Available online on www.ajper.com

Asian Journal of Pharmaceutical Education and Research

Vol -2, Issue-3, July-September 2013

ISSN: 2278-7496

REVIEWARTICLE

BUCCAL FILMS DRUG DELIVERY DEVICE: A REVIEW

Izhar Ahmed Syed [a*], and S.Krishna.

SR College of Pharmacy, Ananthsagar , Hasanparthy Warangal -506371.

Article Received on 21 June 2013.

Accepted on 29 June 2013

***Correspondence for Author:**

Dr. Izhar Ahmed Syed

M.Pharm., PH.D

Associate Prof & Head

SR College of Pharmacy

Ananthsagar, Hasanparthy

Warangal -506371

Tel:+919700139735/ 9966507978

Email
syed.izharahmed@gmail.com

ABSTRACT

Although the oral administration of drugs has been the preferred route of administration for the patients and clinicians, certain disadvantages such as hepatic first pass metabolism, gastric irritation, and enzymatic degradation within the gastrointestinal tract have been identified. The buccal route has been advocated as an alternative route of administration for drugs which undergo extensive hepatic first pass metabolism or which are susceptible to degradation and pre-systemic metabolism in the gastrointestinal tract. This route is well vascularised with venous blood draining the buccal mucosa reaching the heart directly via the internal jugular vein. Moreover, buccal delivery for the transmucosal absorption of drugs into the system circulation provides a number of advantages such rapid onset of action, sustained delivery, high permeability, and high blood flow and is easily accessible for both application and removal of a drug deliver device. In recent times, various mucoadhesive mucosal dosage forms have been developed, which included adhesive tablets, gels, ointments, and more recently films. Adhesive buccal film may be preferred over adhesive tablet in terms of flexibility and comfort. In addition, they can avoid the relatively short residence time of oral gels on the mucosa, which is easily washed away and removed by saliva. Moreover, buccal films also ensure more accurate dosing of drugs when compared to gels and ointments[10]. The buccal films will increases the contact time, achieving controlled release, reducing the frequency of administration and obtain greater therapeutic efficacy.

Key words: Buccal films, bioadhesion, Mucoadhesive polymers

INTRODUCTION:

Despite recent advancements in the inhalable, injectables, transdermal, nasal and several other routes of administration, the unavoidable truth is that oral drug administration has been the preferred route for the drug delivery. Presently, there are certain factors like poor drug solubility and/or absorption, rapid metabolism, high fluctuation in the drug plasma level and variability due to food effect, which are playing major role in unsatisfactory *in-vivo* results that has led to the failure of the conventional delivery system. Since the last decade, the new dimension has achieved by oral drug delivery by using lipid as a carrier for delivering poorly water soluble, lipophilic drugs. Oral drug administration is the preferred and most common route for drug delivery. Several advantages associated with it includes, patient-friendly, painless and easy for self medication. In comparison to parenteral delivery, disease transmission has been suppressed by it along with the reduced cost and patient compliance. Flexible and controlled dosing schedule has also allowed. It is mainly convenient for chronic therapy.

THE STRUCTURE OF THE ORAL MUCOSA [2, 28, 31]

The oral mucosa is composed of an outermost layer of stratified squamous epithelium[28]. 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 about40-50 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.

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 500-800µm, while the mucosal thickness of the hard and soft palates, the floor of the mouth, the ventral tongue, and the gingiva measure at about 100-200µm.

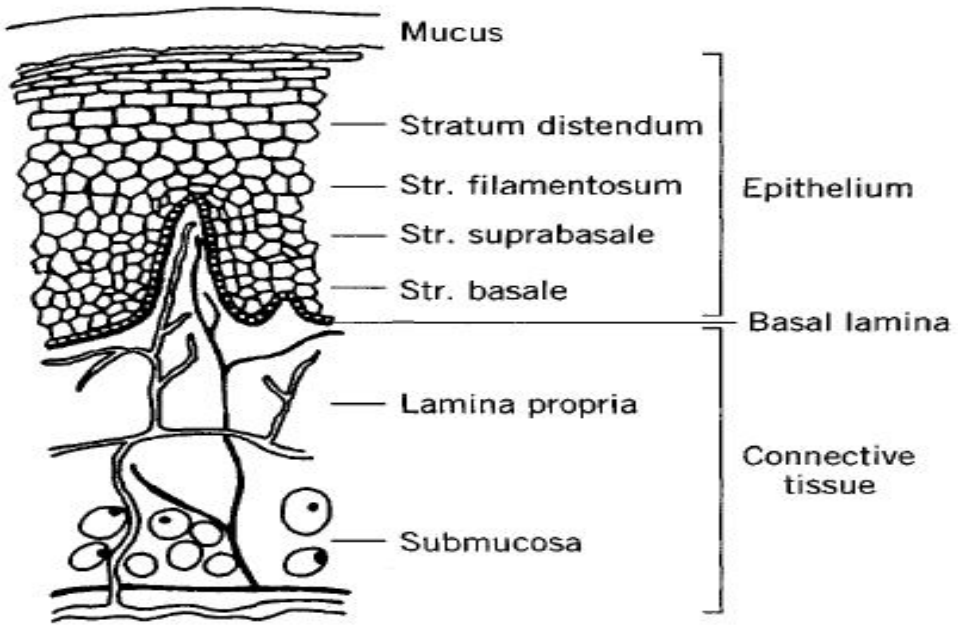

Figure1: Schematic cross section through the oral mucosa showing the epithelium, basal lamina, and connective tissue.

The composition of the epithelium also varies depending on the site in the oral cavity. The mucosa of areas subject to mechanical stress (the gingiva 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 tissues contain neutral lipids like ceramides and acylceramides, which have been associated with the barrier function. These epithelia are relative 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 sulphate and glucosylceramides. These epithelia have been found to be considerably more permeable to water than keratinized epithelia.

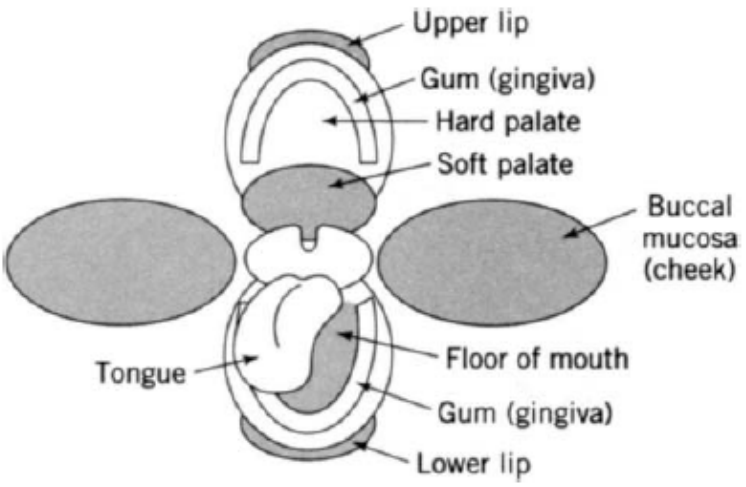

Figure 2: Schematic representation of the "open" oral cavity, showing keratinized (white) and non-keratinized (shaded) regions of the mouth

