*REVIEW ARTICLE*

# Buccoadhesive Drug Delivery - A Potential Route of Drug Administration

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## ABSTRACT

Within the oral mucosal cavity, the buccal region offers an attractive route of administration for systemic drug delivery. The mucosa has a rich blood supply and is permeable to many pharmacologically active agents. The main obstacles that drugs meet when administered via the buccal route derive from the limited absorption area and the barrier properties of the mucosa. The effective physiological removal mechanisms of the oral cavity that take the formulation away from the absorption site are the other obstacles that have to be considered. The strategies studied to overcome such obstacles include the employment of new materials that, possibly, combine mucoadhesive and penetration enhancer properties and the design of innovative drug delivery systems which, besides improving patient compliance, favor a more intimate contact of the drug with the absorption mucosa. The objective of this article is to review buccal drug delivery by discussing the structure and environment of the oral mucosa and highlighting the experimental methods used in the assessment of buccal drug permeation and absorption. The review also assesses the current status of buccal permeation enhancers as well as buccal drug delivery systems.

**Key Words:** Buccoadhesive Drug Delivery, Drug Administration, Buccal

## INTRODUCTION

Among the various routes of drug delivery, the oral route is perhaps the most preferred by patients and clinicians alike. However, peroral administration of drugs has disadvantages, such as hepatic first-pass metabolism and enzymatic degradation within the gastrointestinal (GI) tract, that prohibit oral administration of certain classes of drugs, especially peptides and proteins. Consequently, other absorptive mucosa is considered as potential sites for drug administration. Transmucosal routes of drug delivery (i.e., the mucosal linings of the nasal, rectal, vaginal, ocular, and oral cavities) offers distinct advantages over peroral administration for systemic effect. These advantages include possible bypass of firstpass effects and avoidance of presystemic elimination within the GI tract. Many research groups [1–3] have investigated the nasal cavity as a site for systemic drug delivery, and the route already has reached commercial status with several drugs, including leutinizing hormone-releasing hormone (LHRH), cyanocobalamin, azelastine hydrochloride, desmopressin acetate, and calcitonin [4–5]. However, the potential irritation and the

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irreversible damage to the ciliary action of the nasal cavity from chronic application of nasal dosage forms makes the nasal cavity less attractive for drug delivery. Also, the large intrasubject and intersubject variability in mucus secretion in the nasal mucosa could be a significant factor affecting drug absorption from this site. Even though the rectal, vaginal, and ocular mucosa offer certain advantages, the poor patient acceptability associated with these sites renders them reserved for local applications rather than systemic drug administration. Similar to the nasal route, the oral cavity as a site for drug delivery also has reached commercial status with several drugs, including nitroglycerin as sublingual tablets for angina and fentanyl as a transmucosal buccal device (Actiq,Abbott Laboratories, Abbott Park, IL) for breakthrough cancer pain [6]. However, the mucosal lining of the oral cavity offers some distinct advantages. It is richly vascularized and more accessible for the administration and removal of a dosage form. Additionally, buccal drug delivery has a high patient acceptability compared to other non-oral routes of drug administration. Harsh environmental factors that exist in oral delivery of a drug are circumvented by buccal delivery. Avoiding acid hydrolysis in the gastrointestinal (GI) tract and bypassing the first-pass effect are some of the advantages of this route of drug delivery. Moreover, rapid cellular recovery and achievement of a localized site on the smooth surface of the buccal mucosa are among the other advantages of this route of drug delivery.

The disadvantages associated with this route of drug delivery are the low permeability of the Buccal membrane [7], specifically when compared to the sublingual membrane [8, 9], and a smaller surface area. The total surface area of the membranes of the oral cavity available for drug absorption is 170 cm$^2$ [10], of which ~50 cm$^2$ represents non-keratinized tissues, including the buccal membrane [11]. The continuous secretion of saliva (0.5–2 l/day) leads to subsequent dilution of the drug [9].

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 buccal drug delivery. Moreover, the hazard of choking by involuntarily swallowing the delivery system is a concern, in addition to the inconvenience of such a dosage form when the patient is eating or drinking. Within the oral cavity the two common regions for drug delivery are the sublingual mucosa (area beneath the tongue) and the buccal mucosa (inner lining of the cheeks). Selecting one over the other is mainly based on anatomical and permeability properties of the various oral mucosal sites, the desired residence time, and the desired effects of the drug.

