REVIEW ON MUCOADHESIVE BUCCAL DRUG DELIVERY

Bhandari Heta P.*, Jitendrasingh Yadav

Department of Pharmaceutics, Shree Naranjibhai Lalbhai Patel College of Pharmacy, Umra, Bardoli, Gujarat, India.

ABSTRACT
Buccal delivery is considered to be a major alternative to the peroral route and the unique environment of the oral cavity offers its potential as a site of drug delivery. Buccal drug delivery has lately become an important route of drug administration. The rich in vascularization of oral mucosa and its permeability too many drugs make this route an attractive alternative to the oral and parenteral routes for systemic drug delivery. Absorption through the buccal mucosa overcomes premature drug degradation due to the enzyme activity and pH of gastrointestinal tract, avoids active drug loss due to pre-systemic metabolism (First-pass hepatic metabolism), acid hydrolysis and therapeutic plasma concentration of the drug can be rapidly achieved. There is always increase in demand for the patient convenience and compliance related research and novel methods are the development of mucoadhesive buccal formulations which results the greater bioavailability with reducing dose frequency to mouth plasma peak levels, which in turn minimize adverse/side effects and also make it cost effective. Moreover, rapid onset of action can be achieved.it is also possible to administer the drug to patients who are unconscious and less co-operative. In the present review, recent advancements and literature regarding mucoadhesive buccal patches is compiled and it suggests that this delivery system can be adopted by various pharmaceutical companies in the future at the large scale because it is the novel frontier in drug delivery technology that provides a very convenient means of taking medication. This review also highlight a brief description of advantages, disadvantages, limitation and theories involved in mucoadhesive, and classification of buccal system.

KEYWORDS: Buccal patches, mucoadhesion, buccal mucosa, buccal drug delivery.

INTRODUCTION
Since the early 1980s, the concept of mucoadhesion has gained considerable interest in pharmaceutical technology. The American Society of Testing and Materials has defined adhesion as the state in which two surfaces are held together by interfacial forces, which may consist of valency forces, interlocking action or both (1). The trans mucosal drug delivery (i.e., the mucosal linings of the nasal, rectal, vaginal, ocular, oral cavity) offers distinct advantages over peroral administration for systemic drug delivery. These advantages include possible bypass first pass effect, avoidance of pre-systemic elimination within gastrointestinal tract, and depending on the particular drug, a better enzymatic flora for drug absorption. The potential irritation and the irreversible damage to the ciliary action of the nasal cavity from chronic application of nasal
dosage forms could significantly affect drug absorption from this site. Even through rectal, vaginal and ocular mucosae all offer certain advantages the poor potential acceptability associated with these sites renders them reserved for local applications rather than systemic drug administration. On other hand, the oral cavity is highly acceptable by patients, the mucosae is relatively permeable with a rich blood supply, it is robust and shows short recovery times after stress or damage, and virtual lack of Langerhans cells makes the oral mucosa tolerant to potential allergens. The mucin lining exists in oral mucosa offers an opportunity to develop mucoadhesive system, which retain at absorption site for prolonged time by mucoadhesive binding. The close contact with absorption membrane causes more absorption of the drug and it provides direct entry of drug molecule into the systemic circulation, thus avoiding acid hydrolysis and pre-systemic metabolism.

The buccal mucosa permits a prolonged retention of a dosage form especially with the use of mucoadhesive polymers without much interference in activities such as speech or mastication unlike the sublingual route (2). Buccal films may be preferred over adhesive tablets in terms of flexibility and comfort. In addition they can circumvent the relatively short residence time of oral gels on the mucosa, which are easily washed away and removed by saliva. The continuous secretion of saliva results in rapid removal of released drug and this may desire that the oral cavity should be restricted to the delivery of the drugs, which have a short systemic circulation. Conversely, the thin mucin film, which exists on the surface of oral mucosa, may provide an opportunity to retain for longer time and continuous drug delivery. Moreover, the buccal films are able to protect the wound surface, thus reducing pain and treating oral diseases more effectively (3). The ideal buccal patch should be flexible, elastic and soft yet adequately strong to withstand breakage due to stress from mouth activities. It must also exhibit good mucoadhesive strength so that it can be retained in mouth for desired duration. As such, the mechanical, mucoadhesive, and swelling properties of buccal patches are critical and essential to be evaluated (4).