Buccal film [26, 32]:

A film is generally made by using hydrophilic polymers that has ability to rapidly dissolves on the tongue or with in the buccal cavity, delivering the drug to the systemic circulation via dissolution when contact with liquid is made. Films as dosage forms have gained much importance in the pharmaceutical field as novel, patient friendly and convenient products. Friability of such dosage form is also less, as compared to most common oral disintegrating tablets that usually needs special packaging. More recently, orally disintegrating films(or strips)have come to light. As the muco-adhesive buccal films are small in size and thickness, it has improved patient compliance, compared to tablets. Many muco-adhesive buccal films have formulated to release drug locally in order to treat fungal infections in the oral cavity such as oral candidiasis. Films releasing drug towards the buccal mucosa exhibit the advantage of avoiding the first pass effect by directing absorption through the venous system that drains from the cheek.

When the dry dosage forms is in contact with surfaces with a thin mucous layer, such as a buccal mucoadhesive film, two steps are needed to establish the muco-adhesive bond, a contact and consolidation stage. Mucoadhesion can be defined as the ability of synthetic or biological macromolecules to adhere to mucosal tissues such as mucosa of eyes, nose, oral, intestine, rectum and vagina. Mucoadhesion is considered to occur in three major stages. Wetting, interpenetration and mechanical interlocking between the mucus and the polymer. The strength

of mucoadhesion is affected by various factors such as molecular mass of polymers, contact time with mucus, swelling rate of the polymer.

Fast dissolving buccal films [38, 51, 74]

Fast-dissolving buccal film drug delivery devices have rapidly gained acceptance as an important new way of administering drugs. They are usually used for pharmaceutical and nutraceutical products. It is the newest frontier in drug delivery technology that provides a very convenient means of taking medications and supplements. There are multiple fast-dissolving over the counter and prescribed products on the market worldwide, most of which have been launched recently. There have also been significant increases in the number of new chemical entities under development using a fast-dissolving drug delivery technology.

Now the main question arises that what are fast dissolving buccal films. A fast-dissolving buccal film drug delivery system, in most cases, is a film containing active ingredient that dissolves or disintegrates in the saliva remarkably fast, within a few seconds without the need for water or chewing. Some drugs are absorbed well from the mouth, pharynx and oesophagus as the saliva passes down into the stomach. In such cases, bioavailability of drug is significantly greater than those observed from conventional tablet dosage form. Most fast-dissolving delivery system films must include substances to mask the taste of the active ingredient. This masked active ingredient is then swallowed by the patient's saliva along with the soluble and insoluble excipients.

Fast dissolving buccal films use a dissolving film to administer drugs via absorption in the mouth (buccally or sublingually) and/or via the small intestines (enterically). A film is prepared using hydrophilic polymers that rapidly dissolves on the tongue or buccal cavity, delivering the drug to the systemic circulation via dissolution when contact with liquid is made.

Fast dissolving buccal films drug delivery has emerged as an advanced alternative to the traditional tablets, capsules and liquids often associated with prescription and over the counter medications. Similar in size, shape and thickness to a postage stamp, thin film strips are typically designed for oral administration, with the user placing the strip on or under the tongue or along the inside of the cheek. Different buccal delivery products have been marketed or are proposed for certain diseases like trigeminal neuralgia, meniere's disease, diabetes and addiction. Improved patient compliance is a primary benefit of the fast-dissolving drug delivery systems.

Other benefits of fast-dissolving films include ease of swallowing , no water necessary for administration, and accuracy of dosage. This fast-dissolving action is primarily due to the large surface area of the film, which wets quickly when exposed to the moist oral environment. These additional, superior benefits allow patients to take their medication anytime and anyplace under all circumstances. The fast dissolving buccal film drug delivery system offers a giant leap forward in drug administration by providing a new and easy way of taking medication.

Many fast-dissolving tablets are soft, friable, and/or brittle (such as the lyophilized dosage forms) and often require specialized and expensive packaging and processing. These tablets are either very porous or inherently soft-moulded matrices, or tablets compacted at very low dissolution/disintegration time. The delivery system is simply placed on a patient's tongue or any oral mucosal tissue. Instantly wet by saliva, the film rapidly hydrates and adheres onto the site of application. It then rapidly disintegrates and dissolves to release the medication for oral mucosal absorption or with formula modifications, will maintain the quick-dissolving aspect but allow for gastrointestinal absorption to be achieved when swallowed.

Formulation of fast dissolving buccal film involves the application of both aesthetic and performance characteristics such as strip-forming polymers, plasticizers, active pharmaceutical ingredient, sweetening agents, saliva stimulating agent, flavouring agents, colouring agents, stabilizing and thickening agents. From the regulatory perspectives, all excipients used in the formulation of oral drug strips should be approved for use in oral pharmaceutical dosage forms. In recent application of fast dissolving buccal films it has been made possible that vaccines can be provided to infants in impoverished area against rotavirus.

Advantages of buccal drug delivery [20, 21]

Some of the advantages of buccal drug delivery include:

- Prolongation of the residence time of the dosage form at the site of absorption.
- As the residence time is increased, there is enhanced absorption and therapeutic efficacy of the drug.
- Accessibility is excellent.
- Fast absorption because of enormous blood supply and good blood flow rates.
- Bioavailability is increased due to first pass metabolism avoidance.

- Acidic degradation of the drug in GIT is prevented.
- Improved patient compliance – ease of drug administration.
- Mucosal surface provides, faster onset of action.

Disadvantages of buccal drug delivery [20, 21]

Buccal drug delivery have some disadvantages such as:

- In comparison to the sublingual membrane, buccal membrane has low permeability.
- Surface area is also small. Oral cavity has total surface area of 170cm^2 for drug absorption of which only~50cm2 represents non-keratinized tissues, along with the buccal membrane.
- As the saliva is continuously secreted(0.5-2.1/day),it has diluted the dru to great extent.
- Dissolved and suspended drugs can also be removed during swallowing of saliva, ultimately ,dosage form is removed involuntarily.

Formulation considerations [26, 34, 48, 49, 51]

Formulation involves the intricate application of aesthetic and performance characteristics such as taste masking, fast dissolving, physical appearance, mouth feel etc. Fast dissolving film is a thin film with an area of 5-20 cm containing an active ingredient. The immediate dissolution, in water or saliva respectively, is reached through a special matrix from water-soluble polymers.

Drugs can be incorporated up to single dose of 15 mg . Formulation considerations have been reported as important factors affecting mechanical properties of the films, such as shifting the glass transition temperature to lower temperature. The excipients used in formulation of fast dissolving buccal films are also discussed in detail. From the regulatory perspectives, all excipients used in the formulation should be generally regarded as safe (i.e. GRAS-listed) and should be approved for use in oral pharmaceutical dosage forms.

