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 polymer, Permeation enhancer, 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. 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. Disadvantages of drug delivery by this route are the low permeability of the buccal membrane, specifically when compared to the sublingual membrane, and a smaller surface area. The total surface area of the membranes of the oral cavity available for drug absorption is 170 cm², of which ~50 cm² represents non-keratinized tissues, including the buccal membrane. 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 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.
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. 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 500–800 µ. 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, which are loose intercellular links.

Table 1: Thickness and Surface Area of Oral Cavity Membranes.

<table>
<thead>
<tr>
<th>Oral cavity membrane</th>
<th>Thickness (µm)</th>
<th>Surface area (cm²)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Buccal mucosa</td>
<td>500-800</td>
<td>50.2</td>
</tr>
<tr>
<td>Sublingual mucosa</td>
<td>100-200</td>
<td>26.5</td>
</tr>
<tr>
<td>Gingival mucosa</td>
<td>200</td>
<td>--</td>
</tr>
<tr>
<td>Palatal</td>
<td>250</td>
<td>20.1</td>
</tr>
</tbody>
</table>

Drug delivery across the oral mucosa can be divided into three different type

- **Sublingual drug delivery:** consisting of the administration through the membrane of the ventral surface of the tongue and the floor of the mouth.
- **Buccal drug delivery:** consisting of the administration through the buccal mucosa, mainly composed of the lining of the cheeks and
- **Local drug delivery:** consisting of the administration through all areas other than former two regions.

These site differs anatomically in their permeability to drugs, the rate of drug delivery, and ability to maintain a delivery system for a time required for drug release out of the delivery apparatus and into the mucosa.

**Buccal drug delivery**

The buccal mucosa lines the inner cheek, and buccal formulations are placed in the mouth between the upper gingivae (gums) and cheek to treat local and systemic conditions. The buccal route provides one of the potential routes for typically large, hydrophilic and unstable proteins, oligonucleotides and polysaccharides, as well as conventional small drug molecules. The oral cavity has been used as a site for local and systemic drug delivery.
Buccal mucosa

Amongst the various routes of drug delivery, oral route is perhaps the most preferred to the patient. However, peroral administration of drugs has disadvantages such as hepatic first pass metabolism and enzymatic degradation within the GI tract, that prohibit oral administration of certain classes of drugs especially peptides and proteins. 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 cavity) offer distinct advantages over peroral administration for systemic drug delivery. These advantages include a possible bypass of first pass effect, avoidance of pre-systemic elimination within the GI tract, and, depending on the particular drug, a better enzymatic flora for drug absorption.

Though the nasal rectal, vaginal, and ocular mucosa all offer certain advantages, the poor patient acceptability associated with these sites renders them reserved for local applications rather than systemic drug administration. The oral cavity consists of two regions. Outer oral vestibule which is bounded by cheeks, lips, teeth and gums. Oral cavity proper which extends from teeth and gums back to the faucets (which lead to pharynx) with the roof comprising the hard and soft palate. The tongue projects from the floor of the cavity.

Functions of oral cavity

- It helps in chewing, mastication and mixing of food stuff.
- It is Helps to lubricate the food material and bolus.
- To identify the ingested material by taste buds of the tongue.

- To initiate the carbohydrate and fat metabolism.

As a portal for intake of food material and water.

Basement membrane

Although the superficial layers of the oral epithelium represent the primary barrier to the entry of substances from the exterior, it is evident that the basement membrane also plays a role in limiting the passage of materials across the junction between epithelium and connective tissue. A similar mechanism appears to operate in the opposite direction. The charge on the constituents of the basal lamina may limit the rate of penetration of lipophilic compounds that can traverse the superficial epithelial barrier relatively easily.

Mucus

The epithelial cells of buccal mucosa are surrounded by the intercellular ground substance called mucus with the thickness varies from 40 μm to 300 μm. Though the sublingual glands and minor salivary glands contribute only about 10% of all saliva, together they produce the majority of mucus and are critical in maintaining the mucin layer over the oral mucosa. At buccal pH, mucus can form a strongly cohesive gel structure that binds to the epithelial cell surface as a gelatinous layer. Mucus is composed chiefly of mucins and inorganic salts suspended in water. Mucins are a family of large, heavily glycosylated proteins composed of oligosaccharide chains attached to a protein core. Three-quarters of the protein core are heavily glycosylated and impart a gel-like characteristic to mucus. Mucins contain approximately 70–80% carbohydrate, 12–25% protein and up to 5% ester sulphate.

