Buccal Film Drug Delivery System-An Innovative and Emerging Technology

Radha Madhavi B.*, Varanasi SN Murthy¹, Prameela Rani A¹ and Dileep Kumar Gattu²

¹University College of Pharmaceutical Sciences, Acharya Nagarjuna University, Guntur, India
²Anurag Pharmacy College, Kodad, Nalgonda, India

Abstract

Now days, an extensive research is being carried out on the design and development of innovative drug delivery systems to improve the safety, efficacy and patient compliance. One such delivery system is the buccal film technology. This technology has emerged as an advanced alternative to the other conventional types of drug delivery systems. It is the proven technology for the systemic delivery of active pharmaceutical ingredients [API’s]. The buccal mucosa is the best suited site for local, as well as systemic delivery of drugs due to its large surface area of the film, it allows quick wetting of the film which accelerates disintegration and dissolution in the oral cavity due to which the patients who are mentally retarded, disabled or non-cooperative. The film increases the systemic bioavailability of the drugs, as it bypasses the hepatic first pass metabolism. It is the most suitable for pediatric as well as geriatric patients. The present article provides insight into various issues like benefits of buccal films, manufacturing methods, evaluation parameters and also reviews on the market potentiality of dosage form and its future scenario on global market as an effective pharmaceutical dosage form.

Keywords: Buccal films; Transmucosal drug delivery system; Solvent casting method; Hot melt extrusion technique

Introduction

Among the various routes of drug delivery, transmucosal drug delivery offer distinct advantages over peroral administration for systemic effect. Among various transmucosal routes, buccal mucosa is the most suited for local, as well as systemic delivery of drugs. The unique physiological features make the buccal mucosa as an ideal route for mucoadhesive drug delivery system. These advantages include bypass of hepatic first-pass effect and avoidance of pre systemic elimination within the gastrointestinal tract [1,2]. The use of the oral cavity membranes as sites of drug administration has been the topic of increasing interest for the past decade. It is well known that the absorption of therapeutic compounds from the oral mucosa provides a direct entry of the drug into the systemic circulation, thereby avoiding hepatic first-pass metabolism and gastrointestinal drug degradation, both of which are associated with peroral administration [3-5].

Buccal films are the most recently developed dosage form for buccal administration. They have gained importance as efficacious and novel drug delivery systems and are cost effective with a good patient compliance. As buccal films are implied for attachment to the buccal mucosa, they can be formulated to exhibit local as well as systemic action. Buccal film may be preferred over buccal tablet, in terms of flexibility and comfort. Buccal films have direct access to the systemic circulation through the internal jugular vein, which bypasses the drug from the hepatic first pass metabolism leading to high bioavailability. Further, these dosage forms are self administrable, pharmacoeconomic and have superior patient compliance [6,7]. The film can be defined as a dosage form that employs a water dissolving polymer, which allows the dosage form to quickly hydrate, adhere and dissolve when placed on the tongue, or in the oral cavity, which results in systemic drug delivery [8]. The main property of the buccal film is that due to the large surface area of the film, it allows quick wetting of the film which accelerates absorption of the drug quickly when compared to tablets [9]. Buccal mucosa is rich with blood supply, which acts as a perfect and fast site for absorption of a drug [10]. Mucoadhesive buccal films have also been formulated to show the local action to treat fungal infections in the oral cavity [11-15].

Potential Benefits of Buccal Films

- Buccal films provide large surface area that leads to rapid disintegration and dissolution in the oral cavity due to which it promotes the systemic absorption of Active pharmaceutical ingredient.
- No need of chewing and swallowing.
- No risk of choking.
- Taste masking is possible.
- Accurate dosing compared to liquid dosage forms.
- Self administration is possible.
- Taste masking is possible.
- Prolongs the residence time of the dosage form at the site of absorption, hence increases the bioavailability.
- Ease of administration to pediatric, geriatric patients, and also to the patients who are mentally retarded, disabled or non-cooperative.
- Good mouth feel and good stability.