Active Pharmaceutical agents

The active substance is may be from any class of pharmaceutically active substances that can be administered orally or through the buccal mucosa respectively. According to literature, API canbe added from 5%-25% w/w of total weight of polymer. For the effective formulation, dose of drug should be in mgs (less than 20 mg/day). The drugs which are potent, show high first pass metabolism and patient non- compliant are best candidates for fast dissolving buccal films. Researchers have shown interest in development of fast dissolving films for drugs

like: Pediatrics (antitussive, expectorants, antiasthamatics), Geriatrics (antiepileptic, expectorants), Gastrointestinal diseases, Nausea (e.g. due to cytostatic therapy), Pain (e.g. migraine), CNS (e.g.antiparkinsonism therapy).

Among which preferred active agents include chlorpheniramine maleate, brompheniramine maleate, dexchloropheniramine, triprolidine hydrochloride, acrivastine, azatadine maleate, loratidine, phenylephrine hydrochloride, dextromethorphan hydrochloride, ketoprofen, sumatriptan succinate, zolmitriptan, loperamide, famotidine, nicotine, caffeine, diphenhydramine hydrochloride, and pseudophedrine hydrochloride, and their amounts per strip can be well known in the art.

Polymers [51]

A variety of polymers are available for preparation of fast dissolving buccal films. The polymers can be used alone or in combination to obtain the desired film properties. The film obtained should be tough enough so that there won't be any damage while handling or during transportation. The robustness of the strip depends on the type of polymer and the amount in the formulation. The various polymers to make fast dissolving films include cellulose or cellulose derivatives, pullulan, gelatin, hydroxypropylmethylcellulose, hydroxyethylcellolose, hydroxypropylcellulose, polyvinylpyrrolidone, carboxymethylcellulose, polyvinylalchohal, sodium alginate, xanthane gum, tragacanth gum, guar gum, acacia gum, methylmethacrylate co-polymer and hypromellose are most commonly used for preparation of fast dissolving films.

Modified starches are also used for preparation. Due to low cost of this excipient, it is used in combination of pullulan to decrease the overall cost of the product. Pullulan is a natural polymer obtained from nonanimal origin and does not require chemical modification. About 50 to 80 percent w/w of pullulan can be replaced by starch in the production of fast dissolving films without loss of required properties of Pullulan. Combination of microcrystalline cellulose and maltodextrin has also been used to formulate fast dissolving films. Kulkarni et al., 2010 explored different polymers for use in formulation of oral fast dissolving strips. Different polymers viz., HPMC E15, HPMC K4M, HPMC E5, PVP, PVA, gelatin, eudragit RL100 and pullalan were used to formulate fast dissolving buccal films; by solvent casting method. Results confirmed that pullalan is best polymer for oral fast dissolving strips .

Plasticizers

Plasticizer is a vital ingredient of the fast dissolving buccal films formulation. The mechanical properties such as tensile strength and elongation to the films can be improved by the addition of the plasticizer. It also helps to improve the flexibility of the strip and reduces the brittleness of the strip. They also improve the strip properties by reducing glass transition temperature of the polymer. The flow of polymer also gets better by the addition of the plasticizer. Variations in their concentration affect these properties. The selection of the plasticizer will depend upon its compatibility with the polymer and also the type of solvent employed in its casting. Plasticizers include glycerine, sorbitol, propylene glycol, polyethylene glycol, triacetin, di-butylpthalate, triethyl citrate, acetyl triethyl citrate and other citrate esters. Typically the plasticizers are used in the concentration of 0-20% w/w of the dry polymer weight. Inappropriate use of the plasticizer may lead to film cracking, splitting, peeling of the strip and it may also affect the absorption rate of the drug.

Surfactants

Surfactants are used as solubilizing or wetting or dispersing agents so that the film gets dissolved within seconds and release active agent immediately. Surfactants also improve the solubility of poorly soluble drugs in fast dissolving buccal films. Some of the commonly used are polaxamer 407, sodium lauryl sulfate, benzalkonium chloride, benzthonium chloride, tweens and spans etc.

Sweetening agents

Sweeteners have become the important part of pharmaceutical products intended to be disintegrated or dissolved in the oral cavity. The classical source of sweetener is sucrose, dextrose, fructose, glucose, liquid glucose and isomaltose. The sweetness of fructose is perceived rapidly in the mouth as compared to sucrose and dextrose. Fructose is sweeter than sorbitol and mannitol and thus used widely as a sweetener. Polyhydric alcohols such as sorbitol, mannitol, and isomalt can be used in combination as they additionally provide good mouth-feel and cooling sensation. Polyhydric alcohols are less carcinogenic and do not have bitter after taste which is a vital aspect in formulating oral preparations. The artificial sweeteners have gained more popularity in 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. Acesulfame-K and sucralose have more than 200 and 600 time sweetness. Neotame and alitame have more than 2000 and 8000 time sweetening power as compared to sucrose. Rebiana which is a herbal sweetener, derived from plant Stevia rebaudiana (South American plant) has more than 200 -300 time sweetness.

Saliva stimulating agents

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 strip formulations. Generally acids which are used in the preparation of food can be utilized as salivary stimulants. Citric acid, maliec acid, lactic acid, ascorbic acid and tartaric acids are the few examples of salivary stimulants, citric acid being the most preferred amongst them.

Flavouring agents

Flavouring agents can be selected from the synthetic flavour oils, oleo resins, extract derived from various parts of the plants like leaves, fruits and flowers. Flavours can be used alone or in the combination. Any flavour can be added such as essential oils or water soluble extracts of menthol, intense mints such as peppermint, sweet mint, spearmint, wintergreen, cinnamon, clove, sour fruit flavour such as lemon, orange or sweet confectionary flavours such as vanillin, chocolate ,or fruit essence like apple, raspberry, cherry, pineapple. The amount of flavour needed to mask the taste depends on the flavour type and its strength.

Colouring agents

A full range of colours is available including FD& C colours, EU colours, natural colouring agents, and natural juice concentrates, pigments such as titanium oxide, silicon dioxide and zinc dioxide and custom pantone-matched colours. These all colouring agents should not exceed concentration levels of 1% w/w. these agents are incorporated when some of the formulation ingredients or drugs are present in insoluble or suspension form.

Manufacturing processes involved in making mucoadhesive buccal films

Film casting [26, 35, 40]

The film casting method is the most widely method for the preparation of buccal film, because of easy processing and low cost system setup at the research laboratory scale. The process comprises of six steps:

- Casting solution is prepared
- Solution is then deaerated
- Solution is transferred into a mould
- Casting solution is then dried
- Final dosage form is cut to contain the desired amount of drug
- Packing of the product in suitable package.

