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Review Article

A Comprehensive Review on Mucoadhesive Drug Delivery

Vasu Chauhan*¹ , Abhinav Agrawal² , Umesh Kumar Singh²

¹ Raj Kumar Goel Institute of Technology, Master in Pharmaceutics, Ghaziabad, Uttar Pradesh, India

² Raj Kumar Goel Institute of Technology, Faculty of Pharmacy, Ghaziabad, Uttar Pradesh, India

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*Address for Correspondence:

Vasu Chauhan, Raj Kumar Goel Institute of Technology, Ghaziabad - 201003, Uttar Pradesh, India

Abstract

The two major problems in the development of new drugs are low aqueous solubility and low oral bioavailability. Although, drug delivery via oral route is most preferred for years but it also has some drawbacks. Various techniques for improving the solubility have been developed, however the success of these techniques depends on the physical and chemical properties of the drug under development. In recent years, mucoadhesive drug delivery gained high popularity in comparison to other routes of drug delivery as it can circumvent the drawbacks of conventional delivery system such as first pass metabolism, enzymatic degradation, GI toxicity of some drugs, instability in acidic or alkaline environment and poor bioavailability. Various mucoadhesive dosage forms have been developed recently including tablets, patches, films, ointments, gels etc. The objective of current review is to provide a comprehensive overview of mucoadhesive drug delivery including the mechanism and theories behind mucoadhesion, factors affecting mucoadhesion, different dosage forms, polymers used in mucoadhesive formulations, characterization techniques, marketed products and current scenario & future challenges.

Keywords: Mucoadhesion, Buccal mucosa, Mucoadhesive drug delivery, Mucoadhesive polymers, Mucus membrane, Patents

1. Introduction

Delivery of drug molecules via oral route is most desired in comparison to other administration routes but it also has some restrictions including primary hepatic metabolism, degradation of drug by enzymes within the alimentary canal, and toxicity in GI that limits oral administration of some drugs, mostly peptides, and proteins.¹ Most pharmaceutical dosage forms are designed for immediate release which has some drawbacks such as frequent administration is required for the drugs that have a short half-life, poor patient compliance, and higher chances of adverse effects due to fluctuation in drug levels, particularly in case of drugs with small therapeutic index. Several technological innovations were developed that brought the advancement of delivering drug in controlled way that may modernize drug therapy, offers a variety of therapeutic benefits, and overcome the shortcomings of traditional systems of drug delivery.²

Drug delivery via buccal mucosa is one the good substitute among the a number of routes of administration as it has several merits over the other routes for systemic delivery of medicine such as directly deliver drug to systemic, avoidance of first-pass effect, and circumvention of pre-systemic elimination within the gastrointestinal (GI) tract. These features make it a more appealing and feasible location for medicine delivery directly into the blood. Moreover, the buccal cavity is more convenient for self-medication and the dosage form can be promptly removed from the buccal cavity in case of toxicity.³ Buccal drug delivery systems can be formulated as solid unit dosage forms, ointments, gels etc.⁴

2. Mucoadhesive Drug Delivery

In the previous few years, the mucoadhesive drug delivery system has become popular and gained substantial attention for both local and systemic medication delivery due to exceptional approachability, avoiding first-pass metabolism, large blood supply, safety, and more patient acceptability with enhanced and better treatment.⁵ In 1947 **T.R. Jacoby et al.**, made attempts to formulate bio-adhesive ointment of Penicillin using gum tragacanth for topical purpose which led to an idea for the development of pharmaceutical formulations using mucoadhesive polymers.⁶ Mucoadhesion is a process of interaction between the mucus layer and bioadhesive polymer covering the body tissues where wetting, absorption, and interpenetration of the involved biopolymer chains take place.⁷

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

(a). Sublingual drug delivery: In sublingual delivery, the drug is delivered to the systemic circulation through the mucous membrane covering the floor of oral cavity.

(b). Buccal drug delivery: In this system dosage form is administered through the mucosal linings of the cheeks.

(c). Local drug delivery: This involve transfer of drug locally to the affected tissues (local effect).⁸