*Corresponding author: Radha Madhavi B, University College of Pharmaceutical Sciences, Acharya Nagarjuna University, Guntur-522510, Andhra Pradesh, India, Tel: 8374140020; E-mail: madhavi.pharma@gmail.com

Received October 27, 2013; Accepted November 18, 2013; Published November 25, 2013

Citation: Madhavi BR, Murthy VSN, Rani AP, Kumar GD (2013) Buccal Film Drug Delivery System-An Innovative and Emerging Technology. J Mol Pharm Org Process Res 1: 107. doi: 10.4172/2329-9053.1000107

Copyright: © 2013 Madhavi BR, et al. This is an open-access article distributed under the terms of the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original author and source are credited.
- Ease of transportation, storage and consumer handling.
- Requires less excipient.
- More economical.

However, the main limitation of the buccal films is that high doses cannot be incorporated.

**Anatomy and Physiology of Oral Mucosa**

Oro mucosal region is adhesive in nature and acts as a lubricant, allowing the cells to move relative to one another with less friction. Four sites namely buccal cavity, the lingual area, the palate and gingival region have been used for drug administration. The most commonly used site for drug administration of the four sites mentioned above is the buccal route. The anatomic site for drug administration between the cheek and gingival is known as the buccal mucosa [16]. The oral mucosa is composed of three layers. The first layer is the stratified squamous epithelium, underneath this layer lays the basement membrane. The basement membrane overlies the lamina propria and submucosa. The constitution of the epithelium within the different sites of the oral cavity shows dissimilarity. The epithelium in the soft palate, buccal and sublingual area is not keratinized, therefore not containing ceramides and acylceramidem which are associated with providing a barrier function [17]. The mucosa of the buccal and sublingual region have only small amounts of ceramidem and is thus more permeable when compared to other regions of the oral cavity [18].

A layer of mucus is present on the surface of the epithelial layer of cells. This plays a major role in cell-to-cell adhesion, oral lubrication, as well as mucoadhesion of mucoadhesive drug delivery systems. The buccal area has an expanse of smooth and relatively immobile surface, which is suitable for placement of a retentive system [19]. For buccal drug delivery, adhesion to the oral mucosa permits not only the intimacy of contact and the possibility of improved drug absorption, but also the ability to achieve an optimum residence time at the site of administration [20]. These characteristics make the buccal mucosa as a more appropriate site for prolonged systemic delivery of drugs Figures 1 and 2.

**Formulation Aspects of Buccal Films**

**Active pharmaceutical ingredient [APIs]**

Generally 5% w/w to 30% w/w of active pharmaceutical ingredients can be incorporated in the buccal film. 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. This involves the distribution of water insoluble molecules in water miscible polymer, or the solubility of the drug can be enhanced by complexation with various cyclodextrins. Depending upon the desired release profile, APIs can also be added as milled, micronized, or in the form of nano crystals or particles. The use of micronized API will improve the texture of the film and also for better dissolution and uniformity in the buccal film. The buccal films are more advantageous in certain clinical situations where instantaneous release of the medicaments is necessary for prompt relief. Some of such type of clinical situations includes cough, allergy, motion sickness, pain and other local oral manifestations.

**Mucoadhesive polymers**

Polymers with different characteristics have to be considered depending on the type of formulation. Different situations for buccal mucoadhesion are possible depending on the dosage form. Mucoadhesive polymers are classified into two main groups, such as hydrophilic polymers and hydrogels. The hydrophilic polymers most commonly used in buccal dry or partially hydrated dosage forms include polyvinyl alcohol [PVA], sodium carboxy methylcellulose [NaCMC], hydroxyl propyl methyl cellulose [HPMC], hydroxyl ethyl cellulose and hydroxypropyl cellulose [HPC]. Hydrogels include anionic polymers like carbopol, polyacrylates, cationic polymers like chitosan and non ionic polymers like eudragit analogues (Table 1).