Rheological properties of solution, air bubble entrapped in the solution,residual solvents etc. are few important factors in the preparation of the buccal films. Rate of drying, uniformity of content and final physical appearance of the product is dependent on the viscosity of solution. During the manufacturing process air bubbles get incorporated while mixing and should be removed to maintain the homogeneity of drug content. Films that are prepared by using aerated solutions form films with uneven surface non-uniform thickness. Presence of organic solvent is also an important factor while formulating any film to be used in oral cavity. However, use of organic solvent is generally avoided due to problems of residual solvents and also because of their hazardous nature many formulations rely on the use of organic solvents due to their physicochemical properties. In such cases, organic solvents should be chosen from ICH class3 solvent list. Presently the area of research in developing buccal films are focused on their use for specific drug loading, manufacturing parameters along with the composition of the casting solutions used.

Hot- melt Extrusion of films [24]

In this method of film formation, firstly, a mixture of pharmaceutical ingredients is molten and then it is forced to pass through a vent (the die) so that more homogenous material is produced, such as granules, tablets or films. This process of hot melt extrusion has also been used for the production of controlled-released formulations such as matrix tablets, pellets and granules, along with the orally disintegrating films. However, there are only limited articles of hot melt extrusion process for the preparation of mucoadhesive buccal film. Research has been conducted by Repka *et al* for the production of mucoadhesive buccal film by hot melt extrusion process for the evaluation of additives and matrix formers for blend processing. Earlier publications suggested that the film that contains specially hydroxyl propyl cellulose cannot be formed, however a thin, flexible and stable HPC films has been produced over six months by the addition of several plasticizers, such as PEG 6000, triethyl citrate, or acetyl tri butyl citrate. It has been established that with the increase in the molecular weight of HPC, the release of hot-melt extruded films[24]

decreases following zero order drug release. With the application of several models it has been determined that drug release occurs by erosion of the buccal film.

Table 1: Categories of drugs formulated as Mucoadhesive Buccal films

Drug	Category	Method	Polymer
Diclofenac	NSAID	Solvent casting	HPMC, PVP, Eudragit L-100-55, Ethanol, Glycerine.
Diltiazem	Anti hypertensive	Solvent casting	HPMC, HPC, EudragitL-100, PVP,PVA, sodiumCMC Sodium alginate, Propylene glycol, Sodium chloride, Acetonitrile,methanol.
Felodipine (polyethyleneoxide)	Antihypertensive	Solvent casting	Ethyl cellulose, HPC(polyox%).
Zolmitriptan	Anti migrane (serotonin-5HT1-agonist)	Solvent casting	Polymer,(Sodium CMC,HPMC,HEC, Chitosan) Plasticizer.
Losartan potassium	Antihypertensive (angiotensin-II antagonist)	Solvent casting	Ethyl cellulose, Eudragit RSPO, HPMC, Propylene glycol.
Progesterone	Contraceptive (Fertility control)	Solvent casting	Glutaraldehyde, PVP, Gelatin, Acetic acid.
Miconazole	Anti fungal	Solvent casing	Chitosan, Oliec acid,Potassium dihydrogen phosphate,dihydrogen ortho phosphate, Phosphate buffer saline, Propylene glycol, PEG400, Tween20, Glacial acetic acid, Double,sabourard dextroseagar.
Montelukast Sodium	Anti asthama	Solvent casting	(Eudragit RL-100, Carbapol-971P, Carbapol-974P, HPMC, Propylene glycol PVP-K-30,Carbapol934, Carbapol 940.

Famotidine	Anti ulcers	Solvent evaporation	HPMC, Sodium CMC, PVA, glycerine, Ethanol,water.
Rasagiline mesylate	Anti Parkinson	Solvent casting	Sodium alginate,Carbapol 940P, Glycerine.
Rantidine HCL	Anti ulcer	Solvent casting	Carbopol 934P,HPMCE15, Propylene glycol,Ethanol.

Table 2: Categories of drugs formulated as Fast dissolving Buccal films.

Drug	**Category**	**Method**	**Polymer**
Levocitrizine HCL	Non sedative Anti histamine	Solvent casting	PVA, HPMC.
Domperidone	Anti ulcers	Solvent casting	HPMC, PVA, Beta-cyclodextrins, Xanthane gum.
Dicyclomine	Anti-cholinergic	Solvent casting	HPMC, PVA, Eudragit-RL-100, Aspartame, Organic solvent.
Ondansetron		Solvent casting	PVA, PVP, Carbopol 934P, PEG400, Mnnitol.
Salbutamol	Anti asthma	Solvent casting	HPMC, Glycerol, Aspartame.

Characterization Of Buccal Film [32, 40, 83]

Drug-excipients interaction studies [16, 40]

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 enthalipies of the reaction.

Thickness measurements

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 [78]

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 370C. 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:

$$\%S = (Xt - Xo/Xo) \times 100$$

Where;

Xt is the weight or diameter of the swollen patch after time t,

And Xo is the original patch weight or diameter at zero time.

Surface pH

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

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.

Uniformity of drug content

This parameter can be determined by dissolving known weight of film by homogenization in 100 ml of stimulated saliva of pH 6.8 for 30 min with continuous shaking.

Tensile strength

The tensile strength (psi) is the property of the film that requires a load to cause load deformation failure of film. Nafee et al., 2003 evaluated this mechanical property by using Instron Universal Testing Instrument (model F. 4026), Instron Ltd., Japan, NITK, Surathkal) with a 5-kg load cell. Film strips in special dimension and free from air bubbles or physical imperfections were held between two clamps positioned at a distance of 3 cm. During measurement, the strips were pulled by the top clamp at a rate of 100 mm/min; the force and elongation were measured when the film broke. Results from film samples, which broke at and not between the clamps, were not included in the calculations. Measurements were run in triplicate for each film. Tensile strength is also defined as the maximum stress applied to a point at which the film specimen breaks and can be computed from the applied load at rupture as a mean of three measurements and cross-sectional area of fractured film from the following equation .

Tensile strength (N/mm^2) = breaking force (N) / cross sectional area of sample (mm^2)

Percent elongation

The percent elongation is measured when the film snaps as sufficient force applied so as to exceed the elastic limit. Percentage elongation can be obtained by following equation:

Elongation at break (%) =increase in length at breaking point (mm) / original length(mm)X100%.

Palatability test

Palatability study is conducted on the basis of taste, after bitterness and physical appearance. All the batches are rated A, B and C grades as per the criteria. When the formulation scores at least one A grade, formulation is considered as average. When the formulation scores two A grade then it would be considered as good and the one with all three A grade it would be the very good formulation.

Grades: A= very good, B= good, C=poor.

Surface morphology

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.

Disintegration test [21]

Disintegrating time is defined as the time (second) at which a film breaks when brought into the contact with water or saliva. The disintegration time is the time when a film starts to break or disintegrate. Thickness and mass play a role in determining the dissolvable films physical properties. Disintegration test is done by Disintegration apparatus.

