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A review on bioadhesive buccal drug delivery systems: current status of formulation and evaluation methods

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ABSTRACT

Owing to the ease of the administration, the oral cavity is an attractive site for the delivery of drugs. Through this route it is possible to realize mucosal (local effect) and transmucosal (systemic effect) drug administration. 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 obstacles that drugs meet when administered via the buccal route derive from the limited absorption area and the barrier properties of the mucosa. The effective physiological removal mechanisms of the oral cavity that take the formulation away from the absorption site are the other obstacles that have to be considered. The strategies studied to overcome such obstacles include the employment of new materials that, possibly, combine mucoadhesive, enzyme inhibitory and penetration enhancer properties and the design of innovative drug delivery systems which, besides improving patient compliance, favor a more intimate contact of the drug with the absorption mucosa. This presents a brief description of advantages and limitations of buccal drug delivery and the anatomical structure of oral mucosa, mechanisms of drug permeation followed by current formulation design in line with developments in buccal delivery systems and methodology in evaluating buccal formulations.

Keywords: Buccal delivery, Mucoadhesive polymers, Permeation enhancers, Formulation design.

INTRODUCTION

Among the various routes of drug delivery, the oral route is perhaps the one mostly preferred by patients and clinicians. Based on our current understandings of biochemical and physiological aspects of absorption and metabolism, many drugs, cannot be delivered effectively through the conventional oral route, because after administration are subjected to pre-systemic clearance extensively in liver, which often leads to a lack of significant correlation between membrane permeability, absorption, and bioavailability (1). Difficulties associated with parenteral delivery and poor oral availability promoted the impetus for exploring alternative routes for the delivery of such drugs. Consequently, other absorptive mucosae are considered as potential sites for drug administration. Transmucosal routes of drug delivery (i.e., the mucosal linings of the nasal, rectal, vaginal, ocular, and oral cavities) offer distinct advantages over peroral administration for systemic effect. Among the various transmucosal routes, buccal mucosa has an excellent accessibility, an expanse of smooth muscle and relatively immobile mucosa, hence suitable for administration of controlled release dosage forms. Additionally, buccal drug delivery has a high patient acceptability compared to other non-oral transmucosal routes of drug administration. Direct access to the systemic circulation through the internal jugular vein avoids acid hydrolysis in the gastrointestinal (GI) tract and bypasses drugs from the hepatic first pass metabolism leading to high bioavailability. Moreover, rapid cellular recovery of the buccal mucosa is other advantage of this route (2). Disadvantages of drug delivery by this route are the low permeability of the buccal membrane (3), specifically when compared to the sublingual membrane (4), and a smaller surface area. The total surface area of the membranes of the oral cavity available for drug absorption is 170 cm^2 (5), of which ~50 cm^2 represents non-keratinized tissues, including the buccal membrane (6). Continuous secretion of saliva (0.5–2 l/day) leads to subsequent dilution of the drug. Swallowing of saliva can also potentially lead to the loss of dissolved or suspended drug and, ultimately, the involuntary removal of the

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dosage form. There are some problems associated with buccal drug delivery of which hazard of choking by involuntarily swallowing the delivery system is a concern. Additionally of such a dosage form is inconvenient when the patient is eating or drinking. Nevertheless, the advantages and recent progress in delivering a variety of compounds, render the disadvantages of this route less significant and opts buccal adhesive drug delivery systems as promising option for continued research (7).

Oral cavity: anatomic and physiologic features

Light microscopy reveals several distinct patterns of maturation in the epithelium of the human oral mucosa based on various regions of the oral cavity. Three distinctive layers of the oral mucosa are the epithelium, basement membrane, and connective tissues. The oral cavity is lined with the epithelium, below which lies the supporting basement membrane which in turn is supported by connective tissues. Figure 1 represents the cross sectional area of the buccal mucosa illustrating different cell layers (8). The epithelium, as a protective layer for the tissues beneath, is divided into (a) non-keratinized surface in the mucosal lining of the soft palate, the ventral surface of the tongue, the floor of the mouth, alveolar mucosa, vestibule, lips, and cheeks, and (b) keratinized epithelium which is found in the hard palate and non-flexible regions of the oral cavity. The epithelial cells, originating from the basal cells, mature, change their shapes, and are increased in size while moving towards the surface. The buccal epithelium is classified as a non-keratinized tissue. The thickness of buccal epithelium in humans, dogs and rabbits has been determined to be approximately 500800-µ (9). The term 'buccal', even if is used wrongly to indicate the mucosa of the total oral cavity, refers to the lining of the cheek and the upper and lower lips, which represent one-third of the total oral mucosal surface. Tissue homeostasis requires differentiation followed by migration and desquamation of the superficial cells. The prickle cells (intermediate layer) accumulate lipids and cytokeratins with low molecular weight that do not aggregate to form filaments. The buccal epithelium lack tight junctions common to intestinal and nasal mucosae and is endowed with gap junctions, desmosomes and hemidesmosomes (10), which are loose intercellular links.

Permeability barrier of the oral mucosa

The permeability barrier property of the oral mucosa is predominantly due to intercellular materials derived from the so-called 'membrane coating granules' (MCGs). An intracellular lipid portion is packaged in the membrane coated granules, such MCGs migrate to the apical surface of the cell where their membranes fuse with the cell membranes, and the lipid content is extruded in the extracellular space. Cultured oral epithelium devoid of MCGs has been shown to be permeable to compounds that do not typically penetrate oral epithelium (11). In addition, permeation studies conducted by using tracers of different sizes have demonstrated that these tracer molecules did not penetrate. When the same tracer molecules were introduced sub-epithelially, they penetrated through the intercellular spaces. This limitation of penetration coincides with the level where MCGs are observed. The same pattern is observed in both keratinized and non-keratinized epithelia (4), which indicates keratinization of the epithelia, is not expected to play a major role as a barrier to permeation (12). Another barrier to the drug permeability across buccal epithelium is enzymatic degradation. Saliva contain moderate levels of esterases, carbohydrases, and phosphatases but not proteases (13). However, several proteolytic enzymes have been found in the buccal epithelium (14). It has been reported (15) that endopeptidases and carboxypeptidases are not present on the surface of porcine buccal mucosa, and aminopeptidase is the major enzymatic barrier to the buccal delivery of the peptide drugs. Aminopeptidase N and A (plasma membrane-bound peptidases) and aminopeptidase B (cytosolic enzyme) have been found in the buccal tissue (16). These are some of the permeability barriers for the drug penetration into systemic circulation.

Penetration Enhancers

In order to design penetration enhancers, with improved efficacy and reduced toxicity profile it is required to understand the relationship between enhancer structure and the effect induced in the membrane and the mechanism of action. However, selection of enhancer and its efficacy depends on the physicochemical properties of the drug, nature of the vehicle and other excipients which are drug specific and should be safe and non-toxic, pharmacologically and chemically inert, non-irritant, and non-allergenic. One of the major disadvantages associated with buccal drug delivery is the low flux which results in low drug bioavailability (17). Hence, various compounds have been investigated for their use as buccal penetration enhancers in order to increase the flux of drugs through the mucosa classified in table 1.