Advantages of Buccal Drug Delivery System

The administration of drugs by the buccal route has several main advantages over peroral administration, including the following

- Improves patient compliance by decreasing dosing frequency.
- Better therapeutic effect of short half-life drugs can be achieved.
- Bioavailability enhances despite first pass effect because fluctuations in plasma Drug concentration is maintained by continuous drug release.
Drug release in controlled manner for prolonged period.

Improve the performance of many drugs, as they are having prolonged contact Time with the mucosa.

Increased residence time combined with controlled API release may lead to Lower administration frequency.

Tolerance (in comparison with the nasal mucosa and skin) to potential sensitizer.

It offers a passive system of drug absorption and does not require any activation.

Provides an alternative route for the administration of various hormones, narcotic analgesics, steroids, enzymes, cardiovascular agents etc.

The drug is not subjected to the destructive acidic environment of the stomach.

The oral mucosa is easily accessible, which ensures that a dosage form can be applied to the required site and removed easily in case of emergency.

There is no requirement of medical practitioner to administer the dosage form.

The ease of administration and ability to terminate drug delivery when required Make it either a potential route or an attractive for drug delivery (5) (6).

Disadvantages of Buccal Drug Delivery System

The main challenges of buccal administration are:

Limited absorption area- the total surface area of the membranes of the oral cavity available for drug absorption is 170 cm² of which ~50 cm² represents non-keratinized tissues, including buccal membrane.

The barriers such as saliva, mucus, membrane coating granules, basement membrane etc retard the rate and extent of drug absorption through the buccal mucosa.

Continuous secretion of the saliva (0.5-2 l/day) leads to subsequent dilution of the drug.

The hazard of choking by involuntarily swallowing the delivery system is a concern.

Swallowing of saliva can also potentially lead to the loss of dissolved or suspended drug and ultimately the involuntary removal of the dosage form (5) (6) (7).

Overview of the buccal mucosa

The oral mucosa lines the oral cavity, which is delineated by the lips, cheeks, hard and soft palates, tongue and floor of the mouth. It covers a surface area about 100 cm². Mucus is a translucent and viscid secretion which forms a thin, continuous gel blanket adherent to the mucosal epithelial surface. The mean thickness of this layer varies from about 50 to 450μm in humans. It is secreted by the goblet cells lining the epithelia or by special exocrine glands with
mucus cells acini. The exact composition of the mucus layer varies substantially depending on the species, the anatomical location and the Pathophysiological state. However, it has the following general composition (9).

- Water - 95%
- Glycoproteins and Lipids - 0.5 to 5%
- Mineral salts - 0.5 to 1%
- Free Proteins - 0.5 to 1%

The surface of the buccal mucosa consists of stratified squamous epithelium supported by a connective tissue termed lamina propria and separated from the epithelium by basal membrane. Three different types of oral mucosa are recognized (10).

**Fig. 1: Structure of Oral Cavity** (11)

**Masticatory mucosa**

The masticatory mucosa, representing 25% of the total oral mucosa and being 100-200 μm in thickness covers the gingival and the hard palate regions and is tightly attached to underlying structures. The epithelium of masticatory mucosa in gingival and hard palate regions are keratinized and further subdivided into four layers, namely Keratinized, Granular, Prickle-cell and Basal layers (12).

**Lining mucosa**

The lining mucosa has a thickness of 500-800μm and covers the lips, cheeks, soft palate, the lower surface of the tongue on the floor of the oral cavity, representing 60% of total oral mucosa. This lining provides elastic and deformable surfaces that stretch with the normal functions of the
mouth, such as mastication and speech. It is attached by a loose and elastic connective tissue to the underlying structures \(^{(12)(13)}\).

**Specialized mucosa**

Specialized mucosa accounts for 15% of total oral mucosa and consists of both keratinized and non-keratinized mucosa. It is found on the dorsal of the tongue and is involved in taste \(^{(13)}\).

**Buccal mucosa as a site for drug delivery**

Two sites within the buccal cavity have been used for drug administration to get the systemic effect, Buccal and Sublingual. The buccal delivery allows prolonged localized therapy that enhanced systemic delivery whereas the sublingual route is usually used when a rapid onset of action is required. The sublingual mucosa is relatively permeable, giving rapid absorption and acceptable bioavailability of many drugs, and is convenient, accessible, and generally well accepted. The sublingual route is by far the most widely studied of the 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. Even though the sublingual mucosa is relatively more permeable than the buccal mucosa, it is not suitable for an oral Trans mucosal delivery system. The sublingual region lacks an expanse of smooth muscle or immobile mucosa and is constantly washed by 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 trans mucosal drug delivery \(^{(14)}\).

