Review Article

Buccal Film: An Innovative Dosage Form Designed to Improve Patient Compliance

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ABSTRACT

There is always increasing demands for developing a dosage form which improve patient convince and compliance specially for a buccal drug delivery. Buccal drug delivery system such as film, tablet, micro particle, wafers, lozenges, gel, and liposome are in market pipelines. Due to small size, small dose, thickness of buccal film over other dosage form is most acceptable and palatable. Buccal films provide satisfactory attachment with buccal layers and hence it is most convenient and suitable dosage form as compared to others. It can be enhance absorption of medicament with respect to others. The semi-synthetic and synthetic natural polymer in low concentration can be used for the preparation of buccal film and hence such dosage form are easy to handle, cost effective, fast absorbable, non-irritating, elegant and mostly preferred by consumer.

Keywords: Buccal film, Texture analyzer, Modified physical balance, Solvent casting.

INTRODUCTION[1-12]

The current article focuses on the principles of mucoadhesive drug delivery systems based on adhesion to biological surfaces that are covered by mucus. There is always increasing demand for patient convenience and compliance related research and a novel method is the development of buccal films, which dissolve on the patient buccal mucosa. This drug delivery system (DDS) is suited for the drugs which undergo high first pass metabolism and is used for improving bioavailability with reducing dosing frequency to mouth plasma peak levels, which in turn minimize adverse/side effects and also make it cost effective. Furthermore, films have improved patient compliance due to their small size and reduced thickness, compared for example to lozenges and tablets. Films as dosage forms have gained relevance in the pharmaceutical industry as novel, patient friendly, convenient products.

More recently, orally disintegrating films (or strips) have come to light. This translates into a less friable dosage form compared to most commercialized orally disintegrating tablets, which usually require special packaging. Mucoadhesive buccal films share some of these advantages and more. Moreover, since muco-adhesion implies attachment to the buccal mucosa, films can be formulated to exhibit a systemic or local action. Many mucoadhesive buccal films have been formulated to release drug locally in order to treat fungal infections in the oral cavity such as oral candidiasis. speaking, bioadhesion is an term which broadly includes adhesive interactions with any biological or biologically derived substance, and mucoadhesion is used when the bond is formed with a mucosal surface.

THE STRUCTURE OF THE ORAL MUCOSA[13-19]

Structure

The oral mucosa is composed of an outermost layer of stratified squamous epithelium (Figure 1). Below this lies a basement membrane, a lamina propria followed by the submucosa as the innermost layer. 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.

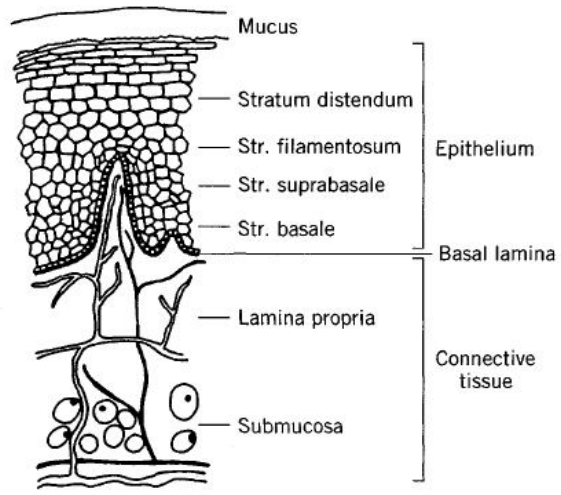

Fig. 1: Schematic cross section through the oral mucosa showing the epithelium, basal lamina, and connective tissue

The turnover time for the buccal epithelium has been estimated at 5-6 days, and this is probably representative of the oral mucosa as a whole. The oral mucosal thickness varies depending on the site: the buccal mucosa measures at 500-800 µm, while the mucosal thickness of the hard and soft palates, the floor of the mouth, the ventral tongue, and the gingivae measure at about 100-200 µm. The composition of the epithelium also varies depending on the site in the oral cavity. The mucosae of areas subject to mechanical stress (the gingivae and hard palate) are keratinized similar to the epidermis.