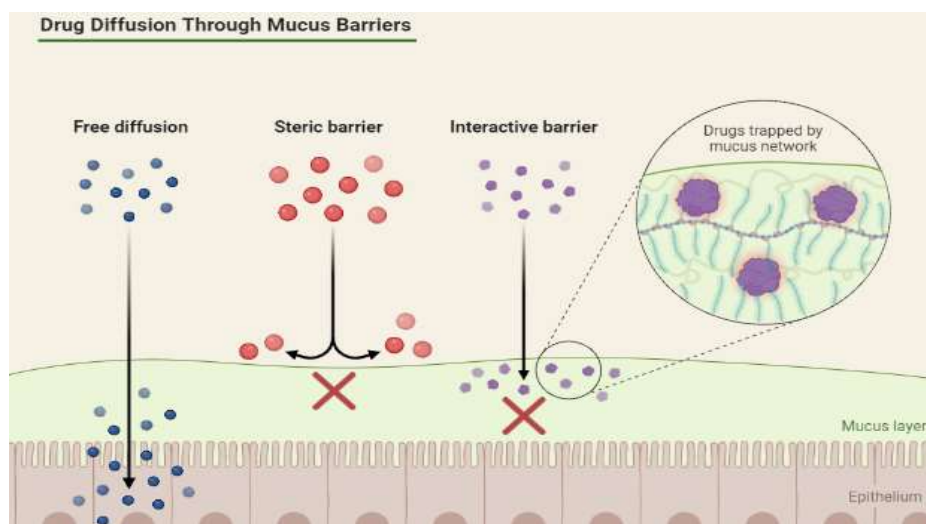


Figure 1: Drug diffusion through Mucous Membrane

2.1 Merits of Mucoadhesive Buccal Drug Administration:⁸

1. It has a relatively larger surface area and a rich blood supply.
2. It bypasses hepatic first-pass metabolism so increases bioavailability.
3. The dosage form is easy to administer and prompt termination of therapy can be facilitated in an emergency.
4. An alternate to administer drug to unconscious patients.
5. Better patient compliance.
6. The prompt onset of action and extended drug release.
7. Buccal route is a better option for delivery of drugs unsuitable for delivery in acidic environment of stomach or prone to enzymatic degradation.
8. Drug absorption by passive diffusion does not require any activation.
9. Buccal mucosa is highly vascularized hence offers more penetrability than skin.

2.2 Limitation of Mucoadhesive Buccal Drug Administration:^{3 4 8 10}

1. This route cannot administer drugs in large doses.
2. Drugs not stable at buccal pH are challenging to deliver.
3. Limits eating and drinking.
4. Possibility of patient's swallowing the formulation.
5. This route cannot administer drugs that have a bitter taste or an unpleasant odour or causes mucosal irritation.
6. Surface area available for absorption is limited.

7. Medicines absorbed by diffusion can only be administered.

8. Continuous salivation (0.5-2 L/Day) causes the medication to dissolve.

9. When saliva is swallowed, the dissolved or suspended drug is lost and eventually the dosage form is unwillingly removed.

3. Oral Mucosa Anatomy and Physiology

Several publications, have extensively discussed the structure and composition of the buccal mucosa.^{11,12} The Buccal mucosa consists of three distinct layers, epithelium, basement membrane, and connective tissues. Connective tissues support oral cavity's basement membrane, which is lined by epithelium. In the oral cavity, two types of epithelium are found: **(I) non-keratinized epithelium** covers the mucosal layer over the soft palate, tongue's ventral surface, mucosa of alveolar, the vestibule, the lips, and the cheeks, and **(II) keratinized epithelium** covers the hard palate and inflexible regions. Originating from the basal cells, epithelial cells mature and modify their shape while expanding in size during the movement toward the surface.

According to the literature, the oral mucosal epithelium in humans, dogs, and rabbits have thickness approximately 500–800 μm .^{13 14} The basement membrane is located between epithelium and connective tissues and provides the necessary adhesion between them, as well as mechanical support to the epithelium. Lamina propria, also known as connective tissue, is made up of fibres of collagen, connective tissues layer, smooth muscles and blood vessels. The external carotid artery provides a rich arterial supply to the buccal mucosa. Among the major arteries supplying blood to the cheek lining in the oral cavity are the buccal artery, few facial artery branches, the posterior alveolar artery, and the infraorbital artery.^{13, 15}

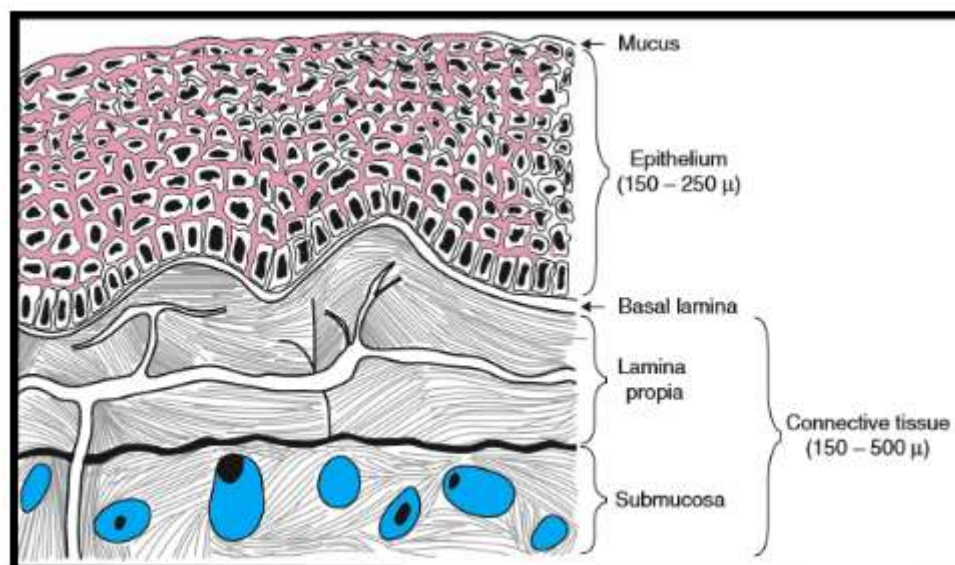


Figure 2: Anatomy of Oral Mucosa¹⁶

Glycoproteins are the water insoluble mucus like secretion protecting the entire oral cavity. A viscoelastic hydrogel consist of 1-5% of water insoluble glycoproteins, 95-99% water, and some other components are like proteins, electrolytes, enzymes, and nucleic acids is present below the apical cell membrane and it act as a protective layer.^{17 18}

