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BUCCAL BIOADHESIVE DRUG DELIVERY- A NOVEL TECHNIQUE

Kumar V, Aggarwal G, Zakir F, Choudhary A*

Department of Pharmaceutics,
Rayat institute of Pharmacy,
Railmajara, Nawashar, Punjab, India.
*Corresponding Author Email: pharmavarinder @gmai.com

Review Article

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ABSTRACT

Oral drug delivery is the most preferable route of drug administration due to ease of administration, patient compliance, flexibility in formulation etc. However in case of the oral route there are several challenges such as first pass metabolism and drug degradation in gastrointestinal environment and poor pharmacological response. Other routes of administration proposed are nasal, pulmonary, transdermal, buccal or rectal drug delivery. These routes offer advantages but they also require some development time. A candidate drug can enter into the development phase but there are problems in delivery of the drug. Drugs having low oral bioavailability show low plasma profile. The buccal mucosa is one of the administration sites that might provide an alternative for peroral administration. This review will provide an insight into this route of drug delivery and the formulations that are, or can be, used, and it will also describe the challenges or possibilities of this route of administration. There is novel drug delivery system like buccal drug delivery system in which drug enters directly in systemic circulation thereby by passing the first pass effect. Contact with digestive food of gastrointestinal tract is avoided which might be unsuitable for stability of many drugs. This is painless and without discomfort, precise dosage form and facilitates ease of removal without significant associated pain. Moreover it shows better stability, patient compliance; uniform and sustained drug release and above all easy and cheap methods of preparation which can be done with various commonly available biocompatible polymers.

KEYWORDS: Buccal delivery, Formulation, Polymer, Mechanism of action, Characterisation

Introduction

The buccal region of the oral cavity is an attractive target for administration of the drug of choice. Buccal delivery involves the administration of the desired drug through the buccal mucosal membrane lining of the oral cavity. Because after oral administration many drugs show first-pass metabolism, which leads to a lack significant correlation between membrane permeability, absorption, and bioavailability[1]. Difficulties associated with parenteral delivery and poor oral bioavailability provides alternative route for delivery of such drugs. These include routes such as pulmonary, ocular, nasal, rectal, buccal, sublingual, vaginal, and transdermal[2]. Among the varies transmucosal routes 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. Direct access to the systemic circulation through the internal jugular vein bypass drugs from the hepatic first pass metabolism leading to high bioavailability. Other advantages such as low enzymatic activity, suitability for drugs or excipients that mildly and reversibly damages or irritates the mucosa, painless administration, pH modifier in the formulation and designing as multidirectional or unidirectional release system. Additionally, buccal drug delivery has a high patient acceptability compared to other non-oral routes of drug administration. The disadvantages associated with this route of drug delivery are the low permeability of the buccal membrane, specifically when compared to the sublingual membrane, and a smaller surface area. The total surface area of the membranes of the oral cavity available for drug absorption is 170 cm^2, of which ~50 cm^2 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 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. So we are discussing the implication of various approaches for buccal adhesive delivery strategies applied for the systemic delivery of orally less/in efficient drugs, in addition to the widely used other drug delivery.

Overview of the oral mucosa

Structure:

The oral cavity is lined with mucous membranes with a total surface area of 100 cm^2. It is possible to observe several distinct areas: the floor of mouth (sublingual), the buccal mucosa (cheeks), the gums (gingival), the palatal mucosa and the lining of the lips. The epithelium is similar to stratified squamous epithelia found in the rest of the body in that it has a mitotically active basal cell layer, advancing through a number of differentiating intermediate layers to the superficial layers, where cells are shed from the surface of the epithelium. The epithelium of the buccal mucosa is about 40–50 cell layers thick, while that of the sublingual epithelium contains somewhat fewer. The epithelial cells increase in size and become flatter as they travel from the basal layers to the superficial layers.

- Permeability
- 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

There are two possible routes of drug absorption through the squamous stratified epithelium of the oral mucosa in passive diffusion:

i.Transcellular (intracellular, passing through the cell) and

ii.Paracellular (intercellular, passing around the cell).

Permeants may traverse these two routes simultaneously, but one route usually is more effective than the other, depending on the

physicochemical properties of the diffusant. 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.

