The Pharmaceutical and Chemical Journal, 2015, 2(4):16-26

Available online www.tpcj.org

Review Article

ISSN: 2349-7092
CODEN(USA): PCJHBA

Buccal films: Design and *in vitro* characterization

Udichi Kataria, Chandraprakash Jain

Department of Pharmaceutical Sciences, Mohanlal Sukhadia University, Udaipur, Rajasthan, India.

Abstract The oral cavity is an attractive site for the delivery of drugs owing to the ease with which it can be administered. It is now possible to administer drug through mucosal (local effect) and transmucosal (systemic effect) route. In the first case, the aim is to achieve a site-specific release of the drug on the mucosa, whereas the second case involves drug absorption through the mucosal barrier to reach the systemic circulation. The main barrier to this route is limited absorption through buccal route. Various strategies exist and are studied to overcome the obstacles and nowadays use of new materials have increased that, possibly, combine mucoadhesive, enzyme inhibitory and penetration enhancer properties to enhance the desired delivery of drugs. Many designs on innovative drug delivery systems are achieved which, besides improving patient compliance, favor a more intimate contact of the drug with the absorption mucosa. This review throws light on advantages and limitations of buccal drug delivery with the brief anatomical structure of oral mucosa, and explains various available buccal dosage forms, in particularly explaining the development of buccal films with their detailed possible *in vitro* characterization methodology for films.

Keywords buccal, film, mucoadhesive, dosage forms

Introduction

Traditionally, oral dosage forms refer to tablets, capsules and liquid preparations taken orally, swallowed and transiting the gastrointestinal tract (GIT) for post buccal absorption. However, some undesirable physiological properties of the gastrointestinal (GI) tract limit the feasibility of administration of some molecules by this route (i.e., proteins, polypeptides, etc.). The relatively poor absorption, presence of abundant digestive enzymes in the GI lumen and epithelium, post absorption efflux (i.e., by P-glycoprotein etc.), and first-pass metabolism by the hepatic enzymes and subsequent elimination, limit the ability of many drugs to reach therapeutic levels by this route. For the last few decades, the controlled delivery of macromolecules represents one of the greatest challenges in pharmaceutical sciences. Difficulties associated with parenteral delivery and poor oral bioavailability provided the impetus for exploring alternative routes for the delivery of the drugs with first-pass effect. Transmucosal delivery across the tissues of the oral cavity may be an attractive means for non-invasively administering such drugs and is considered as an alternative method of systemic administration for several classes of pharmaceutical agents [1]. The delivery of drugs through the buccal mucosa has attracted much research interest over the past two decades and numerous approaches, both conventional and complex, have been developed in an attempt to deliver a variety of pharmaceutical compounds via the buccal route.

I. Mucoadhesive Drug Delivery Systems:

The different oral mucosal sites differ greatly from one another, in terms of anatomy, permeability to an applied drug and their ability to retain a delivery system for desired length of time [2-3].

Drug delivery via the membranes of the oral cavity can be subdivided as follows:

1) *Sublingual delivery:* is the administration of drug via the sublingual mucosa, (the membrane of the ventral surface of the tongue and the floor of the mouth) to the systemic circulation.
2) *Buccal delivery*: is administration of drug via the buccal mucosa (the lining of the cheek) to the systemic circulation
3) *Local delivery*: For the treatment of condition of the oral cavity, principally aphthous ulcers, fungal conditions and periodontal diseases by application of the bioadhesive system either to the palate, the gingiva or the cheek.

The permeability of buccal mucosa is 4-4000 times greater than that of the skin. In general, the permeability of the oral mucosa decreases in the order: Sublingual > buccal > palatal. Absorption across the sublingual epithelium was likely to be greater than across the buccal epithelium because the former is thinner and is immersed in a larger volume of saliva [1].

II. Buccal drug delivery systems

Buccal drug delivery specifically refers to the delivery of drugs within/ through the buccal mucosa to affect local/ systemic pharmacological actions. Buccal-delivered drugs may be used for treatment of diseases in the oral cavity or for systemic use.

1. Anatomy and physiology of buccal mucosa

Oral mucosa is lined with an epithelium supported by a connective tissue termed lamina propria and separated from the epithelium by a basal membrane [4-6]. The epithelium of oral mucosa is stratified with regional variation in terms of structure and function. Three types of oral mucosa are referred to as masticatory, lining, and specialized mucosa. Small vessels and capillaries that open to the internal jugular vein distribute within the lamina propria, thus avoiding the hepatic first-pass clearance of buccal-delivered drugs. Blood flow in the oral mucosa is generally faster and richer than that in the skin [6].