Mucosal membranes line the stomach, intestines, ureters, and bladders, in addition to the mouth, nose, eyelids, trachea (windpipe), and lungs. Mucous membranes contain a layer of epithelial cells, either stratified squamous epithelium or simple columnar epithelium. Mucus, which primarily contains mucopolysaccharides, is the major constituent of mucous membranes. Mucous membranes and Mucus serve as lubricants (to keep underlying tissues moist) and act as a barrier against bacteria, fungi, and viruses. Mucous membranes possess specialized functions, such as digestion and absorption of food by the intestinal and gastric mucosae. Nasal and olfactory mucosae contribute to the breakdown of

odor particles in the nose, allowing these substances to be smelled. Additionally, mucosae are also found in the reproductive system such as the vagina. Vaginal discharge is produced by the mucosa of the vagina to self-clean and stays moist. (Bhalerao & Shinde, 2013; Boddupalli et al., 2010; Harris & Robinson, 1992; Shaikh et al., 2011a).^{19 20}

4. Mechanism of Mucoadhesion: 3 4 8 20

It can be described by the two stage mentioned below:

4.1 Contact stage: It involves interaction between mucoadhesive material and mucous layer, the formulation swells and spread over mucus membrane.

4.2 Consolidation stage: Mucoadhesive material is activated by the moisture which further plasticize the system and allows the mucosal adhesive molecules to separate and connect via weak Vander walls and hydrogen bonds.

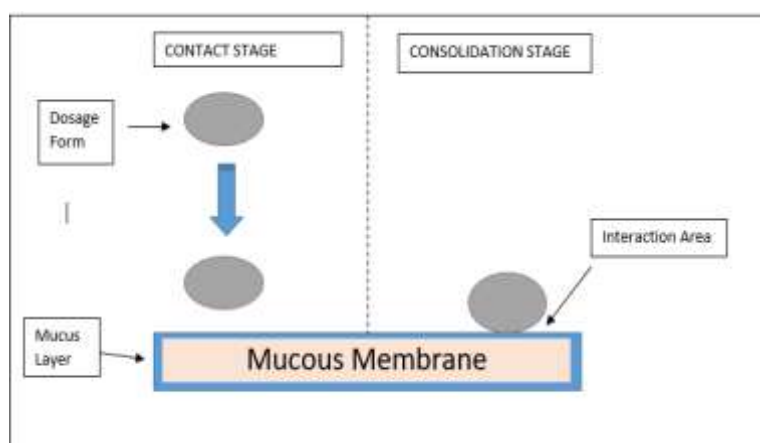


Figure 3: Steps involve in mucoadhesion

Two theories are involved in explaining the consolidation steps:

(a) Diffusion theory: It state mutual interaction between mucoadhesive molecules and glycoprotein of mucus caused by interaction of their chains and the formation of secondary bonds.

(b) Dehydration theory: In aqueous environment while materials come in contact with mucus, it gets jellified and water filled into the dosage form because of concentration gradient till the osmotic equilibrium is achieved. As a result, mucus membrane's contact time between the formulation mixture and mucus increases. Therefore, it is the movement of water, not the interpenetration of macromolecule chains that

causes adhesive connections to strengthen.

5. Theories of Bioadhesion:

Mucosal adhesion is a complicated process and several concepts have been suggested that play an important role in adhesion.

5.1 Adsorption theory^{3,8,20}

According to this theory, when the two surfaces come in contact, the atoms present in two surfaces form chemical bonds due to the surface force acting between them and the adhesion of materials occur. There are 2 types of chemical bonding involved:

5.1.1 Strong Primary bonds: Covalent bonds are undesirable because they are permanent in nature.

5.1.2 Weak Secondary bonds: This involves electrostatic forces, hydrogen, Vander Waals forces, and hydrophobic bonds. These bonds have semi-permanent nature and require less amount of energy to break that makes them the most projecting surface interaction form in adhesion.

5.2 Electronic theory^{3,10,20}

The electronic theory indicates that an attractive electrostatic force occurs when glycoprotein mucin network interacts with bio-adhesive material that results in electrons transfer through the adhesive boundary and adhering surface because of variations in their electronic structure. This creates an electric double layer or charge at the interface responsible for adhesion between the two layers.

5.3 Diffusion theory^{10,20-22}

The basis of "Diffusion theory" lies in interaction between strands of mucin and polymer chains. This theory describes that the polymer and mucous chains penetrate to a sufficient depth and are driven by a concentration gradient to form a semi-permanent adhesive bond. Mobility, diffusivity, contact time, flexibility and nature of mucoadhesive strands are the reasons which impact the inter-diffusion of polymer network. According to the literature, for efficient bioadhesive bonds, the depth of interpenetration ranges from 0.2 – 0.5 μm . To calculate the depth following equation is used:

$$l = (tD_b)^{1/2}$$

Where, **t** is **contact time** and **D_b** is **diffusion coefficient** of the mucoadhesive material in the mucus. In order for diffusion to occur, both the mucoadhesive and the mucus must have comparable chemical structures. Greater structural similarity results in better mucosal adhesion.

5.4 Wetting theory^{3,8,22}

This theory is predominantly relevant to liquid systems or bio-adhesives with low viscosity. This theory defines the affinity of bioadhesive polymer to the surface in order to spread over it and develop intimate contact with the biological surfaces. The liquid bioadhesive material should have an equal to or zero contact angles for proper spreading and diffusivity of polymer must be positive. Lower the contact angle, greater will be affinity. The work of adhesion (W_a) given by the Dupres equation:

$$W_a = \gamma_A + \gamma_B - \gamma_{AB}$$

Where, **A** is **biological membrane** and **B** is **bioadhesive formulation**.