## Buccal mucosal structure and its suitability

Buccal region is that part of the mouth bounded anteriorly and laterally by the lips and the cheeks, posteriorly and medially by the teeth and/or gums, and above and below by the reflections of the mucosa from the lips and cheeks to the gums. Numerous racemose, mucous, or serous glands are present in the submucous tissue of the cheeks. The buccal glands are placed between the mucous membrane and buccinator muscle: they are similar in structure to the labial glands, but smaller. About five, of a larger size than the rest, are placed between the masseter and buccinator muscles around the distal extremity of the parotid duct; their ducts open in the mouth opposite the last molar tooth. They are called molar glands [12]. Maxillary artery supplies blood to buccal mucosa and blood flow is faster and richer (2.4ml/min/cm2) than that in the sublingual, gingival and palatal regions, thus facilitates passive diffusion of drug molecules across the mucosa. The thickness of the buccal mucosa is measured to be 500–800 μm and is rough textured, hence suitable for retentive delivery systems [13]. The turnover time for the buccal epithelium has been estimated at 5–6 days[14]

Buccal mucosa composed of several layers of different cells as shown in Fig. 1. The epithelium is similar to stratified squamous epithelia found in rest of the body and is about 40–50 cell layers thick [12]. Lining epithelium of buccalmucosa is the nonkeratinized stratified squamous epithelium that has thickness of approximately 500–600 µ and surface area of 50.2 cm$^2$. Basement membrane, lamina propria followed by the submucosa is present below the epithelial layer [15]. Lamina propria is rich with blood vessels and capillaries that open to the internal jugular vein. Lipid analysis of buccal tissues shows the presence of phospholipid 76.3%, glucosphingolipid 23.0% and ceramide NS at 0.72%. Other lipids such as acyl glucosylated ceramide, and ceramides like Cer AH, CerAP, Cer NH, CerAS, and EOHP/NP are completely absent [16].

The primary function of buccal epithelium is the protection of the underlying tissue. In nonkeratinized regions, lipid-based permeability barriers in the outer epithelial layers protect the underlying tissues against fluid loss and entry of potentially harmful environmental agents such as antigens, carcinogens, microbial toxins and enzymes from foods and beverages [17] (**Fig. 1**).

A gel-like secretion known as mucus, which contains mostly water-insoluble glycoproteins, covers the entire oral cavity. Mucus is bound to the apical cell surface and acts as a protective layer to the cells below [18]. It is also a visco-elastic hydrogel, and primarily consists of 1–5% of the above-mentioned water insoluble glycoproteins, 95–99% water, and several other components in small quantities, such as proteins, enzymes, electrolytes, and nucleic acids. This composition can vary based on the origin of the mucus secretion in the body [19, 20].

**Buccal mucosa as a site for drug delivery (Absorption pathways)**

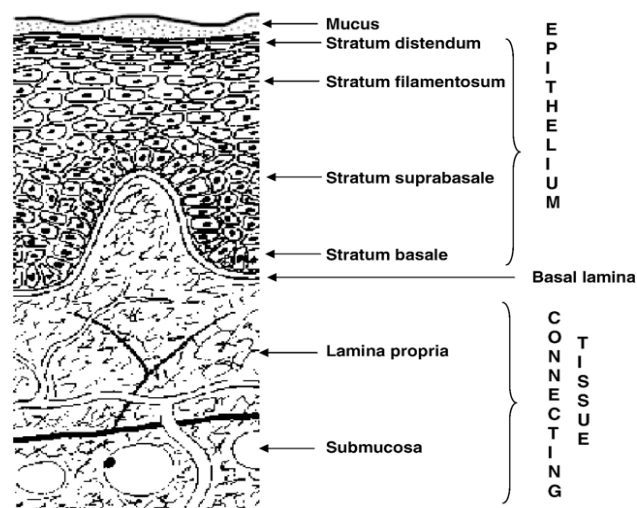The major pathway across stratified epithelium of large molecules is via the



**Fig 1: Cross-section of buccal mucosa.**

intercellular spaces and that there is a barrier to penetration as a result of modifications to the intercellular substance in the superficial layers. However, rate of penetration varies depending on the physicochemical properties of the molecule and the type of tissue being traversed. This has led to the suggestion that materials uses one or more of the following routes simultaneously to cross the barrier region in the process of absorption, but one route is predominant over the other depending on the physicochemical properties of the diffusant [21].