The non-keratinized buccal mucosa was reported to have approximately a thickness of 500 – 600 mm and surface area of 50.2 cm^2.

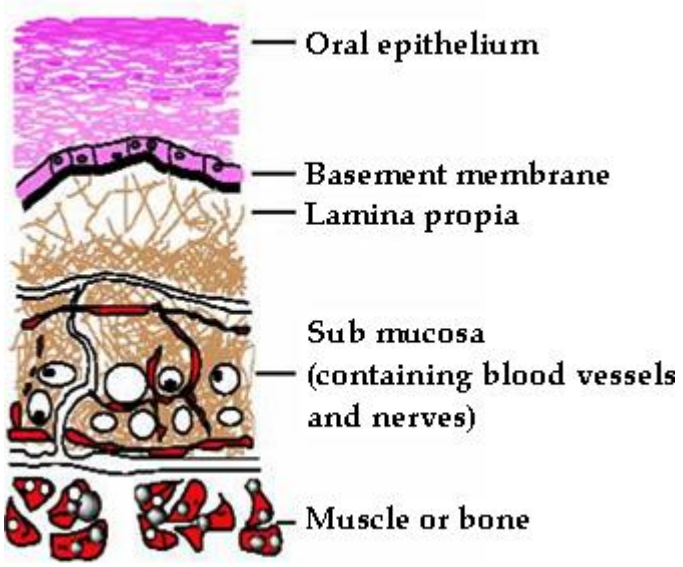

Figure 1: Schematic representation of physiological structure of buccal layer [7].

2. Advantages and Limitations of Buccal Dosage forms

The advantages of delivering the drugs through Buccoadheisve dosage forms are numerous. The most common are that they are easy and painless to administer and well accepted by the patient. Precise dosage form localization is possible and there is ability to terminate delivery when required. Buccal dosage forms are flexible in physical state, shape, size and surface. For patient suffering with nausea or vomiting or in the state of unconsciousness, with an upper gastrointestinal tract disease or surgery which affects oral drug absorption, the oral cavity a useful site for drug delivery for upper symptoms. Maximized absorption rate is achieved due to intimate contact with the absorbing membrane and decreased diffusion barriers. It is an excellent route for the systemic delivery of drug with high first pass metabolism, thereby offering a greater bioavailability. A significant reduction in dose can be achieved, thereby reducing dose dependent side effects. Drugs which are unstable in the acidic environment of the stomach or are destroyed by the enzymatic or alkaline environment of the intestines can be administered by this route. It offers a passive system for drug absorption and does not require any activation. It allows for the local modification of tissue permeability, inhibition of protease activity or reduction in immunogenic response. Thus, selective use of therapeutic agents like peptides, proteins and ionised species can be achieved. The oral mucosa lacks prominent mucus secreting goblets cells and therefore there is no problem of diffusion limited mucus buildup beneath the applied dosage form. The presence of saliva ensures relatively large amount of water for drug dissolution unlike in case of rectal and transdermal routes. It satisfied several features of the controlled release system. It can be made unidirectional to ensure only buccal absorption. The buccal mucosa is highly perfused with blood vessels and offers a greater permeability than the skin. Bioadhesion prolongs the residence time at the site of drug absorption, and thus improves bioavailability and dosing interval and it exhibits rapid onset of action [8-9].

While there are enormous advantages achieved by formulating the buccal dosage form but a formulator needs to keep in mind few limitations [9-12] of these dosage forms and route of delivery before proceeding forward for his/her work. Drugs which irritate the mucosa or have a bitter or unpleasant taste or an obnoxious odour cannot be administered by this route. Drugs which are unstable at buccal pH cannot be administered by this route. Only drugs with a small dose requirement can be administered. Drug contained in the swallowed saliva follows the peroral route and advantages of buccal route are lost. Only those drugs which are absorbed by passive diffusion can be administered by this route. Eating and drinking may become restricted on using buccal dosage forms. There is an ever present possibility of the patient swallowing the buccal tablet. Over hydration may lead to formation of slippery surface and structural integrity of the formulation may get disrupted by this swelling and hydration of bioadhesive polymer.