Mechanism of permeation enhancers

(i) Changing mucus rheology

Mucus forms viscoelastic layer of varying thickness that affects drug absorption. Further, saliva covering the mucus layers also hinders the absorption. Some permeation enhancers› act by reducing the viscosity of the mucus and saliva overcomes this barrier.

(ii) Increase in the fluidity of lipid bilayer membrane

The most accepted mechanism for drug absorption

Table 1: Penetration enhancers and their mechanism of action.

Category	Examples	Mechanism of action
Surfactants	Anionic: Sodium lauryl sulfate Cationic: Cetyl pyridinium chloride Nonionic: Poloxamer, Brij, Span, Myrj, Tween	Perturbation of intercellular Lipids and protein domain integrity
Bile salts	Sodium glycol deoxycholate, Sodium glycocholate, Sodium tauro deoxycholate, Sodium tauro cholate	Perturbation of intercellular Lipids and protein domain integrity
Fatty acids	Oleic acid, Caprylic acid, Lauric acid, Lyso phosphatidyl choline, Phosphatidyl choline	Increase fluidity of phospholipid domains
Cyclodextrins	α, β, γ, Cyclodextrin, methylated β –cyclodextrins	Inclusion of membrane Compounds
Chelators	EDTA, Citric acid, Sodium salicylate, Methoxy salicylates	Interfere with Ca^{+}
Positively charged Polymers	Chitosan, Trimethyl chitosan	Ionic interaction with negative charge on the mucosal surface
Cationic Compounds	Poly-L-arginine, L-lysine	Ionic interaction with negative charge on the mucosal surface

through buccal mucosa is intracellular route. Some enhancers disturb the intracellular lipid packing by interaction with either lipid or protein components.

(iii) Action on the components at tight junctions
Some permeation enhancers act on desmosomes by disturbing and or interacting with the components of the desmosomes, a major component at the tight junctions.

(iv) Overcoming the enzymatic barrier
The buccal permeation enhancers act by inhibiting the various peptidases and proteases present within buccal mucosa, thereby overcoming the enzymatic barrier. In addition, changes in membrane fluidity also alter the enzymatic activity indirectly.

(v) Increase in the thermodynamic activity of drugs
Some permeation enhancers alter the partition coefficient of the drug there by increase the solubility. This leads to increased thermodynamic activity resulting better drug absorption.

Enzyme inhibitors
Co-administration of a drug with enzyme inhibitors is another strategy to improve the buccal absorption of drugs, particularly peptides. Enzyme inhibitors, such as aprotinin, bestatin, puromycin and some bile salts stabilize protein drugs by different mechanisms, including change in the activities of enzymes, altering the conformation of the peptides or proteins and/or rendering the drug less accessible to enzymatic degradation (18). In addition, some mucoadhesive polymers, such as polyacrylic acid and chitosan derivatives, have been proved to inhibit enzyme activity even if are not in the buccal mucosa (19, 20). In particular, polyacrylic acid (carbomer) is able to bind the essential enzyme cofactors such as calcium and zinc and by change in conformational cause enzyme autolysis and loss of enzyme activity. Moreover, the chemical modification of chitosan (cationic polymer) with EDTA produces polymer conjugate chitosan–EDTA that is a very potent inhibitor of metallopeptidases, such as carboxypeptidase (20). In recent years, the polymer derivatization with thiol groups on poly (acrylates) or chitosans has been demonstrated to improve polymer enzyme inhibitory properties (21).

Solubility Modifiers
In spite of the increase in bioavailability of hepatically metabolized drugs by buccal delivery, poor solubility of drug in saliva may impede drug release from its device for uptake by buccal mucosa. Solubilization of poorly water-soluble drugs by complexation with cyclodextrins and delivering via the buccal mucosa is advantageous in increasing drug absorption and bioavailability. It has been reported that the release of felodipine from buccal tablets comprising hydroxypropyl-β-cyclodextrin-felodipine complex and hydroxylpropyl methyl cellulose and is a complete and sustained release of the drug associated with an enhanced buccal permeation. These results could be attributed to the ability of hydroxypropyl-β-cyclodextrin to form a complex with felodipine, resulting in an increase in apparent drug solubility, dissolution rate and permeability (22). The results demonstrate that these

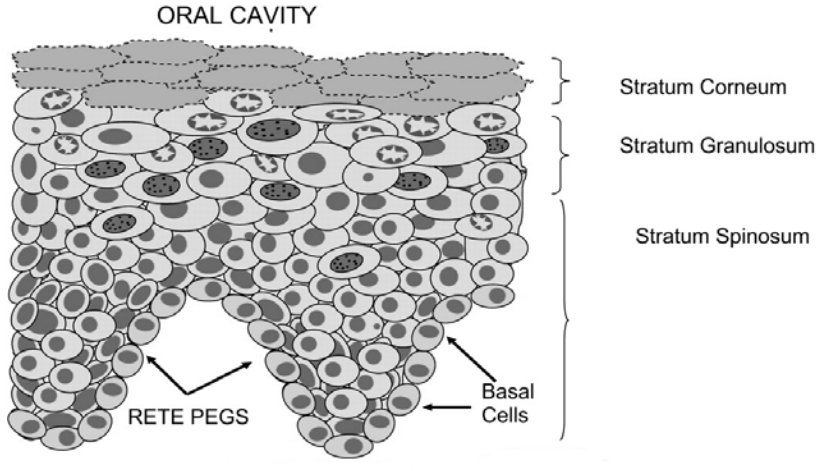

Figure 1. Cross sectional area of the buccal mucosa.

polymeric formulations with inclusion complexes afford high utility as a transmucosal drug delivery system for a complete and sustained drug release with enhanced permeability. Imidazole antimycotics (e.g., miconazole, clotrimazole) are extensively used in the local treatment of fungal infections in the oral cavity. Due to their low water solubilities and high lipophilicities, they were released extremely slowly from the lipophilic chewing gum bases. Formulating hydroxypropyl-β-cyclodextrin inclusion complex of these antimycotics into chewing gums was found to increase the drug release from the chewing gums (23).