✓ Passive diffusion
 ◦ Transcellular or intracellular route (crossing the cell
  membrane and entering the cell)
 ◦ Paracellular or intercellular route (passing between the
  cells)
✓ Carrier mediated transport
✓ Endocytosis

The flux of drug through the membrane under sink condition for paracellular route can be written as Eq. (1)

$$J_p = \frac{D_p{}^{\varepsilon}}{h_p} \cdot C_d$$

Where, Dp is diffusion coefficient of the permeate in the intercellular spaces, hp is the path length of the paracellular route, ε is the area fraction of the paracellular route and Cd is the donor drug concentration.

Similarly, flux of drug through the membrane under sink condition for transcellular route can be written as Eq. (2).

$$Jc = \frac{(1-\varepsilon)\, D_c K_c}{h_c} \cdot C_d$$

Where, $K_c$ is partition coefficient between lipophilic cell membrane and the aqueous phase, $D_c$ is the diffusion coefficient of the drug in the transcellular spaces and $h_c$ is the path length of the transcellular route [22].

Because the intercellular spaces are less lipophilic in character than the cell membrane, hydrophilic compounds have higher solubilities in this environment. The cell membrane, however, is highly lipophilic in nature, and hydrophilic solutes have great difficulty permeating the cell membrane because of a low partition coefficient. Therefore, the intercellular spaces pose the major barrier to passive permeation of lipophilic compounds, and the cell membrane acts as the major transport barrier for hydrophilic compounds. Because the oral epithelium is stratified, solute permeation may involve a combination of these two routes. The route that predominates, however, is generally the one that provides the least amount of hindrance to passage.

In very few cases absorption also takes place by the process of endocytosis where the drug molecules were engulfed by the cells. It is unlikely that active transport processes operate within the oral mucosa; however, it is believed that acidic stimulation of the salivary glands, with the accompanying vasodilatation, facilitates absorption and uptake into the circulatory system [23].

The absorption potential of the buccal mucosa is influenced by the lipid solubility and molecular weight of the diffusant. Absorption of some drugs via the buccal mucosa is found to increase when carrier pH is lowered and decreased with an increase of pH. However, the pH dependency that is evident in absorption of ionizable compounds reflects their partitioning into the epithelial cell membrane, so it is likely that such transcellularly compounds will tend to penetrate [24]

## 2. BUCCAL MUCOSA AS A SITE OF DRUG DELIVERY

As stated above, there are three different categories of drug delivery within the oral cavity (i.e., sublingual, buccal, and local drug delivery). Selecting one over another is mainly based on anatomical and permeability differences that exist among the various oral mucosal sites. The sublingual mucosa is relatively permeable, giving rapid absorption and acceptable bioavailabilities of many drugs, and is convenient, accessible, and generally well accepted [25]. The sublingual route is by far the most widely studied of these routes. Sublingual dosage forms are of two different designs, those composed of rapidly disintegrating tablets, and those consisting of soft gelatin capsules filled with liquid drug. Such systems create a very high drug concentration in the sublingual region before they are systemically absorbed across the mucosa. The buccal mucosa is considerably less permeable than the sublingual area, and is generally not able to provide the rapid absorption and good bioavailabilities seen with sublingual administration. Local delivery to tissues of the oral cavity has a number of applications, including the treatment of toothaches [28], periodontal disease [26], bacterial and fungal infections, aphthous and dental stomatitis, and in facilitating tooth movement with prostaglandins [27].

Even though the sublingual mucosa is relatively more permeable than the buccal mucosa, it is not suitable for an oral transmucosal delivery system. The sublingual region lacks an expanse of smooth muscle or immobile mucosa and is constantly washed by a considerable amount of saliva making it difficult for device placement. Because of the high permeability and the rich blood supply, the sublingual route is capable of producing a rapid onset of action making it appropriate for drugs with short delivery period requirements with infrequent dosing regimen. Due to two

important differences between the sublingual mucosa and the buccal mucosa, the latter is a more preferred route for systemic transmucosal drug delivery [25]. First difference being in the permeability characteristics of the region, where the buccal mucosa is less permeable and is thus not able to give a rapid onset of absorption (i.e., more suitable for a sustained release formulation). Second being that, the buccal mucosa has an expanse of smooth muscle and relatively immobile mucosa, which makes it a more desirable region for retentive systems, used for oral transmucosal drug delivery.

Thus the buccal mucosa is more fitted for sustained delivery applications, delivery of less permeable molecules, and perhaps peptide drugs. Similar to any other mucosal membrane, the buccal mucosa as a site for drug delivery has limitations as well. One of the major disadvantages associated with buccal drug delivery is the low flux, which results in low drug bioavailability. Various compounds have been investigated for their use as buccal penetration enhancers in order to increase the flux of drugs through the mucosa. Since the buccal epithelium is similar in structure to other stratified epithelia of the body, enhancers used to improve drug permeation in other absorptive mucosae have been shown to work in improving buccal drug penetration [29].