3. Types of Buccal Drug Delivery Systems

a) Buccal tablets

Tablets have been the most commonly investigated dosage form for buccal drug delivery to date [13]. Buccal tablets are small, flat, and oval, with a diameter of approximately 5–8 mm. Unlike conventional tablets, buccal mucoadhesive tablets allow for drinking and speaking without major discomfort [14].

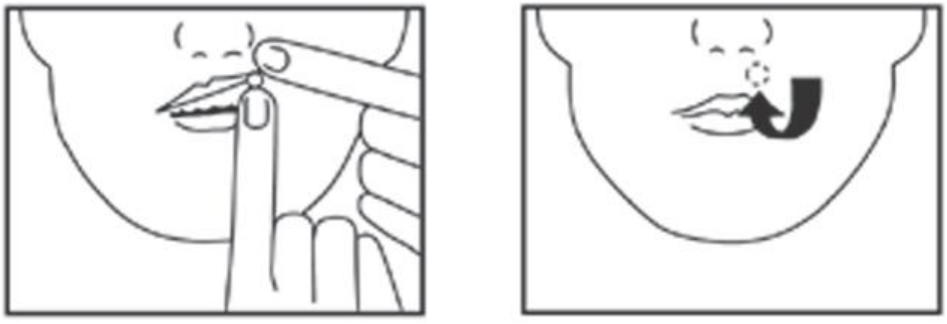

Figure 2: Figure illustration of placing the buccal tablet on mucosa

They soften, adhere to the mucosa, and are retained in position until dissolution and/or release is complete. These tablets can be applied to different sites in the oral cavity, including the palate, the mucosa lining the cheek, as well as between the lip and the gum. Successive tablets can be applied to alternate sides of the mouth. [15-16]

The major drawback of buccal bioadhesive tablets is their lack of physical flexibility, leading to poor patient compliance for long-term and repeated use. If necessary, the drug may be formulated in certain physical states, such as microspheres, prior to direct compression in order to achieve some desirable properties, For instance an enhanced activity and prolonged drug release was shown by Giunchedi *et al*., in 2002 [17]. Some newer approaches use tablets that melt at body temperatures. The matrix of the tablet is solidified while the drug is in solution. After melting, the drug is automatically in solution and available for absorption, thus eliminating dissolution as a rate-limiting step in the absorption of poorly soluble compounds.

b) Buccal patches

Patches are laminates consisting of an impermeable backing layer, a drug-containing reservoir layer from which the drug is released in a controlled manner, and a bioadhesive surface for mucosal attachment. Buccal patch systems are similar to those used in transdermal drug delivery. Two methods used to prepare adhesive patches include solvent casting and direct milling. In the solvent casting method, the intermediate sheet from which patches are punched is prepared by casting the solution of the drug and polymer(s) onto a backing layer sheet, and subsequently allowing the solvent(s) to evaporate. In the direct milling method, formulation constituents are homogeneously mixed and compressed to the desired thickness, and patches of predetermined size and shape are then cut or punched out [18]. An impermeable backing layer may also be applied to control the direction of drug release, prevent drug loss, and minimize deformation and disintegration of the device during the application period.

c) Buccal gels and ointments

Semisolid dosage forms, such as gels and ointments, have the advantage of easy dispersion throughout the oral mucosa. However, drug dosing from semisolid dosage forms may not be as accurate as from tablets, patches, or films. Poor retention of the gels at the site of application has been overcome by using bioadhesive formulations. Certain bioadhesive polymers, e.g., poloxamer 407 Miller & Donovan in 1982 [19], sodium carboxymethylcellulose Wong *et al.*, in 1999 [18], Carbopol, hyaluronic acid [16], undergo a phase change from a liquid to a semisolid. This change enhances the viscosity, which results in sustained and controlled release of drugs. However, these polymers have been investigated for this purpose primarily in ocular drug delivery.

Hydrogels are also a promising dosage form for buccal drug delivery. They are formed from polymers that are hydrated in an aqueous environment and physically entrap drug molecules for subsequent slow release by diffusion or erosion as shown by Cui & Mumper in 2003 [20]. It has been suggested that hydrogels with mucoadhesive polymers might be useful for periodontitis therapy when incorporated in antimicrobial-containing formulations that are easily introduced into the periodontal pocket with a syringe in many research works by Jones *et al*. in 2000 [21, 22]. Mucoadhesion helps ensure formulation retention within the pocket.

d) Buccal Mucoadhesive Films

These are two ply laminates or multilayered thin film, round or oval consistently basically of bioadhesive polymeric layer and impermeable basically layer to provide a unidirectional flow of drug across buccal mucosa.