Barriers to penetration across buccal mucosa [3]

Basement membrane: Although the superficial layers of the oral epithelium represent the primary barrier to the entry of substances from the exterior, it is evident that the basement membrane also plays a role in limiting the passage of materials across the junction between epithelium and connective tissue. A similar mechanism appears to operate in the opposite direction. The charge on the constituents of the basal lamina may limit the rate of penetration of lipophilic compounds that can traverse the superficial epithelial barrier relatively easily [4].

Mucus: The epithelial cells of buccal mucosa are surrounded by the intercellular ground substance called mucus with the thickness varies from 40 µm to 300 µm[5]. Mucus is composed chiefly of mucins and inorganic salts suspended in water. Mucins are a family of large, heavily glycosylated proteins composed of oligosaccharide chains attached to a protein core. Three quarters of the protein core are heavily glycosylated and impart a gel like characteristic tomucus. Mucins contain approximately 70–80% carbohydrate, 12–25% protein and up to 5% ester sulphate[6]. The dense sugar coating of mucins gives them considerable water-holding capacity and also makes them resistant to proteolysis, which may be important in maintaining mucosal barriers[7].

Saliva: The mucosal surface has a salivary coating estimated to be 70 µm thick, which act as unstirred layer[8]. Within the saliva there is a high molecular weight mucin named MG1 that can bind to the surface of the oral mucosa so as to maintain hydration, provide lubrication, concentrate protective molecules such as secretory immunoglobulins, and limit the attachment of microorganisms[9]. Several independent lines of evidence suggest that saliva and salivary mucin contribute to the barrier properties of oral mucosa[10]. A constant flowing down of saliva within the oral cavity makes it very difficult for drugs to be retained for a significant amount of time in order to facilitate absorption in this site.

Formulation design

Buccal adhesive drug delivery systems with the size 1–3 cm2 and a daily dose of 25 mg or less are preferable. The maximal duration of buccal delivery is approximately 4–8 h [11].

Buccal adhesive polymers

A polymer is a molecule made up of a chain of repeating units which are chemically bonded together. Adhesives are substances which are used to glue things together. A polymer adhesive is a synthetic bonding substance made from polymers and is considered to be stronger, more flexible and have greater impact resistance than other forms of adhesives. The term is derived from the Greek words: polys meaning many, and meros meaning parts. 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 [12].

Ideal characteristics

- Polymer and its degradation products should be non-toxic, non-irritant and free from leachable impurities.
- Should have good spreadability, wetting, swelling and solubility and biodegradability properties.
- pH should be biocompatible and should possess good viscoelastic properties.
- Should adhere quickly to buccal mucosa and should possess sufficient mechanical strength.
- Should possess peel, tensile and shear strengths at the bioadhesive range.
- Polymer must be easily available and its cost should not be high.
- Should show bioadhesive properties in both dry and liquid state.
- Should demonstrate local enzyme inhibition and penetration enhancement properties.
- Should demonstrate acceptable shelf life.
- Should have optimum molecular weight.
- Should possess adhesively active groups.
- Should have required spatial conformation.
- Should be sufficiently cross-linked but not to the degree of suppression of bond forming groups.
- Should not aid in development of secondary infections such as dental caries.

Physiological considerations

Physiological considerations such as texture of buccal mucosa, thickness of the mucus layer, its turn over time, effect of saliva and other environmental factors are to be considered in designing the dosage forms [13]. Saliva contains moderate levels of esterases, carbohydrases, and phosphatases that may degrade certain drugs. Although saliva secretion facilitates the dissolution of drug, involuntary swallowing of saliva also affects its bioavailability. Hence development of unidirectional release systems with backing layer results high drug bioavailability.