Drugs investigated for buccal delivery using various permeation /absorption enhancers range in both molecular weight and physicochemical properties. Small molecules such as butyric acid and butanol, ionizable low molecular weight drugs such as acyclovir, propranolol, and salicylic acid, large molecular weight hydrophilic polymers such as dextrans and a variety of peptides including octreotide, leutinizing hormone releasing hormone (LHRH), insulin, and α- interferon have all been studied.

## 3. FORMULATION DESIGN

Buccal adhesive drug delivery systems with the size 1–3 cm$^2$ and a daily dose of 25 mg

or less are preferable. The maximal duration of buccal delivery is approximately 4–6 h.

## Pharmaceutical considerations

Great care needs to be exercised while developing a safe and effective buccal adhesive drug delivery device. Factors influencing drug release and penetration through buccal mucosa, organoleptic factors, and effects of additives used to improve drug release pattern and absorption, the effects of local drug irritation caused at the site of application are to be considered while designing a formulation. Other than the low flux associated with buccal mucosal delivery, a major limitation of the buccal route of administration is the lack of dosage form retention at the site of absorption. Consequently, bioadhesive polymers have extensively been employed in buccal drug delivery systems.

Bioadhesive formulations use polymers as the adhesive component. These formulations are often water soluble and when in a dry form attract water from the biological surface and this water transfer leads to a strong interaction. Bioadhesive polymers are defined as polymers that can adhere onto a biological substrate. The term mucoadhesion is applied when the substrate is mucosal tissue [30]. These polymers also form viscous liquids when hydrated with water that increases their retention time over mucosal surfaces and may lead to adhesive interactions. Bioadhesive polymers should possess certain physicochemical features including hydrophilicity, numerous hydrogen bond-forming groups, flexibility for interpenetration with mucus and epithelial tissue, and visco-elastic properties [31]. Polymers, which can adhere to either hard or soft tissue, have been used for many years in surgery and dentistry. Diverse classes of polymers have been investigated for their potential use as mucoadhesives. These include synthetic polymers such as monomeric α- cyanoacrylate, polyacrylic acid, hydroxypropyl methylcellulose, and poly methacrylate derivatives as well as various naturally occurring polymers such as

hyaluronic acid and chitosan.

Other synthetic polymers such as polyurethanes, epoxy resins, polystyrene, and natural-product cement have also been extensively investigated. In general, dosage forms designed for buccal administration should not cause irritation and should be small and flexible enough to be accepted by the patient. These requirements can be met by using hydrogels. Hydrogels are hydrophilic matrices that are capable of swelling when placed in aqueous media.

A Polyacrylic acid derivative shows the best mucoadhesion properties. For e.g. Carbpol-971p is best polymer used for the preparation of mucoadhesive formulation such as veginal cream, gels and mucoadhesive patch.

## Permeation enhancers

The buccal mucosa offers several advantages for controlled drug delivery for extended periods of time. The mucosa is well supplied with both vascular and lymphatic drainage and first-pass metabolism in the liver and pre-systemic elimination in the gastrointestinal tract is avoided. The area is well suited for a retentive device and appears to be acceptable to the patient. With the right dosage form design and formulation, the permeability and the local environment of the mucosa can be controlled and manipulated in order to accommodate drug permeation. However, the need for safe and effective buccal permeation/absorption enhancers is a crucial component for a prospective future in the area of buccal drug delivery.

Membrane permeation is the limiting factor for many drugs in the development of buccal adhesive delivery devices. The epithelium that lines the buccal mucosa is a very effective barrier to the absorption of drugs. Substances that facilitate the permeation through buccal mucosa are referred as permeation enhancers. As most of the penetration enhancers were originally designed for purposes other than absorption enhancement, a systemic search for safe and effective penetration enhancers must be a priority in drug delivery. The goal of designing penetration enhancers, with improved efficacy and reduced toxicity profile is possible by understanding the relationship between enhancer structure and the effect induced in the membrane and of course, the mechanism of action. However, the selection of enhancer and its efficacy depends on the physicochemical properties of the drug, site of administration, nature of the vehicle and other excipients. In some cases usage of enhancers in combination has shown synergistic effect than the individual enhancers. The efficacy of enhancer in one site is not same in the other site because of differences in cellular morphology, membrane thickness, enzymatic activity, lipid composition and potential protein interactions are structural and functional properties. Penetration enhancement to the buccal membrane is drug specific [33]. Effective penetration enhancers for transdermal or intestinal drug delivery may not have similar effects on buccal drug delivery because of structural differences; however, enhancers used to improve drug permeation in other absorptive mucosae improve drug penetration through buccal mucosa. These permeation enhancers should be safe and non-toxic, pharmacologically and chemically inert, non-irritant, and non-allergenic [34]. However, examination of penetration route for transbuccal delivery is important because it is fundamental to select the proper penetration enhancer to improve the drug permeability. The different permeation enhancers available are [34-36].