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 Trans mucosal 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 \(^{(15)}\).
**Delivery of drugs within the oral mucosal cavity**

It is classified into three categories

1. **Sublingual delivery:** Is the administration of drug via sublingual mucosa (membrane of the ventral surface of the tongue and floor of the mouth) to systemic circulation. The sublingual mucosa is relatively permeable, giving rapid absorption and acceptable bioavailability of many drugs, and is convenient, accessible, and generally well accepted. The sublingual route is by far the most widely studied of these routes. Sublingual dosage forms are most often one of two 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.

2. **Buccal delivery:** Is the administration of drug via buccal mucosa (the lining of cheek) to the systemic circulation. The buccal mucosa is considerably less permeable than sublingual area, and is generally not able to provide rapid absorption and good bioavailability seen with sublingual administration.

3. **Local delivery:** For the treatment of conditions of oral cavity, principally ulcers, fungal conditions and periodontal disease. These oral mucosal sites differ greatly from one another in terms of anatomy, permeability to an applied drug and their ability to retain a delivery system for a desired length of time. Even though sublingual mucosa is relatively more permeable than buccal mucosa, it is not suitable for a retentive oral trans mucosal delivery system. The sublingual region lacks an expanse of smooth and immobile mucosa and is constantly washed by a considerable amount of saliva, making device placement difficult. The preferred site for retentive oral Trans mucosal delivery systems and for sustained and controlled-release delivery devices is the buccal mucosa, mainly because of differences in permeability characteristics between the two regions and the buccal mucosa expanse of smooth and relatively immobile mucosa\(^{16}\)\(^{17}\)\(^{18}\).

**Buccal routes of drug absorption**

The mechanisms by which the drugs cross biologic lipid membranes are passive diffusion, active transport, and pinocytosis. The main mechanism involved in drug transfer across the oral mucosa, is passive diffusion, although facilitated diffusion has also been shown to take place, primarily with nutrients. Passive diffusion involves the movement of a solute from a region of low concentration within the buccal tissues. Further diffusion then takes into the venous capillary system, with the drug eventually reaching the systemic circulation via jugular vein\(^5\). There are two permeation pathways for passive drug transport across the oral mucosa: paracellular
(intercellular) and trans cellular (intracellular) routes. Permeants can use these two routes simultaneously, but one route is usually preferred over the other depending on the physicochemical properties of the diffusant. Since the intercellular spaces and cytoplasm are hydrophilic in character, lipophilic compounds would have low solubilities in this environment. The cell membrane, however, is rather lipophilic in nature and hydrophilic solutes will have difficulty permeating through the cell membrane due to a low partition coefficient. Therefore, the intercellular spaces pose as the major barrier to permeation of lipophilic compounds and the cell membrane acts as the major transport barrier for hydrophilic compounds. Since 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\(^{(15)}\). Compounds with partition coefficient in the range 40-20000 and Pka 2-10 are considered optimal to be absorbed through buccal mucosa\(^{(23)}\). However the administration site is also a factor. Large size patches can be administrated at the central position of the buccal mucosa (center of cheek), whereas the sublingual and gingival sites require a rather small sized patches\(^{(24)}\)\(^{(25)}\). The size of systems typically varies from 1-16 cm, depending upon the specific purpose of the application. Usually, 1-3 cm patches are commonly used because of patient convenience and comfort\(^{(26)}\)\(^{(27)}\).

**Characteristics of an Ideal mucoadhesive System**

An ideal buccal adhesive system should possess the following characteristics:

1. Quick adherence to the buccal mucosa and sufficient mechanical strength.
2. Drug release in a controlled fashion.
3. Facilitates the rate and extent of drug absorption.
4. Should have good patient compliance.
5. Should not hinder normal functions such as talking, eating and drinking.
6. Should accomplish unidirectional release of drug towards the mucosa.
7. Should not aid in development of secondary infections such as dental caries.
8. Possess a wide margin of safety both locally and systemically.
9. Should have good resistance to the flushing action of saliva\(^{(5)}\).

