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Trends in Buccal Film: Formulation Characteristics, Recent Studies and Patents

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Abstract: Administration of drug via buccal route serves several advantages including bypass of gastrointestinal tract, hepatic first pass effect and improved patient compliance. The buccal mucosa provides direct entry into the systemic circulation. Film casting technique is the most commonly employed process for the manufacture of the buccal film. This article deal with the various prospects of buccal drug delivery such as advantages, formulation methodologies, recent studies and various patents concerning formulation of buccal film.

Key words: Buccal film · Buccal drug delivery · Patents

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 [1]. 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 [2].

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 [3-6].

Buccal Film: A film is generally made by using hydrophilic polymers that has ability to rapidly dissolves on the tongue or within 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 [7]. As the mucoadhesive buccal films are small in size and thickness, it has improved patient compliance, compared to tablets [8-10]. Many mucoadhesive buccal films have formulated to release drug locally in order to treat fungal infections in the oral cavity such as oral candidiasis [11-15]. 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 [16].

When the dry dosage forms is in contact with surfaces with a thin mucus layer, such as a buccal mucoadhesive film, two steps are needed to establish the mucoadhesive bond, viz. a contact and a 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 mucus and 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 [17].

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Advantages of Buccal Drug Delivery: 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 [18].

Disadvantages of Buccal Drug Delivery: Buccal Drug Delivery Have Some Disadvantages Such As:

- In comparison to the sublingual membrane, buccal membrane has low permeability [19].
- Surface area is also small. Oral cavity has total surface area of 170cm^2 for drug absorption [20] of which only ~50 cm^2 represents non-keratinized tissues, along with the buccal membrane [21].
- As the saliva is continuously secreted (0.5-2 l/day), it has diluted the drug to a great extent. [22].
- Dissolved and suspended drugs can also be removed during swallowing of saliva, ultimately, dosage form is removed involuntarily [23].

Manufacturing Processes Involved in Making Mucoadhesive Buccal Films

Film Casting: 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 mold;
- 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 [24]. 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 [25]. Films that are prepared by using aerated solutions form films with uneven surface and 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 [24]. In such cases, organic solvents should be chosen from ICH Class 3 solvent list [26]. 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 [27-30].

Hot-melt Extrusion of Films: 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 homogeneous material is produced, such as granules, tablets, or films [31]. This process of Hot-melt extrusion has also been used for the production of controlled-release formulations such as matrix tablets, pellets and granules [32], along with the orally disintegrating films [33]. 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 [34-36]. 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 8000, triethyl citrate, or acetyltributyl citrate [37]. It has been established that with the increase in the molecular weight of HPC, the release of hot-melt extruded films decreases following zero-order drug release [38]. With the application of several models it has been determined that drug release occurs by erosion of the buccal film [39-40].

Recent Studies on Buccal Film:

Doshi *et al.*: [41] 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* bioadhesion and *in vivo* mucoadhesion. Films formed have good tensile strength and elasticity and the drug content was also uniform. Satisfactory residence time has been obtained with HPMC containing film, along with good bioadhesive 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, whereas HPMC containing films are used for the sustained release of the drug .

Choudhury *et al.*: [42] formulated mucoadhesive buccal film of ciprofloxacin hydrochloride using different concentrations of hydroxypropylmethyl 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.*: [43] formulated five different film formulations containing 20 mg of miconazole nitrate, along with the drug solubilizers (propylene glycol 10% w/w, polyethylene 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 albicans*. The prepared film thickness ranged from 0.11 to 0.23 mm and the weight of the film ranged from 152.5 to 188 mg 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 h reached 32.1%. The drug release mechanism was mainly governed by Fickian 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 0.524 mg/cm2, PG 10% w/w and chitosan 2% w/w) can be efficiently used for the management of oral candidiasis.

Goudanavar *et al.*: [44] prepared mucoadhesive buccal films of glibenclamide 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 behavior 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 result.

Koland *et al.*: [45] prepared Mucoadhesive buccal films of losartan potassium using hydroxypropyl methyl cellulose and retardant polymers ethyl cellulose or eudragit RS 100. 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 hours. 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 whereas EC containing films were smooth in nature and when Eudragit is used in the preparation of film, a slightly rough texture was obtained. HPMC containing films showed higher mucoadhesive force, swelling index, 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 to 97.40 % for a period of 6 hours. Pharmacokinetically, the data indicates non fickian diffusion for all formulations except E2.