Permeation enhancers

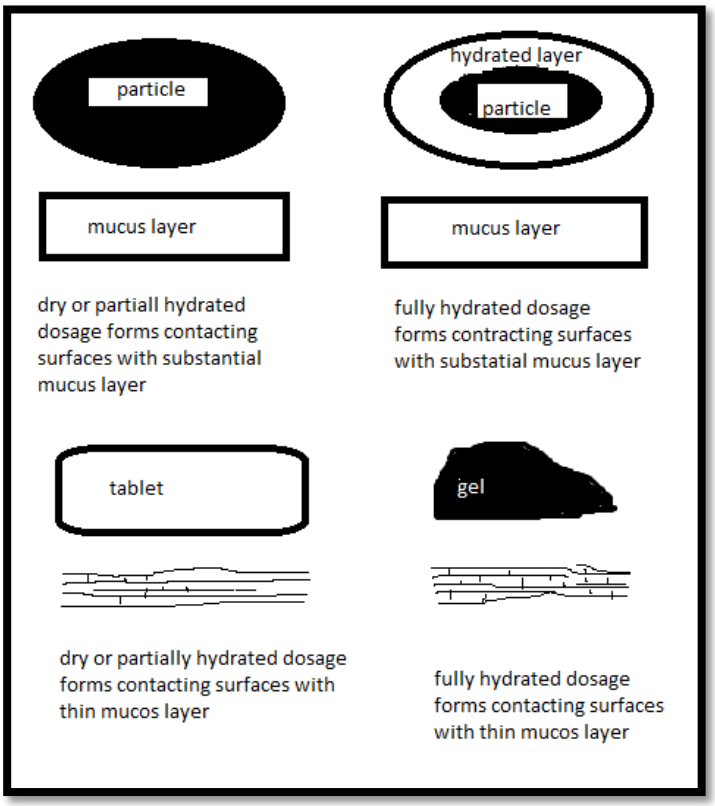
Substances that help to promote drug permeation through the buccal epithelium are referred to as penetration enhancers, permeation promoters or absorption enhancers[14]. The chemicals used as penetration enhancers ideally should be safe and non-toxic, pharmacologically and chemically inert, non-irritant, and non-allergenic[15]. Penetration enhancers can be divided into many categories according to their structure, mechanism of action, and the type of drugs whose permeation they enhance. Most of the compounds used as buccal mucosal penetration enhancers are the ones generally used to compromise barrier function. **Table 1** provides an overview of some of the different chemical classes that have been used, with examples of materials and the proposed mechanisms of action.

Mucosal penetration enhancers and mechanisms of action

Classification	Examples	Mechanism
Surfactants	**Anionic:** sodium lauryl sulfate, sodium laurate **Cationic:** cetylpyridinium Chloride Nonionic: poloxamer, Brij, Span, Myrj, Tween **Bile salts:** sodium glycodeoxycholate, sodium glycocholate, sodium taurodeoxycholate, sodium taurocholate	Perturbation of intercellular lipids, protein domain integrity
Fatty acids	Oleic acid, caprylic acid	Increase fluidity of phospholipid Domains
Cyclodextrins	a-, b-, g-cyclodextrin, methylated b-cyclodextrins	Inclusion of membrane compounds
Chelators	EDTA, sodium citrate, Polyacrylates	Chelators EDTA, sodium citrate Interfere with Ca^{2+}
Positively charged polymers	Chitosan, trimethyl chitosan	Ionic interaction with negative
Cationic compounds	Poly-L-arginine, L-lysine	charge on the mucosal surface

Mechanisms of action

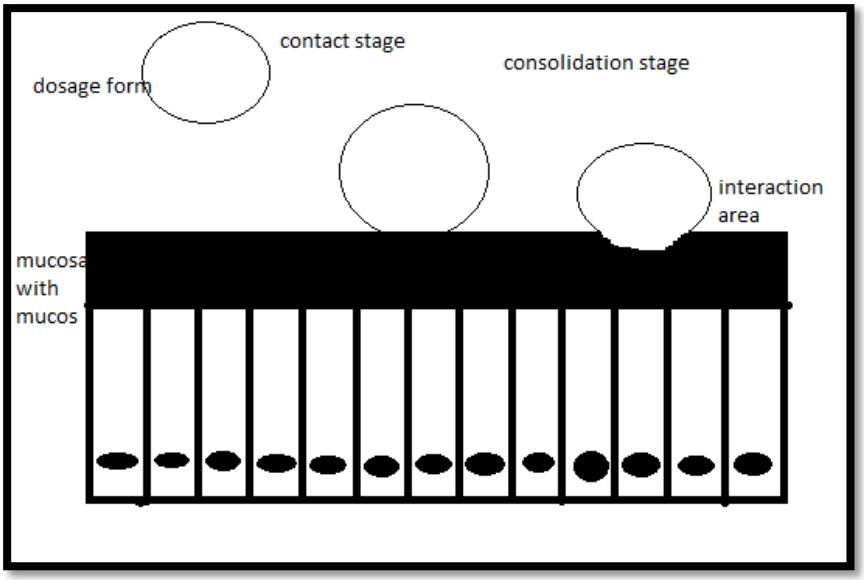
Due to its relative complexity, the process of mucoadhesion cannot be described by just one of the theories. In considering the mechanism of mucoadhesion, a whole range of scenarios for in-vivo mucoadhesive bond formation are possible



In the study of adhesion generally, two steps are identified, which have been adapted to described the interaction between mucoadhesive materials and a mucous membrane [16,17].