**Ideal characteristics of buccal adhesive polymers**

1. Polymer and its degradation products should be non-toxic, non-irritant and free from leachable impurities.
2. Should have good spreadability, wetting, swelling and solubility and biodegradability properties.
3. Should adhere quickly to buccal mucosa and should possess sufficient mechanical strength.
4. Should possess peel, tensile and shear strengths at the bioadhesive range.
5. Polymer must be easily available and its cost should not be high.
6. Should show bioadhesive properties in both dry and liquid state.
7. Should demonstrate local enzyme inhibition and penetration enhancement properties.
8. Should demonstrate acceptable shelf life.
9. Should have optimum molecular weight.
10. Should possess adhesively active group \(^{28}\) \(^{29}\)

**Mucoadhesive polymers**

Mucoadhesive polymers can be classified as following:

1. **Synthetic polymers**: Cellulose derivatives (methylcellulose, ethyl cellulose, hydroxyethylcellulose, Hydroxyl propyl cellulose, hydroxyl propyl methylcellulose, sodium carboxy methylcellulose, Poly (acrylic acid) polymers (carbomers, polycarbophil), Poly (hydroxyethyl methylacrylate), Poly (ethylene oxide), Poly (vinyl pyrrolidone), Poly (vinyl alcohol), Natural polymers, Tragacanth, Sodium alginate, Karaya gum, Guar gum, Xanthan gum, Lectin, Soluble starch, Gelatin, Pectin, Chitosan.

2. **Hydrophilic Polymers**: These are the water-soluble polymers that swell indefinitely in contact with water and eventually undergo complete dissolution, e.g. Methyl Cellulose, Hydroxyl Ethyl Cellulose, Hydroxyl Propyl Methyl Cellulose, Sodium Carboxy Methyl Cellulose, Carbomers, Chitosan and Plant gums.

3. **Hydrogels**: These are water swellable materials, usually a cross-link polymer with limited swelling capacity, E.g. poly (acrylic acid co acrylamide) copolymers, carrageenan, sodium alginate, guar gum and Modified guar gum etc.

4. **Thermoplastic Polymers**: These polymers include the non-erodible neutral polystyrene and semi-crystalline bio-erodible polymers, which generate the carboxylic acid groups as they degrade, e.g. polyanhydrides and polylactic acid. Various synthetic polymers used in mucoadhesive formulations include polyvinyl alcohol, polyamides, polycarbonates, polyalkylene glycols, polyvinyl ethers, esters and halides, polymethacrylic acid, polymethylmethacrylic acid, Methyl Cellulose, Hydroxyl Propyl Cellulose, Hydroxyl Propyl Methyl Cellulose, and Sodium Carboxy Methyl Cellulose. Various biocompatible polymers used in mucoadhesive formulations include cellulose-based polymers, ethylene glycol polymers and its copolymers, oxyethylene polymers, polyvinyl alcohol, polyvinyl acetate and esters of hyaluronic acid. Various
Biodegradable polymers used in mucoadhesive formulations are poly (lactides), poly (Glycolides), poly (lactides-co-glycolides), polycaprolactones, and polyalkyl cyanoacrylates. Polyorthoesters, polyphosphoesters, polyanhydrides, polyphosphazenes are the recent additions to the polymers.\(^{(19)}\)\(^{(20)}\).

**Buccal dosage forms**

**Buccal mucoadhesive tablets:**

Buccal mucoadhesive tablets are dry dosage form that have to be moistened prior to placing in contact with buccal mucosa. Example: a double layer tablet, consisting of adhesive matrix layer of hydroxyl propyl cellulose and polyacrylic acid with an inner core of cocoa butter containing insulin and a penetration enhancer (sodium glycocholate).

**Patches and Films**

Buccal patches consist of two laminates, with an aqueous solution of the adhesive polymer being cast onto an impermeable backing sheet, which is then cut into the required oval shape. A novel mucosal adhesive film called “Zilactin” – consisting of an alcoholic solution of hydroxy propyl cellulose and three organic acids. The film which is applied to the oral mucosal can be retained in place for at least 12 hours even when it is challenged with fluids.\(^{(30)}\).

**Semisolid Preparations (Ointment and Gels):**

Bioadhesive gels or ointment have less patient acceptability than solid bioadhesive dosage form, and most of the dosage forms are used only for localized drug therapy within the oral cavity. One of the original oral mucoadhesive delivery systems- “orabase”- consists of finely ground pectin, gelatin and sodium carboxy methylcellulose dispersed in a poly (ethylene) and a ground pectin, gelatin and sodium carboxy methylcellulose dispersed in poly (ethylene) and a mineral oil gel base, which can be maintained at its site of application for 15-150 minutes.\(^{(31)}\).