Saliva

The mucosal surface has a salivary coating estimated to be 70 μm thick, which act as a unstirred layer. Within the saliva, there is a high molecular weight mucin named MG1 that can bind to the surface of the oral mucosa so as to maintain hydration, provide lubrication, concentrate protective molecules such as secretory immunoglobulins, and limit the attachment of microorganisms. Several independent lines of evidence suggest that saliva and salivary mucin contribute to the barrier properties of oral
mucosa.[26] The major salivary glands consist of lobules of cells that secrete saliva; parotids through salivary ducts near the upper teeth, submandibular under the tongue, and the sublingual through many ducts in the floor of the mouth. Besides these glands, there are 600–1000 tiny glands called minor salivary glands located in the lips, inner cheek area (buccal mucosa), and extensively in other linings of the mouth and throat.[27]

Mechanism of bioadhesion
The process of bioadhesion can be viewed as occurring in two steps. First intimate contact between the polymers and membrane followed by formation of bonds. The bonding occurs chiefly through both physical and mechanical bonds results from the entanglement of the adhesive material and the extended nucus chain.

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.[28] 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.[29] Another barrier to the drug permeability across buccal epithelium is enzymatic degradation. Saliva contain moderate levels of esterases, carbohydrases, and phosphatas but not proteases.[30] However, several proteolytic enzymes have been found in the buccal epithelium.[31] It has been reported[32] that endopeptidases and carboxypeptidases are not present on the surface of porcine buccal mucosal, 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.[33]

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.[34]

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.

Table 2: Penetration Enhancers and Their Mechanism of Action.

<table>
<thead>
<tr>
<th>Category</th>
<th>Example</th>
<th>Mechanism Of Action</th>
</tr>
</thead>
<tbody>
<tr>
<td>Surfactants</td>
<td>Anionic: Sls</td>
<td>Perturbation of intracellular lipids and protein domain integrity</td>
</tr>
<tr>
<td></td>
<td>Cationic: Cetyl Pyridinium Chloride</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Non-Ionic: Poloxamer, Brij, Span, Myrj, Tween</td>
<td></td>
</tr>
<tr>
<td>Bile Salt</td>
<td>Sodium Glycocholate, Sodium Tauro, Deoxycholate, Sodium Tauro Cholate</td>
<td>Perturbation of intracellular lipids and protein domain integrity</td>
</tr>
<tr>
<td>Fatty Acid</td>
<td>Oleic Acid, Caprylic Acid, Lauric Acid, Lysophosphotidy Choline, Phasphatidyl Choline</td>
<td>Increase fluidity of phospholipid domain</td>
</tr>
<tr>
<td>Cyclodextrins</td>
<td>A, B, Cyclodextrin, Methylated B-Cyclodextrins</td>
<td>Inclusion of membrane compounds</td>
</tr>
<tr>
<td>Chelators</td>
<td>EDTA, Citric Acid, Sodium Salicylate, Methoxy Salicylates</td>
<td>Interfere with Ca⁺</td>
</tr>
<tr>
<td>Positively Charged Polymer</td>
<td>Chitosan, Trimethyl Chitosan</td>
<td>Ionic interaction with negative charge on the mucosal surface</td>
</tr>
<tr>
<td>Cationic Compound</td>
<td>Poly-L-Arginine, L-Lysine</td>
<td>Ionic interaction with negative charge on the mucosal surface</td>
</tr>
</tbody>
</table>

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, 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.[35] 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.[36] 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.[37] Factors such as saliva secretion, food intake, local pH, and compositions of delivery systems also strongly affect bioadhesion.

Table 3: Mucoadhesive Polymers Used In Buccal Delivery.

<table>
<thead>
<tr>
<th>Criteria</th>
<th>Category</th>
<th>Example</th>
</tr>
</thead>
<tbody>
<tr>
<td>Source</td>
<td>Semi-natural/natural</td>
<td>Agaros, chitosan, gelatin hyaluronic acid, various gum (guar, hakea, gellan, carrageenan, pectin and sodium alginate) cellulose derivative (HPMC, MC, CMC, HPC, HEC, Sodium CMC, Thiolated CMC)</td>
</tr>
<tr>
<td>Aqueous solubility</td>
<td>Synthetic</td>
<td>(CP, PC, PAA, copolymer of acrylic acid and PEG)</td>
</tr>
<tr>
<td></td>
<td>Water-soluble</td>
<td>CP, HEC, HPC (water&lt; 38C), HPMC (cold water), PAA, sodium CMC, sodium alginate</td>
</tr>
<tr>
<td></td>
<td>Water-insoluble</td>
<td>Chitosan</td>
</tr>
<tr>
<td>Charge</td>
<td>Cationic</td>
<td>Aminodextran, chitosan, dimethylaminoethyl (DEAE)-dextran, trimethylated chitosan</td>
</tr>
<tr>
<td></td>
<td>Anionic</td>
<td>Chitosan-EDTA, CP, CMC, pectin, PAA, PC, sodium alginate, sodium CMC, xanthan gum</td>
</tr>
<tr>
<td></td>
<td>Non-ionic</td>
<td>Hydroxyethyl starch, HPC, poly(ethylene oxide), PVA, PVP, scleroglucan</td>
</tr>
</tbody>
</table>