Drug absorption pathways

The drug transport mechanism through the buccal mucosa involves two major routes: transcellular (intracellular) and paracellular (intercellular) pathways (Fig.2). Studies with microscopically visible tracers such as small proteins and dextrans suggest that the major pathway across stratified epithelium of large molecules is via the intercellular spaces where there is a barrier to penetration as a result of modifications of the intercellular substance in the superficial layers. It is generally recognized that the lipid matrix of the extracellular space plays an important role in the barrier function of the paracellular pathway, especially when the compounds such as peptides are hydrophilic and have a high molecular weight (10). The absorption potential of the buccal mucosa is influenced by the lipid solubility and molecular weight of the diffusant. Absorption of some drugs via the buccal mucosa is found to increase when carrier pH is lowered and decreased by an increase in pH (24). In general, for peptide drugs, permeation across the buccal epithelium is thought to be through paracellular route by passive diffusion. Recently, it was reported that the drugs having a monocarboxylic acid residue could be delivered into systemic circulation from the oral mucosa via its carrier (25). The permeability of oral mucosa and the efficacy of penetration enhancers have been investigated in numerous in vitro and in vivo models. Various kinds of diffusion cells, including continuous flow perfusion chambers, Ussing chambers, Franz diffusion cells and Grass–Sweetana, have been used to determine the permeability of oral mucosa (26). Cultured epithelial cell lines have also been developed as an in vitro model to study drug the transport and metabolism at biological barriers as well as to elucidate the possible mechanisms of action of penetration enhancers (27). Recently, TR146 cell culture model was suggested as a valuable in vitro model of human buccal mucosa for permeability and metabolism studies with enzymatically labile drugs, such as leu-enkefalin, intended for buccal drug delivery.

Formulation design for buccal delivery

For mucosal and transmucosal administration, conventional dosage forms are not able to assure therapeutic drug levels in the mucosa and circulation because of the physiological removal of the oral cavity (washing effect of saliva and mechanical stress), which take the formulation away from the mucosa, resulting in a very short exposure time and unpredictable distribution of the drug on the site of action/absorption. To obtain the therapeutic action, it is therefore necessary to prolong and improve the contact between the active substance and the mucosa. To fulfill the therapeutic requirements, formulations for buccal administration should contain: mucoadhesive agents, to maintain an intimate and prolonged contact of the formulation with the absorption site; penetration enhancers,

Table 2: Mucoadhesive polymers in buccal delivery systems.

Criteria	Category	Examples
Source	Semi-natural/natural	Agarose, chitosan, gelatin Hyaluronic acid Various gums (guar, hakea, xanthan, gellan, carragenan, pectin, and sodium alginate)
	Synthetic	Cellulose derivatives [CMC, thiolated CMC, sodium CMC, HEC, HPC, HPMC, MC] Poly(acrylic acid)-based polymers [CP, PC, PAA, copolymer of acrylic acid and PEG] Others PVA, PVP, thiolated polymers
Aqueous solubility	Water-soluble	CP, HEC, HPC (water<· ٣٨C), HPMC (cold water), PAA, sodium CMC, sodium alginate
	Water-insoluble	Chitosan (soluble in dilute aqueous acids), EC, PC
Charge	Cationic	Aminodextran, chitosan, dimethylaminoethyl (DEAE)-dextran, trimethylated chitosan
	Anionic	Chitosan-EDTA, CP, CMC, pectin, PAA, PC, sodium alginate, sodium CMC, xanthan gum
	Non-ionic	Hydroxyethyl starch, HPC, poly(ethylene oxide), PVA, PVP, scleroglucan
Potential bioadhesive forces	Covalent	Cyanoacrylate
	Hydrogen bond	Acrylates [hydroxylated methacrylate, poly(methacrylic acid)], CP, PC, PVA
	Electrostatic interaction	Chitosan

to improve drug permeation across mucosa (transmucosal delivery) or into deepest layers of the epithelium (mucosal delivery), enzyme inhibitors, to protect the drug from the degradation by means of mucosal enzymes and solubility modifiers to enhance solubility of poorly soluble drugs.

Buccoadhesive polymers used in the oral cavity

The major advantages of bioadhesive systems are increase in the residence time of the drug containing device in the oral cavity and localization of drugs in a particular region. The bioadhesion process has been explained by electronic, adsorption, wetting, diffusion, and fracture theories (28). Generally, some of the necessary structural characteristics for bioadhesive polymers include strong hydrogen bonding groups, strong anionic or cationic charges, high molecular weight, chain flexibility, and surface energy properties which favor spreading on mucus layer (29). In general, adhesive polymers sources should be natural or synthetic, water-soluble and water insoluble, charged and uncharged polymers. Examples of the recent bioadhesive buccal polymers are listed in table 2. The polymers classified in table 2 are represented as nonspecific bioadhesives and are considered as first-generation bioadhesives. The duration of bioadhesion is largely determined by the fast turnover of mucus layer (30). Factors such as saliva secretion, food intake, local pH, and compositions of delivery systems also strongly affect bioadhesion.

Novel Second-generation mucoadhesive polymers

Lectins, bacterial adhesions and thiolated polymers are classified and considered as second-generation mucoadhesive polymers.

Lectins

Lectins are naturally occurring proteins that play a fundamental role in biological recognition phenomena involving cells and proteins. These are proteins/glycoproteins that possess high specific affinity for carbohydrates. After initial mucosal cell binding, lectins can either remain on the cell surface or in the case of receptor-mediated adhesion possibly become internalized via endocytosis (31). Although lectins offer significant advantages in relation to site targeting, many are toxic or immunogenic, and the effects of repeated lectin exposure are largely unknown. It is also feasible that lectin induced antibodies could block subsequent adhesive interactions between mucosal epithelial cell surfaces and lectin delivery vehicles. Moreover, such antibodies may also render individuals

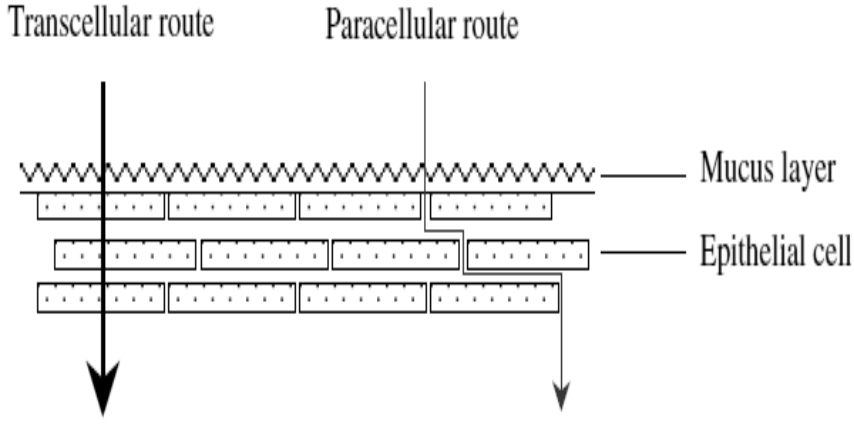

Figure 2. Schematic representation of penetration routes in buccal drug delivery.

susceptible to systemic anaphylaxis on subsequent exposure. Recently, lectin-based second-generation bioadhesives have attracted considerable interests for oral drug delivery (32). It has been found that lectin binding on human buccal cells occurred within 20 second and was not detached by saliva flushing (33).

Bacterial adhesions

The adhesive properties of bacterial cells have been investigated recently. The ability of bacteria to adhere to a specific target is rooted from particular cell-surface components or appendages, known as fimbriae, that facilitate adhesion to other cells or inanimate surfaces. These are extracellular, long threadlike protein polymers of bacteria that play a major role in many diseases. Bacterial fimbriae adhere to the binding moiety of the specific receptors. A significant correlation has been found between the presence of fimbriae on the surface of bacteria and their pathogenicities (34). The attractiveness of this approach lies in the potential increase in the residence time of the drug on the mucus and its receptor-specific interaction, similar to those of the plant lectins.