Design of Buccal Mucoadhesive Film

The following consideration are taken while designing buccal mucoadhesive films: [23]

- Convenient to apply and unobtrusive when in place.
- Not to incorporate a bitter tasting drug.
- It should have smooth surface rather than textured surface.
- Preferably it should achieve unidirectional release of drug.
- It should not irritate buccal mucosa.

The different components of buccal mucoadhesive films are,

Drug: The important drug properties that affect its diffusion through the patch as well as buccal mucosa include molecular weight partition coefficient, dissociation constant of drug. The selection of suitable drug to design buccal drug delivery system is based on pharmacokinetic properties. Following are the properties for candidature to mucoadhesive buccal drug delivery system.

- Conventional dose of drug should be less.
- The drug should not adversely affect the natural microbial flora of oral cavity.
- Drug should not have bad taste and free from irritancy, allerginicity, discolouration or erosion of teeth.

Buccal adhesive polymers: Polymer is a very long molecule consisting of structural units connected by covalent chemical bonds. Bioadhesive formulations use polymers as adhesive component. These formulations are often water soluble and when in dry form attract water from biological surface and this water transfer leads to strong interaction. These polymers also form viscous liquids when mixed with water. Bioadhesive polymers should possess certain physicochemical feature including hydrophilicity, hydrogen bonding and visco-elastic properties.

Plasticizer: These are the materials used to achieve softness and flexibility of thin films of polymer or blend of polymers. The plasticizer which helps in release of drug from polymer base as well as it acts as penetration enhancer. Usually the concentration of polymer will be the 10-50% of the total polymer weight. Ex: glycerol, Propylene glycol, PEG-200, PEG-400.

Permeation enhancer: The substances that facilitate the permeation through buccal mucosa are referred as permeation enhancers. Most of the permeation enhancers were designed for purposes other than absorption enhancement, a systemic search for safe and effective penetration enhancers must be priority in drug delivery. The selection of enhancer and its efficacy depends on physicochemical properties of drug, site of administration, nature of vehicle and other excipients.

The different permeation enhancers available are,

Chelators: EDTA, citric acid, sodium salicylate, methoxy salicylates.

Surfactants: sodium lauryl sulphate, polyoxyethylene, cetylpyridinium chloride.

Bile salts: sodium glycoholate, sodium deoxycholate, sodium taurocholate.

Fatty acids: oleic acid, capric acid, lauric acid, propylene glycol, methyloleate, phosphatidylcholine.

Non-surfactants: unsaturated cyclic ureas.

Inclusion complexes: cyclodextrins.

Thiolated polymers: chitosan-cystiene, poly-homocystiene, polycarbophil-cystiene/GSH, chitosan-4-thioglycholic acid.

Backing membrane: It is also one component which provides unidirectional drug flow to buccal mucosa. It prevents the drug to be dissolved in saliva and hence swallowed avoiding the contact between drug and saliva. The thickness of backing membrane must be around 75-100 µ. The material used for backing membrane must be inert and impermeable to drugs and penetration enhancers. Ex: ethyl cellulose, Cellophane-325, Polyglassine paper.

III. Characterization of Buccal Films:

The various research work done till date shows buccal film offers several advantages including convenient dosing and better patient compliance. However, the greatest challenge is to develop a high quality buccal film which also necessitates constant evaluation and understanding the performance of the dosage form, the critical steps to achieve a successful product development. Despite the intense focus on buccal film based drug delivery system, there are no official standardized methods for its evaluation. Significant efforts have been made to demonstrate and improve the efficacy, potency and safety of buccal film using *in vitro*, *ex vivo* and *in vivo* assessments. However, various research groups have employed different methods and experimental conditions to evaluate the formulation, which has limited the comparison of data between the research groups. The ideal buccal film should exhibit adequate

flexibility, elasticity, softness, resist the breakage due to stress from oral activities, good mucoadhesive strength, endure the movement of buccal cavity etc. All these parameters need to be evaluated during the formulation development stage and required standard protocols. Several techniques can be applied to characterize and evaluate the buccal films and are based on methods ranging from the physical properties through buccoadhesive, *in vitro* permeation to *in vivo* absorption in humans.

Table 1: Types of Buccal dosage forms and their testing requirements [24].

