interaction mucoadhesive develops red colour on its surface. The

mucoadhesive properties of the mucoadhesive device can be compared by measuring the intensity of red colour.

Fluorescent Probe Method: In this method lipid bilayer of cultured human conjunctiva cells is labelled with pyrene which is used as a fluorescent probe. If the polymer can adhere to this cell, it can cause change in fluorescence due to change in surface compression when compared with control cell. This change in degree of fluorescence is directly proportional to amount of polymer binding. To determine density on adhesion, polymer charge, and charge sign another probe can also be used. It states that determination of bioadhesive bond is based on molecular interaction of polymer with mucus

4.4 In-Vivo Methods Of Evaluation:

Gamma Scintigraphy Techniques: It is a non destructive method for the evaluation of pharmaceutical dosage forms. This technique is used to get the different information of the different areas of GI tract, the site of drug absorption, the time and site of disintegration of dosage forms. This instrument also used to check the effect of disease and food size on the biopharmaceutical characteristics of the dosage forms. Generally this method is used to study the distribution and the retention time of mucoadhesive tablets.

GIT Transit Using The Radio-Opaque Technique: In this technique radio opaque markers are used to determine effect of polymer in GI transit time. Non invasive method such as faeces examination and xray evaluation can provide sufficient data to study GI residence time. Cr 51, Tc99 m, In113 m or I123 these are some examples of marker which are used for mucoadhesive drug delivery.

Moisture Absorption Studies For Buccal Patches: The determination of moisture absorption by the buccal films or patches is necessary for evaluation of the drug absorption and drug release parameters. Moisture absorption studies can be performed in 5% w/v agar in distilled water. Heat the solution and then transferred to petri plates and allowed to solidify. Then select the six buccal patches from each batch weigh properly. After solidification of agar positioned them on the surface of agar plate and incubate at 37°C in incubator. Weigh all the patches again, and calculate the percentage of the absorbed moisture by using the following formula-

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

Thickness: Select randomly five different patches and with the help of screw gauge measure the thickness.

Folding endurance: Select a patch and fold it repeatedly at the same point until it ruptures. The total number of folding required for cracking or breaking a patch is called as its folding endurance. The folding endurance of the buccal patch should be greater than 150 times.

Swelling study for tablet: Weigh the mucoadhesive dosage form accurately and place in a beaker containing 200 ml of buffer media. Remove the dosage form after each interval and weigh it again. Follow this process up to 8 hours. The following formula can be used for calculating the swelling index:

$$\text{Swelling Index (S.I.)} = (W_t - W_o) / W_o$$

Where,

- S.I.=Swelling index
- W_t =Weight of the dosage form at time t
- W_o =Initial weight of dry dosage form.

Surface pH Study: The surface pH of the buccal dosage form is calculated in order to examine the possibility of any side effects that may be arise in-vivo because of acidic or basic pH. In this method a glass electrode is used for determining pH. Allow the dosage form to swell by keeping it in contact with distilled water at room temperature for 2 hrs. Then measure the pH by taking the electrode in contact with the surface of the dosage form.

Residence Time: For determining the residence time of the buccal dosage forms the modified disintegration apparatus. 800 ml isotonic buffer pH 6.75 solution can be used as disintegration medium 3 cm long rabbit mucosa was attached to glass slide and it was vertically attached to side arm. One surface of mucoadhesive tablet was hydrated with 15 ml of isotonic phosphate buffer solution then it was taken in mucosal contact. The movement of glass slide was allowed to up and down for complete immersion. Then time for detachment of tablet from mucosal surface can be noted.

Future Perspectives:

A buccal adhesive system offers countless advantages in terms of economy, accessibility, administration, withdrawal and patient compliance. Research scientists are now looking out the traditional polymers for novel drug transport systems. From the recent years,

pharmaceutical experts are finding various methods to develop buccal adhesive dosage forms and to improve the bioavailability of less orally bioavailable drugs. It is found that the second generation muco adhesive polymer having great potential. Micro particulate or nanoparticulate systems of less bioavailable drugs are being designing in the bio adhesive systems are showing much more satisfactory results as compared to conventional buccal drug delivery systems.

DISCUSSION

Mucoadhesive drug delivery systems significantly improve drug bioavailability by increasing the residence time of formulations at mucosal surfaces. The interaction between polymeric materials and mucus is governed by physicochemical bonding mechanisms such as hydrogen bonding, van der Waals forces, and mechanical interlocking. Several theories, including electronic, adsorption, wetting, diffusion, and fracture theories, explain the adhesion process between polymers and mucin.

The performance of mucoadhesive systems is strongly influenced by polymer properties such as molecular weight, chain flexibility, swelling behavior, and cross-linking density. Environmental factors such as pH, mucin turnover, and saliva flow also play a critical role in determining adhesion strength and drug retention. Among various mucosal routes, the buccal cavity is most favorable due to its large vascular surface, ease of administration, and avoidance of hepatic first-pass metabolism.

Buccal drug delivery systems can be formulated in solid, semi-solid, and liquid forms, including tablets, films, patches, gels, and microspheres. Each system offers unique advantages depending on the drug characteristics and therapeutic requirements. However, limitations such as low permeability, saliva dilution, and taste masking challenges still restrict broader applications.

Evaluation techniques including in-vitro, ex-vivo, and in-vivo methods are essential for assessing mucoadhesive strength, drug release, swelling behavior, and residence time. Advanced methods such as gamma scintigraphy and rheological studies provide deeper insights into polymer-mucus interactions. Continued research in polymer science and nanotechnology is expected to further enhance the effectiveness of buccal mucoadhesive systems.

5. CONCLUSION

Mucoadhesive drug delivery systems represent a promising approach for improving therapeutic outcomes by enhancing drug retention and absorption at mucosal sites. Buccal delivery, in particular, offers significant advantages including patient convenience, rapid onset of action, and avoidance of first-pass metabolism. Despite certain limitations such as permeability barriers and formulation challenges, advancements in polymer technology and formulation strategies are expanding their clinical potential. Future developments in nanoparticulate and second-generation mucoadhesive polymers are expected to further improve drug targeting efficiency and bioavailability, making mucoadhesive systems an important focus in modern pharmaceutical research.

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