The **work of cohesion** (W_c) is given by:

$$W_c = 2\gamma_A \text{ or } \gamma_B$$

5.5 Fracture theory^{3,4,22}

It states the requisite force for the detachment of polymer from the mucus after adhesion is established. It calculates the maximum tensile strength (fracture strength) during detachment which is equal to adhesive strength is given by:

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

Where, **E** refers to **Young's modulus of elasticity**, **ε** refers to **Fracture energy**, **L** refers to **Critical crack length** of two separated surfaces.

This concept doesn't require any physical interaction between polymer chains and mucus strands that makes it suitable for studying the bioadhesion of rigid polymers that lack flexible chains.

6. Factors affecting mucoadhesion^{20,23,24}

Mucoadhesion properties depend upon the bioadhesive polymer and the surface on which polymer is present. Factors that affect the mucoadhesive properties of a polymer are summarized below.

6.1 Molecular weight: Molecular weight increases mucoadhesion strength for linear polymers, but not for non-linear polymers, for example mucoadhesive strength of polyethylene glycols will increase in order of their increasing molecular weight: $2 \times 10^4 < 2 \times 10^5 < 4 \times 10^5$. High molecular weight polymers promote physical entanglement whereas low molecular weight polymers favoured better mucus layer penetration.

6.2 Hydrophilicity: Mucoadhesive polymers own hydrophilic functional groups having low hydrogen bonding with the substrate, swell in aqueous media, and thus aid in mucoadhesion by maximum exposure to their mucoadhesive sites. In addition, disentangled state and maximum distance between the chains of swollen polymers leads to high chain flexibility and efficient penetration.

6.3 Flexibility: Polymer chain's flexibility plays vital role to facilitate the penetration and attachment of mucoadhesive polymer with mucus. Mucoadhesion is caused by the diffusion of polymer chains in the interfacial regions, and greater the flexibility of polymers larger will be the diffusion into the mucus network. Thus the polymer flexibility may relate to their viscosity and diffusion coefficients.

6.4 Concentration of polymer: This factor has its importance in forming a strong adhesive bond between the polymer and mucus. If polymer concentration is too low, the interaction in polymer and mucus will be unstable and the number of invading polymer chains per mucus unit will be low. In high concentration of polymer, the adhesion property decreased as the polymer creates an "unperturbed" state at a critical concentration due to apparently coiled structure. Therefore, solvent accessibility to the polymer decreases, resulting in reduction of chain penetration of the polymer.

6.5 Hydrogen bonding capacity: Another factor plays an important role in polymer bioadhesion is hydrogen bonding. For the mucoadhesion to take place the polymers must have the functional groups (OH, COOH etc.) which are capable to form hydrogen bonds and the hydrogen bonding potential will improve by the flexibility of the polymer.

6.6 Cross linking density and Swelling: Three significant and inter-related structural considerations of a polymer network are the typical size of pore, crosslink density and the amount and average molecular weight of the cross-linked polymers. In a study Flory suggest that polymer swelling is inversely related to the polymer cross-linking. Therefore, it seems equitable as crosslinking density increases, polymer

swelling decreases due to slow water diffusion into the polymer and this result in lower interpenetration rate between mucin and polymer.

6.7 Charge and pH: Some simplifications regarding the bioadhesive polymers charge have been made earlier, where non-ionic polymers have less amount of adhesion in comparison to anionic polymers. According to **Peppas and Buri**, the strong anionic charge of the polymer is one of the prerequisite properties for mucoadhesion. Some cationic

polymers like chitosan shows higher bioadhesive properties, primarily in a neutral or to some extent in alkaline medium. There is no imperative literature on the effect of membrane charge on the mucoadhesion but the membrane pH can influence the ionized or un-ionized forms of the polymer and hence it may affect the mucoadhesion. The membrane charge has no influence but the membrane pH can affect the mucoadhesion as it has impact on the ionized or un-ionized forms of the polymers.