In figure 2 white portions represent non keratinized region while dark portions represent keratinized region. The keratinized epithelia contain neutral lipids like ceramides and acylceramides which have been associated with the barrier function. These epithelia are relatively impermeable to water. In contrast, non-keratinized epithelia, such as the floor of the mouth and the buccal epithelia, do not contain acylceramides and only have small amounts of ceramide . They also contain small amounts of neutral but polar lipids, mainly cholesterol sulfate and glucosyl ceramides. These epithelia have been found to be considerably more permeable to water than keratinized epithelia.

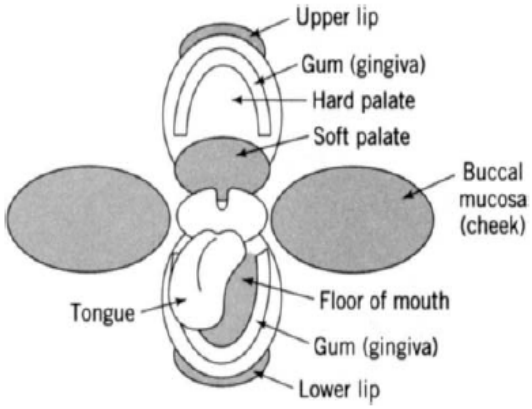

Fig. 2: Schematic representation of the "open" oral cavity, showing keratinized (white) and nonkeratinized (shaded) regions of the mouth

Formulation and manufacture of buccal films

Formulation design[19-92]

Formulation of buccal film involves following excipients should be Generally Regarded as Safe (i.e. GRAS-listed) and should be approved for use in oral pharmaceutical dosage forms.

Active pharmaceutical ingredient

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 film.

While water soluble APIs are present in the dissolved state in the buccal film or in the solid solution form, the water insoluble drugs are dispersed uniformly in the film. The distribution of water insoluble molecules in water miscible polymer becomes important from the large scale manufacture point of view. APIs can also be added as milled, micronized or in the form of nanocrystals or particles depending upon the ultimate release profile desired. It is always useful to have micronized API

which will improve the texture of the film and also for better dissolution and uniformity in the buccal film. Many APIs, which are potential candidates for buccal film technology, have bitter taste. This makes the formulation unpalatable especially for pediatric preparations. Thus before incorporating the API in the buccal film, the taste needs to be masked. Various methods can be used to improve the palatability of the formulation. Among the techniques employed, the simplest method involves the mixing and co-processing of bitter tasting API with excipients with pleasurable taste. This is often termed as obscuration technique. Barrier technologies that can be used to mask the bitter taste include complexation, polymeric coating, conversion into microparticles/microcapsules, coated particles or coated granules. However, in the cases where the drug is encapsulated, the instantaneous release of medicament will not be achieved. Depending on the material employed in encapsulation and the manufacturing technique, the rate of drug release varies. Hence, the issue of palatability and drug response needs to be balanced to achieve maximum advantage of the developed buccal film formulation.

Complexation technology involves use of cyclodextrins, resins which surround the bitter API and prevents the direct contact with saliva. Matrixing of the bitter drug or coating of drug with water insoluble polymer has been used widely for taste masking of drugs. The results rendered a good taste masked product which did not affect the bioavailability of the drug confirming the potential of the developed technology.

Recently a novel salting out technology was developed for the taste masking of API. The technology involved coating of drug substance with salting out layer consisting of salt and water soluble polymer. The salt reduced the dissolution of water soluble polymer and drug from the system resulting into taste masking of the drug. As the concentration of salt decreases in the system, the polymer and drug was released and resulted into immediate release of the drug. This salting-out taste-masking system generates lag time with subsequent immediate release. The technology was successfully utilized for the taste masking of paracetamol used as model drug.