Escherichia coli (*E.coli*) has been reported to specifically adhere to the lymphoid follicle epithelium of the ileal Peyer's patch in rabbits (35). Additionally, different staphylococci possess the ability to adhere to the surface of mucus gel layers and not to the mucus-free surface (36). Thus, it appears that drug delivery based on bacterial adhesion could be an efficient method to improve the delivery of particular drugs or carrier systems. Antigen K99-fimbriae, an attachment protein derived from *E. coli*, has been covalently attached to polyacrylic acid networks (37). The formulated polymer–fimbriae platform exhibited a significant increase in adhesion in vitro in comparison to the control (unmodified polymer These).

Thiolated Polymers

Thiolated polymers (thiomers) are of the second-generation mucoadhesive derived from hydrophilic polymers such as polyacrylates, chitosan or deacetylated gellan gum (38). The presence of thiol groups allows the formation of covalent bonds with cysteine- rich sub-domains of the mucus gel layer, leading to increase in the residence time and improvement of the bioavailability (39).Thiomers mimic the natural mechanism of secreted mucus glycoproteins that are also covalently anchored in the mucus layer by the formation of disulphide bonds (40). While first-generation mucoadhesive polymers are involved in non-covalent secondary interactions, the covalent bonding mechanisms involved in second-generation systems lead to interactions that are less susceptible to changes in ionic strength and/or the pH (41). Moreover the presence of disulphide bonds may significantly alter the mechanism of drug release from the delivery system due to increase in rigidity and cross-linking. In such platforms a diffusion-controlled drug release mechanism is more typical, whereas in the first-generation polymers anomalous transport of API into bulk solution is more common (42).

Investigations on the buccal drug delivery systems

Several buccal drug delivery devices have been developed at the laboratory scale by many researchers either for local or systemic actions. They are broadly classified into (i) Solid buccal adhesive dosage forms (ii) Semi-solid buccal adhesive dosage forms (iii) Liquid buccal adhesive dosage forms. Buccal mucoadhesive dosage forms can also be categorized into three types on the basis of geometry. Type I is a single layer device with multidirectional drug release. This type of dosage form suffers from significant drug loss due to swallowing. In the type II devices, an impermeable backing layer is superimposed on top of the drug-loaded bioadhesive layer, creating a double-layered device, preventing

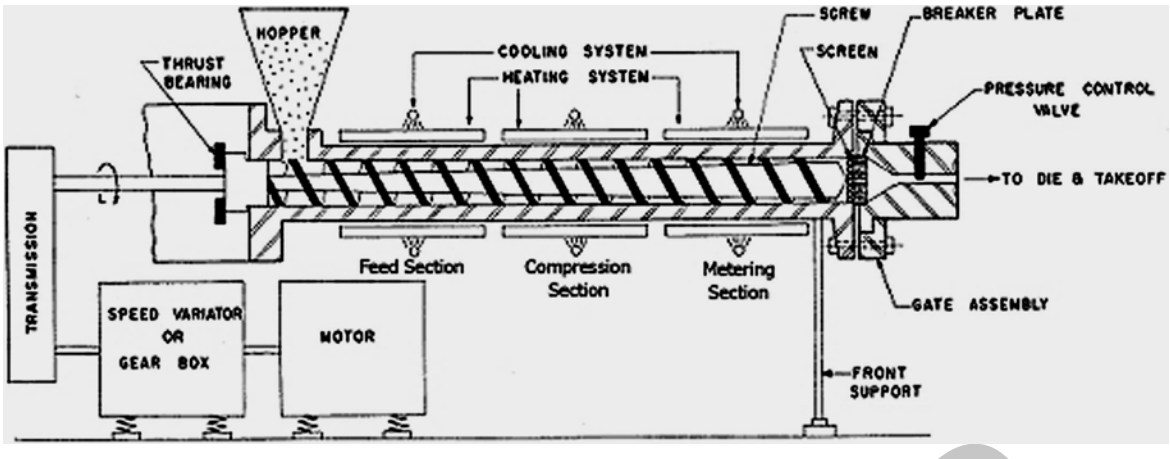

Figure 3. Schematic representation of a single-screw hot melt extruder.

drug loss from the top surface of the dosage form into the oral cavity. Type III is a unidirectional release device, from which drug loss is minimal, since the drug is released from the side adjacent to the buccal mucosa. This can be achieved by coating every face of the dosage form, except the one that is in contact with the buccal mucosa (43). The device should be fabricated so that the swelling rate of bioadhesive polymer is optimized to ensure a prolonged period of bioadhesion as well as a controlled or sustained drug release.

Solid buccal adhesive dosage forms

They are dry formulations which achieve bioadhesion via dehydration of the local mucosal surface.

(i). Buccal Tablets

Tablets have been the most commonly investigated dosage forms for buccal drug delivery. Several bioadhesive buccal tablet formulations have been developed by direct compression method in recent years either for local or systemic drug delivery. They are designed to release the drug either unidirectionally by targeting buccal mucosa or multi-directionally into the saliva (43). Alternatively, the dosage form can contain an impermeable backing layer to ensure that drug is delivered unidirectionally. Disadvantages of buccal tablets may be patient acceptability (mouth feel, taste and irritation) and the nonubiquitous distribution of drug within saliva for local therapy. It is important to point out the possible problems that children and the elderly may experience by the use of adhesive tablets such as possible discomfort provoked by the material applied to the mucosa and the possibility of the separation of dosage form the mucosa, swallowing, and then adherence to the wall of the esophagus. A typical bioadhesive formulation of this type consists of a bioadhesive polymer (such as polyacrylic acids or a cellulose derivative), alone or in combination, incorporated into a matrix containing the active agent and excipients, and perhaps a second impermeable layer to allow unidirectional drug delivery (44, 45). Results of some studies for development of buccal tablets are listed in table 3.

(ii). Bioadhesive Micro/nanoparticles

Bioadhesive micro/nanoparticles offer the same advantages as tablets but their physical properties enable them to make intimate contact with a lager mucosal surface area. These are typically delivered as an aqueous suspension or are incorporated into a paste or ointment or applied in the form of aerosols. Particulates have the advantage of being relatively small and more likely to be acceptable by the patients. Bioadhesive polymeric microparticles of carbopol, polycarbophil, chitosan or Gantrez are to adhere to porcine esophageal mucosa, with particles prepared from the polyacrylic acids exhibiting greater mucoadhesive strength during tensile testing studies. However in elution studies, particles of chitosan or Gantrez were found to persist on mucosal tissue for longer periods of time (74, 75). It has been reported (76). The use of nanoparticles for local delivery to the oral mucosa has been reported. Two types of nanoparticles, solid lipid nanoparticles incorporating either idarubicin or BODIPY®FL C12 as model fluorescent probes and polystyrene nanoparticles (Fluo-Spheres®), were investigated using monolayer-cultured human oral squamous cell carcinoma (OSCC) cell lines and normal human oral mucosal explants in a proof of concept study. The results demonstrated that OSCC cells internalized solid lipid nanoparticles. The observed penetration of nanoparticles through the epithelium and basement membranes into the underlying connective tissue suggested the possibility of oral transmucosal nanoparticle delivery for systemic therapy. Monti and co-workers (77) produced an atenolol containing microsphere using Poloxamer 407 and evaluated the formulation in vivo in rabbits against a marketed tablet formulation as a reference. After administration of the

Table 3. List of the drugs investigated for buccal mucoadhesive tablets.