7. Classification of Mucoadhesive dosage forms: 4,8,19,20,25

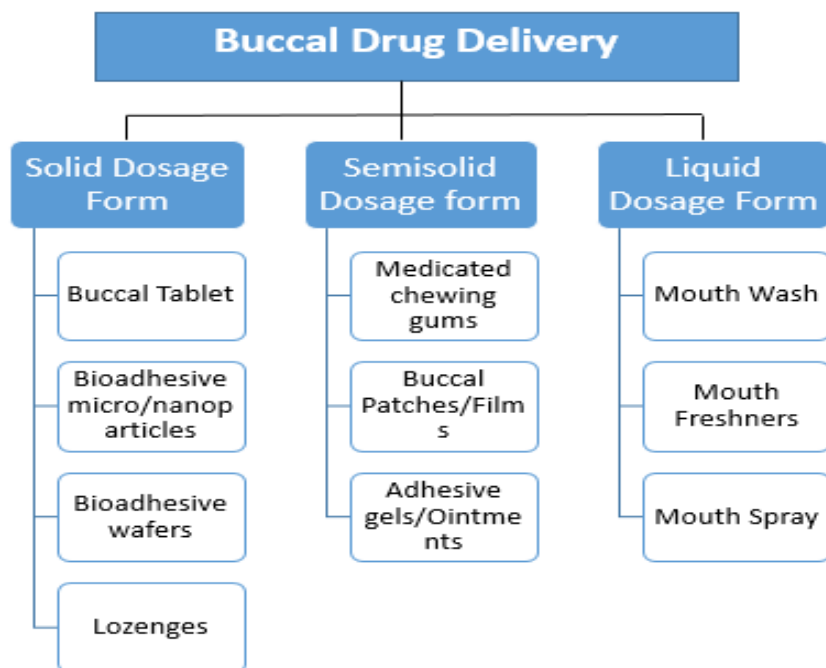


Figure 4: Classification of Mucoadhesive Dosage Form

7.1 Tablets:

Buccal tablets are most widely studied dosage form for oral delivery of drugs. These are small size, flat and oval shape dry dosage forms that are applied directly to the surface of mucosa for local or systemic therapeutic effects. They become soft, stick to the mucous membrane and remain in place until dissolution and/or release is complete. Mucosal adherent tablets can also be used as controlled drug delivery, but additional mucoadhesive properties of tablet has further benefits. For instance, the high surface area-to-volume ratio improves effective drug absorption and bioavailability, allowing for closer contact with the mucosal membrane. These are designed to stick to any mucosal tissue, thus providing the potential for local and systemic release of drug in controlled way. Application of mucosal adhesive tablets to the gastric mucosa helps in localized effect of the medicine. Mucosal adherent tablets are broadly used to release the drug over longer time duration, decrease dosing frequency, and improve patient acceptability. The main disadvantage of these tablets is their poor physical flexibility, which results in poor patient acceptability with long-term repeated use.

7.2 Buccal Patches:

A buccal patch is a laminates made up of an impervious backing membrane, a reservoir layer that contains drug and release the drug in a controlled way, and a mucoadhesive sheet which helps in adhesion to the mucosa. These can be

used to deliver the drug directly to the mucosa similarly like transdermal drug delivery.

Solvent casting and direct milling are the two methods used in the manufacturing of bioadhesive patches. In solvent casting, drug and polymer solution cast on a backing membrane sheet from which patches are punched, and then allow evaporating the solvent. In the direct milling method, first step is to mix all the materials evenly, compress them to the preferred thickness and the cut the patches of desired size and shape. An impermeable backing membrane is used for the unidirectional release of drug, avoid drug loss and to reduce distortion and disintegration of the patch throughout the time-period of use. Buccal patches have significant merits over creams and ointments because they deliver a fixed amount of drug to the site.

7.3 Buccal Films:

In past few years, many bioadhesive dosage forms have been established for buccal drug delivery for example tablets, patches, films, discs, ointments and gels. However, mucosal adhesive films are preferred over adhesive discs and tablets in terms of patient flexibility and acceptability, and they provide more precise dosing and extended residence time in comparison to gels and ointments. Oral films provide the added benefit of decreasing discomfort and increasing therapy effectiveness by preserving the wound surface. A good film should have good flexibility, elasticity, softer, and good

strength to hold the tension from mouth movements without breaking.

7.8 Gels and Ointments:

These are semi-solid dosage formulations that are less preferred patients when compared to solid bioadhesive dosage forms. A feature of these formulations is easy dispersion in the entire oral mucosal membrane and also overcome the problem of poor retention of the conventional gels at the site of action. However, administration of the formulation in semi-solid dosage form may not be as accurate as from tablets, patches, or films. Some mucoadhesive polymers, such as Sodium CMC, Carbopol, hyaluronic acid, and xanthan gum, undergo a phase change from liquid to semisolid that leads to viscosity enhancement, which results in

sustained and controlled delivery of drugs. One of the most important uses of adhesive gel is to treat periodontitis, an inflammatory and contagious disease that causes pockets between the gums and teeth and can ultimately lead to tooth loss. It has been suggested that mucosal adhesive polymers combined with antibacterial dosage forms that can be easily injected into the periodontal pocket using a syringe may be useful in the treatment of periodontitis.

8. Bioadhesive polymers used in the oral cavity

Adhesive polymers are classified on the basis of their sources, solubility in water, charge, and forces. A few examples of latest polymers categorised in following categories are shown in the figure 5.