**Plasticizers**

Typically, the plasticizers are used in the concentration of 0-20% w/w of dry polymer. Plasticizer is an important ingredient of the film, which improves the flexibility of the film and reduces the bitterness of the film by reducing the glass transition temperature of the film. The selection of plasticizer depends upon the compatibility with the polymer and type of solvent employed in the casting of film. Plasticizers should be carefully selected because improper use of the plasticizers affects the mechanical properties of the film. PEG 400, Propylene glycol, Glycerol, castor oil is most commonly used plasticizers.
Apple, raspberry, cherry, pineapple are few examples of fruit essence oils, while vanilla, cocoa, coffee, chocolate and citrus are fruity flavors. Flavoring agents are very important in case of oral dissolving drug delivery system. 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 natural sweeteners include sucrose, dextrose, fructose, glucose, liquid glucose and maltose. The sweetness of fructose is perceived rapidly in the mouth as compared to sucrose and dextrose. Artificial sweeteners should be used if the dosage form is meant for diabetic patients. Saccharin, cyclamate and aspartame are the first generation of the artificial sweeteners, followed by acesulfame-K, sucralose, alitame and neotame, which come under aspartame are the first generation of the artificial sweeteners, followed by acesulfame-K, sucralose, alitame and neotame, which come under aspartame are the first generation of the artificial sweeteners, followed by acesulfame-K, sucralose, alitame and neotame, which come under the second generation artificial sweeteners.

Flavoring agents

The flavoring agents are very important in case of oral dissolving systems. The acceptance of the oral disintegrating formulation by a patient 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. Peppermint few seconds after the product has been consumed and the after taste of the formulation which lasts for at least about 10 min. Flavors can be used alone or in the combination. 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. To improve the flavor strength and to enhance the mouth-feel effect of the product, cooling agents like monomethyl succinate can be added.

**Table 1:** Various categories of Mucoadhesive polymers.

| S. No. | Type                  | Examples of mucoadhesive polymers                                      |
|-------|-----------------------|------------------------------------------------------------------------|
| 1.    | Non-ionic polymers    | Hydroxy ethyl cellulose, Hydroxy propyl cellulose, Poly vinyl pyrrolidone, Hydroxy propyl methyl cellulose, Polyvinyl alcohol, Polycarboxphil, Polyethylene oxide, Eudragit analogues |
| 2.    | Anionic polymers      | Sodium alginate, Sodium carboxy methyl cellulose, carbopil, polyacrylates |
| 3.    | Cationic polymer      | Chitosan                                                               |

**Penetration enhancers**

Penetration enhancers are also the important excipients to be added in the buccal film formulation. These are 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, bile salts, and alcohols.

**Taste masking agents**

Taste masking agents or taste masking methods should be used in the formulation if the APIs have bitter taste, as the bitter drugs 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, such as complexation technology, salting out technology, etc.

**Sweetening agents**

Sweeteners have become the important excipients for oral disintegrating drug delivery system. Generally, acids which are used in the preparation of food can be utilized as salivary stimulants. 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. 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.

**Saliva stimulating agent**

Generally, acids which are used in the preparation of food can be utilized as salivary stimulants. 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. 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.

**Manufacturing Methods**

The buccal film manufacturing process includes the following techniques.

1. Solvent casting technique
2. Hot melt extrusion technique

**Solvent casting method**

The solvent casting method is widely preferred for the manufacture of buccal films. This process involves the following steps:

- Water soluble ingredients (polymers) are dissolved in water to form homogenous viscous solution.
- API and other excipients are dissolved in suitable solvent to form a clear viscous solution.
- Both the solutions are mixed and the resulting solution is casted as a film and allowed to dry (Figure 3) [46-51].

**Hot melt extrusion technique**

Hot melt extruder is used in this process. This technique involves shaping a polymer into a film via the heating process. A blend of pharmaceutical ingredients including API in dry state is filled in the hopper, conveyed, mixed and subjected to the heating process, and then extruded out in molten state melted by the extruder. The molten mass thus formed is used to cast the film. A critical step is the casting and drying process. This technique has many advantages, such as this process involves lower temperature and shorter residence times of the drug carrier mix, absence of organic solvents, continuous operation.
Evaluation of Buccal Films

The buccal films are evaluated by

Weight and thickness of the film

For evaluation of film weight, three films of every formulation are taken and weighed individually on a digital balance. The average weights are calculated. Similarly, films of each formulation were taken and the film thickness is to be measured using micrometer screw gauge at three different places, and the mean value is to be calculated [54,55].