Drug	Bioadhesive polymer used	Reference
Buprenorphine	HEMA and Polymeg	46
Buspirone HCL	Carbopol 974, HPMCK4M	47
Chlorhexidine diacetate	Chitosan and sodium alginate	48
Chlorpheneramine maleate	Hakea gum, Carbopol 934, HPMC	48, 49
Clotrimazole	Carbopol 974P, HPMC K4M	50
Carvedilol	Carbopol 934 with HPC, HPMC	51
Carbamazepine	HPMC and Carbopol	52
Cetylpyridinium chloride	Sodium CMC and HPMC	53
Diltiazem HCl	Carbopol 934, HPMCK4M	54
Ergotamine tartrate	Carboxyvinyl polymer and HPC	55
Felodipine and Pioglitazone	HPMC,Sodium CMC, and carbopol	56
Felodipine	HP-β-CD - felodipine complex and HPMC	29
Hydralazine HCL	Carbopol 934P and CMC	57
Hydrocortisone acetate	HPMC, Carbopol 974P, or PC	58
Insulin	Carbopol 934 with HPC or HPMC	59
Luteinizing hormone	PVP K30, PVP K90, Carbopol 934P	60
Metaclopromide	Carbopol, HPMC, PC, Sodium CMC	61
Metronidazole	HEC, HPC, HPMC, or Na CMC combined with Carbopol 940,	62
Miconazole nitrate	HPMC, sodiumCMC, Carbopol, sodium Alginate	63
Nalbuphine	Carbopol 934 and HPC	64
Nifedipine	CMC and Carbopol	65
Nystatin	Carbomer, HPMC	66
Omeprazole	Sodium alginate, HPMC	67
Pindolol	Carbopol 934 and sodium CMC; HPMC and HPC	68
Piroxicam	HPMC and Carbopol 940	69
Propranolol HCl	HPMC and PC	70
Sodium fluoride	Eudragit® and/or EC	71
Triamcinolone acetonide	Carbopol 934P and sodium CMC	72
Zinc sulfate	EC and Eudragit®	73
Sumatriptan succinate	HPMC and Carbopol	111

microsphere formulations, the atenolol concentration remained higher than the reference tablet during the entire elimination phase showing a sustained release profile from the microspheres. Moreover, the absolute bioavailability of microsphere formulations was higher than that of reference tablets in spite of a lower drug dose, suggesting a possible dose reduction by atenolol microparticles via oral transmucosal administration. Liposomes are one of the alternatives for drugs which are poorly soluble and hence are not efficiently delivered from a solid dosage form. For example, silamyrin liposomal buccal delivery showed steady state permeation through a chicken buccal pouch for 6 hrs and which was higher than free drug powder (78).

The small size of microparticles compared to tablets means that they are less likely to cause local irritation at the site of adhesion and the uncomfortable sensation of a foreign object within the oral cavity is reduced (79).

(iii). Bioadhesive Wafers

The delivery system is a composite wafer with surface layers possessing adhesive properties, while the bulk layer consists of antimicrobial agents, biodegradable polymers and matrix polymers. A conceptually novel periodontal drug delivery system (80) intended for the treatment of microbial infections associated with periodontitis has been reported.

(iv). Bioadhesive Lozenges

A slow release bioadhesive lozenge offers the potential for prolonged drug release with

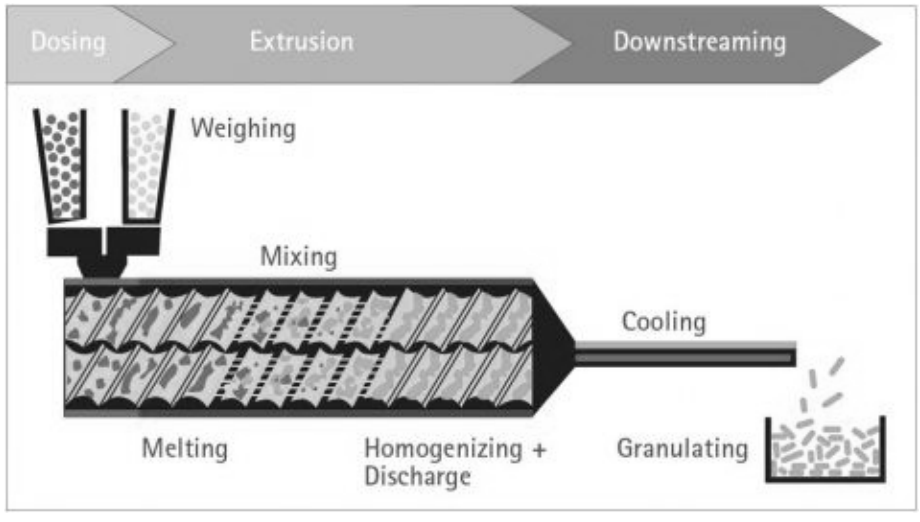

Figure 4. Schematic representation of twin screw extruder and processing of hot melt extrusion

improved patient compliance. Bioadhesive lozenges may be used for the delivery of drugs that act within the mouth including antimicrobials, corticosteroids, local anaesthetics, antibiotics and antifungals. A Bioadhesive lozenge has been reported as a means to deliver antifungal agents to the oral cavity (81). The limitation of these bioadhesive lozenzes is the short residence time at the site of absorption which depends to the size and type of formulation and since dissolve within 30min, the total amount of the drug that can be delivered is limited. The dissolution or disintegration of lozenges is usually controlled by the patient, i.e. how hard they suck the unit. Increased sucking and saliva production causes uncontrolled swallowing and loss of drug down the GI tract. Thus, solid dosage forms generally have a much higher inter- and intra-individual variations in absorption and bioavailability. Also these types of system are not able to provide unidirectional release of drugs. Continuous secretion of saliva is another major hurdle to the performance of such dosage forms.

Semi-solid dosage forms

(i). Medicated chewing gums

Although medicated chewing gums pose difficulties in regulation of the administered dose, they still have some advantages as drug delivery devices, particularly in the treatment of diseases of the oral cavity and in nicotine replacement therapy. Some commercial products are available in the market. Caffeine chewing gum, Stay Alert®, was developed recently for alleviation of sleepiness. It is absorbed at a significantly faster rate and its bioavailability was comparable to the capsule formulation. Nicotine chewing gums (e.g., Nicorette® and Nicotinell®) have been marketed for smoking cessation.