The buccal film technology offers advantages in certain critical clinical situations. For drugs that are projected as local anesthetic or pain killer, the buccal film has demonstrated improved clinical benefits. Certain pathologies require instantaneous release of the medicament for prompt relief. For instance, in the case of migraine a rapid clinical effect is desired by the individual. Regiospecific delivery of the medicament would be required in the cases of sore throat, cough, allergy and other local oral manifestations. Breath films also offer superior consumer compliance. Similarly, cases of motion sickness need immediate attention. Also since buccal film technology does not require water during administration as compared to the regular tablet dosage forms; it is very handy during travel. This dosage form can also be used for natural extracts and neutraceuticals including vitamin B12, chromium picolinate, melatonin and possibly CoQ10.

Mucoadhesive agents

Different situations for buccal mucoadhesion are possible depending on the dosage form. In the case of dry or partially hydrated formulations, 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. The spreading coefficient and the capability to form physical or chemical bonds with mucin (which results in a strengthening of the mucoadhesive interface) increase when fully hydrated dosage forms (e.g. aqueous gels or liquids) are considered. So, depending on the type of formulation, polymers with different characteristics have to be considered.

The polymers most commonly used in buccal dry or partially hydrated dosage forms include polyacrylic acid (PAA), polyvinyl alcohol (PVA), sodium

carboxymethylcellulose (NaCMC), hydroxypropylmethyl cellulose (HPMC), hydroxyethyl cellulose (HEC), hydroxypropyl cellulose (HPC) and sodium alginate. Various copolymer of acrylic acid, such as acrylic acidpolyethylene glycol monomethyl ether copolymer (P(AAco-EHA)) and acrylic acid-2 ethylhexyl acrylate copolymer (P(AA-co-PEG)) have also been studied. PAA, chitosan and its derivatives, HPC, PVA, gelatine, carrageenan, NaCMC, hyaluronic acid, when tested in fully hydrated state, have been proved to interact with buccal mucosa. Recently, lamellar and cubic liquid crystalline phases of glyceryl monooleate (GMO) have shown mucoadhesive properties and feasibility to be used as carriers for buccal delivery of peptides.

In recent years, lectins have been studied as specific bioadhesives for drug delivery in the oral cavity. Their peculiarity lies in the mucoadhesion mechanism: such substances are able to recognize and bind some specific sugar residues on mucosal surface without altering the structure of the recognized ligand.

Sr.no	Mucoadhesive polymer	Properties
1	Hydroxyethyl cellulose(HEC)	Non-ionic polymer
2	Hydroxypropyl cellulose(HPC)	Non-ionic polymer
3	Hydroxypropyl methylcellulose(HPMC)	Non-ionic polymer
4	Sodiumcarboxymethylcellulose(SCMC)	Anionic polymer
5	Poly(vinyl pyrrolidone) (PVP)	Non-ionic polymer
6	Poly (vinyl alcohol)	Non-ionic polymer
7	Chitosan	Cationic polymer
8	Alginate, sodium	Anionic polymer
9	Polycarbophil	Non-ionic polymer
10	Poly(ethylene oxide)	Non-ionic polymer

Plasticizers

Plasticizer is a vital ingredient of the film formulation. It helps to improve the flexibility of the film and reduces the brittleness of the film. Plasticizer significantly improves the film properties by reducing the glass transition temperature of the polymer. The selection of plasticizer will depend upon its compatibility with the polymer and also the type of solvent employed in the casting of film. The flow of polymer will get better with the use of plasticizer and enhances the strength of the polymer. Glycerol, Propylene glycol, low molecular weight polyethylene glycols, phthalate derivatives like dimethyl, diethyl and dibutyl phthalate, Citrate derivatives such as tributyl, triethyl, acetyl citrate, triacetin and castor oil are some of the commonly used plasticizer excipients. Typically the plasticizers are used in the concentration of 0–20%w/w of dry polymer weight. However inappropriate use of plasticizer may lead to film cracking, splitting and peeling of the film. It is also reported that the use of certain plasticizers may also affect the absorption rate of the drug.

The Plasticizer employed should impart the permanent flexibility to the film and it depends on the volatile nature plasticizer and the type of interaction with the polymer. It should be noted that the properties of plasticizer are important to decrease the glass transition temperature of polymer in the range of 40–60^{0}C for non aqueous solvent system and below 75^{0}C for aqueous systems. Plasticizer should be compatible with drug as well as other excipients used for preparation of film.