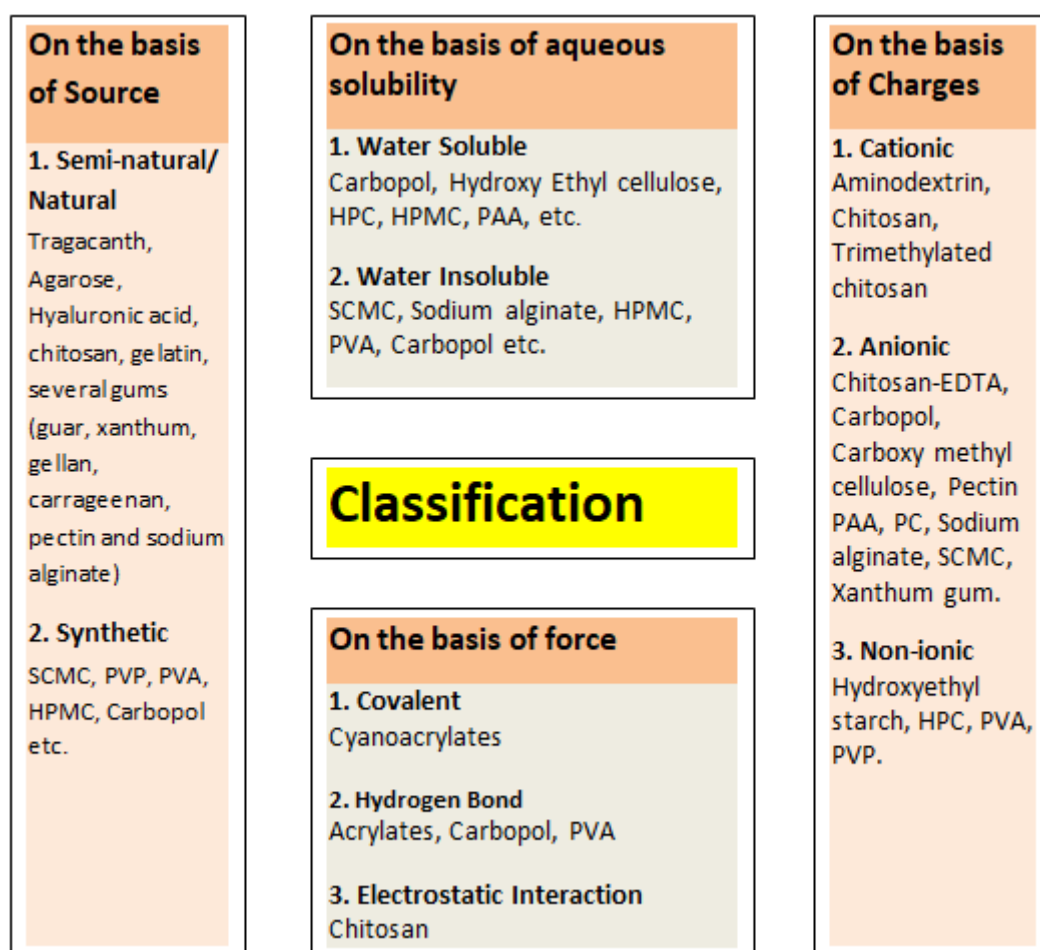


Figure 5: Bioadhesive polymers used in bucco-adhesive formulations

8.1 Features of an ideal mucoadhesive polymer: ^{11 22 26}

1. It adheres to the mucosa membrane in a short time.
2. Interact vigorously with mucin epithelial tissue.
3. Excellent ability to spread, moistening, swelling, solubility, and biodegradability.
4. Minimal effect on release of drug.
5. Not affected by changes in hydrodynamic conditions, food, or pH.
6. Simple to incorporate into a variety of drug formulations.
7. Have peel, tensile, and shear strengths within the bioadhesive range.
8. Demonstrate mucoadhesive properties in both the dry and liquid states.
9. Exhibit the ability to inhibit local enzymes and improve penetration.
10. Show satisfactory shelf life.
11. Be endowed with adhesively active groups.
12. Have Optimum molecular weight.
13. Have the necessary spatial conformation.
14. Adequately cross-linked, but not to the extent that bond forming groups are suppressed.
15. Possess good viscoelastic properties and no mucosal breakdown.

Table 1: Investigated mucoadhesive buccal tablets

Active Ingredient	Polymers Used	Investigators
Acelofenac	Carbopol 934, HPMC, SCMC	Baral P. Kalpana et al. ²⁷
Felodipine	Cyclodextrin, Carbopol 934, Na CMC	Balamurugan K. et al. ²⁸
Carvedilol	Hydroxypropyl cellulose (HPC) and polyethylene oxide WSR-1105	Patel S. Keyur et al. ²⁹
Chlorhexidine	HPMC, Poloxamer 407	Hill J. David et al. ³⁰
Captopril	Acritamer 940, Manugel, Hypromellose K100	Begum SK Asha et al. ¹
Valsartan	Carbopol 934, Xanthum Gum	Shaikh T.A. et al. ³¹
Ivabradine Hydrochloride	Hydroxypropyl methylcellulose (HPMC K100M), carnauba wax	Mohanty C. et al. ³²
Furosemide	HPMC K 100, Carbopol 940	Shrestha S. et al. ³³
Furosemide	Xanthan gum, karaya gum, guar gum, Carbopol 934-P	Ambarish G Shardor et al. ³⁴
Nystatin	Cashew Gum	Carmo F.A. et al. ³⁵
Domperidone Maleate	Carbopol 940, Sodium alginate	Dixit D.Y. et al. ³⁶
Propranolol HCL	Carbopol 940, HPMC, Na CMC	Zain A.F. et al. ³⁷
Pantoprazole sodium	HPMC, Xanthum Gum	Dr. Ramalingam N. et al. ³⁸
Mefenamic acid	HPMC K4 M, SCMC	Li K.L. et al. ³⁹
Nisoldipine	carbopol 934P HPMC K4M and K15M	Ramarao A. et al. ⁴⁰

9. Evaluation Parameters of bioadhesive tablets

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9.1 Weight variation ^{33 36}

Weigh 20 tablets separately and then together. Calculate average weight of the tablets and determine the % weight variation using the following formula.

$$\%Wt \text{ Variation} = \frac{\text{Weight of each tablet} - \text{Average weight of tablet}}{\text{Average weight of tablet}} \times 100$$

Average weight of tablet	Deviation (%)	No. of tablets
Less than 80 mg	± 10	Min. 18
	± 20	Max. 2
80 mg to 250 mg	± 7.5	Min. 18
	± 15	Max. 2
More than 250 mg	± 5	Min. 18
	± 10	Max. 2

9.2 Thickness & Hardness ⁴²

Thickness is an important parameter for the uniform size of tablets and it can be calculated by Vernier Caliper. Randomly select the tablets and hardness of the tablets from each batch will determine using a Monsanto hardness tester. It is measured in kg/cm³.