Permeation studies

Permeation studies are carried using the modified Franz diffusion cell by using porcine buccal mucosa. The mucosa is mounted between the donor and receptor compartment of Franz diffusion cell. The receptor compartment is filled with buffer and maintained at 37 °C ± 0.2 °C and the hydrodynamics were maintained by stirring with a magnetic bead at 50 rpm. One previously weighed film is placed in intimate contact with the mucosal surface of the membrane that should be previously moistened with a few drops of simulated saliva. The donor compartment is filled with 1 ml of simulated saliva of pH 6.8. Samples are withdrawn at suitable interval, replacing the same amount with the fresh medium. The percentage of drug permeated is determined by measuring the absorbance by selected analytical method.

Stability study [69]

Stability study of fast dissolving films is carried out for all the batches according to ICH guidelines. After predetermined time intervals, the films are evaluated for the drug content, disintegration time and physical appearance..

Determination of mucoadhesion

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 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.

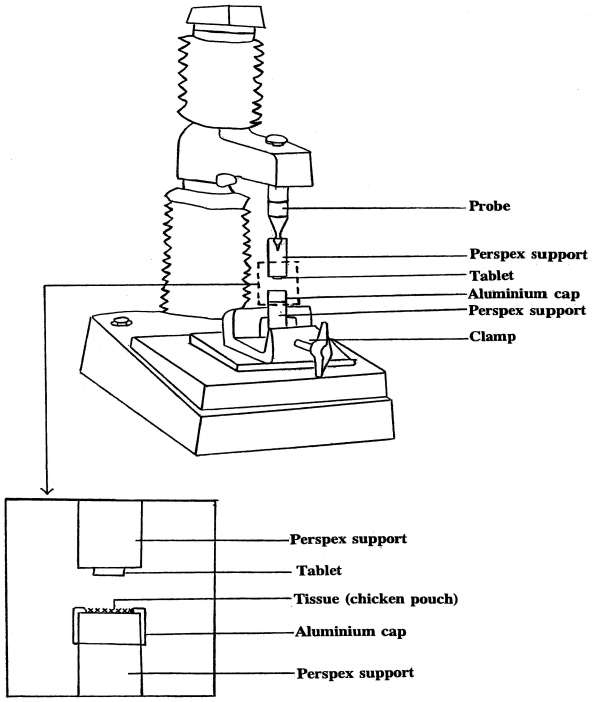

Figure 3: TX2 texture analyzer (Stable Micro Systems) to measure the mucoadhesion strength of buccal films

***In vitro* Release Study [58, 61, 62]:**

In vitro dissolution studies were carried out in USP XXIV type II apparatus under sink conditions. The dissolution medium was 500mL of simulated saliva solution pH 6.75 at 37±0.50c 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.

Packaging [80]

In the pharmaceutical industry it is vital that the package selected adequately preserve the integrity of the product. Expensive packaging, specific processing, and special care are required during manufacturing and storage to protect the dosage of other fast dissolving dosage forms. A variety of packaging options are available for fast dissolving films. Single packaging is mandatory for films, which are pharmaceutical products; an aluminium pouch is the most commonly used packaging format. APR- Lab tech, has developed the Rapid card, a proprietary and patented packaging system, which is specially designed for the Rapid films. The rapid card has same size as a credit card and holds three raid films on each side. Every dose can be taken out individually.

The material selected must have the following characteristics

1. They must protect the preparation from environmental conditions.
2. They must be FDA approved.
3. They must meet applicable tamper-resistant requirement.
4. They must be non-toxic.
5. They must not be reactive with the product.
6. They must not impart to the product tastes or odours.

Foil, paper or plastic pouches

The flexible pouch is a packaging concept capable of providing not only a package that is temper- resistance, but also by the proper selection of material, a package with a high degree of environmental protection. A flexible pouch is usually formed during the product filling operation by either vertical or horizontal forming, filling, or sealing equipment. The pouches can be single pouches or aluminium pouches.

Single Pouch and Aluminium pouch

Soluble film drug delivery pouch is a peelable pouch for "quick dissolve" soluble films with high barrier properties. The pouch is transparent for product display. Using a 2 structure combination allows for one side to be clear and the other to use a cost-effective foil lamination. The foil lamination has essentially zero transmission of both gas and moisture. The package provides a flexible thin film alternative for nutraceutical and pharmaceutical applications. The single dose pouch provides both product and dosage protection. Aluminium pouch is the most commonly used pouch.

Blister Card with multiple units

The blister container consists of two components: the blister, which is the formed cavity that holds the product, and the lid stock, which is the material that seals to the blister. The blister package is formed by heat –softening a sheet of thermoplastic resin and vaccum-drawing the softened sheet of plastic into a contoured mould. After cooling the sheet is released from the mould and proceeds to the filling station of the packaging machine. The semi –rigid blister previously formed is filled with the product and lidded with the heat sealable backing material. The film selection should be based upon the degree of protection required. Generally the lid stock is made of aluminium foil. The material used to form the cavity is typically a plastic, which can be designed to protect the dosage form from moisture.

Barrier Films

Many drug preparations are extremely sensitive to moisture and therefore require high barrier films. Several materials may be used to provide moisture protection such as Polychloro-trifluoro-ethylene (PCTFE) film, Polypropylene. Polypropylene does not stress crack under any conditions. It is an excellent gas and vapour barrier. Lack of clarity is still a drawback.

Applications of fast dissolving buccal films [22,38]

Vaccines

Fast dissolving buccal films film can be delivered in the form of vaccine which is stable at room temperature so it is quickly dissolved in mouth and in saliva. Rotavirus vaccine prepared in United states is a room temperature stable fast-dissolving buccal film delivery system for vaccines that will make vaccinations almost as simple as freshening your breath. This delivery system exhibits many advantages which include: improved patient

compliance, improved bioavailability, reduction in the costs associated with storage and distribution, handling and administration.

Controlled and Sustained release film

Sustained release buccal film is applicable in hospital preparations and various polymers like chitin and chitosan[30] derivatives are used as excipients. They contribute to expansion of application, decrease toxicity, wound dressings, oral mucoadhesive and water-resisting adhesive by virtue of their release characteristics and adhesion.

Taste masking

Taste masking is an essential requirement for fast dissolving tablets for commercial success. Fast dissolving buccal films dissolve or disintegrate in patient's mouth, thus releasing the active ingredients which come in contact with the taste buds and hence this property becomes critical for the patient compliance. In taste masking, drugs with unacceptable bitter taste can be microencapsulated into pH sensitive acrylic polymers by solvent evaporation and solvent extraction techniques. These polymers microspheres showed efficient taste masking and complete dissolution in a short period .

Orally disintegrating films

Fast dissolving buccal films are based on a water-soluble polymer. The film has the ability to dissolve rapidly without the need for water provides an alternative to the patients with swallowing disorders and to patient suffering from nausea, such as those patients receiving chemotherapy.