Penetration enhancers

Penetration enhancers are also required when a drug has to reach the systemic circulation to exert its action. These must be non-irritant and have a reversible effect: the epithelium should recover its barrier properties after the drug has been absorbed. The most common classes of buccal penetration enhancers include fatty acids (that act by disrupting intercellular lipid packing), surfactants and, among these, bile salts (by extracting membrane protein or lipids, by membrane fluidization, by producing reverse micellization in the membrane and creating aqueous channels), azone (by creating a region of fluidity in intercellular lipids) and alcohols (by reorganizing the lipid domains and by changing protein conformation). Recently, chitosan and its derivatives, polymers already known for their mucoadhesive properties, have been shown to be the potential penetration enhancers for transmucosal (intestinal, nasal, buccal and

vaginal) absorption of drugs. Although the penetration enhancement properties of chitosan through mucosae (intestinal and nasal) are mainly owing to a transient widening of the tight junctions between the cells, the mechanism of penetration enhancement through the mucosa of the oral cavity has still to be clarified. A hypothesis that has still to be demonstrated is that chitosan acts on the intercellular lipid domain, recognized as being the main barrier to drug transport via paracellular pathway in the buccal mucosa. It must be emphasized that different in vitro and ex vivo methods have been used for characterizing the penetration enhancement properties of the different materials, but they do not always appropriately simulate the in vivo conditions. The establishment of standardized biological models alternative to animal studies is needed for the evaluation and comparison of different materials.

Enzyme inhibitors

The coadministration of a drug with enzyme inhibitors is another strategy for improving the buccal absorption of drugs, particularly peptides. Enzyme inhibitors, such as aprotinin, bestatin, puromycin and some bile salts stabilize protein drugs by different mechanisms, including affecting the activities of the enzymes, altering the conformation of thepeptides or proteins and/or rendering the drug less accessible to enzymatic degradation. some mucoadhesive polymers, such as polyacrylic acid and chitosan derivatives, have been proved to inhibit enzyme activity even if not in buccal mucosa. In particular, polyacrylic acid (carbomer) is able to bind the essential enzyme cofactors calcium and zinc, causing a conformational change resulting in enzyme autolysis and loss of enzyme activity. Moreover, the chemical modification of chitosan (cationic polymer) with ethylene diamine tetraacetic acid (EDTA) produces polymer conjugate chitosan–EDTA that is a very potent inhibitor of metallopeptidases, such as carboxypeptidase. In recent years, the polymer derivatization with thiol groups on poly(acrylates) or chitosans has been demonstrated to improve polymer enzyme inhibitory properties.

Sweetening agents

Sweeteners have become the important part of the food products as well as pharmaceutical products intended to be disintegrated or dissolved in the oral cavity. The sweet taste in formulation is more important in case of pediatric population. Natural sweeteners as well as artificial sweeteners are used to improve the palatability of the mouth dissolving formulations. The classical source of sweetener is sucrose (derived from cane or beet in the form of liquid or dry state), dextrose, fructose, glucose, liquid glucose and maltose. The sweetness of fructose is perceived rapidly in the mouth as compared to sucrose and dextrose. However it should be noted that the use of natural sugars in such preparations need to be restricted in people who are on diet or in the case of diabetic patients.

Due to this reason, the artificial sweeteners have gained more popularity in food and pharmaceutical preparations. Saccharin, cyclamate and aspartame are the first generation of the artificial sweeteners followed by acesulfame-K, sucralose, alitame and neotame which fall under the second generation artificial sweeteners. Rebiana which is a herbal sweetener, derived from plant *Stevia rebaudiana* (South American plant) is about 200–300 time sweet than other. Stevia plant is best alternative to synthetic one. All artificial sweetener have toxic and carcinogenic effects.

Saliva stimulating agent

The purpose of using saliva stimulating agents is to increase the rate of production of saliva that would aid in the faster disintegration of the rapid dissolving film formulations. Generally acids which are used in the preparation of food can be utilized as salivary stimulants. Citric acid, malic acid, lactic acid, ascorbic acid and tartaric acid are the few examples of salivary stimulants, citric acid being the most preferred amongst them. These agents are used alone or in combination between 2 to 6%w/w of weight of the film.