Surface pH of films

For determination of surface pH, three films of each formulation are allowed to swell for 2 h on the surface of an agar plate. The surface pH is to be measured by using a pH paper placed on the surface of the swollen patch. A mean of three readings is to be recorded [56].

Swelling index

After determination of the original film weight and diameter, the samples are allowed to swell on the surface of agar plate kept in an incubator maintained at 37 ± 0.2°C. Weight of the films (n=3) is determined at different time intervals (1-5 h). The percent swelling, % S is to be calculated using the following equation:

\[
\text{Percent swelling (} \% \text{ S)} = \left[ \frac{X_t - X_o}{X_o} \right] \times 100
\]

Where, \(X_t\) = The weight of the swollen film after time t, \(X_o\) = The initial film weight at zero time [57-59].

Folding endurance

Three films of each formulation of required size are cut by using a sharp blade. Folding endurance is to be determined by repeatedly folding the film at the same place, till it is broken. The number of times, the film could be folded at the same place without breaking gives the value of folding endurance [60].

Moisture content

The prepared films are to be weighed individually and kept in a desiccators containing calcium chloride at room temperature for 24 h. The films are to be weighed again after a specified interval, until they show a constant weight. The percent moisture content is to be calculated by using following formula [61].

\[
\% \text{ Moisture content} = \left[ \frac{\text{Initial weight} - \text{Final weight}}{\text{Final weight}} \right] \times 100
\]

Moisture uptake

Weighed films are kept in desiccators at room temperature for 24 h. These are then taken out and exposed to 84% relative humidity using saturated solution of potassium chloride in desiccators, until a constant weight is achieved. % moisture uptake is calculated as given below.

\[
\% \text{ Moisture uptake} = \left[ \frac{\text{Final weight} - \text{Initial weight}}{\text{Initial weight}} \right] \times 100
\]

In-vitro residence time

The in vitro residence time is determined using IP disintegration apparatus using 900 mL of the disintegration medium maintaining at 37 ± 2°C. The segments of rat intestinal mucosa, each of 3 cm length, are to be glued to the surface of a glass slab, which is then vertically attached to the apparatus. Three mucoadhesive films of each formulation are hydrated on one surface and the hydrated surface is brought into contact with the mucosal membrane. The glass slab is vertically fixed to the apparatus and allowed to move up and down. The film is completely immersed in the buffer solution at the lowest point, and is out at the highest point. The time required for complete erosion or detachment of the film from the mucosal surface is to be recorded [62].

Drug content uniformity

Three film units (each of 20 mm diameter) of each formulation has to be taken in separate 100 mL volumetric flasks, 100 mL of solvent has to be added and continuously stirred for 24 h. The solutions have to be filtered, diluted suitably and analyzed at specified nm in UV spectrophotometer. The average of drug contents of three films has to be taken as final reading.

Surface characterization studies

The scanning electron photomicrograph of the film is taken at 6000 X magnification. The prepared film containing drug is examined for clear and colorless surface. The photomicrographs of the film with the drug and the blank film are compared, and are examined whether the drug is distributed uniformly throughout the film in an amorphous form [63].

In-vitro dissolution studies

Dissolution studies are carried out for all the formulations, employing USP dissolution apparatus at 37 ± 0.5°C, rotated at constant speed of 50 rpm using 900 mL of dissolution medium. A sample of drug film is used in each test. An aliquot of the sample is periodically withdrawn at suitable time interval and the volume is replaced with fresh dissolution medium. The sample is analyzed spectrophotometrically at specified nm [64-66].