Step 1 – contact stage: An intimate contact (wetting) occurs between the mucoadhesive and mucous membrane.

Step 2 – consolidation stage: various physicochemical interaction occur to consolidate and strengthen the adhesive joint, leading to prolonged adhesion.



Muco/Bioadhesion

Adhesion is defined as the state in which surfaces are held together by interfacial forces, which may consist of valence forces interlocking action, or both. The term Bioadhesion is used to describe adhesion between two materials where atleast one of the material is of the biological origin. In case of Bioadhesive drug delivery system, Bioadhesion often refers to adhesion between the excipient of the formulation and biological tissue. Mucoadhesive drug delivery systems utilize the property of certain water-soluble polymers, which become adhesive on hydration and hence can be used for targeting a drug to a particular region of body for an extended period of time [18,19].

The mucoadhesion interaction

Chemical bonds: the molecule must bond across the interface for adhesion to occur. These bonds can arise in the following ways [20].

- Ionic bonds
- Covalent bonds
- Hydrogen bonds
- Vander wall bonds
- Hydrophobic bonds
- Hydrogen bonding
- Disulphide bridging
- Hydration forces
- Electrostatic double-layer forces
- Steric forces

Theories of Bioadhesion

There are various general theories of adhesion, which have been adapted for investigation of mucoadhesion [21,22,23].

a) **Adsorption theory:** according to this theory, after an initial contact between two surfaces, the material adheres because of surface forces. Two types of chemical bonds resulting from these forces can be distinguished:

I. Primary chemical bonds of covalent nature which are undesirable in Bioadhesion because there high strength may result in permanent bond.

II. Secondary chemical bonds having many different forces of attraction, including electrostatic force, vander-wall forces, hydrogen and hydrophobic bonds.

b) Diffusion theory: According to this theory, polymer chains and the mucus mix to a sufficient depth to form a semi-permanent bond. The depth of interpenetration depends on the diffusion coefficient and time of contact. This diffusion coefficient depends on the molecular weight between cross-links and decreases significantly as the cross linking density decreases.

c) **Electronic theory:** According to this theory, an electronic transitions occurs upon contact of adhering surfaces and due to differences in there electronic structure. This is proposed to result in the formulation of an electrical double layer at the interface with subsequent adhesion due to attractive forces.

d) **Mechanical theory:** According to this theory, adhesion arises from an interlocking of a liquid adhesive into irregularities on a rough surface. However, rough surfaces provide an increase area available for interaction along with an enhanced

viscoelastic and plastic dissipation of energy during joint failure, which are though to be more important in adhesion process than a mechanical effect.

e) **Wetting theory:** this theory is predominantly applicable to liquid and solid Bioadhesive systems. It analyses adhesive and contact behaviour in terms of the ability of liquid or paste to spread over biological system.

Various theories exist, but it is clear that all the mechanisms of adhesion require high intimate contact between the polymer and mucin and expanded network in both substances favours strong adhesion. Although these theories have provided some insight, no single theory has been successful in explaining the mucoadhesion phenomenon, this is due to the fact that in actual process a number of factors are involved simultaneously.

Methods to study mucoadhesion

The evaluation of mucoadhesive properties is fundamental to the development of novel Bioadhesive drug delivery system. Measurement of the mechanical properties of a Bioadhesive material after interaction with a substrate is one of the most direct ways to quantify the Bioadhesive performance. Testing is essential for the development, quantification, processing and proper use of the Bioadhesive. Several methods have been developed for the determination of Bioadhesive bond strength. These tests are also important during the design and development of Bioadhesive controlled release system as they ensure compatibility, physical and mechanical stability, surface analysis, and Bioadhesive strength [24].

The test methods can be classified into two major categories:

- ***In vitro/Ex vivo* methods**

-***In vivo* methods**

***In vitro/Ex vivo* methods:** The *in vitro* methods are based on the measurements of either tensile stress or shear stress.