9.3 Friability test ⁴³

A friabilator is used to perform this test. Weigh randomly selected 10 tablets and record the initial weight. Tablets are then placed in plastic chamber of friabilator for the combine effect of abrasion and shock, revolve the friabilator at a speed of 25 rpm for 4 min. Then, remove the tablets, dusted off the fines and record the weight. Percentage Friability can be calculated using the formula:

$$\% \text{ Friability} = \frac{\text{Initial weight of tablets} - \text{Final weight of tablets}}{\text{Initial weight of tablets}} \times 100$$

9.4 Content uniformity ⁴¹

Ten tablets are accurately weighed and crush in mortar pestle to the powder form. An equivalent amount of powder will be taken and dissolved in the desired solvent. Filter and perform assay using UV-Visible spectroscopy.

9.5 Surface pH ³⁶

This is done to determine any side effect due to alteration in pH as an acidic or basic pH may result in mucosal irritation. The tablets will be kept in contact of distilled water for 2 hours, then bring the electrode to the tablet surface and allow to equilibrate for 1 min and note down the pH.

9.6 Swelling studies ³⁶

Individually weigh the tablets (W1) and keep them in separate petri plates containing 5 ml of phosphate buffer (pH 6.8) solution. Remove the tablet at regular intervals (0.5, 1, 2, 3, 4, 5 and 6 hr), clean excess water using filter paper and weigh again (W2). Calculate the Swelling Index (SI) by the following formula:

$$\text{Swelling Index (SI)} = \frac{W2 - W1}{W1} \times 100\%$$

9.7 In-vitro drug release ⁴¹

This evaluation is done using USP type II dissolution apparatus and isotonic phosphate buffer (IPB) pH 6.8 as the release media to simulate the physiological condition of the oral cavity. The drug release will be conducted at 37.5 ± 0.5°C, at a rotation speed of 50 rpm. At time intervals of 15, 30, 60, 90, 120, 180, 240, 300, 360, 420, and 480 minutes sample (5ml) will be withdrawn and replace it with fresh buffer to maintain a constant volume and sink state. Filter the samples using Whatman filter paper, and measure the concentration of drug by UV-Visible spectrophotometer.

9.8 Mucoadhesive study ²⁷

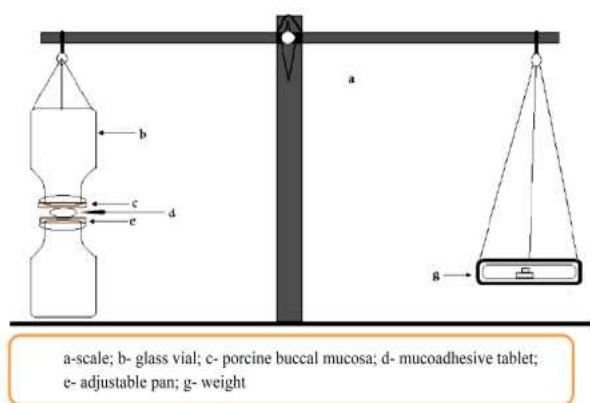


Figure 6: Layout of modified pan balance

Bovine buccal mucosa or porcine buccal mucosa can be employed as a model mucosal membrane. Keep the mucosal membrane in tyrode solution immediately after slaughter at room temperature. A modified pan balance will be used to determine the mucoadhesive forces of the tablets. Cut the buccal mucosa into pieces of applicable size and wash with tyrode solution. A piece of buccal mucosa (c) having diameter about 1 cm will be fixed on the upper glass vial (b) using a rubber band and keep it in the tyrode solution for 10 minutes at room temperature. After that, vial with buccal mucosa (b) and another vial (e) will be fixed at a height so that the gap between two vials will be equal to the tablet thickness. A tablet will be placed at the lower vial with the help of bilayered

adhesive tape. A constant force for 2 min will be applied to the upper vial so as to the tablet attach to the buccal mucosa. Then, weigh in the right pan will be slowly increased until the two vials get separated from each other. Mucoadhesive force then calculate using the equation:

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

9.9 Stability studies ⁴¹

Put appropriate number of tablets in a screw capped bottle and keep it in the stability chamber maintained at a temperature of $40 \pm 1^\circ\text{C}$ & Relative humidity $75 \pm 5\%$ for a period of 3 months. Take samples monthly to estimate the drug content and at the end of 3 months drug release profile and drug content will be checked.

10. Current scenario ¹⁶

Mucoadhesive drug delivery systems are attaining popularity around the world, with more inventors and researchers working on the design and development of new adhesive devices. A large number of new formulations are being developed on a daily basis, and their demand is increasing, examples are mucoadhesive formulations and the use of peptides as drugs. Mucoadhesive drug formulations available in the market include Oralone tablet (Triamcinolone acetone), Susadrin tablet (Nitroglycerin), Buccostem tablet (Prochlorperazine maleate), Salcoat powder sprays (Beclomethasone dipropionate), Rhinocort powder spray (Budesonide) and Sucralfate (Aluminum hydroxide). However, very few formulations have been in the market to the date, as they become more popular, more new types of formulation can be expected in the future.