Organoleptic evaluation

The prepared buccal film should possess the desired features of sweetness and flavor, which is acceptable to a large mass of population. Controlled human taste panels are used for psychophysical evaluation of the product. In-vitro methods of utilizing taste sensors, specially designed electronic tongue measurement devices can be used for this purpose [67,68].

Packaging

Many options are available for buccal films packing, such as single pouch, blister card with multiple units, multiple-unit dispenser and continuous roller dispenser. Single packaging is mandatory for films. An aluminium pouch is the most commonly used packaging system. There are some patented packaging systems for oral films. Labtec company has patented packaging technology called Rapid card and Amcor Flexibilities Company has patented Core-peel technology.

Ex-vivo Permeation Studies

The modified Franz diffusion cell is used for permeation studies. It
consists of two compartments, one is donor compartment and another is receptor compartment of 18 mL capacity and having 0.785 cm² effective diffusion area. The receptor compartment was covered with water jacket to maintain 37°C.

The porcine or rabbit buccal mucosa can be used for these studies. The buccal mucosa is carefully separated from fat and muscles using scalpel. The buccal epithelium is isolated from the underlying tissue. The buccal epithelium was used within 2 hrs upon removal. The separated buccal epithelium is mounted between two chambers and receptor chamber is filled with PBS pH 7.4. The buccal epithelium is allowed to stabilize for the period of 1 hr. After stabilization of buccal epithelium, the film is kept on buccal epithelium and periodically samples are withdrawn and some fresh volume is replaced. The aliquots are analyzed spectrophotometrically (Figure 5).

Flexibility in Formulation of Buccal Films

There is wide range of flexibility in developing the buccal films. The main benefits of buccal film formulation includes that many of the eligible Active pharmaceutical ingredients (APIs) can be formulated as buccal films and many of the physical properties can be altered, such as material composition, film dissolution rates and API absorption rates. The formulation of buccal films includes film forming polymers and other additives. Formulators can design the films to release the drug immediately in seconds as immediate drug release formulations, or to deliver the dose over a period of hours as controlled release formulations by modifying the combination of film-forming polymers and film thickness. The buccal mucosal area, as it has an expanse of smooth and relatively immobile surface, the area is well suited for placement of a retentive device and appears to be acceptable to the patient. The anatomical features of buccal mucosa make it as an appropriate site for prolonged systemic delivery of drugs. The buccal mucosa permits not only the intimacy of contact and the possibility of improved drug absorption, but also the ability to achieve an optimum residence time at the site of administration. Buccal film formulation is more feasible drug delivery method even for the systemic delivery of orally inefficient drugs, and it as an attractive alternative for the delivery of protein and peptide drug molecules.

Applications

- Multilayer drug film construction is possible, which an emerging area for immediate application. Two or more drugs could be combined into one format and the layers may be formulated to have the same or various dissolution rates.
- The films can be formulated in such a way that the dissolution rates of the drugs can range from minutes to hours.
- Films acts as gastro retentive dosage forms, in which the dissolution of the films could be triggered by the pH or enzyme secretions of gastro intestinal tract, and could be potentially used to treat gastro intestinal disorders.

Conclusion

The present review concludes that the buccal film is the most accurate and acceptable dosage form, which bypasses the hepatic first pass effect and shows good bioavailability. This is the most promising and innovative technology, which is useful to all the age groups, specifically pediatric, geriatric patients and also to the patients with swallowing difficulties. Buccal films can replace the conventional dosage forms, including fast disintegrating tablets due to its advantages over the conventional dosage forms, and they can be manufactured with low cost. This technology provides a good tool for maintenance of drug therapeutic value, as well as pharmacoeconomic value.