(ii). Adhesive Gels

Various adhesive gels may be used to deliver drugs *via* the buccal mucosa and allow sustained release. Gel forming bioadhesive polymers include cross-linked polyacrylic acid that has been used to adhere to the mucosal surfaces for extended periods of time and provide controlled release of drug at the site of absorption. Designed of a novel, hydrogel based, bioadhesive, intelligent response system for controlled drug release has been reported (82). This system combined several desirable facets into a single formulation; a poly (hydroxyethyl methacrylate) layer as barrier, poly (methacrylic acid-g-ethylene glycol) as a biosensor and poly (ethylene oxide) to promote mucoadhesion. The limitations for gel formulations are inability to deliver a measured dose of drug to the site and as a result have limited uses for drugs with narrow therapeutic window.

(iii). Buccal patches/films

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. Flexible films/patches have been prepared either by solvent casting or hot melt extrusion technique to deliver drugs directly to a mucosal membrane. Compared to creams and ointments they offer advantages in delivering a measured dose of drug to the site (83).

(a). Solvent casting technique

In this technique the required quantity of mucoadhesive polymer is treated with required volume of solvent system and vortexed to allow

Table 4. List of some drug substances processed by solvent casting technique

Drug	Bioadhesive Polymer Used	Reference
Felodipine	HPMC E15, Eudragit RL100	84
β-galactosidase	Noveon, Eudragit S-100	85
Buprenorphine	CP-934, PIB and PIP	86
Carvedilol	HPMC E15, HPC	87
Chlorpheniramine Maleate	HEC	88
Chlorhexidine	Chitosan	89
Isosorbide dinitrate	HPC, HPMC	90
Ipriflavone	PLGA, chitosan	91
Miconazole nitrate	SCMC, Chitosan, PVA, HEC and HPMC	92
Nifedipine	Sodium alginate	93
(Protirelin (TRH	HEC, HPC, PVP, or PVA	94
Oxytocin	CP 974P	95
Terbutaline sulfate	CP 934, CP 971, HPMC, HEC, or SCMC	96
Triamcinolone acetonide	CP, poloxamer, and HPMC	97

polymer to swell. After swelling, mixture was treated with, measured quantity of plasticizer (propylene glycol or glycerin or dibutyl phthalate) and vortexed. Finally the required quantity of drug was dissolved in small volume of solvent system and added to the polymer solution and mixed well. It was set aside for some time to remove any entrapped air and transferred into a previously cleaned anumbra petri plate. Drying of these patches was carried out in an oven at 40^0C. The formed patches were stored in a desiccator till the evaluation tests were performed (84). Some of the studies in the development of buccal patches by solvent casting technique is listed in table 4.

(b). Hot melt extrusion technique

The Hot-melt extrusion (HME) technique is an attractive alternative to traditional processing methods and offers many advantages over the other pharmaceutical processing techniques (98). Molten polymers during the extrusion process can function as thermal binders and act as drug depots and/or drug release retardants upon cooling and solidification.

Since solvents and water are not necessary, the numbers of processing and time-consuming drying steps are reduced. A matrix can be massed into a larger unit independent of compression properties. The intense mixing and agitation imposed by the rotating screw cause de-aggregation of suspended particles in the molten polymer resulting in a more uniform dispersion and the process is continuous and efficient. Bioavailability of the drug substance may be improved when it is solubilized or dispersed at the molecular level in HME dosage forms. Pharmaceutical Hot-Melt Extrusion processes can be categorized as either ram extrusion or screw extrusion (99, 100).

(a). Ram extrusion

It operates with a positive displacement ram capable of generating high pressures to push materials through the die. During ram extrusion, materials are introduced into a heated cylinder. After an induction period for softening of the materials, a ram (or a piston) pressurizes the soft materials through the die and transforms them into the desired shape. High-pressure is the operating principle of ram extrusion. This technique is well suited for the precision extrusion of highly valuable materials. The ram exerts modest and repeatable pressure as well as a very consistent extrudate diameter. The major drawback of ram extrusion in comparison with extrudates processed by screw extrusion is limited melting capacity that causes poor temperature uniformity in the extrudate and resulting in lower homogeneity.

(b). Screw Extruders are of two types *i).* Single Screw Extruder, *ii).*Twin-Screw Extruders

i). Single Screw Extruder

The single screw extruder is the most widely used extrusion system in the world. One screw rotates inside the barrel and is used for feeding, melting, devolatilizing, and pumping. Mixing is also accomplished for less demanding applications. Single screw extruders can be either flood or starve fed, depending upon the intended manufacturing process (99). Single screw extruders (Fig. 3) are continuous, high-pressure pumps for viscous materials that can generate thousands of pounds of pressure while melting and mixing. Most extruder screws are driven from the hopper end. However, when screws are reduced to less than 18 mm, they become weak and solids transportation is far less

Table 5. List of drug substances processed by hot melt extrusion techniques.

Drug	Melting temperature (^{0}C)
Carbamazepine	192.0
Cetylsalicylic Acid	135.0
Chlorpheniramine Maleate	135.0
Diclofenac Sodium	284.0
Ethinyl estradiol	144.0
Hydrochlorothiazide	274.0
Hydrocortisone	220.0
Itraconazole	166.0
Ketoconazole	150.0
Ketoprofen	94.0
Lacidipine	184.8
Nifedipine	175.0
Piroxicam	204.9
Tolbutamide	128.4
Indomethacin	162.7
Lidocaine	68.5
Ibuprofen	76.0
Diltiazem Hydrochloride	210.0
Acetaminophen	168.0
Zidovudine	127.5
Lamivudine	176.8
Theophylline	272.5
Phenylpropanolamine HCl	192.0
Nimodipine	130.0
Metoprolol tartrate	120.0
ketoprofen	94.0

reliable. To overcome these shortcomings, a vertical screw, driven from the discharge end, may be used. The strength of discharge of such screws is 24- times higher than solids transport.

There are three basic functions of a single screw extruder: solids conveying, melting and pumping. The forwarding of the solid particles in the early portion of the screw is a result of friction between the material and the feed section's bore. After solids conveying the flight depth begins to taper down and the heated barrel causes formation of a melt. The energy from the heaters and shearing contribute to melting. Ideally, the melt pool will increase as the solid bed reduces in size until all is molten at the end of the compression zone. Finally, the molten materials are pumped against the die resistance to form the extrudate.

ii). Twin-Screw Extruders

Twin-screw extruders have several advantages over single screw extruders, such as easier material feeding, high kneading, and dispersing capacities, less tendency to over-heat and shorter transit time. The first twin-screw extruders were developed in the late 1930's in Italy, with the concept of combination of the machine actions of several available devices into a single unit. As the name implies, twin-screw extruders utilize two screws usually arranged side by side (Fig. 4). The use of two screws allows a number of different configurations and imposes different conditions on all zones of the extruder, from the transfer of material from the hopper to the screw, all the way to the metered pumping zone (99). In a twin-screw extruder, the screws can either rotate in the same (co-rotating extruder) or the opposite (counter-rotating extruder) direction. The counter-rotating designs are utilized when very high shear regions are needed since they subject materials to very high shear forces as the material is squeezed through the gap between the two screws when they come together. Also, the extruder layout is good for dispersing particles in a blend. Generally, counter-rotating twin-screw extruders suffer from disadvantages of potential air entrapment, high-pressure generation, and low maximum screw speeds and output. Co-rotating twin-screw extruders on the other hand are generally of the intermeshing design, and are thus self-wiping. Industrially they are the most important type of extruders and can be operated at high screw speeds to achieve high outputs, while maintaining good mixing and conveying characteristics. Unlike counter-rotating extruders, they generally experience lower screw and barrel wear as they do not experience the outward "pushing" effect due to screw rotation. These two primary types can be further classified as non-intermeshing and fully intermeshing. The fully intermeshing type of screw design is the most popular type used for twin-screw extruders.