Parmar *et al.*: [46] developed various formulations of Carvedilol by using polymers like Eudragit RL-100, PVP, HPMC, NaCMC and Carbopol 934 in several combinations by solvent casting technique along with the addition of plasticizer propylene glycol, with and without penetration enhancers' addition like DMSO, Tween 60 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 10h. 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.

Divyen *et al.*: [47] formulated mucoadhesive film in such a manner, using lycopene as a model drug by solvent casting method, so that higher concentration was achieved in buccal cavity for the treatment of leukopenia. As the film was intended for local effect, no drug release was performed. Lycopene is completely water insoluble in nature, while other excipients are completely water soluble, so major challenge arises for the uniform preparation of film. Viscosity of vehicle, thickness of the film, tensile strength, bending strength, film swelling and erosion properties and *ex vivo* mucoadhesion time and force were the criteria to characterize and evaluate the film formation using propylene glycol as plasticizer.

Basalious *et al.*: [48] prepared mucoadhesive buccal films of Fluconazole using film forming polymers namely; hydroxypropyl methyl cellulose, hydroxyethyl cellulose, chitosan, Eudragit and sodium alginate either alone or in combination with bioadhesive polymers such as sodium carboxymethyl cellulose, Carbopol 974P and polycarbophil. The prepared films were characterized by means of film thickness, surface pH, swelling capacity, *in vitro* adhesion, *in vivo* residence time, *in vitro* drug release and *in vivo* drug release to determine the amount of drug release from selected film formulae using microbiological assay and HPLC. The films that contain 2% HPMC and 1% SCMC showed optimum release behaviour, convenient bioadhesion and acceptable elasticity. The drug released in the saliva determines the ability of film to deliver the drug over a period of 5 hours that would be beneficial in the treatment of oral candidiasis.

Alagusundaram *et al.*: [49] prepared buccal films of Ranitidine using polymers of Hydroxy Propyl Methyl Cellulose - 15 cps (HPMC) and Poly Vinyl Pyrrolidone (PVP) by solvent casting technique employing 'O' shape ring placed on a glass surface as substrate. Polymers were dispersed in ethanol and dichloromethane and 30 % w/w propylene glycol that can be used as plasticizer as well as penetration enhancer. The prepared ranitidine buccal films were evaluated or characterized for surface pH, PMA, PML, swelling percentage, WVT, thickness, weight, folding endurance and drug content. During the in vitro release studies, the buccal film of ranitidine showed significant controlled release profile, along with improved bioavailability.

Semalty *et al*: [50] prepared mucoadhesive buccal films of glipizide using polymers of hydroxy propylmethylcellulose, sodium carboxymethylcellulose, carbopol- 934P and Eudragit RL-100, by solvent casting technique. Films were evaluated for their weight, thickness, surface pH, swelling index, *in vitro* residence time, folding endurance, *in vitro* release, *ex vivo* permeation studies and drug content uniformity. During the in vitro studies the films showed controlled release over more than 6 h. From the study it was concluded that, the films that contain 5 mg glipizide in 4.9 % w/v hydroxy propylmethylcellulose and 1.5 % w/v sodium carboxymethylcellulose exhibited significant swelling, an optimum residence time and promising drug release thus proved to be potential candidate for the development of buccal films for therapeutic use.

Nappinnai *et al.*: [51] developed the mucoadhesive buccal films of nitrendipine using mucoadhesive polymer such as hydroxypropyl methyl cellulose K-100, hydroxypropyl cellulose, sodium carboxymethyl cellulose, sodium alginate, polyvinyl alcohol, polyvinyl pyrrolidone K-30 and carbopol 934P, by solvent casting technique. The prepared films were evaluated for their weight; percentage moisture absorbed and lost, thickness, folding endurance, surface pH, drug content uniformity, *in-vitro* residence time, *in-vitro* release and *ex-vivo* permeation. From the study it was concluded that buccal films made of hydroxypropyl cellulose and sodium carboxymethyl cellulose exhibits the best results. These films showed 50% w/w drug release at the end of 2 hr.