References

1. Akbari J, Nokhodchi A, Farid D, Adrangui M, Siah-Shadbad MR, et al. (2004) Development and evaluation of buccoadhesive propranolol hydrochloride table formulations: Effect of fillers. Farmaco 59: 155-161.
2. Remunan-Lopez C, Portofo A, Vila-Jalio JL, Alonso MJ (1998) Design and evaluation of chitosan/ethyl cellulose mucoadhesive bilayered devices for buccal drug delivery. J Control Release 55: 143-152.
3. Rathborne M, Drummond B, Tucker I (1994) Oral cavity as a site for Systemic drug delivery. Adv Drug Deliv Rev 13: 1-22.
4. Hao J, Heng PWS (2003) Buccal delivery systems. Drug Dev Ind Pharm 29: 821-832.
5. Kurosaki Y, Kimura T (2000) Regional variation in oral mucosal drug permeability. Crit Rev Ther Drug Carrier Syst 17: 467-508.
6. Lee JW, Park JH, Robinson JR (2000) Bioadhesive-based dosage forms: the next generation. J Pharm Sci 89: 850-866.
7. Veuliez F, Kalia YN, Jacques J, Dleshusses, Buri P (2001) Factors and strategies for improving buccal absorption of peptides. Eur J Pharm Biopharm 51: 93-109.
8. Sudhakar Y, Kuotsu K, Bandypadhyay AK (2006) BuccalBioadhesive drug delivery- a promising option for orally less effective drug. J Control Release 114: 15-40.
9. Joseph RR, Vincent K L (1987) Lee controlled drug delivery. (2ndEdn), MarcelDekkerinc, New York, USA 42-43.
10. Pfister WR, Ghosh TK (2005) Drug delivery to the oral cavalmucolocytes to market. Marcel Dekker, New York, USA.
11. Bhura N, Sanghi K, Patel U, Parmar B, Patel D (2012) A review on fast dissolving film. IJPRBS 1: 68-89.
12. RathaAdhikani SN, Nayak BS, Nayak AK, Mohanty B (2010) Formulation and evaluation of buccal patches for delivery of atenolol. AAPS Pharm Sci Tech 11: 1043-1044.
13. Donnelly R, McCarron P, Tunney M, Woolfson A (2007) Potential of photodynamic therapy in treatment of fungal infections of the mouth. Design and characterisation of a mucoadhesive patch containing toluidine blue O. J Photochem Photobiol B 86: 59-69.
14. Khanna R, Agarwal SP, Ahuja A (1997) Preparation and evaluation of mucoadhesivebuccal films of clortimazole for oral Candida infections, Indian J Pharm Sci 59: 299-305.
15. Repta M, Produturi S, Stodghill S (2003) Production and characterization of hot melt ectruded films containing clortimazole. Drug Dev Ind Pharm 29: 757-765.
16. Senel S, Ikinci G, Kas S, Yousef-Rad A, Sargon M, et al. (2000) Chitosan films and hydrogels of chlorhexidinegluconate for oral mucosal delivery. Int J Pharm 193: 197-203.
17. Singh S, Jain S, Muthu MS, Twari S, Tilak R (2008) Preparation and evaluation of buccalbioadhesive films containing clortimazole. AAPS Pharm Sci Technol 9: 660-667.
18. Danckwerts MP (2003) Intrarot drug delivery: A comparative review. Ann J Drug Deliv 1: 149-224.
19. Squier CA (1991) The permeability of oral mucosa. Crit Rev Oral Biol Med 2: 13-32
20. Shojaei AH (1998) Buccal mucosa as a route for systemic drug delivery: A review. J Pharm Sci 87: 10-30.
21. Papolin-Vilhohl, Kolhiyalpreetii (2003) Waters Technology-A new approach to smart drug delivery system. Ind J Res Pharm Biotechnol 1.
22. Guo JH (1994) Investigating the surface properties and bioadhesion of buccal patches. J Pharm Pharmacol 46: 647-650.
23. Dixit RP, Puthli SP (2009) Oral strip technology: Overview and future potential. J Control Release 139: 94-107.
24. Rossi Silvia, Sandri Giuseppina, Caramella Carla M (2005) Buccal drug delivery: A challenge already won?. Drug Discov Today Technol 2: 59-65.