Methods based on measurement of tensile strength: In these methods the force required to break the adhesive bond between a model membrane and the test polymer is measured.

Tensinometer: This instrument consists of two jaws from flat glasses. The upper glass was fixed, but the lower glass had been mounted on a screw-elevating surface. The upper fixed glass was attached to a sensitive digital balance. Tablets from each formulations were suspended in water (pH 7) for 15 min. Then these adhesive tablets were located on the surface of lower glass and were elevated until they contact the surface of upper glass. The lower glass was then lowered until the tablet clearly was pulled free from the upper glass. The maximum tensile force needed to detach the jaws was recorded in gram/cm and mean values were calculated and recorded [25].

Modified balance method: Modified double beam physical balance was used as the Bioadhesion test apparatus. The right pan of the balance was replaced with lighter one and pan was prepared with the Teflon ring hanging by a number of metallic rings. A cylinder at whose base a tablet was attached was hung from this ring. The two sides of the balance were then balanced with a fixed weight on the right hand side. The mucus membrane was tied with mucosal side upward using a thread over a Teflon block. The block was then lowered into the jacketed beaker which was then filled with phosphate buffer such that buffer just reached the surface of the balance. The balance beam was raised by removing the fixed weight kept on the right side of the pan. This lowered the Teflon cylinder along with the

tablet over the mucosa. The balance was kept in this position for a fixed time and then slowly increased on the right pan till the tablet separated from the mucus surface. The excess weight on right hand side gave the Bioadhesive strength of the tablet in grams. It was observed that assembly gave reproducible results and performed efficiently [26].

In vitro methods

1. **Adhesion weight method:** A system where suspension of an exchange resin particles flowed over the inner mucosal surface of a section of guinea pig intestine and the weight of adherent particles was determined. Although the method has limited value due to poor data reproducibility resulting from fairly rapid degradation and biological variation of the tissue, it was possible to determine the effect of particle size and charge on the adhesion after 5 minutes contact with the adverted intestine [27].

2. **Flow channel method:** Mikos and Peppas developed this method which utilizes a thin channel made up of glass which is filled with 2% w/w aqueous solution of bovine submaxillary mucin, thermostated at 37^0C. Humid air at 37^0C was passed through glass channel. A particle of Bioadhesive polymer was placed on the mucin gel, and its static and dynamic behaviour was monitored at frequent intervals using a camera, thereby calculating its adhesive property [28].

3. **Fluorescent probe method:** In order to examine a large number of polymers for their Bioadhesive potential, the technique of labelling the lipid bilayer and memberane protein with the fluorescent probes namely pyrene and fluorescein isothiocynate, respectively, was used. Addition of polymers to this substrate surface compressed the lipid bilayer or protein causing a change in fluorescence, as compared to control cells. By using the fluorescent probes, it was possible to compare charge type and density and backbone structure and their influence on polymer adhesion. Charged carboxylated polyanions were found to have a good potential for Bioadhesive drug delivery [29].

4. **Mechanical spectroscopic method:** Mechanical spectroscopy was used to investigate the interaction between glycoprotein gel and polyacrylic acid, and the effect of pH and polymer chain length on this. Mortazavi et al., used a similar method to investigate the effect of carbopol 934 on the rheological behaviour of mucus gel. They also investigated the role of mucus glycoproteins and the effect of various factors such as ionic concentration, polymer molecular weight and its concentration, and the introduction of anionic, cationic and neutral polymers on the mucoadhesive mucus interface [30].

5. **Thumb test:** it is simple test method used to quantify mucoadhesiveness. The difficulty of pulling the thumb from the adhesive as a function of pressure and contact time gives a measure of adhesiveness. It is most likely that any mucoadhesive system is adhesive to fingers, since most mucoadhesives are non-specific and not mucin specific and like mucin the skin has also many hydroxyl groups for interaction with Bioadhesive systems. Although the thumb test may not be conclusive, it provides useful information on mucoadhesive potential [19].

6. **Colloidal Gold Staining:** This technique employed red colloidal gold particles, which were stabilized by the absorbed mucin molecules to form mucin gold conjugates. Upon interaction with mucin-gold conjugates, Bioadhesive hydrogel

developed a red colour on the surface. Thus the interaction between them could easily be quantified, either by measurement of the intensity of the red colour on the hydrogel surface or by the measurement of the decrease in the concentration of the conjugates from the absorbance changes at wavelength [31].