**Powders**

Hydroxypropyl cellulose and beclomethasone in powder form when sprayed onto the oral mucosa of rats, a significant increase in the residence time relative to an oral solution is seen, and 2.5% of beclomethasone is retained on buccal mucosa for over 4 hours.\(^{(32)}\).

**Micro particle**

Micro particles 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 causeless 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.\(^{(33)}\).
Wafer
Wafer is a novel periodontal drug delivery system. This is used for the treatment of microbial infection.

Lozenges
Lozenges are used as topically within mouth including antimicrobials, corticosteroids, local anesthetics, 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 sub therapeutic levels.

Composition of buccal patches

A. Active Pharmaceutical ingredient (API):
The buccal film technology has the potential for delivery of variety of APIs. However since the size of the dosage form has limitation, high dose molecules are difficult to be incorporated in buccal film. Generally 5%w/w to 30%w/w of active pharmaceutical ingredients can be incorporated in the buccal patches (34).

B. Polymers (adhesive layer)
Polymer hydration and swelling properties probably play the main role. The polymer hydration and consequently the mucus dehydration could cause an increase in mucous cohesive properties that promote mucoadhesion. Swelling should favor polymer chain flexibility and interpenetration between polymer and mucin chains. So, depending on the type of formulation, polymers with different characteristics have to be considered. Examples: Hydroxy ethyl cellulose, hydroxyl propyl cellulose, polyvinyl pyrrolidone, polyvinyl alcohol, Carbopol and other mucoadhesive polymers (35).

C. Diluents
Lactose DC is selected as diluent for its high aqueous solubility, its flavoring characteristics, and its Physico-mechanical properties, which make it suitable for direct compression. Other example: microcrystalline starch and starch.

D. Sweetening agents
Sucralose, aspartame, mannitol, etc.

E. Flavoring agents
Menthol, vanillin, clove oil, Peppermint oil, cinnamon oil, spearmint oil, oil of nutmeg are examples of flavor oils while vanilla, cocoa, coffee, chocolate and etc (36).

F. Backing layer
Ethyl cellulose, etc.
G. Penetration enhancer
Cyanoacrylate, EDTA, Citric acid etc.

H. Plasticizers
PEG-100, 400, propylene glycol, etc.\(^{(37)}\).

Characteristics of polymer
- Size of the flexible buccal patch may be as large as 10–15 cm\(^2\) in area.
- Mucoadhesive buccal patches with a surface area of 1–3 cm\(^2\) are most acceptable.
- It has been estimated that the total amount of drug that can be delivered across the buccal mucosa from a 2-cm\(^2\) system in 1 day is approximately 10–20 mg.
- Shape of the delivery system may also vary, although for buccal drug administration, an ellipsoid shape appears to be most acceptable.
- Thickness of the delivery device is usually restricted to only a few millimeters. The location of delivery device also needs to be considered.
- Maximal duration of buccal drug retention and absorption is approximately 4–6 h because food and/or liquid intake may require removal of delivery device.
- Physiology of mucous membrane under disease condition need to be accounted (for e.g.: Cancer patients suffer from oral candidiasis) \(^{(21)}\).

Designs of buccal patches
1. Matrix design: (Bi directional) the buccal patch designed in a matrix configuration containing drug, adhesive, and additives mixed together. Bi-directional patches release drug in both the mucosa and the mouth.

2. Reservoir design: (Uni direction) the buccal patch designed in a reservoir system contains a cavity for the drug and additives separate from the adhesive. An impermeable backing is applied to control the direction of drug delivery; to reduce patch deformation and disintegration while in the mouth; and to prevent drug loss. Basically unidirectional types of buccal patches are used for both local as well as systemic effect \(^{(22)}\).
Methods of preparation of buccal patches

1. Solvent casting
   In this method, all patch excipients including the drug co-dispersed in an organic solvent and coated onto a sheet of release liner. After solvent evaporation a thin layer of protective backing material is laminated onto the sheet of coated release liner to form a laminate that is die-cut to form patches of desired size and geometry.

2. Direct milling
   In this, patches are manufactured without the use of solvents. Drug and excipients are mechanically mixed by direct milling or by kneading, usually without the presence of any liquids. After the mixing process, resultant material is rolled on a release liner until desired thickness is achieved. The backing material is then laminated as previously described. While there are only minor or even no differences in patch performance between patches fabricated by two processes, solvent-free process is preferred because there is no possibility of residual solvents and no associated solvent-related health issues.