11. Marketed buccal drug delivery systems ^{11 16 44}

Table 2: Marketed Buccal drug delivery Products

Dosage Form	Product	Active Pharmaceutical Ingredient	Manufacturer	Therapeutic Category
Tablet	Loramyc	Miconazole	BioAlliance Pharma	Antifungal
	Buccastem	Prochlorperazine Meleate	Reckitt Benckiser	Antipsychotic
	Aphtach	Triamcinolone Acetonide	Tejin Ltd.	Corticosteroid
	Suboxone	Buprenorphine Hydrochloride - Naloxone HCl	Reckitt Benckiser	Opioid Analgesic
	Straint SR	Testosterone	Adrana Bioscience Ltd.	Androgenic Hormone
	Effentora	Fentanyl Citrate	Cephalon	
	Sabutex	Buprenorphine Hydrochloride	Reckitt Benckiser	Opioid Analgesic
	Suscard	Glyceryl Trinitrate	Forest Laboratories	Vasodilator
Spray	Zolpimist	Zolpidem	Novadel Pharmaceuticals	Sedative & Hypnotics
	Sativex	Cannabis based	GW Pharmaceuticals	Cannabinoids
	Nitrostat	Nitroglycerine	Pfizer	Vasodilator
Gel	Bonjela	Cetalkonium Chloride, Choline Salicylate	Reckitt Benckiser	Antiulcer
	Corsodyl	Chlorhexidine Digluconate	GlaxoSmithKline	Antimicrobial
	Fastum	Ketoprofen	Menarini	NSAIDS
Lozenge	Actiq	Fentanyl Citrate	Cephalon	Opioid Analgesic
Pellets	Coralan	Hydrocortisone Sodium Succinate	Celltech	Corticosteroid
Patch	Dentipatch	Lidocaine	Noven	Analgesic
	Coreg	Carvedilol	GlaxoSmithKline	Antihypertensive

12. Future Challenges and Opportunities

Buccal drug delivery research has grown and advanced dramatically over the last few years. The buccal mucosa presents great potential for systemic delivery of drugs which are ineffective via orally administration and also a feasible and attractive alternative to administer the protein and peptide drugs non-invasively. Mucoadhesive delivery systems offers an exceptional carrier system for many drugs and can be tailored to stick to any mucosal tissue, including those found in the oral cavity, alimentary canal, vagina, eye etc. One area of interest is the novel buccal adhesive delivery system, which directs delivery of drug to the buccal mucosa while shielding the surroundings. Looking into the future, researchers believe that buccal adhesive drug delivery will be replaced by

formulation of vaccines and the delivery of small proteins and peptides. Microparticulate bioadhesive systems are particularly intriguing because they provide therapeutic entities with protection as well as enhanced absorption as a result of the increased contact time provided by the bioadhesive component. Bioadhesion can undoubtedly play a critical role in non-parenteral protein formulations, in addition to vaccines that can adhere to mucosal membranes to incite local immunity.²⁵ As a result of broad research in this field many novel devices such as nanoparticulate devices, buccal sprays, and phospholipid vesicles. Different techniques have been used to create sustained or controlled delivery systems. Some newly invented and patented devices are mentioned in the table below.²⁴

Table 3: Patents available for Buccal drug delivery

Patent Title	Pharmacological Action	Dosage Form	References
Buccal delivery of glucagon-like insulinotropic peptides	Reduces blood sugar level	Buccal spray	Sonia J. Heiber et al., ⁴⁵
Buccal drug administration in the treatment of female sexual dysfunction	Female hormone replacement therapy, female contraception, to treat female sexual dysfunction, etc	Buccal estrogen toothpaste	Virgil A. Place ⁴⁶
Bilayered buccal tablets comprising nicotine	Termination of Smoking	Buccal tablet	Park C. et al., ⁴⁷
Buccal, polar, and nonpolar spray containing sumatriptan	To treat migraine	Buccal spray	Dugger Harry et al., ⁴⁸
Buccal, polar, and nonpolar spray containing ondansetron	Chemotherapy induced nausea and vomiting	Buccal spray	Dugger Harry A. et al., ⁴⁹
Buccal, polar, and nonpolar spray containing testosterone	Hormone replacement therapy	Buccal spray	Dugger Harry et al., ⁵⁰
Propofol containing buccal polar and nonpolar spray	Sedatives & Hypnotics	Buccal spray	Dugger Harry ⁵¹
Lozenge composition comprising an oral nicotine active ingredient and process for manufacturing it	Smoking termination	Lozenges	Chen Li-Lan ⁵²
Chewing gum compositions providing rapid release of nicotine	To end smoking	Chewing gum	Axelsson Anders et al., ⁵³
Canker sore patch	For the treatment of mouth sores	Buccal patch	Malcovati L. ⁵⁴
Patches for teeth whitening	Whitening of teeth	Patch	Young J Kim et al., ⁵⁵
Propellant-free polar buccal spray of zolpidem	Sedative & Hypnotics	Oral spray	Dugger Harry ⁵⁶
Buccal spray containing sildenafil	Antihypertensive, erectile dysfunction therapies	Buccal spray	Dugger Harry ⁵⁷
Dendrobium buccal tablets and preparation method for buccal tablets containing phenothiazine derivatives	Improve immune system, Antipyretic, Analgesic	Buccal tablet	Zhan, Yong ⁵⁸
Oral transmucosal administration forms of s-ketamine	Analgesic	Buccal film/ buccal tablet	Salama B. Zoser ⁵⁹
Chewing gum compositions comprising cannabinoids	Antiemetic, Analgesic, Anesthetics	Chewing gum	Phillipus Anne ⁶⁰
Fentanyl double-layer buccal tablet and preparation method thereof	Analgesic	Buccal tablet	Yijie S. et al., ⁶¹
Multilayer nicotine-containing pharmaceutical composition	Smoking termination	Trilayered Buccal patch	Duggins D. Walker ⁶²

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