7. **Electronic conductance**: This method is used to test the semisolid mucoadhesive ointments. The adhesion of Orabase, carbopol, eudispert, guar gum and methylcellulose to artificial membranes in artificial saliva was studied by using a modified rotational viscometer capable of measuring electrical conductance. In the presence of adhesive the conductance was comparatively low, as the adhesive was removed, the value increased to final value, which corresponds to the conductance of saliva, which indicates the absence of adhesion [19].

Buccal adhesive drug delivery system

Recent buccal mucoadhesive formulations prove to be an alternative to the conventional oral medications as they can be readily attached to the buccal cavity retained for a longer period of time and removed at any time. Mucoadhesive adhesive drug delivery systems using tablets, films, layered systems, discs, microparticles, ointments, wafers, lozenges and hydrogel systems has been studied by various research groups.

Buccal tablet is the tablet which dissolves when held between the cheek and gum, permitting direct absorption of the active ingredient through the oral mucosa but tablets have some limitations such as size for tablet due to requirement for the dosage form.

Microparticles have more advantages than tablet. The physical properties of microspheres enable to make them closely contact with a large mucosal surface. They can also be delivered to less accessible sites like GI track and nasal cavity and they cause less local irritation at the site of adhesion but the success of these microspheres is limited due to their short residence time at site of absorption.

Wafers is a novel periodontal drug delivery system. This is used for the treatment of microbial infection.

Lozenges are used as topically within mouth including antimicrobials, corticosteroids, local anaesthetics, antibiotics and antifungals. In lozenges multiple daily dosing is required because the release of drug in oral cavity is initially high and then rapidly decline to the subtherapeutic levels.

Buccal patches: These are flexibles which deliver the drugs directly in to systemic circulation through mucos membrane thereby by passing the first pass effect. Buccal patch formulations are placed in the mouth between the upper gingivae (gums) and cheek to treat local and systemic conditions. Contact with digestive food of gastrointestinal tract is avoided which might be unsuitable for stability of many drugs. This is painless and without discomfort, precise dosage form and facilitates ease of removal without significant associated pain. Moreover it shows better stability, patient compliance; uniform and sustained drug release and above all easy and cheap methods of preparation which can be done with various commonly available biocompatible polymers.

An ideal buccal adhesive system must have the following properties:

- The drug release should be in a controlled fashion,
- Drug release should be in unidirectional way towards the mucosa,

- The rate and extent of drug absorption should be facilitated,
- Should not cause any irritation or inconvenience to the patient,
- Should not interfere with the normal functions such as talking, drinking etc,
- Should adhere to the site of attachment for a few hours.

Reported buccoadhesive drug delivery system

Drug	Dosage	Action	Bioadhesive polymer
Betamethasone	Tablet	Local	Scmc
Benzydamine	Patch	Local	Pectin, PAA
Benzocaine	Bioadhesive gel	Local	HPMC
Carvedilol	Buccal patch	Systemic	HPMC
Clotrimazole	Bioadhesive liposome gel	Local	Carbopol
Cetylpyridinium chloride	Buccal patch	Local	PVA, HEC and chitosan
Captopril	Tablet	Systemic	Carbopol, chitosan
Clotrimazole	Disk	local	Carbopol, HPMC
Diltiazem HCL	Tablet	systemic	Carbopol, PVP
Diclofenac sodium	Buccal disk	local	Carbopol, SCMC
Fentanyl	Buccal film	systemic	PVP k30, PVP k90
Flurbiprofen	Emulgels	local	Pemulen, compritol
Metronidazole	Bioadhesive liposome gel	local	Carbopol
Metronidazole	Buccal tablet	local	SCMC,polycarbophil, carbopol, HEC, HPMC
Miconazole nitrate	Tablet	systemic	HPMC,SCMC, cabbopol, sodium alginate
Ibuprofen	Mucoadhesive patch	systemic	PVP, NaCMC

Characterisation of Buccal patches:

Masss uniformity: Mass uniformity was tested in 10 different randomly selected patches from each batch (32).

Thickness: Thickness was measured at 5 different randomly selected spots on patches using a screw gauge [32].

Folding endurance: Folding endurance of patches was determined by repeatedly folding one patch at the same place till it broke or folded up to 200 times without breaking [33].