Other buccal film ingredients such as sweeteners also act as salivary stimulants. Food grade sugars as well as synthetic sugars are useful salivary stimulants along with acidulents. Glucose, fructose, xylose, maltose, lactose are few examples of such sweeteners.

The stimulation of salivation can be measured by comparing the amount of resting flow and stimulated flow at equal time under same conditions. The stimulant action of sweeteners is dependent on the sweetness value. Fructose has the sweetness value of 1.1 as compared to 0.7 of glucose and 1.0 of sucrose. The artificial sweetener is preferred over natural sugars because lower concentration is required and multiple uses don't result in dental caries in individuals.

Flavoring agents

Perception for the flavors changes from individual to individual depending upon the ethnicity and liking. It was observed that age plays a significant role in the taste fondness. The geriatric population like mint or orange flavors while younger generation like flavors like fruit punch, raspberry etc. The selection of flavor is also dependant on the type of drug to be incorporated in the formulation. For example, mint flavor is generally added in products used for gastric related ailments like indigestion. The acceptance of the oral disintegrating or dissolving formulation by an individual by and large depends on the initial flavor quality which is observed in first few seconds after the product has been consumed and the after taste of the formulation which lasts for at least about 10 min.

Flavoring agents can be selected from synthetic flavor oils, oleo resins, extract derived from various parts of the plants like leaves, fruits and flowers. Flavors can be used alone or in the combination. Peppermint oil, cinnamon oil, spearmint oil, oil of nutmeg are examples of flavor oils while vanilla, cocoa, coffee, chocolate and citrus are fruity flavors. Apple, raspberry, cherry, pineapple are few examples of fruit essence type. The amount of flavor needed to mask the taste depends on the flavor type and its strength. Preferably up to 10%w/w flavors are added in the buccal film formulations. Cooling agents like monomethyl succinate can be added to improve the flavor strength and to enhance the mouth-feel effect of the product. Other cooling agents likeWS3, WS23 and Utracoll II can also be used in conjunction with flavors.

Coloring agents

Pigments such as titanium dioxide or FD&C approved coloring agents are incorporated (not exceeding concentration levels of 1%w/w) in buccal film when some of the formulation ingredients or drugs are present in insoluble or suspension form.

Methods of manufacture of films

1. Solvent casting
2. Hot-melt extrusion

Solvent Casting[93-98]

Buccal films are preferably formulated using the solvent casting method, whereby the water soluble ingredients are dissolved to form a clear viscous solution and the drug along with other excipients is dissolved in suitable solvent then both the solutions are mixed and stirred and finally casted in to the Petri plate and dried.

Steps in film casting

- Water soluble ingredients are dissolved in water
- API and other agents are dissolved in suitable solvent to form a clear viscous solution
- Both the solutions are mixed
- resulting solution is cast as a film and allowed to dry
- film is collected

Water soluble hydrocolloids used to prepare films are HPMC, HPC, SA, CMC, Pullulan and Pectin.

Sr.no.	Drug	Polymers	Solvent
1	Lidocaine	EC, HPC	Ethanol
2	Propranolol	Eudragit RS100	Acetone, water
3	Paractamol	SA,CMC	Water
4	Metoprolol	Eudragit NE40D, HPMC K4M, HPMC K15M, SCMC 400, Cekol 700, Cekol 10000, CP 934P, CP 971P, CP 974P	Water

Hot-melt extrusion[99-101]

In hot-melt extrusion, a blend of pharmaceutical ingredients is molten and then forced through an orifice (the die) to yield a more homogeneous material in different shapes, such as granules tablets, or films. Hot metal extrusion is commonly used to prepare granules, sustained release tablets, transdermal and transmucosal drug delivery systems. However, only a handful of articles have reported the use of hot-melt extrusion for manufacturing mucoadhesive buccal films. Repka and coworkers have extensively conducted research on the use of hot-melt extrusion for the manufacture of mucoadhesive buccal films, evaluating different matrix formers and additives for the processing of the blend.