✓ Chelators: EDTA, citric acid, sodium salicylate, methoxy salicylates.
✓ Surfactants: sodium lauryl sulphate, polyoxyethylene, Polyoxyethylene-9-laurylether, Polyoxythylene-20-cetylether, Benzalkonium chloride, 23-lauryl ether, cetylpyridinium chloride, cetyltrimethyl ammonium bromide.
✓ Bile salts: sodium glycocholate, sodium deoxycholate, sodium taurocholate, sodium glycodeoxycholate, sodium taurodeoxycholate.

- ✓ Fatty acids: oleic acid, capric acid, lauric acid, lauric acid/ propylene glycol, methyloleate, lysophosphatidylcholine, phosphatidylcholine.
- ✓ Non-surfactants: unsaturated cyclic ureas.
- ✓ Inclusion complexes: cyclodextrins.
- ✓ Others: aprotinin, azone, cyclodextrin, dextran sulfate, menthol, polysorbate 80, sulfoxides and various alkyl glycosides.
- ✓ Thiolated polymers: chitosan-4-thiobutylamide, chitosan- 4-thiobutylamide/GSH, chitosan-cysteine, Poly (acrylic acid)-homocysteine, polycarbophil-cysteine, polycarbophil-cysteine/GSH, chitosan-4-thioethylamide/GSH, chitosan- 4-thioglycholic acid.

## 4. BUCCAL MUCOADHESIVE DOSAGE FORMS

Buccal mucoadhesive dosage forms can be categorized into three types based on their geometry. Type I is a single layer device with multidirectional drug release. This type of dosage form suffers from significant drug loss due to swallowing. In type II devices, an impermeable backing layer is superimposed on top of the drug-loaded bioadhesive layer, creating a double-layered device and preventing drug loss from the top surface of the dosage form into the oral cavity. Type III is a unidirectional release device from which drug loss is minimal, since the drug is released only from the side adjacent to the buccal mucosa. This can be achieved by coating every face of the dosage form, except the one that is in contact with the buccal mucosa.

Buccal dosage forms can also be classified as either a "reservoir" or "matrix" type (**Fig.2**). In the reservoir type, an excessive amount of the drug is present in the reservoir surrounded by a polymeric membrane, which controls the drug's release rate. In the matrix type systems, the drug is uniformly dispersed in the polymer matrix, and drug release is controlled by diffusion through the polymer network. In general, dosage forms designed for buccal drug and

should not cause irritation. Other desired delivery should be small and flexible enough to be acceptable for patients,
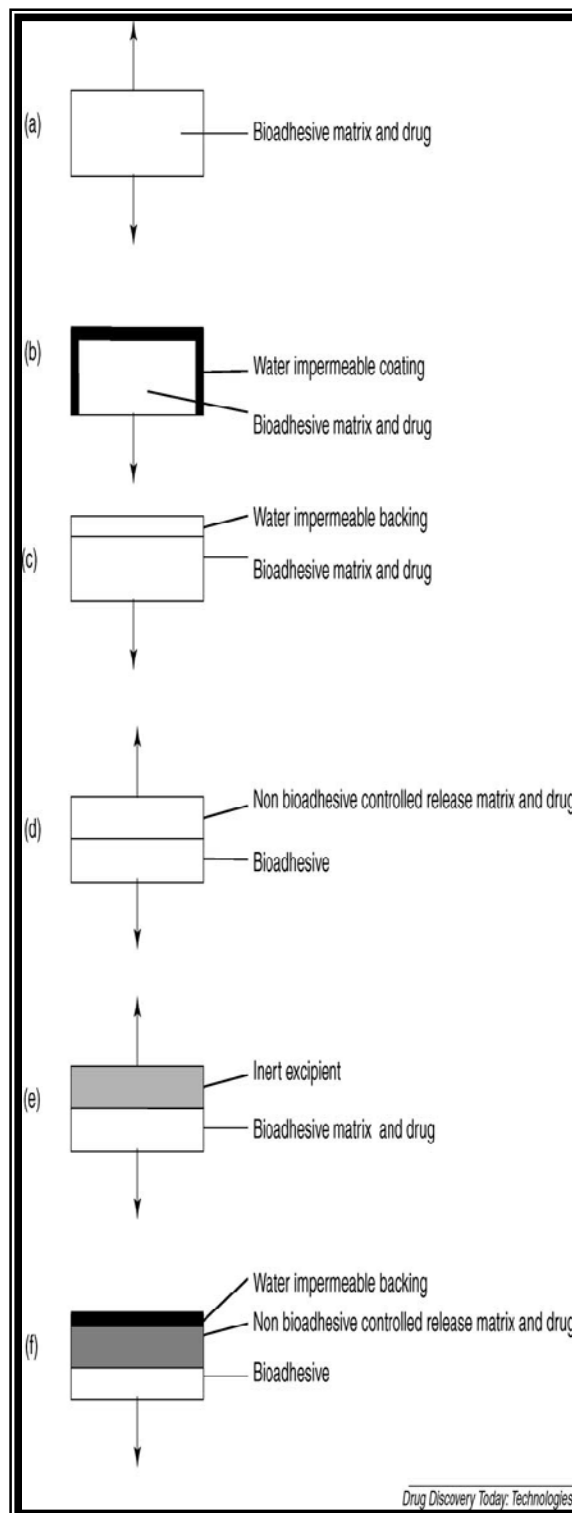