Test Method	Tablets/ Lozenges	Films/Wafers/Patches	Liquids/gel/cream/ointments	Spray
IN VITRO EVALUATION				
Weight Variation	Y	Y	-	-
Uniformity of content	Y	Y	Y	Y
Friability	Y	-	-	-
Resistance to crushing	Y	-	-	-
Tensile strength	Y	Y	-	-
Thickness	Y	Y	-	-
Film Endurance	-	Y	-	-
Viscosity	-	-	Y	-
Droplet size	-	-	-	Y
Disintegration test	Y	Y	-	-
Dissolution test	Y	Y	Y	-
Residence time	Y	Y	Y	-
Mucoadhesion Strength	Y	Y	Y	-
Permeability study	Y	Y	Y	Y
IN VIVO EVALUATION				
Buccal Absorption test	Y	Y	Y	Y
Perfusion study	Y	Y	Y	Y
Residence time	Y	Y	Y	Y
Pharmacokinetic study	Y	Y	Y	Y

1. Evaluation of Physical properties of Buccal films

a) Thickness and weight variations

The thickness of the films is usually measured using well calibrated electronic digital micrometer, screw gauge, vernier caliper or by SEM images. Indeed, the measurement of thickness of the film is essential to ascertain the uniformity of the film thickness as it is directly related to the accuracy of dose in the film [24-26]. Moreover, an optimum thickness is necessary to provide adequate bioadhesion. In general, an ideal buccal film should exhibit a thickness between 50 and 1000 μm. For weight variation, individual patches are weighed and the average weights are calculated. A large variation in weight indicates the inefficiency of the method employed and is likely to have non-uniform drug content.

b) Tensile strength

Ongoing studies use this parameter to measure the mechanical strength of the films during formulation optimization. The sample under test is stretched until it tears and the stress needed represents the tensile strength [27]. It is calculated by dividing the force (N) at which the film breaks with the cross sectional area (m^2) of the film.

c) Elongation at break and percent elongation

Elongation is a kind of deformation. It is a simple change in shape that anything undergoes when under stress, which can be measured using a texture analyzer. In other words, when a sample is put under tensile stress, the sample deforms, becomes longer or gets elongated. Ultimate elongation measures the amount to which a material can be stretched before it breaks. It has been reported that the type and content of polymer, amount of plasticizer and drug have a profound effect on the percent elongation of the film [24, 27].

***Tear resistance and porosity*:** Tear resistance of a film is a function of its resistance to rupture and is calculated by subjecting the film to a constant rate of deformation. The maximum stress or force required to tear the film is recorded in Newton's or pound–force [28]. Porosity denotes a number of pores per unit area of thematerial, the greater the porosity the lesserwill be the strength of thematerial. It also affects the wetting properties of the material and has a profound effect on the permeation of active pharmaceuticals' ingredient through it and from it. Porosity is moreover a surface phenomenon and depends upon the type of drying and drying rate [29].

d) Folding endurance

The flexibility of the buccal patches is an important physical character that can be measured quantitatively in terms of folding endurance and is determined by repeatedly folding the film at 180° angle of the plane at the same plane until it breaks or folded to 300 times without breaking. The number of times the film is folded without breaking is computed as the folding endurance value [30].

e) Water absorption capacity

The absorption of water by the film is essential to provide better bioadhesion of the film with the buccal mucosa, which is dependent on the nature of the polymer matrix. Secondly, it facilitates the drug release from the films, which is mainly by two mechanisms (diffusion and erosion). The formulated films are generally evaluated for its water absorption capacity and erosion of polymer [24, 31].

f) Degree of hydration

The hydration of polymer is essential for the relaxation and interpenetration of polymer chains but, excess hydration generally leads to decreased mucoadhesion and/or retention due to the formation of slippery mucilage [32]. As films uptake water, swelling starts, bonding starts and adhesion occurs. Initially the bond formed will be weak but it increases with hydration. However, finally it reaches a point where over hydration leads to the disentanglement and distortion of polymer molecules at the interface and decreases the adhesion [33]. The swelling properties of films are generally determined by evaluating the percentage hydration.

g) Moisture content

The amount of moisture affects the brittleness and friability of buccal films. Basically, the contents in the product regulate the degree of moisture in a particular film [24]. The amount of moisture present in the film is generally determined using moisture content testing equipment, Karl fisher titration method or by weighing method. The moisture content in an ideal buccal film should be <5%.