This design is self-wiping by itself, where it minimizes the non-motion and prevents localized overheating of materials within the extruder. The extruder operates by a first in/first out principle since the material does not rotate along with the screw. Non-intermeshing extruders, on the other hand, are often used for processing when large amounts of volatiles need to be removed and when processing highly viscous materials. Non-intermeshing extruders allow large volume de-volatization via a vent opening since the screws are positioned apart from one another. Non-intermeshing extruders are not susceptible to high torques generated while processing highly viscous materials for the same reasons (99). List of drug substances processed by hot melt extrusion techniques is listed in table 5.

Liquid dosage forms

They are solutions or suspensions of drugs in suitable aqueous vehicles. Such types of dosage forms are usually employed to exert local action into the oral cavity and several antibacterial mouthwashes and

mouth-freshener are commercially available for this purpose. The limitation associated with these liquid dosage forms are that they are not readily retained or targeted to buccal mucosa and can deliver relatively uncontrolled amounts of drug throughout oral cavity. From the wide range of polymer solutions, chitosan represents the greatest binding, followed by methylcellulose, gelatin, carbopol and polycarbophil. Viscous liquids may be used to coat buccal surface either as protectants or as drug delivery vehicles to the mucosal surface. Dry mouth is treated with artificial saliva solutions that are retained on mucosal surfaces to provide lubrication. These solutions contain sodium CMC as bioadhesive polymer.

Recent developments in buccal drug delivery systems
Recent developments in buccal drug delivery systems, such as lipophilic gel, buccal spray and phospholipid vesicles have been recently proposed to deliver peptides via the buccal route. In particular, some authors proposed the use of cubic and lamellar liquid crystalline phases of glyceryl monooleate as buccal drug carrier for peptide drugs (101). A novel liquid aerosol formulation (Oralin, Generex Biotechnology) has been developed recently (102). Phospholipid deformable vesicles, transfersomes, have been recently devised for the delivery of insulin in the buccal cavity (103).

Commercial buccal adhesive drug delivery systems
Commercial formulations or formulations in clinical trials, intended for buccal delivery are presented in table 6. Only few formulations are available on market or under clinical evaluations which indicate the difficulty to develop drug delivery systems with clear efficacy and safety profiles.

Evaluation of Buccal Delivery Systems
Buccal adhesive drug delivery devices are subjected to the routine evaluation tests such as weight variation, thickness variation, friability, hardness, content uniformity, in vitro dissolution for tablets; tensile strength, film endurance, hygroscopicity etc. for films and patches; viscosity, effect of aging etc. for gels and ointments. They should also to be evaluated specifically for their bioadhesive strengths and permeabilities (69).

Moisture absorption studies for buccal patches
The moisture absorption studies for the buccal patches give an indication about the relative moisture absorption capacities of polymers and an idea whether the buccal patches maintain their integrity after absorption of moisture. Moisture absorption studies have been performed in 5 % w/v agar in distilled water, which while hot was transferred to petri plates and allowed to solidify (112). Then six buccal patches from each formulation were selected and weighed. Buccal patches were placed in desiccator overnight prior to the study to remove moisture if any and laminated on one side with water impermeable backing membrane. Placed on the surface of the agar plate and incubated at 37° C for 2 hrs in incubator. The patches were weighed again and the percentage of the absorbed moisture was calculated using the formula:

$$\% \text{ Moisture absorbed} = \frac{\text{Final weight} - \text{Initial weight}}{\text{Initial weight}} \times 100$$

Swelling and erosion studies for buccal tablets
Swelling and erosion studies for buccal tablets were determined gravimetrically in phosphate buffer, of pH 6.6 (56, 111). The tablets were attached to pre-weighed glass supports using a cyanoacrylate adhesive sealant. The supports with tablets were immersed into the phosphate buffer at 37 ˚C. At pre-determined time intervals, the devices were removed from the media, blotted with tissue paper to remove excess water, and weighed. After determination of the wet weight, the tablets were dried at 40°C until constant mass. Swelling index (S.I) and erosion were determined gravimetrically according to the following equations.

$$\text{Swelling index (\%)} = \frac{W_s - W_d}{W_d}$$

$$\text{Erosion (\% mass loss)} = \frac{\text{Original weight} - \text{remaining dry weight}}{\text{Original weight}} \times 100$$

Where W_d and W_s are the weights of dry and swollen devices, respectively.

Study of the surface pH
The bioadhesive buccal tablets were covered with 1ml of distilled water and allowed to swell for 1-2h at room temperature. The surface pH of the tablets or patches was measured by bringing the pH meter electrode in contact with the surface of the patch or tablet and allowing it to equilibrate for one minute (113).

Measurement of Mechanical Properties
Mechanical properties of the films has been reported (84) and has been performed by using a microprocessor based advanced force gauze equipped with a motorized test stand (Ultra Test, Mecmesin, West Sussex, UK), equipped with a 25 kg load cell. Film strips with the dimensions of 60 x 10 mm were held between two clamps positioned at a distance of 3 cm. A cardboard has been attached on the surface of the clamp to prevent the film from being cut by the grooves of the clamp. During

measurement, the strips were pulled by the top clamp at a rate of 2.0 mm/s to a distance till the film broke. The force and elongation were measured when the films were broken. Results from film samples, which were broken at end and not being present between the clamps were not included in observations. Measurements were run in six replicates for each formulation. The following equations were used to calculate the mechanical properties of the films.

$$\text{Tensile strength } (\text{kg.mm}^{-2}) = \frac{\text{Force at break (kg)}}{\text{Initial cross sectional area of the sample } (\text{mm}^2)}$$

$$\text{Elongation at break } (\%.\text{mm}^{-2}) = \frac{\text{Increase in the length (mm)}}{\text{Original length}} \times \frac{100}{\text{Cross sectional area } (\text{mm}^2)}$$

Bioadhesion measurement

Methods available for the measurement of bioadhesion are limited, and their selections depend on applicability, reproducibility, and providing useful information. It is unnecessary to compare the absolute values of different methods and is more meaningful to examine the relative bioadhesive performance using each technique. In addition, some factors, including saliva secretion, mastication, and mucus turnover that can markedly affect the adhesion strength and duration of in vivo adhesion are not present in in vitro testing (110).