Alanazi *et al.*: [52] formulated buccoadhesive film of ketorolac tromethamine, the non-steroidal anti-inflammatory drug, using various bioadhesive polymers namely sodium carboxymethyl cellulose (Na-CMC), hydroxypropyl cellulose (HPC), hydroxypropylmethyl cellulose (HPMC) and Carbopol 934, by solvent casting technique. The prepared films were characterized for their physical and mechanical properties, swelling behaviors, in vitro bioadhesion, drug permeation via bovine buccal mucosa and in vitro drug release.. Films that contain

Table 1: Patent concerning buccal film

Patent no.	Inventors	Work	References
20110033541	Myers, Garry L. Hilbert, Samuel D. Boone, Bill J. Bogue, Arlie B. Sanghvi, Pradeep Hariharan, Madhusudan	Used the polymers of cellulose or cellulose derivatives for the preparation of mucoadhesive buccal film of buprenorphine. This invention was developed for the treatment of narcotic dependence in a user along with sufficient buccal adhesion.	www.freepatentsonline.com/y 2011/0033541.html
4900552	Sanvordeker, Dilip R. Leung, Sau-hung S.	Lead to the development of a trilaminate film showing sustained release of active ingredient in a buccal cavity. The base layer is provided with a nonadhesive reservoir layer, a hydratable mucoadhesive base layer and a water-impermeable carrier film that has been sandwiched and bonded to it.	http://www.freepatentsonline.com/4900552.html
594294	Repka, Michael A. Repka, Staci L. McGinity, James W.	Prepared the film using water soluble or swellable thermoplastic polymers such as hydroxypropyl cellulose and/or polyethylene oxide along with a bioadhesive polymer. Controlled delivery of a therapeutic agent depends upon the size and shape of the film. The film prepared lead to the controlled release of therapeutic agent to the buccal, vaginal, cranial, nasal, otic cavities etc. The film is also used for treatment of wounds.	http://www.patentstorm.us/patents/6375963.html.
20110033542	Myers, Garry L. Hilbert, Samuel D. Boone, Bill J. Bogue, Arlie B. Sanghvi, Pradeep Hariharan, Madhusudan	The present invention provides the information relating to development of self-supporting dosage form that will deliver active therapeutic agent with sufficient buccal adhesion. This invention has also reduced the likelihood of diversion abuse of active agent. It has also been used in the treatment of pain suffered by a patient.	http://www.freepatentsonline.com/y2011/0033542.html
20100266669	Meyer, Stephan Slominski, Greg Fankhauser, Christopher Edward Ouis, Nicole	This invention has led to the development of single-layer oral disintegrating films that have at least two different zones, which consist of nicotine that allows sufficient buccal absorption thereof.	http://www.freepatentsonline.com/y2010/0266669.html
20070172515	Fuisz, Richard C	The present invention relates to the development of multi-component delivery systems that shows good adherence to mucosal surface. This delivery system consists of two delivery vehicles. The first delivery vehicle comprises of one or more mucoadhesive films that adheres to mucosal surface. The second one comprised of active substance, for delivery through the mucosal surface.	http://www.freepatentsonline.com/y2007/0172515.html
6592887	Zerbe, Horst Georg. Guo, Jian-hwa. Serino, Anthony	Disclosed a composition that contains breath freshening agent and/or therapeutic agents for use in the oral cavity. Water soluble polymers along with certain ingredients were used as carriers that were responsible for therapeutic and cosmetic effect. Using coating technology the film was coated and dried further which results in instant wettability and rapid dissolution/disintegration upon oral administration.	http://www.freepatentsonline.com/6592887.html
20090186107	Haber, Meir. Kristmundsdottir, Thordis. Skulason, Skuli.	This invention relates to the preparation of mucoadhesive film for oral administration. The film consists of major film-forming polymer, at least one alginate that forms low viscous aqueous solution, as carrier and one or more bioactive ingredients.	http://www.freepatentsonline.com/y2009/0186107.html
20100063110	Meyer, Stephan. Slominski, Greg. Fankhauser, Christopher Edward	This invention relates to the development of mucoadhesive oral disintegrating film that completely disintegrates in mouth within one to ten minutes. The film is composed of alkaline substance and pharmaceutical active substance which may be present optionally	http://www.freepatentsonline.com/y2010/0063110.html