Approaches for drug delivery on buccal films [76, 80]

Doshi *et al*: Formulated buccal films of Diclofenac sodium using mucoadhesive polymers like PVA and HPMC. Evaluation of the films mainly comprises of mechanical strength, folding endurance, drug content uniformity, swelling, *in vitro* residence time, *in vitro* release, *in vitro* bio adhesion and *in vivo* muco adhesion. Films formed have good tensile strength and elasticity and the dru content was also uniform.Satisfactory residence time has been obtained with HPMC containing film, along with good bio adhesive strength and the release of drug was found to be matrix diffusion type. Less bioadhesion has been achieved with the films containing PVA. PVA

containing film generally used for fast release of drug, so fast action, where as HPMC containing films are used for the sustained release of the drug.

Choudhury *et al* : Formulated mucoadhesive buccal film of ciprofloxacin HCL using different concentrations of hydroxy propyl methyl cellulose for the treatment of periodontal diseases. Films prepared were evaluated in terms of determination of weight, thickness, surface pH, folding endurance, swelling index, mucoadhesion time, mucoadhesion strength, drug content,*in vitro* drug release study, *ex-vivo* release study and release kinetic behaviour. Evaluation results lead to the conclusion that all the prepared films have good flexibility and mucoadhesive properties, along with that, they showed desired *in vitro* and *ex vivo* drug release profile. Prepared films shows sustained drug release phenomenon as required in buccoadhesive drug delivery.

Rasool *et al***:** Formulated five different film formulations containing 20mg of miconazole nitrate, along with the drug solubilizers(propylene glycol10% w/w, poly ethylene glycol 3%w/w, tween20 6%w/w and oleic acid 5%w/w) and chitosan as film forming polymer, casting-solvent evaporation technique has been employed for film preparation and further it is evaluated in terms of weight uniformity, film thickness, surface pH, swelling capacity, *in vitro* drug release and *in vitro* microbiological effectiveness against *candida*[25] *albicans.* The prepared film thickness ranged from 0.11-0.23mm and the weight of he film ranged from 152.5-188mg and the pH values of all films were in the range of 5.84-6.63 which is favourable for oral mucosa. Films that contain propylene glycol 10% showed optimum release pattern and adequate elasticity. The percent swelling of the selected film after 6 hrs reached 32.1%. The drug release mechanism was mainly governed by fickian[53] diffusion. Furthermore, the selected film showed good antifungal activity($p<0.05$)superior to the reference miconazole oral gel(Daktarin). Mucoadhesive buccal film prepared from chitosan for the topical delivery of miconazole nitrate could be a utilized for the effective management of oral candidiasis. Further, it was concluded that the selected film formulation(MC 0.524mg/cm ^{2}, PG10%w/w and chitosan 2%w/w) can be efficiently used for the management of oral candidiasis.

Goudanavar *et al* :Prepared mucoadhesive buccal films of glibenclamide[30] with improved bioavailability using different polymer combinations such as hydroxy propyl cellulose (HPC),polyvinyl pyrrolidone (PVP) and ethyl cellulose(EC) by solvent casting technique. Prepared films were evaluated and characterized by means of drug release, bioadhesive strength,

content uniformity, film thickness, percentage elongation, surface pH and folding endurance. Conclusion was made that type of polymer and their concentration influences the release behaviour of drug. Films that contain HPC had shown maximum drug release while incorporation of PVP or EC showed decrease in the release rate of Glibenclamide from the buccal films. Studies showed that various formulations that contain polymers hydroxy propyl cellulose, polyvinyl pyrrolidone and ethyl cellulose showed good results.

Koland *et al*: Prepared mucoadhesive buccal films of losartan potassium using hydroxy propyl methyl cellulose and retardant polymers ethyl cellulose or eudragit RS100. No interaction was found between drug and polymer when thermal analysis by DSC was done. During the ex vivo permeation studies of losartan potassium, it was found that buccal mucosa showed 90.2% absorption at the end of 2 hrs. The films were further evaluated for uniformity of thickness, weight, drug content, folding endurance, tensile strength, elongation at break, surface pH and mucoadhesive strength. Normally the films formed were flexible in nature where as EC containing films were smooth in nature and when eudragit is used in the preparation of films, a slightly rough texture was obtained. HPMC containing films showed higher mucoadhesive force, swelling index, folding endurance, tensile strength and percentage elongation at break. All films show sustained release phenomena during in vitro drug release studies, in the range of 90.10-97.40% for a period of 6 hrs. Pharmacokinetically, the data indicates non-fickian diffusion for all formulations.

Parmar *et al* : Developed various formulations of carvedilol by using polymers like Eudragit RL-100, PVP,HPMC, Na CMC and carbapol934P in several combinations by solvent casting technique along with the addition of plasticizer propylene glycol, with and without penetration enhancers addition like DMSO, Tween60 and Castor oil. A backing layer formed using EC 10%w/v in ethanol along with the addition of propylene glycol was applied on the film for the unidirectional release. The most acceptable formulations had retained on buccal cavity for maximum duration of 10 hr. Ex vivo diffusion studies concluded that the formulation containing DMSO as penetration enhancer that increase the permeability of the drug through buccal mucosa up to 15% was chosen as best formulation. The most acceptable formulation followed zero order kinetics while the SEM showed that drug release mechanism was anomalously diffused. The most acceptable formulations is the one that shows no significant changes in the physicochemical parameters.

CONCLUSION

The buccal mucosa is found to be the most promising delivery route for those drugs that have sufficient gastro intestinal degradation and has significant first pass metabolism. It can be concluded from the whole literature survey that buccal film has good opportunity as a drug delivery devices for various drug entity. Fast dissolving buccal films have gained popularity because of better patient compliance, rapid drug delivery system. Fast dissolving buccal films can be a better option to optimize therapeutic efficacy of various active pharmaceutical ingredients in the future.

ACKNOWLEDGEMENT

The Principal and Management of SR College of Pharmacy, Warangal for his constant encouragement.

REFERENCES

1. Slowson M., Slowson S. Pharma Times, 1985; 51: 90-96.
2. Tripathi KD. In Essentials of Medical Pharmacology, 6th edition, JP Medical Publishers, 2003; 606-607.
3. Drug Delivery via Dissolving Strips, Drug Discovery and Development, 2007, 10 (7), 10. Available from URL: http//en.wikipedia.org/wiki/ thin film drug delivery.
4. Dixit R, Puthli SJ. of Controlled Release: (Mumbai, India) Official J. of Controlled Release Society, 139(2), 94-107.
5. Patel R, Shardul N, Patel J, Baria A. Arch Pharm. Science and Research, 2009; 1 (2): 212-217.
6. Sumitha CH, Karunasree N, Divya B, Madhavi K. Vimal Kumar VM, Charbu NN. Int. Chemical Research, 2009; 1(2): 24-27.
7. Reddy LH, Ghose B. Rajneesh. Indian J. Pharma. Science, 2002; 64(4): 331-336.
8. Kuchekar BS, Arumugam V. Indian J. Pharma. Edu, 2001; 35: 150.
9. Bhaskaran S, Narmada GV, Indian Pharmacist, 2002; 1(2): 9-12.