Sr.no.	Drug	Polymers
1	Lidocaine	HPMC, HPC
2	Maltodextrins	PEG 400

CHARACTERIZATION OF BUCCAL FILM

Drug-excipients interaction studies[102,103]

Assessment of possible incompatibilities between an active drug substance and different excipients plays an important part of the formulation stage during the development of solid dosage form. Fourier Transformer Infra Red Spectrum (FTIR), Differential scanning calorimeter (DSC), thin layer chromatography and X Ray Diffraction (X-RD) can be used to assess possible drug excipients interaction. DSC allows the fast evaluation of possible incompatibilities, because it shows changes in appearance, shift of melting endotherms and exotherms, and variation in the corresponding enthalpies of the reaction.

Thickness measurements[104]

The thickness of each film was measured at five different locations (centre and four corners) using an electronic digital micrometer. Data are represented as a mean ± S.D. of five replicate determinations.

Swelling study[105]

After determination of the original patch weight and diameter, the samples were allowed to swell on the surface of agar plate kept in an incubator maintained at 37^0C. Increase in the weight and diameter of the patches (n = 5) was determined at preset time intervals (1–5 h). The percent swelling, %S, was calculated using the following equation:

$\%S = (X_t - X_o/X_o) \times 100$

where X_t is the weight or diameter of the swollen patch after time t, and X_o is the original patch weight or diameter at zero time.

Surface pH [106]

The surface pH of the films was determined in order to investigate the possibility of any side effects, in vivo. As an acidic or alkaline pH may cause irritation to the buccal mucosa, it was our attempt to keep the surface pH as close to neutral as possible. The films were first allowed to swell by keeping them in contact with 1.0 ml of distilled water (pH 6.5 ± 0.05) for 2 h in specially fabricated glass tubes. The surface pH was then noted by bringing a combined glass electrode near the surface of the film and allowing it to equilibrate for 1 min.

Folding endurance [107,108]

The test is performed by repeated folding of the film at the same place until film failure. A maximum of 300 times is sometimes reported as a limit to the test, and the value is reported as the number of times the film can be folded prior to rupture.

Surface morphology [109]

The cross section of the films was examined by scanning electron microscopy (SEM). The dried films were coated with gold sputter and then observed under scanning electron microscope.

Determination of mucoadhesion [109-148]

There are different models are used for mucoadhesive measurement. The earliest approaches to measure bioadhesion were indirect and provided an idea of the trend that different formulations followed. The studies were focused on determining the force of adhesion, time of adhesion or retention time of the dosage form in various models. In vitro experiments usually consist of attaching a film to a glass plate, or to the sides of a beaker, and a mechanical force is applied either by moving the plate or by stirring the media in the beaker. The first approach is normally done by modifying a standard USP disintegration apparatus. In which a suitable substrate is attached to the surface of a glass slab, which is connected with the mobile arm of the disintegration apparatus. The film is then allowed to adhere to the substrate, and the time necessary for complete erosion or detachment is recorded as the in vitro residence time. Conditions such as the medium composition, pH, temperature, salts addition, or nature of the substrate can be controlled and will modify the results; hence, it is important to report the conditions used to obtain reproducible data. The second approach often used in the literature requires the adhesion of the film into a static surface, normally the side of a beaker, and detachment force is applied by the stirring media. Modifications of this approach include the adhesion of a biological substrate to the side of the beaker, normally a non-keratinized tissue layer such as porcine buccal mucosa to further mimic the physiology of the human buccal epithelium. Again, controlling the composition of the media, temperature, pH, or the nature of the substrate (from either a biological or a synthetic source) will determine the final mucoadhesion or in vitro residence time.