**Fig. 2. Schematic representation of different matrix tablets for buccal delivery. Arrows indicate the direction of drug release**.

characteristics of a buccal mucosadhesive dosage form include high drug loading

capacity, controlled drug release (preferably unidirectional release), good bioadhesive properties, smooth surface, tastelessness, and convenient application. Erodible formulations can be beneficial because they do not require system retrieval at the end of desired dosing interval.

A number of relevant buccal mucoadhesive dosage forms have been developed for a variety of drugs. Several peptides, including thyrotropin-releasing hormone (TRH), insulin, octreotide, leuprolide, and oxytocin, have been delivered via the buccal route, albeit with relatively low bioavailability (0.1–5%) owing to their hydrophilicity and large molecular weight, as well as the inherent permeation and enzymatic barriers of the buccal mucosa. Several buccal adhesive delivery devices were developed at the laboratory scale by many researchers either for local or systemic actions. They are broadly classified in to:

- ✓ Solid buccal adhesive dosage forms
- ✓ Semi-solid buccal adhesive dosage forms
- ✓ Liquid buccal adhesive dosage forms

**Solid buccal adhesive formulations**
Dry formulations achieve bioadhesion via dehydration of the local mucosal surface.

**Tablets:** Several bioadhesive tablet formulations were developed in recent years either for local or systemic drug delivery. Tablets that are placed directly onto the mucosal surface have been demonstrated to be excellent bioadhesive formulations. However, size is a limitation for tablets due to the requirement for the dosage form to have intimate contact with the mucosal surface. These tablets adhere to the buccal mucosa in presence of saliva. They are designed to release the drug either unidirectionally targeting buccal mucosa or mutidirectionally in to the saliva.

**Microparticles:** Bioadhesive microparticles offer the same advantages as tablets but their physical properties enable them to make intimate contact with a lager mucosal surface area. In addition, they can also be delivered to less accessible sites including the GI tract and upper nasal cavity. The small size of microparticles compared with tablets means that they are less likely to cause local irritation at the site of adhesion and the uncomfortable sensation of a foreign object within the oral cavity is reduced.

**Wafers:** Bromberg et al. [37] described a conceptually novel periodontal drug delivery system that is intended for the treatment of microbial infections associated with peridontitis. The delivery system is a composite wafer with surface layers possessing adhesive properties, while the bulk layer consists of antimicrobial agents, biodegradable polymers and matrix polymers.

**Lozenges:** Bioadhesive lozenges may be used for the delivery of drugs that act topically within the mouth including antimicrobials, corticosteroids, local anaesthetics, antibiotics and antifungals. Conventional lozenges produce a high initial release of drug in the oral cavity, which rapidly declines to subtherapeutic levels, thus multiple daily dosing is required. A slow release bioadhesive lozenge offers the potential for prolonged drug release with improved patient compliance. Codd and Deasy investigated bioadhesive lozenges as a means to deliver antifungal agents to the oral cavity [38].