h) Surface pH

A film with too much acidic or basic pH affects the area of application and causes damages to oral mucosal membrane leading to patient discomfort. In general, the surface pH of the prepared films was measure after allowing it to swell by keeping it in contact with distilled water for a short period (~2 h) at room temperature. It is likely that the chemical nature of the drug and the excipients influences the pH of the prepared films [34].

i) Drug polymer interaction

Interaction between the drug and polymer is always possible in films due to the intact contact between them. Hence the prepared films are generally assessed for this interaction. Analytical techniques such as FTIR can easily detect

the chemicals and assess the compatibility of drug with the excipients by scanning the mixture using this instrument [24].

j) Residence time:

This method determines the retention time rather than measuring the force of adhesion. This is done by sticking the buccal films to the sides of a container or to a glass plate and a mechanical force is applied by stirring the media or moving the plate or rotating the container itself, until the film detaches or completely eroded [35-37]. However, this method is not widespread.

2. Mucoadhesive studies

Mucoadhesive strength is measured as the work of adhesion or the maximum force required for detaching the applied films from the buccal cavity which in turn provides better insight into the retention of the prepared films at the site of application. However, there is no universally agreed test method to determine mucoadhesion.

***a) Determination of shear stress*:** This measure the force (per unit area) required to slide the film over the mucus layer in a direction parallel to their plane of contact of adhesion [38].

***b) Determination of peel strength*:** This test measures the force required to detach the film from the substrate material attached through the mucoadhesive material by peeling [31].

***c) Determination of tensile strength*:** This test usually measures the force required to detach the test film from the model membrane. The testing conditions and operation variables should be optimized in order to obtain reliable and reproducible results [39].

3. *In vitro* drug release

Release of drug from the prepared films is a prerequisite for permeation through the buccal epithelium. Release studies determine the cumulative drug release from the formulation in a given period of time. No specific *in vitro* method has yet been developed for the drug release studies of buccal films [40]. Standard or modified dissolution apparatus with certain modifications or Franz diffusion cells is used by different workers in investigating the drug release from buccal films. Most of the studies have used paddle over disc method (similar to USP 23 apparatus 5) to assess the release of drug from the prepared films [39].

4. Permeation studies

Assessment of the permeation of drug molecules following application of a buccal patch means establishing the absorption of this compound across the buccal epithelium to the systemic circulation. Physiochemical properties of the drug molecules and the physiological property of the buccal barrier have identical role in the transportation of drug into and through the membrane. The permeability of oral mucosa and the efficacy of penetration enhancers have been investigated in numerous *in vitro* and *in vivo* models. *Ex-vivo* permeation studies, in general, provide the information regarding the pathways and possible mechanisms of drug transport across the buccal epithelium, and are directly related to the physicochemical properties of the drug. Further, this study provides better insight into the absorption kinetics and bioavailability of drug molecules during the preformulation study [24]. This preliminary data can be used for gathering the required information for optimizing a successful buccal delivery system. A typical permeability chamber consists of donor and receiver compartments. The freshly excised buccal mucosa of animal origin is usually used as the barrier membrane in permeation studies since it most closely simulates the *in vivo* situation.

5. *In vivo* studies

In the development and assessment of an oral mucosal delivery system through film there is a need for experimental methods which allow the absorption characteristics (rate, extent and mechanisms) of a drug to be determined. The *in vivo* studies are used generally to determine the residence time, drug release, irritation, absorption, bioavailability, pharmacokinetic parameters etc. Studies are carried out in both animal models and human subjects. The primary

choice among the animal models remains the rabbit, probably due the presence of para-keratinized buccal membrane [40]. Further, one should keep in mind that the buccal mucosa of most of the animal models is different from the human and the data observed in animal models do not necessarily correlate with human studies. Limitation of animal models still remains their unsuitability for the prediction of human oral mucosal drug absorption.