Drug content uniformity: Drug content uniformity was determined by dissolving the patch by homogenization in 100 ml of an isotonic phosphate buffer (pH 7.4) for 8 h under occasional shaking. The 5 ml solution was taken and diluted with isotonic phosphate buffer pH 7.4 up to 20 ml, and the resulting solution was filtered through a 0.45 µm Whatman filter paper. The drug content was then determined after proper dilution at UVspectrophotometer[34]. The experiments were carried out in triplicate.

Surface pH Determination: The surface pH was determined by the method similar to that used by Bottenberg et al. 1991. A combined glass electrode was used for this purpose. The patches were allowed to swell by keeping them in contact with 1 ml of distilled water (pH 6.5±0.1) for 2 h at room temperature, and pH was noted down by bringing the electrode in contact with the surface of the patch, allowing it to equilibrate for 1 minute. The surface pH of the patches was determined in order to investigate the possibility of any side effects, in the oral cavity. As acidic or alkaline pH is bound to cause irritation to the buccal mucosa, hence attempt was made to keep the surface pH of the patch close to the neutral pH [35].

***In vitro* Swelling Studies of Buccoadhesive patch:** The degree of swelling of bioadhesive polymer is important factor affecting adhesion. Upon application of the bioadhesive material to a tissue a process of swelling may occur. The swelling rate of buccoadhesive patch was evaluated by placing the film in phosphate buffer solution pH 7.4 at 37°C. Buccal patch was weighed, placed in a 2% agar gel plate and incubated at 37±1°c. At regular one-hour time intervals (upto 3 h), the patch was removed from the petri dish and excess surface water was removed carefully using the filter paper. The swollen patch was then weighed again and the swelling index was calculated [36].

$$\text{Swelling index} = \frac{W_2 - W_1}{W_1}$$

***In vitro* release Studies:** In order to carry out *In-vitro* release studies dissolution test apparatus type II (USP) rotating paddle method was used. The studies were carried out for all formulation combination in triplicate, using 900 ml of isotonic phosphate buffer (pH 7.4) as the dissolution medium. The release was performed at 37°C, at 50rpm. To provide unidirectional release, one side of buccal patch was attached to a glass disk with the help of two sided adhesive tape then disk was put in the bottom of the dissolution vessel so that patch remained on the upper side of the patch remained on the upper side of the disk. An aliquot of 5ml sample was withdrawn at predetermined time intervals and similar volume was replaced with fresh phosphate buffer (pH 7.4) maintained at same temperature. Samples were then analyzed with the help of UV spectrophotometer[37].

***Ex vivo* mucoadhesion time:** The selected batch was subjected to ex vivo mucoadhesion test. The disintegration medium was composed of 800 ml isotonic phosphate buffer pH 7.4 maintained at 37°C. A segment of porcine cheek mucosa, 3 cm long, was glued to the surface of a glass slab, vertically attached to the apparatus. The mucoadhesive patch was hydrated from one surface using 15 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 patch was completely immersed in the buffer solution at the lowest point and was out at the highest point. The time necessary for complete erosion or detachment of the patch from the mucosal surface was recorded. The experiment was carried out in triplicate [32].

Permeation studies

The *in vitro* study of venlafaxine permeation through the sheep buccal mucosa was performed using a Franz diffusion cell at 37 ± 0.2°C. Sheep buccal mucosa was obtained from a local slaughterhouse (used within 2 h of slaughter). Freshly obtained goat buccal mucosa was mounted between the donor and receptor compartments so that the smooth surface of the mucosa faced the donor compartment. The patch was placed on the mucosa and the compartments clamped together. The donor compartment was filled with 1 mL of isotonic phosphate buffer pH 7.4. The receptor compartment (15 mL capacity) was filled with isotonic phosphate buffer pH 7.4 and the hydrodynamics in the receptor compartment was maintained by stirring with a magnetic bead at 100 rpm. One mL sample was withdrawn at predetermined time intervals and analyzed for drug content at 224 nm.

Bioadhesion strength

The tensile strength required to detach the bioadhesive patch from the mucosal surface was applied as a measure of the bioadhesive performance. The apparatus was locally assembled. The device was mainly composed of a two-arm balance.

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Address for the Correspondence:

Kumar V*

Department of Pharmaceutics,
Rayat institute of Pharmacy,
Railmajara, Pin: 144533,
Nawashar, Punjab,
India.
E-mail: pharmavarinder @gmai.com