**Semi-solid dosage forms**
**Gels:** Gel forming bioadhesive polymers include crosslinked polyacrylic acid that has been used to adhere to mucosal surfaces for extended periods of time and provide controlled release of drugs. Gels have been widely used in the delivery of drugs to the oral cavity. Advantages of gel formulations include their ability to form intimate contact with the mucosal membrane and their rapid release of drug at the absorption site. A limitation of gel formulations lies on their

inability to deliver a measured dose of drug to the site. They are therefore of limited use for drugs with narrow therapeutic window. [39] designed a novel, hydrogelbased, bioadhesive, intelligent response system for controlled drug release. This system combined several desirable facets into a single formulation; a poly (hydroxyethyl methacrylate) layer as barrier, poly (methacrylic acid-g-ethylene glycol) as a biosensor and poly (ethyleneoxide) to promote mucoadhesion.

**Patches/films:** Flexible films may be used to deliver drugs directly to a mucosalmembrane. They also offer advantages over creams and ointments in that they provide ameasured dose of drug to the site. Buccal adhesive films are already in use commercially for example, Zilactin used for the therapy of canker sores, cold sores and lip sores.

**Liquid dosage forms**
Viscous liquids may be used to coat buccal surface either as protectants or as drug vehicles for delivery to themucosal surface. Traditionally, pharmaceutically acceptable polymerswere used to enhance the viscosity of products to aid their retention in the oral cavity. Dry mouth is treated with artificial saliva solutions that are retained on mucosal surfaces to provide lubrication. These solutions contain sodium CMC as bioadhesive polymer.

**EVALUATION**
In addition to the routine evaluation tests such as weight variation, friability, hardness, content uniformity, in vitro dissolution for tablets; tensile strength, film endurance, hygroscopicity etc for films and patches; viscosity, effect of aging etc for gels and ointments; buccal adhesive drug delivery devices are also to be evaluated specifically for their mucoadhesive strength and permeability. Some other parameters are:

**Water sorption studies**      A previously weight polymer disk was put on a 10 cm diameter wet filter paper surface soaked in phosphate buffer pH 7.4 in a Petri dish at $25^0$C for 8 hours (n=2). During this interval, the polymer disc reached equilibrium and exhibited swelling. Increase in weight of polymer was determined at end of 8 hours and % water sorption calculated as-

$$W_{(Water\ absorption)} = W_s - W_d/\ W_d \times 100$$

Where,
$W_s$= weight of swollen polymer
$W_d$= initial weight of polymer
and subsequently expressed in terms of per unit area or per unit volume. A water sorption study of polymer disk of was carried out to determine the swelling indices at present time interval (1-24h). The swelling indices was determined by [40]

$$Swelling\ indices = W_s - W_d/\ W_d$$

***Ex vivo* mucoadhesive strength**
Mucoadhesive strength of polymer disk with buccal mucosa was measured using a modified 2-arm balance. Buccal mucosa was obtained from slaughterhouse, stored in Kreb's buffer at $4^0$C upon collection. The experiments were performed within 3 hours of procurement of mucosa. The mucosa was cut into pieces and washed with phosphate buffer pH 7.4. A piece of buccal mucosa was tied to the open mouth of a glass vial, which was filled completely with phosphate buffer pH 7.4, and held on the left side of the balance tightly fitted in the center of glass beaker containing phosphate buffer (pH 7.4, $37^0$C$\pm1^0$C) just touching the mucosal surface. The polymer disk was applied to the lower side of the rubber stopper of the glass vial which was held in inverted position with the help of clamp and then lower beaker was raised slowly until contact between mucosa and polymer disk established. The left and right pans were balanced by adding a 5 gm weight on the right hand pan. When the 5 gm weight was removed from the right hand pan, the left hand pan along with was lowered over the mucosa. The balance was kept in this

position for 5 minutes. Water (equivalent to weight) was added slowly at 100 drops/min to the right hand pan until the disk detached from the mucosal surface. The weight of water required to detach the polymer disk was noted as mucoadhesive strength. These experiments were repeated along with the optimized formulation (with fresh mucosa) in an identical manner (n=3) [41,42]. The force of adhesion in Newton (N) was calculated by the formula-

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

Bond strength $(N/m^2)$ = Force of adhesion (N) / Surface area of disk $(m^2)$

### Ex-vivo residence time

The *Ex-vivo* residence time was determined using a locally modified USP disintegration apparatus, based on the apparatus applied by Nakamura *et al.*. The disintegration medium was composed of 800 mL isotonic phosphate buffer of pH 7.4 (IPB) maintained at $37^0$C. A segment of goat buccal mucosa, 3 cm long, was glued to the surface of a glass slab, vertically attached to the apparatus. The formulation was hydrated from one surface using 15 µl IPB and then the hydrated surface was brought into contact with the mucosal membrane. The glass slab was vertically fixed to the apparatus and allowed to move up and down so that the formulation was completely immersed in the buffer solution at the lowest point and was out at the highest point [43]. The time necessary for complete erosion or detachment of the disk from the mucosal surface was recorded (mean of triplicate determinations).