Table 1: Continue

Patent no.	Inventors	Work	References
20070155774	Moormann, Joachim. Opitz, Klaus. Hoffmann, Hans-rainer.	The invention relates to the development of film shaped medicament active for oral administration which consists of deoxypeganine and its derivatives as ingredients which can be further utilized for transmucosal administration.	http://www.freepatentsonline.com/y2007/0155774.html
20040006111	Widder, Kenneth. Hall, Warren. Olmstead, Kay.	This invention relates to the development of methods for transmucosal delivery of PPIs (proton pump inhibitors). The pharmaceutical composition consists of antacid core and therapeutically effective amount of proton pump inhibitor as outer layer. The other composition comprised of unidirectional film as outer layer and effective amount of proton pump inhibitor as inner layer.	http://www.freepatentsonline.com/y2004/0006111.html
20060182786	Rademacher, Tina	This invention relates to the formation of film for transmucosal administration of active moiety using at least one matrix forming polymer as a carrier. pH values of the base mass is mainly considered for the production of the administration form and several processes were used for the production of such preparations. Further the study showed that the irritation to the mucosa was significantly reduced or prevented.	http://www.freepatentsonline.com/y2006/0182786.html
20070298087	Biegajski, James E.	This invention relates to the development of mucoadhesive film of pharmaceutically active agent using polymeric backing layer. This mucoadhesive film can be used for the release of therapeutic active ingredients to skin or mucosal surface.	http://www.freepatentsonline.com/y2007/0298087.html
20080152695	Clark, Richard T. Durschlag, Maurice E.	The present invention relates to disclosure of buccal transmucosal delivery method. It includes an edible thin film strip and significant amount of xylitol. The edible thin film further consists of sodium chloride, potassium chloride, trisodium citrate and also glucose.	http://www.freepatentsonline.com/y2008/0152695.html

carbopol (0.5%) and HPMC (0.5%) was found to be the best film as it shows good adhesion, acceptable pH and gives a reasonable ketorolac release (about 85-90% at 6 h). From the results, it was concluded that the ketorolac concentration in the oral cavity was maintained above 4.0μg/mL for a period of at least 6h.

Jacques *et al.*: [53] made mucoadhesive buccal films of fentanyl using polyvinylpyrrolidone (PVP) of two different molecular weights: PVP K30 and PVP K90. Determination of release of fentanyl across full-thickness mucosa and across heat-separated epithelium (where the permeability barrier was shown to be located) was done. Further it was found that, the fentanyl permeation is directly related to the pH i.e. increase in pH causes increase in fentanyl permeation. However, at the pH values studied, fentanyl was predominantly ionized suggesting that transport pathways offering a hydrophilic, or polar, environment across the mucosa were available. The transport rates achieved from the PVP films providing the highest delivery suggest that a buccal system of only 1-2 cm^2 in surface area could achieve a therapeutic effect equivalent to a 10 cm^2 transdermal patch, with a much shorter lag-time.

Hashida *et al*: [54] prepared mucoadhesive buccal films of lidocaine and ketoprofen by using β-cyclodextrin as a polymer. β-cyclodextrin shows some sort of interaction with several other polymers i.e. When β-cyclodextrin was added to hydroxypropylcellulose (HPC) or polyvinylalcohol (PVA) film dosage forms, the release of lidocaine into artificial saliva (pH 5.7) was reduced by 40% of the control while the release of ketoprofen from the polymer film was enhanced by addition of β-cyclodextrin polymer. It was found that, when lidocaine and ketoprofen was incubated with β-cyclodextrin polymer in the artificial saliva, there was decrease in concentration of the free lidocaine molecules, the reason behind this may be due to the decrease in thermodynamic activity by inclusion complex formation. Whereas enhanced release of the lipophilic ketoprofen by the β-cyclodextrin polymer may be due to prevention of recrystallization occurring after contacting the film with aqueous solution. Thus, result suggested that effects of low molecular-weight β-cyclodextrin polymer to the drug release rate from film dosage forms would vary according to the strength of interaction with and the solubility of active ingredient.

Perioli *et al.*: [55] formulated buccal mucoadhesive film for the delivery of ibuprofen using sodium CMC and PVP as film forming material. The films formed were evaluated

in terms of swelling, mucoadhesion and organoleptic characteristics. Those films that contain polyvinylpyrrolidone as film-forming polymer and sodium carboxymethyl cellulose as mucoadhesive polymer exhibits best result. Statistical investigation of *in-vitro* release revealed that the main process involved in the drug release mechanism was diffusion and the Higuchi's model provided the best fit. *In-vivo* studies showed that the ibuprofen can be placed in saliva (70-210 μg/ml) for 5 h with no irritation.

CONCLUSION

The buccal mucosa is found to be the most promising delivery route for those drugs that have sufficient gastrointestinal 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 system for various drug entity.

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