Conclusion

The need for research into drug delivery systems extends beyond ways to administer new pharmaceutical therapies. From both a financial and global healthcare perspective, finding ways to administer injectable medications is costly and sometime leads to serious hazardous effects. Hence inexpensive multiple dose formulations with better bioavailabilities are needed. Improved methods of drug release through transmucosal methods would be of great significance, as by such routes, the pain factor associated with parenteral routes of drug administration can be totally eliminated. Buccal adhesive films offer innumerable advantages in terms of accessibility, administration and withdrawal, retentivity, low enzymatic activity, economy and high patient compliance. Adhesion of buccal adhesive drug delivery devices to mucosal membranes leads to an increased drug concentration gradient at the absorption site and therefore improved bioavailability of systemically delivered drugs. In addition, buccal adhesive films have been used to target local disorders at the mucosal surface (e.g., mouth ulcers) to reduce the overall dosage required and minimize side effects that may be caused by systemic administration of drugs. Researchers are now looking beyond traditional polymer networks to find other innovative drug transport systems. Scientists are finding ways to develop buccal adhesive systems through various approaches to improve the bioavailability of orally less/inefficient drugs by manipulating the formulation strategies like inclusion of pH modifiers, enzyme inhibitors, permeation enhances etc. The future direction of buccal adhesive drug delivery lies in vaccine formulations and delivery of small proteins/peptides. Exciting challenges remain to influence the bioavailability of drugs across the buccal mucosa. Many issues are yet to be resolved before the safe and effective delivery through buccal mucosa. Conclusively, developing a buccal dosage form with the optimum pharmacokinetics is a promising area for continued research as it is enormously important and intellectually challenging. Advances in experimental and computational methodologies will be helpful in shortening the processing time from formulation design to clinical use.

References

1. Johnston TP. Anatomy and Physiology of the Oral Mucosa. In: Rathbone MJ Senel S, Pather I. eds. Oral Mucosal Drug Delivery and Therapy, New York: CRS Springer, 2015; 1-12.
2. Harris D, Robinson JR. Drug delivery via the membrane of the oral cavity. Indian J Pharma Sci. 1992; 81:1-10.
3. Chidambaram N, Srivatsava AK. Buccal drug delivery system. Drug Development and Industrial Pharmacy. 1995; 21: 1009-1036
4. Michael JR, Jonathan H. Absorption of drug from the human oral cavity. Int J Pharmaceutics. 1991; 74: 9-24.
5. Lee JW, Park JH, Robinson JR. Bioadhesive-based dosage forms: The next generation. J Pharm Sci. 2000; 89:850-866.
6. Veuillez F, Kalia YN, Jacques Y, Jacques D, Buri P. Factors and strategies for improving buccal absorption of peptides. European Journal of Pharmaceutics and Biopharmaceutics. 2001; 51: 93-109.
7. Smart JD. Buccal drug delivery. Expert Opin Drug Deliv. 2005; 2: 507-517.
8. Gupta A, Garg S, Khar K. Mucoadhesive Buccal drug delivery system. Indian Drug. 1992; 29:586-593.
9. Singh BN, Kim KH. Drug Delivery: Oral Route. In: Swarbrick J. ed. Encyclopedia of Pharmaceutical Technology Vol.1, 3rd edn. New York: Informa Healthcare Inc, 2007, 1254.
10. Gandhi RB, Robinson JR. Bioadhesin in drug delivery. Indian J Pharm Sci. 1988; 50: 145-152.
11. Longer MA, Robinson JR. Fundamental aspects of Bioadhesion. International Journal of pharmaceutics. 1986; 7:114.
12. Lee JW, Park JH, Robinson JR. Bioadhesive-based dosage forms: the next generation. J Pharm Sci. 2000; 89:850-866.