### In-vitro drug permeation studies

The buccal epithelium was carefully mounted in between the two compartments of a Franz diffusion cell with internal diameter of 2.1 cm ($3.46cm^2$ area) with a receptor compartment volume of 15.0 ml. 15 ml of phosphate buffer pH (7.4) was placed in the receptor compartment. The donor compartment contained formulation. The

entire set up was placed over magnetic stirrer and temperature was maintained at 37°C by placing the diffusion cell in a water bath. 1 ml sample was collected at predetermined time intervals from receptor compartment and replaced with an equal volume of the buffer solution. Drug permeated through the buccal mucosa was then determined by measuring the absorbance using a UV spectrophotometer. The experiments were performed in triplicate (n=3) and mean value was used to calculate the permeability coefficient. Amount of drug in donor compartment was determined and plotted as a function of time. The permeability coefficient (P) and flux was ($J_{ss}$) calculated from the linear part of the curve as equation-

$$P = (\Delta M/\Delta t) / A. C_0$$
$$J_{ss} = (\Delta M/\Delta t) / A$$

Where, A= diffusion surface area$\Delta M/\Delta t$ = amount of drug permeated, $C_0$= total amount of drug (Vishnu *et al.*, 2007).

### Surface pH study

The surface pH of formulation was determined in order to investigate the possibility of any side effects in vivo. As an acidic or alkaline pH may irritate the buccal mucosa therefore neutral pH was maintained. The method reported by Bottenberg *et al* was used to determine the surface pH of the formulation. The formulation was allowed to swell by keeping it in contact with 1 ml of distilled water for 2 hours at room temperature. The pH was identified by bringing the pH paper over the surface of formulation [41].

### CONCLUSION

The need for research into drug delivery systems extends beyond ways to administer new pharmaceutical therapies. The safety and efficacy of current treatments may be improved if their delivery rates, biodegradation, and site specific targeting can be predicted, monitored and controlled. From both a financial and global healthcare perspective, finding ways to administer injectable medications is costly and some

time leads to serious hazardous effects. Hence inexpensive multiple dose formulations with better bioavailabilies are needed. Improved methods of drug release through transmucosal and transdermal methods would be of great significance, as by such routes, the pain factor associated with parenteral routes of drug administration can be totally eliminated. Buccal adhesive systems offer innumerable advantages in terms of accessibility, administration and withdrawal, retentivity, low enzymatic activity, economy and high patient compliance. Adhesion of buccal adhesive drug delivery devices to mucosal membranes leads to an increased drug concentration gradient at the absorption site and therefore improved bioavailability of systemically delivered drugs. In addition, buccal adhesive dosage forms have been used to target local disorders at the mucosal surface (e.g., mouth ulcers) to reduce the overall dosage required and minimize side effects that may be caused by systemic administration of drugs. Researchers are now looking beyond traditional polymer networks to find other innovative drug transport systems. Much of the development of novel materials in controlled release buccal adhesive drug delivery is focusing on the preparation and use of responsive polymeric system using copolymer with desirable hydrophilic/hydrophobic interaction, block or graft copolymers, complexation networks responding via hydrogen or ionic bonding and new biodegradable polymers especially from natural edible sources. At the current global scenario, scientists are finding ways to develop buccal adhesive systems through various approaches to improve the bioavailability of orally less/inefficient drugs by manipulating the formulation strategies like inclusion of pH modifiers, enzyme inhibitors, permeation enhances etc. Novel buccal adhesive delivery system, where the drug delivery is directed towards buccal mucosa by protecting the local environment is also gaining interest. Currently solid dosage forms, liquids and gels applied to oral cavity are commercially successful. The future direction of buccal adhesive drug delivery lies in vaccine formulations and delivery of small proteins/peptides. Microparticulate bioadhesive systems are particularly interesting as they offer protection to therapeutic entities as well as the enhanced absorption that result from increased contact time provided by the bioadhesive component. Exciting challenges remain to influence the bioavailability of drugs across the buccal mucosa. Many issues are yet to be resolved before the safe and effective delivery through buccal mucosa. Successfully developing these novel formulations requires assimilation of a great deal of emerging information about the chemical nature and physical structure of these new materials.

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