25. Patel D, Smith AW, Grist N, Barnett P, Smart JD (1999) An in vitro mucosal model predictive of bioadhesive agents in the oral cavity. J Control Release 61: 175-183.
26. Lee J, Kellaway IW (2002) Peptide washout and permeability from glyceryl mono oleatebuccal delivery systems. Drug Dev Ind Pharm 28: 1155-1162.
27. Smart JD (2004) Lectin-mediated drug delivery int he oral cavity. Adv Drug Deliv Rev 56: 481-489.
28. Smart JD, Nantwi PK, Rogers DJ, Green KL (2002) A quantitative evaluation of radio labelledlectin retention on oral mucosa in vitro and in vivo. Eur J Pharm Biopharm 53: 289-292.
29. Sandri G, Rosai S, Ferrari F, Bonferoni MC, Muzzarelli C, et al. (2004) Assessment of chitosan derivatives as buccal and vaginal penetration enhancers. Eur J Pharm 21: 351-359.
30. Ganem-Quintanar A (1997) Mechanisms of oral permeation enhancement. Int J Pharm 155: 127-142.
31. Hao J, Heng PW (2003) Buccal delivery systems. Drug Dev Ind Pharm 29: 821-832.
32. Bernkop-Schnurrch A (2000) Chitosan and its derivatives: potential excipients for peroral peptide delivery systems. Int J Pharm 194: 1-13.
33. Dodane V, Amin Khan M, Merwin JR (1999) Effect of chitosan on epithelial permeability and structure. Int J Pharm 182: 21-32.
34. Hamman J (2000) Enhancement of paracellular drug trasport across mucosal epithelia by N-trimethyl chitosan chloride. STP PharmaSci 10: 35-38.
35. Tengamnuay P, Sahamethapat A, Sailasuta A, Mitra AK (2000) Chitosan as nasal absorption enhancers of peptides; Comparison between free amine chitosans and soluble salts. Int J Pharm 197: 53-67.
36. Lueben HL (2003) Mucoadhesive polymers in peroral peptide drug delivery. I Influence of mucoadhesive excipients on the porolytic activity of intestinal enzymes. Eur J Pharm Sci 4: 117-128.
37. Bernkop-Schnurrch A (2004) Thiomers: Potential excipients for noninvasive peptide delivery systems. Eur J Pharm Biopharm 58: 253-263.
38. Kulkarni N, Kumar LD, Suresh K (2003) Fast dissolving orally consumable films containing an antitussive and a mucosa coating agent. U.S. Patent 2003/206942.
39. Ai S, Quadir A (2007) High molecular weight povidone polymer-based films for fast dissolving drug delivery applications. Drug Del Technol 7: 36-43.
40. Citruso F, Cunope IE, Minghetti P, Selmin F, Montanari L (2008) Fast dissolving films made of maltodextrins. Eur J Pharm Biopharm 70: 895-900.
41. Nishimura M, Matsuura K, Tsukioka T, Yamashita H, Inagaki N, et al. (2009) In vitro and in vivo characteristics of prochloorperazine oral disintegrating film. Int J Pharm 368: 98-102.
42. Consuelo ID, Falcon F, Guy RH, Jacques Y (2007) Ex vivo evaluation of bioadhesive films for buccal delivery of fentanyl. J Control Release 122: 135-140.
43. Agresti C, Tu Z, Ng C, Yang Y, Liang JF (2008) Specific interactions between dipherhydramine and n-helical polyglycylamide-A new ion-pairing complex for tastmasking and pH-controlled dipherhydramine release. Eur J Pharm Biopharm 70: 226-233.
44. Suzuki H, Onishi H, Takahashi Y, Iwata M, Machida Y (2003) Development of oral acetaminophen chewable tablets with inhibited bitter taste. Int J Pharm 251: 123-132.
45. Sugah N, Yamazaki S, Shiozawa H, Yano K (1998) Taste masking of bitter drug powder without loss of bioavailability by heat treatment of wax-coated micro particles. J Pharm Sci 87: 96-100.
46. Xu J, Bovet LL, Zhao K (2008) Taste masking microspheres for orally disintegrating tablets. Int J Pharm 359: 63-69.