In vitro bioadhesion measurement

In vitro bioadhesion measurement method was first reported (104) in evaluation of the adhesive properties of patches using a microprocessor based on advanced force gauze equipment with porcine buccal membrane as a model tissue under simulated buccal conditions. Data collection and calculations were performed using the Data Plot software package of the instrument. Two parameters, namely the work of adhesion and peak detachment force were used to study the buccal adhesiveness of patches. The work of adhesion was determined from the area under force-distance curve while the peak detachment force was the maximum force required to detach the film from the tissue.

Determination of the residence time

Ex vivo residence time

Ex vivo residence time was determined using a modified USP disintegration apparatus. Nakamura et al. (105) applied this method by taking the disintegration medium composed of 800 ml phosphate buffer of pH 6.6 maintained at 37 °C. The porcine buccal tissue was tied to the surface of a glass slab, vertically attached to the apparatus. The time which was taken for complete erosion or detachment of the tablet from the mucosal surface was recorded and considered as ex vivo residence time.

In vivo residence time

The experiment was performed in eight healthy adult male volunteers, aged between 22 and 28 years. The volunteers were asked to record the residence time of the film on buccal mucosa in the oral cavity, which was taken as the time for the patch to dislodge completely from the buccal mucosa by continual sensation of the patch as well as the backing membrane. In vivo residence time was recorded in each case (83).

Permeation studies

Buccal absorption/permeation studies must be conducted to determine the feasibility of this route of administration for a drug candidate and to determine the type of enhancer and its concentration which were to control the rate of permeation of drugs during the pre-formulation studies. Similar to an in vitro permeation study in transdermal drug delivery, different types of diffusion cells with certain modifications are suitable to conduct permeation studies, except that the buccal mucosa dissected from model animals are used as diffusion barriers for buccal delivery. Despite the careful endeavor in tissue preparation to maintain viability and integrity of oral mucosa, the loss of mucus layer on the surface of the oral mucosal membrane is unavoidable since the mucus network is extremely sensitive to environmental changes. These studies involve methods that would examine in vitro, ex vivo and/or in vivo buccal permeation profile and kinetics of absorption of the drug. Porcine buccal mucosa has been extensively used as an in vitro model to study the permeability of various diffusants and to assess their potentials to be delivered through the buccal route by using Franz diffusion cell. A mucosal tissue thickness of about 500 µm is recommended for in vitro transbuccal permeation studies since the epithelium remained the major permeability barrier for all diffusants at this thickness (106).

Buccal absorption test

A method (107) for the measurement of the developed a method to measure the kinetics of the drug absorption by swirling a 25 ml sample of the test solution for 15 min by human volunteers followed by the expulsion of the solution. The amount of the drug remaining in the expelled volume is then determined to assess the amount of drug absorbed. The drawbacks of this method are inability to localize the drug solution within a specific site of the oral cavity, accidental swallowing of a portion of the sample solution and the salivary dilution of the drug.

Table 6. Commercial formulations or under clinical trials formulation intended for buccal delivery.

Manufacturer	Product	Present status
Generex Biotechnology Corporation	Insulin Buccal Spray ORALGEN (US) ORALIN (Canada) Heparin Buccal Delivery System Fentanyl Buccal Delivery Systems	 Commercially available Clinical Trials Completed Clinical Trials Completed
Columbia Laboratories Inc.	Testosterone Buccal Tablet (Straint) Desmopressin Buccal Tablet	Commercially available Commercially available
Ergo Pharm	Androdiol Buccal Tablets (Cyclo-Diol SR) Norandrodiol Buccal Tablets (Cyclo-Nordiol SR)	Commercially available Commercially available
Cytokine Pharma Sciences Inc.	Pilocarpine Buccal Tablet (PIOLOBUC)	Commercially available
Britannia Pharmaceuticals Ltd	Prochlorperazine Buccal Tablet (Buccastem)	Commercially available
Pharmax Limited	Glyceryl Trinitrate (Suscard Buccal Tablet)	Commercially available
Cephalon, Inc.	Oral Transmucosal Fentanyl Citrate Solid Dosage Form (ACTIQ)	Commercially available
Wyeth Pharma Ceuticals	Lorazepam Buccal Tablets (Temesta Expidet) Oxazepam Buccal Tablets (Seresta Expidet)	Commercially available Commercially available
IVAX Corporation	Estrogen Buccal Tablet	Under Phase III clinical trials
Regency Medical research	Vitamins Trans Buccal Spray	Commercially available
Leo Pharmaceuticals	Nicotine Mucoadhesive Tablet (Nicorette) Nicotine Chewing Gum (Nicotinell)	Commercially available Commercially available
Teijin Ltd.	Triamcinolone acetonide(Aftach)	Commercially available
Rhone-Poulenc Rorer	Prochlorperazine Bioadhesive Buccal Tablet (Tementil)	Commercially available
Reckitt Benckiser	Prochlorperazine Bioadhesive Buccal controlled release Tablet (Buccastem)	Commercially available
Reckitt Benckiser	Buprenorphine HCl Tablets (Subutex)	Commercially available
Reckitt Benckiser	Buprenorphine HCl & Naloxone HCl (Suboxane)	Commercially available
Ciba-Geigy	Methyltestosterone Buccal Tablets (Metandren)	Commercially available

Modified Beckett's test

The test has been modified (108) by addition of phenol red as a marker for drug dilution by saliva secretion as well as for accidental swallowing of the drug solution. The 'Schurmann and Turner Test' has also been modified (109) by taking a small sample of the solution in the oral cavity every few minutes, without removal of the residual solution. In this way he was able to study kinetics of the absorption in a single test for 15-20 minutes. Advantages of this type of test over the original absorption test are; corrections for saliva secretion, accidental swallowing and changes in pH can be made and that a complete absorption curve can be measured in one single test. Still, the disadvantage is the uncertainty with respect to the amount of drug that actually reaches the systemic circulation.

CONCLUSION

Buccal adhesive systems offer innumerable advantages in terms of accessibility, administration and withdrawal, retentivity, low enzymatic activity, economy and high patient compliance. Adhesions of these drug delivery devices to mucosal membranes lead to an increased drug concentration gradient at the absorption site and therefore improve bioavailability of systemically delivered drugs. In addition, buccal adhesive dosage forms have been used to target local disorders at the mucosal surface (e.g., mouth ulcers), to reduce the overall required dosage and minimize side effects that may be caused by systemic administration of drugs. Investigations are continuing beyond traditional polymer networks to find other innovative drug transport systems. At the current global scenario, scientists are finding ways to develop buccal adhesive systems through various approaches to improve the bioavailability of drugs used orally by manipulation of 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. Another important aspect concerns the in vitro and ex vivo techniques which are employed for evaluation of the performance of the materials and dosage forms. Efforts should be made to develop standard in vitro and ex vivo biological models that allow one to characterize and compare different material and formulation in terms of their capability to promote drug absorption via the buccal route.

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