10. Indurwade NH, Rajyaguru TH, Nakhat PD. Indian Drugs, 2002; 39(8): 405-09.
11. Devrajan PV, Gore SP. Express Pharma Pulse, 2000; 7(1): 16.
12. Kulkarni AS, Deokule HA, Mane MS, Ghadge DM. J. of current Pharma. Research, 2010; 2 (1): 33-35.
13. Sakellariou P, Rowe RC. Prog. Polymer Science, 1995; 20: 889 -942.
14. Banker GS. J. Pharma. Science, 1966; 55: 81-88.
15. McIndoe LME, Rowe RC, Sheskey PJ, Owen SC. Handbook of Pharmaceutical Excipients.
16. Wale A, Weller PJ, Handbook of Pharmaceutical Excipients, 2nd edition, 1994; 24, 27, 352,448.
17. Prakash., DuBois GE, Clos JF, Wilkens KL, Fosdick LE. Food Chem. Toxicol, 2008; 46: 75- 82.
18. Chapdelaine AH, Zyck DJ, Dzija MR. US Patent 6740332, 2004.
19. Barnhart S, Slaboda MS. Drug Dev. Tech, 2007; 1: 34-35.
20. Repka M, Swarbrick J, Boylan J, In Encyclopedia of Pharmaceutical Technology, 2nd Edition, 2002; 1488–1504. Pharmaceutical press, London, 2006; 128 -130.
21. Lachmann L., In The Theory & Practical of Industrial Pharmacy, 3rd edition, Varghese Publishing house, Fourth Indian Reprint, 1991; 344-348.
22. Mehnert W and Mader K.. Solid lipid nano particles: Production charecterization and applications. advance drug delivery Rev. 2001;47:165-196.
23. Gaucher G, Satturwar P, Jones MC, Furtos A and Leroux JC. Polymeric micelles for oral drug delivery. European J. Pharmaceutics and biopharmaceutics, 2010;76:147-158.
24. Repka M, Prodduturi S and Stodghill S. Production and charecterization of hot-melt extruded films containing Clotrimazole. Drug development and industrial pharmacy. 2003;9:757-765.
25. Lee Y and Chien Y. Oral mucosa controlled delivery of LHRH by bilayer mucoadhesive polymer systems J. Controlled release, 1995; 37:251-261.

26. Khanna R, Agarwal SP and Ahuja A. Preparation and evaluation of mucoadhesive buccal films of Clotrimazole for oral candida infections. Indian J.pharmaceutical Science. 1997;59:299-305.

27. Dixit R and Puthli S . Oral strip technology: Overview and future potential, J. Controlled release. 2009; 139:94-107.

28. Goodman and Gillman. The Pharmacological Basis of Therapeutics, 2009; 5-6.

29. Ahuja A and Khanna R. Mucoadhesive buccal drug delivery; A potential alternative to conventional therapy. J.Controlled Release, 1998;1-11.\

30. Ilango R, Jeyakar B, Kavimani S and Mullaicharam AR (1997) In-vivo studies on buccal strips of Glibenclamide using Chitosan. J.Controlled Release, 59, 232-235.

31. Remington. The science and practice of pharmacy, 2005; 1157.

32. Mohamed Magdy I, Mohamed Haider. Buccal Mucoadhesive films containing antihypertensive drug: invitro/invivo Evaluation, Journal of chemical and pharmaceutical research. 2011; 3(6): 665-686.

33. Tripathi KD, Essential of medical pharmacology: Antihypertensive Drugs, 6th edn. Jaypee brother's medical publishers New Delhi, 2008; 531-533

34. Patel Vishnu M, Prajapati BG and Patel Madhabhai M. Formulation, Evaluation and Comparison of Bilayered and Multilayered Mucoadhesive Buccal Devices of Propranolol Hydrochloride, AAPS PharmSciTech. 2007; 8(1): E1-8.

35. Patel DJ and Patel JK., Mucoadhesive effect of Polyethylene Oxide on Famotidine nanosuspension prepared by solvent evaporation method, International journal of Pharmacy and Pharmaceutical Sciences. 2010; 2: 122-127

36. Koland M**,** Charyulu RN and Prabhu P. Mucoadhesive films of Losartan Potassium for Buccal delivery: Design and Characterization, Indian J.Pharm. 2010; 315-323.

37. Brahmankar DM, Jaiswal SB. biopharmaceutics and pharmacokinetics a treatise. 1st ed. Delhi: Vallabh Prakashan; 2003; 230-72.

38. Mashru RC, Sutariya MG. Development and evaluation of fast dissolving film of salbutamol sulphate. Drug Dev. Ind. Pharm 2005; 1: 25-34.

39. Sudhakar Y, Kuotsu K, Bandyopadhyay AK. Buccal bioadhesive drug delivery: A promising option for orally less efficient drugs. J Control Release 2006; 114: 15-40.

40. Morales JO, McConville JT. Manufacture and characterization of mucoadhesive buccal films. Eur J Pharm Biopharm 2011; 77: 187-199.

41. Andrew GP, Laverty TP, Jones DS. Mucoadhesive polymeric platform for controlled drug delivery. Eur J Pharm Biopharm 2009; 71: 505-518.

42. Gandhi RB, Roninson JR. Bioadhesion in drug Delivery. Indian J Pharm Sci 1988; 50: 145- 152.

43. Shojaei AH, Li X. Determination of transport route of acyclovir across buccal mucosa. Proc Int Symp Control Release Bioact Mater 1997; 24: 427-428.

44. Ana F, Juliane H, Andreas BS. In-vitro evaluation of natural and methylated cyclodextrin as Buccal permeation enhancing system for omeprazole delivery. Eur J Pharm Biopharm 2009; 71: 339-345.

45. Henrihsen I, Green LK Bioadhesion of hydrated chitosan: an in vitro and in vivo study. Int J Pharm 1996; 145: 231-240.

46. Lehr CM, Bouwstra JA. In vitro evaluation of mucoadhesive properties of chitosan and some other natural polymer. Int. J. Pharma. 1992; 78: 43-48.

47. Biradar SS. Bhagvati ST, kuppasad IJ. Fast dissolving drug delivery systems; a brief review. Internet J Pharmcol. 2006; 4(2). 56-68.

48. Ivory AA, Rossman JM, Lee KM. Rapidly dissolving edible film compositions with cellulose film forming polymers. United states patent application publication. 2004:1-9.