47. Morales JO, McConville JT (2011) Manufacture and characterization of mucoadhesivesub Buccal films. Eur J Pharm Biopharm 77: 187-199.
48. Perumal VA, Tuchman D, Mackraj I, Govender T (2008) Formulation of monolayered films with drug and polymers of opposing solubilities. Int J Pharmaceut 358: 184-191.
49. Yukioka K, Hishiti K, Yasuyuki B, Hiroshi Y, Tetsuya O, et al. (1997) Controlled release of lidocaine hydrochloride from buccal mucosa-adhesive films with solid dispersion. In J Pharmaceut 158: 47-155.
50. Wong CF, Yuen KH, Peh KK (1999) Formulation and evaluation of controlled release Eudragit buccal patches. Int J Pharm 176: 11-22.
51. Khanna Rajesh, Agarwal S P, Ahuja A (1996) Preparation and evaluation of bioerodiblebuccal tablets containing clotrimazole. Int J Pharmaceut 138: 67-73.
52. Morales Javier O, McConville Jason T (2011) Manufacture and characterization of mucoadhesivebuccal films. Eur J Pharm Biopharm 77: 187-199.
53. Dixit RP, Puthli SP (2009) Oral strip technology: Overview and future potential. J Control Release 139: 94-107.
54. Anders R, Merkle H (1989) Evaluation of laminated muco-adhesive patches for buccal drug delivery. Int J Pharmaceut 49: 231-240.
55. Chun M, Kwak B, Choi H (2003) Preparation of buccal patch composed of carbopol, poloxamer and hydroxypropl methylcellulose. Arch Pharm Res 26: 973-978.
56. Repka MA, Gupta K, Prudduttoh S, Munjal M, Stodgill SP (2005) Characterization of cellulose hot-melt extruded films containing lidocaine. Eur J Pharm Biopharm 59: 189-196.
57. Citruso F, Cunope IE, Minghetti P, Selmin F, Montanari L (2008) Fast dissolving films made of maltodextrins. Eur J Pharm Biopharm 70: 895-900.
58. Shidhaye SS, Saindane NS, Sutar S, Kadam V (2008) Mucoadhesiveblayered patches for administration of sumatriptan succinate. AAPS Pharm Sci Tech 9: 909-916.
59. Pernoli L, Ambrogli V, Angelici F, Ricci M, Giovagnoniset al. (2004) Development of mucoadhesive patches for buccal administration of ibuprofen. J Control Release 99: 73-82.
60. Patel VM, Prapajigil BG, Patel MM (2007) Effect of hydrophilic polymers on bucoadhesive Eudragit patches of propranolol hydrochloride using factorial design. AAPS Pharm Sci Tech 8.
61. Satishbhu BK, Srinivasan BP (2008) Preparation and evaluation of bucoadhesive films of atenolol. Ind J Pharm Sci 70: 175-179.
62. Khanna R, Agarwal SP, Ahuja Alka (1996) Preparation and evaluation of bioerodiblebuccal tablets containing clotrimazole. J Pharm Pharmaceutics 138: 67-73.
63. Morales Javier O, McConville Jason T (2011) Manufacture and characterization of muco adhesive buccal films. Eur J Pharm Biopharm 77: 187-199.
64. Dixit RP, Puthli SP (2009) Oral strip technology: Overview and future potential. J Control Release 139: 94-107.
65. Ratha Adhikari Surya N, Nayak Bhabani S, Nayak Amit K, Mohanty Biswaranjan (2010) Formulation and evaluation of buccal delivery of fentanyl. AAPS Pharm Sci Tech 11: 1038-1044.
66. Anders R, Merkle H (1989) Evaluation of laminated muco-adhesive patches for buccal drug delivery. Int J Pharmaceut 49: 231-240.
67. AnandV, Kataria M, Kukkar V, Saharan V, Choudhury PK (2007) The latest trends in the taste assessment of pharmaceuticals. Drug Discov Today 12: 257-265.
68. Murray OJ, Dang W, Bergstrom D (2004) Using an electronic tongue to optimize taste masking in a lyophilized orally disintegrating tablet formulation. Pharm Technol.