13. Salamat M, Nazila, Montakarn C, Thomas PJ. The use of mucoadhesive polymers in buccal drug delivery. Advanced Drug Delivery Reviews. 2005; 57:1666-1691.
14. Shojaei AH. Buccal mucosa as a route for systemic drug delivery: a review. J Pharm Sci. 1998; 1:15-30.
15. Madhav NV, Ashok KS, Pragati S, Kuldeep S. Orotransmucosal drug delivery systems: a review. Journal of Controlled Release. 2009; 140:2-11.
16. Gurny R, Meyer JM, Peppas NA. Bioadhesive Intraoral Release Systems: Design, Testing and Analysis. Biomaterials. 1984; 5:336-340.
17. Giunchedi P, Juliano C, Gavini E, Cossu M, Sorrenti M. Formulation and *in vivo* evaluation of chlorhexidine buccal tablets prepared using drug-loaded chitosan microspheres. European Journal of Pharmaceutics and Biopharmaceutics. 2002; 53:233-239.
18. Wong CF, Yuen KH, Peh KK. Formulation and evaluation of controlled release Eudragit buccal patches. International Journal of Pharmaceutics. 1999; 178:11-22.
19. Miller SC, Donovan MD. Effect of poloxamer 407 gel on the miotic activity of pilocarpine nitrate on rabbits. Int J Pharm. 1982; 12:147-152.
20. Cui ZR, Mumper RJ. Buccal transmucosal delivery of calcitonin in rabbits using thin-film composites. Pharm Res. 2002; 19:1901–1906
21. Jones DS, Woolfson AD, Brown AF, Coulter WA, McClelland C, Irwin CR. Design, characterization and preliminary clinical evaluation of a novel mucoadhesive topical formulation containing tetracycline for the treatment of periodontal disease. J Control Release. 2000; 67:357–368.
22. Ikinci G, Senel S, Akincibay H, Kaş S, Erciş S, Wilson CG, Hincal AA. Effect of chitosan on a periodontal pathogen Porphyromonas gingivalis. Int J Pharm. 2002; 235:121-7.
23. Mitra AK, Alur HH, Johnston TP. Peptides and Proteins: Buccal Absorption In: James S, James CB eds. Encyclopedia of pharmaceutical technology 2nd edn. New York: Marcel Dekker Inc, 2002; 2664
24. Nair AB, Rachna K, Sree H, Attimarad M, Bandar EAD, Ibrahim AA. *In vitro* techniques to evaluate buccal films. Journal of Controlled Release. 2013; 166:10-21.
25. Cilurzo F, Cupone IE, Minghetti P, Selmin F, Montanari L. Fast dissolving films made of maltodextrins. Eur J Pharm Biopharm. 2008; 70:895–900.
26. Cao N, Yang X, Fu Y. Effects of various plasticizers on mechanical and water vapor barrier properties of gelatin films. Food Hydrocoll. 2009; 23:729–735.
27. Felton L, Donnell PO, McGinity J. Mechanical properties of polymeric films prepared from aqueous dispersions. In: McGinity J, Felton L. eds. Aqueous Polymeric Coatings for Pharmaceutical Dosage Forms 3rdedn. NewYork,:Informa Healthcare, 2008; 105–128.
28. Dixit RP, Puthli SP. Oral strip technology: overview and future potential. J Control Release. 2009; 139:94–107.
29. Narisava S, Yoshino H, Hirakawa Y, Noda K. Porosity controlled ethyl cellulose film coating 1. Formation of porous ethyl cellulose film in the casting process and the factors effecting film density. Chem Pharm Bull. 1993; 41:329–334.
30. Nafee NA, Boraie NA, Ismail FA, Mortada LM. Design and characterization of mucoadhesive buccal patches containing cetylpyridinium chloride. Acta Pharm. 2003; 53:199–212.
31. Guo JH. Bioadhesive polymer buccal patches for buprenorphine controlled delivery: formulation, *in vitro* adhesion and release properties. Drug Dev Ind Pharm. 1994; 20:2809–2821
32. Mortazavi SA, Smart J. An investigation into the role of water movement and mucus gel dehydration in Mucoadhesion. J Control Release. 1993; 25:197–203.
33. Bottenberg P, Cleymaet R, Muynck C, Remon JP, Coomans D, Michotte Y, Slop D. Development and testing of bioadhesive, fluoride-containing slow release tablets for oral use. J Pharm Pharmacol. 1991; 43:457–464.
34. Anders R, Merkle HP. Evaluation of laminated muco-adhesive patches for buccal drug delivery. Int J Pharm. 1989; 49:231–240.

35. Khanna R, Agarwal SP, Ahuja A. Preparation and evaluation of mucoadhesive buccal films of clotrimazole for oral candida infections. Indian J Pharm Sci. 1997; 59:299–305.
36. Jay S, Fountain W, Cui Z, Mumper RJ. Transmucosal delivery of testosterone in rabbits using novel bi-layer mucoadhesive wax-film composite disks. J Pharm Sci. 2002; 91:2016–2025.
37. Chary RB, Vani G, Rao YM. *In vitro* and *in vivo* adhesion testing of mucoadhesive drug delivery systems. Drug Dev Ind Pharm. 1999; 25:685–690.
38. Vasir JK, Tambwekar K, Garg S. Bioadhesive microspheres as a controlled drug delivery system. Int J Pharm. 2003; 255:13–32.
39. Patel VM, Prajapati BG, Patel MM. Effect of hydrophilic polymers on buccoadhesive eudragit patches of propranolol hydrochloride using factorial design. AAPS Pharm Sci Technol. 2007; 8:E119–E126.
40. Khar RK, Ahuja A, Ali J. Mucoadhesive Drug delivery. In: Jain NK eds. Controlled and Novel Drug Delivery. New Delhi: CBS Publishers and Distributors, 2009; 365-370.