3. Solid dispersion extrusion
   In this method immiscible components are extrude with drug and then solid dispersions are prepared. Finally the solid dispersions are shaped in to films by means of dies.

4. Semisolid casting
   In semisolid casting method first a solution of water soluble film forming polymer is prepared. The resulting solution is added to a solution of acid insoluble polymer (cellulose acetate phthalate, cellulose acetate butyrate), which was prepared in ammonium or sodium hydroxide. Then appropriate amount of plasticizer is added so that a gel mass is obtained .Finally the gel mass is casted in to films or ribbons using heat controlled drums. Thickness of the film is about 0.015-0.05 inches. The ratio of the acid insoluble forming polymer should be 1:4.

5. Rolling Method
In rolling method solution or suspension containing drug is rolled on a carrier. The solvent is mainly water and mixture of water and alcohol. The film is dried on rollers and cut into desired shapes and sizes.

6. Hot melt extrusion

In hot melt extrusion method, first the drug is mixed with carriers in solid form. Then the extruder having Heaters melts the mixture. Finally the melt is shaped into films by dies. There are certain benefits of hot melt extrusion, Fever operation units, Better content uniformity, and anhydrous process (38).

Evaluation parameter of buccal patches

a. Weight variation

For evaluation of film weight, three films of every formulation are selected randomly and individual weight of each 1x1cm patch was taken on digital balance. The average weight was calculated (39).

b. Film thickness

Thickness of the film is measured by using screw gauge with a least count of 0.01 mm at different places on the film. The thickness of the film was measured at three different places and the average of thickness is measured (40).

c. Surface pH

For determination of surface pH three films of each formulation is allowed in contact with 1ml of distilled water. The surface pH was noted by bringing a combined glass electrode or pH paper near the surface of films and allowing equilibrate for 1 min. A mean of three reading is recorded (41).

d. Folding endurance

Folding endurance of the film is determined by repeatedly folding one film at the same place till it broke, which was considered satisfactory to reveal good films properties. The number of times of films could be folded at the same place without breaking gave the value of the folding endurance. This test was done on randomly selected three films from each formulation (39).

e. Drug content uniformity

This parameter was determined by dissolving film of 1 × 1cm diameter containing drug in 50 ml simulated salivary fluid with occasional shaking. Filtration was carried out to remove insoluble residue, 1 ml of the filtrate was diluted to 10 ml with simulated salivary fluid (pH 6.8). The
absorbance was measured at specified nm using an UV spectrophotometer. The experiments were carried out in triplicate for the films of all formulations \(^{42}(43)\).

\textbf{f. In-vitro dissolution studies}

Dissolution study was carried out in USP basket type apparatus using the stimulated salivary fluid (pH 6.8) as a dissolution medium at 50 rotations per minute. 10 ml aliquots were withdrawn at one minute time intervals and same amount of fresh dissolution medium was added. The aliquots were assayed for drug content at specified wavelength using UV-spectrophotometer. The cumulative percentage drug release was calculated \(^{44}\).

\textbf{g. In vitro residence/mucoadhesion time}

The in vitro adhesion time of films was evaluated by assessing the time for the patch to detach from goat buccal mucosa in a well stirred beaker filled with 500 ml phosphate buffer pH 6.8 at 37 °C. The mucosal membrane was fixed on the side of the beaker with cyanoacrylate glue. The patch was attached to the membrane by applying light force with fingertip for 60 sec. The beaker was then magnetically stirred at an approximate rate of 150 rpm to simulate buccal and saliva movement. The time necessary for complete erosion or detachment of the films from the mucosal membrane was taken as an indication of the in vitro adhesion time \(^{45}(46)\).

\textbf{h. Tensile strength}

Tensile strength of these buccal films was determined by using universal strength testing machine. The sensitivity of the machine is one gram. It consists of 2 load cell grips. The lower one is fixed and upper one is movable as shown in the figure. The test patch of specific size is fixed between these cell grips and force was gradually applied, till the patch breaks. The tensile strength of the patch was taken directly from the dial reading \(^{43}\).

\textbf{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 sometime leads to serious hazardous effects. Hence inexpensive multiple dose formulations with better bioavailability are needed. Improved methods of drug release through trans mucosal 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. 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.

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