Even though the measurement of the in vitro mucoadhesion or residence time provides information to optimize formulations, it does not elicit the real strength of the mucoadhesive bond. There is another model in which freshly excised rabbit buccal mucosa was glued onto a stainless steel platform. Likewise, a buccal film sample was attached to another platform, and following the addition of a drop of water, the film and the substrate were allowed to adhere for a predetermined amount of time. The mucoadhesion strength was measured as the maximum applied force needed in order to detach the film from the substrate. The development of the bench top texture analyzer that allowed for accurate measurement of very small variations, as well as being able to control the contact force and time, increased the number of publications that reported on mucoadhesion and tensile properties of buccal films. The first report on the use of the TA.TX2 texture analyzer (Stable Micro Systems) to measure the mucoadhesion strength of buccal films utilized chicken pouch as the biological membrane upon which the films were allowed to adhere. The instrument measures detachment forces from its mobile arm, which after normalizing is considered as adhesive forces, and the maximum force is normally referred to as mucoadhesive force. The use of this type of texture analyzer for the measurement of mucoadhesion on different dosage forms, such as buccal tablets, had already been published. This previous research had focused on the importance of the method variables, which ultimately determine, together with the film and the substrate properties, the value of mucoadhesion strength. Some other approaches to measure mucoadhesion include the modification of different mass balance apparatuses to determine the

detachment force from the mucoadhesive joint between the buccal film and usually a biological substrate. khana et al used modified physical balance for mucoadhesive measurement.

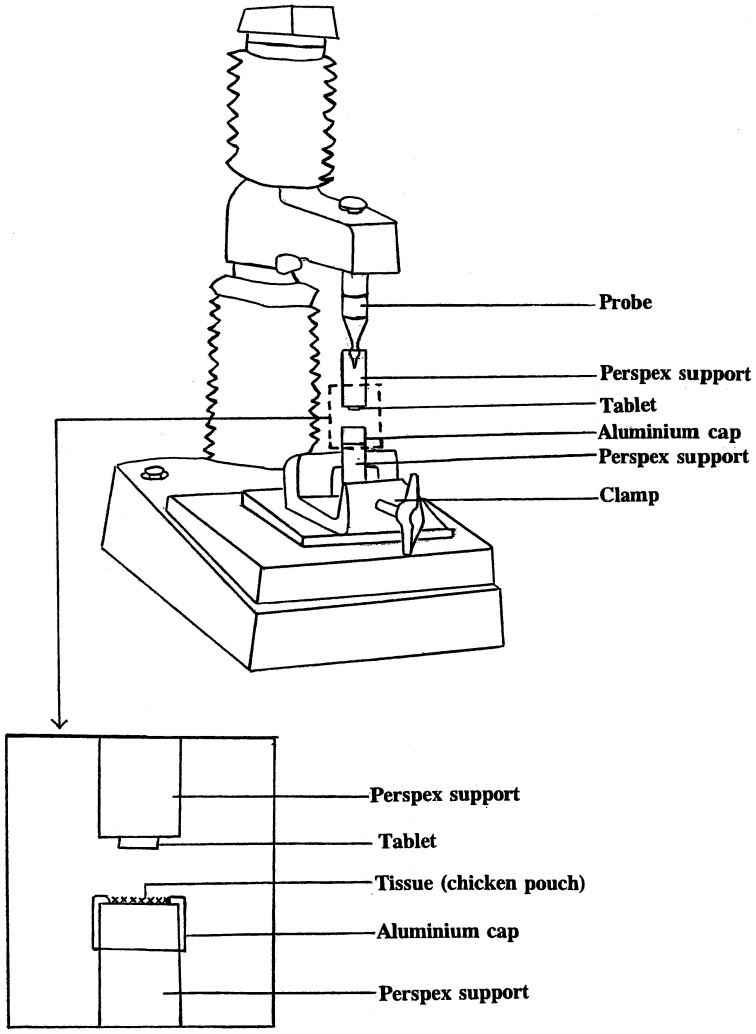

Fig. 3

In vitro release study [149,150]

In vitro dissolution studies were carried out in USP XXIV type II apparatus under sink conditions. The dissolution medium was 500 mL simulated saliva solution pH 6.75 at37±0.5^{0}c with stirring speed depends upon dosage form for fixed time intervals. The samples are withdrawn at fixed intervals and replaced by equivalent amount of fresh dissolution medium. The amount of drug released in dissolution medium was determined by UV spectroscopy.

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