49. Dinge A, Nagarsenker M, "Formulation and evaluation of fast dissolving films for delivery of triclosan to the oral cavity", AAPS. Pharma. Science and Tech, 2008; 9(2), 349-56.

50. Koland M, Charyulu RN and Prabhu P. Mucoadhesive films of Losartan Potassium for Buccal delivery: Design and Characterization, Indian J.Pharm. Educ. Res. 2010; 44(4), 315- 322.

51. Chen M, Tirol G, Schmitt R, Chien C and Dualeh A, Film forming polymers in fast dissolve oral films, AAPS Annual meetings-posters and papers, 2006; T3200,

52. Cilurzo F, Cupone IE, Minghetti P, Selmin F and Montanari L. Fast dissolving films made of maltodextrins. Eur. J. Pharmaceut and Biopharmaceut 2008; 70, 895–900

53. Peppas NA, Analysis of Fickian and non Fickian drug release from polymers, Pharm. Acta Helv. 1985; 60: 110–111.

54. Jain N.K. Controlled and Novel Drug Delivery, 1st Edition, published by CBS publishers and Distributors, New Delhi; 1997: 52-81.

55. Semalty A, Bhojwani M, Bhatt GK, Gupta GD and Shrinivas AK. Design and evaluation of mucoadhesive buccal film of dilitazem hydrochloride. Ind. J Pharm. Sci. 2005; 67(5): 548-552.

56. Mona Semalty, A. Semulty and G. Kumar. Formulation and characterization of mucoadhesive buccal films of glipizide. Indian Journal of pharmaceutical sciences, 2008; 43-48.

57. Khurana R, Ahuja A and Khar RK. Development and evaluation of mucoadhesive films of miconazole nitrate. Ind. J. Pharm. Sci. 2000; 447-453.

58. Dandagi PM, Manvi FV, Mustiholimath VS, Hiremath SP and Thomas PT. Formulation and *in vitro* evaluation of Diltiazem hydrochloride buccal films. The Indian Pharmacist, 2005;37: 59-62.

59. Satishbabu BK and Srinivasan BP: Preparation and evaluation of buccoadhesive films of atenolol. Indian Journal of Pharmaceutical Sciences 2008; 70(2):175-179.

60. Parmar VJ, Lumbhani AN, Vijaylakshmi P, Jha S. Formulation development and evaluation of buccal films of carvedilol . International journal of pharmaceutical sciences and research, 2010; 1(8) (Suppl.).

61. Giradkar KP, Channawar MA, Kajale AD, Sridhar E, Kamble RS, Bakde BV and Chandewar AV. Design development and *in-vitro* evaluation of bioadhesive dosage form for buccal route. International Journal of Pharma. Research and Develop; 2010; 26.

62. Alagusundaram, M, Chengaiah, B, Ramkanth, S, Parameswari, SA, Chetty CM and Dhachinamoorthi, D. Formulation and evaluation of mucoadhesive buccal films of ranitidine International Journal of Pharma Tech Research. 2009; 1(3): 557-563.

63. Raghavendra Rao NG, Suryakar VB and Thube K.. Development of mucoadhesive films for buccal administration of montelukast International Journal of Pharmacy and Technology. 2010;2 (1): 1-15.

64. Johnston T.P, Miller S, Chittchang M, Theuse of mucoadhesive polymers in buccal drug delivery, Adv. Drug Deliv. Rev., 2005; 57:1666-1691.

65. Semalty A. Mucoadhesive polymers: a review, Available at: http://www.pharmainfo.net/reviews/mucoadhesive-polymers-review [updated on 2006Dec].

66. Alagusundaram M, Chengaiah B, Ramkanth S, Parameswari S.A, Madhu C, Formulation and evaluation of mucoadhesive buccal films of ranitidine, Int. J. Pharm. Tech. Res., 2009; 1(3): 557-563.

67. Hariharan M and Bogue A. Orally dissolving film strips: the final evalution of orally dissolving dosage forms, Drug Delivery Technology 2009; 9: 24–29.

68. Dixit R and Puthli S. Oral strip technology: overview and future potential, Journal of Controlled Release, 2009; 139: 94–107.

69. ICH Harmonised Tripartite Guideline. Stability Testing of New drug substances and products Q1A (R2). Current step 4 version, 8. 2003.

70. Dixit R and Puthli S. Oral strip technology: overview and future potential, Journal of Controlled Release, 2009; 139: 94–107.

71. Harris, D. and Robinson, J.R., Drug delivery via the mucous membranes of the oral cavity, J. Pharm. Sci.1992; 81: 1-10.

72. Wertz PW and Squier CA. Cellular and molecular basis of barrier function in oral epithelium, Crit. Rev. Ther. Drug Carr. Sys.1991; 8: 237-269.

73. Rossi S. Buccal delivery of acyclovir from films based on chitosan and poly acrylic acid, Pharm. Dev. Technology. 2003; 8: 199–208.

74. Cilurzo F, Cupone I E, Minghetti P, Selmin F and Montanari L. Fast dissolving films made of maltodextrins, Eur. J. Pharm. Biopharm. 2008; 70(3): 895–900.

75. Consuelo ID, Falson F, Guy RH and Jacques Y. Ex vivo evaluation of bioadhesive films for buccal delivery of fentanyl, J. Control. Release, 2007; 122: 135–140.

76. Jian-Hwa G and Karsten C. Development of Bioadhesive Buccal Patches. Swarbrick J, Mathiowitz editors, Bioadhesive Drug Delivery Systems: Fundamentals, Novel Approaches and Development. Marcel Dekker Inc., 1999: 541-59.

77. Sang-Chul Shin. and Ja-Young Kim. Enhanced permeation of triamcinolone acetonide through the buccal mucosa. Eur. J. Pharm Biopharm 2000; 50(2): 217-20.

78. Peh KK and Wong CF. Polymeric fims as vehicles for buccal delivery: Swelling, Mechanical and Bioadhesive properties. J. Pharma. Science.1999; 2(2): 53-61.

79. NK Jain. Oral trans-mucosal drug delivery, CBS publishers and distributors, New Delhi, 2002: 52-81.

80. JT McConville. Recent trends in oral drug delivery. Industry overviews and deals, Drug delivery report autumn/winter, 2005;24-26.

81. Mathiowitz E, Chickering D, Jacob JS and Santos C. Bioadhesive drug delivery systems. In: E. Mathiowitz, editor. Encyclopedia of controlled drug delivery systems. New York: John Wiley and Sons, Inc. 1998; 9-13.

82. Hoogstraate J, Benes L and Burgaud S. Oral transmucosal drug delivery systems. In: AM Hillery, AW Lioyd, J Swarbrick , editors. Drug delivery and targeting. London: Taylor and Francis; 2001; 186-200.

83. Kashappa Goud Desai H, Pramod Kumar TM. Preparation and Evaluation of a Novel Buccal Adhesive System. AAPS Pharm. Sci.Tech, 2004;5(3):35-38.