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.[38]

Bacterial adhesions
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.[39]

Escherichia coli (E.coli)
It has been reported to specifically adhere to the lymphoid follicle epithelium of the ileal Peyer’s patch in rabbits. Additionally, different staphylococci possess the ability to adhere to the surface of mucus gel layers and not to the mucus-free surface.[40] 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.[41] 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.[42] The presence of thiol groups allows the formation of covalent bonds with cysteine-rich subdomains of the mucus gel layer, leading to increase in the residence time and improvement of the bioavailability.[43]
**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 mucosaladhesive 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 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.[44] 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.[45] 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.

(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, polyacrylsol, 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.[45] It has been reported. 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.[47]

(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[48] 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 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.[49] The limitation of these bioadhesive lozenges 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.

**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.[50] This system combined several desirable facets into a single formulation; a poly (hydroxethyl methacrylate) layer as barrier, poly (methacrylic acid-g-ethylene glycol) as a biosensor and poly (ethylene oxide) to promote mucoadhesion.

(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.[51]

**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-fresheners 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.[52] A novel liquid aerosol formulation (Oralin, Generex Biotechnology) has been developed recently.[53] Phospholipid deformable vesicles, transfersomes, have been recently devised for the delivery of insulin in the buccal cavity.[54]

**Commercial buccal adhesive drug delivery systems**

Commercial formulations or formulations in clinical trials, intended for buccal delivery are presented in table 3. 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.

**Table 4.**

<table>
<thead>
<tr>
<th>Manufacturer</th>
<th>Product</th>
<th>Present Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>Generex biotechnology corporation</td>
<td>Insulin Buccal Spray</td>
<td>Commercially available</td>
</tr>
<tr>
<td></td>
<td>ORALGEN (US)</td>
<td>Commercially available</td>
</tr>
<tr>
<td></td>
<td>ORALIN (Canada)</td>
<td>Clinical trial completed</td>
</tr>
<tr>
<td></td>
<td>Heparin buccal delivery system</td>
<td>Clinical trial completed</td>
</tr>
<tr>
<td></td>
<td>Fentanyl buccal delivery system</td>
<td></td>
</tr>
<tr>
<td>Colombia lab Inc.</td>
<td>Testeron buccal tablet (straint)</td>
<td>Commercially available</td>
</tr>
<tr>
<td></td>
<td>Demopresin buccal tablet</td>
<td>Commercially available</td>
</tr>
<tr>
<td>Ergo pharm</td>
<td>Androdial buccal tablets (Cyclo-Diol SR)</td>
<td>Commercially available</td>
</tr>
<tr>
<td></td>
<td>Norandrodil buccal tablet (Cyclo-Nordiol SR)</td>
<td>Commercially available</td>
</tr>
<tr>
<td>Cytokin pharma sciences Inc.</td>
<td>Pilocarpin buccal tablet (PILBUC)</td>
<td>Commercially available</td>
</tr>
<tr>
<td>Britannia Pharmaceutical Ltd.</td>
<td>Prochlorperazin buccal tablet (Buccatem)</td>
<td>Commercially available</td>
</tr>
<tr>
<td>Pharmax limited</td>
<td>Glyceryl trinitrate (Suscard buccal tablet)</td>
<td>Commercially available</td>
</tr>
<tr>
<td>Cephalon Inc.</td>
<td>Oral Transmucosal fentanyl citrate solid dosage form (ACTIQ)</td>
<td>Commercially available</td>
</tr>
</tbody>
</table>

**EVALUATION OF BUCCAL DRUG DELIVERY SYSTEMS**

**Surface pH**

Buccal patches are left to swell for 2 hr on the surface of an agar plate. The surface pH is measured by means of a pH paper placed on the surface of the swollen patch.[55]

**Thickness measurements**

The thickness of each film is measured at five different locations (centre and four corners) using an electronic digital micrometer.[56]

**Swelling study**

Weighed the buccal patches individually (W1), and placed separately in 2% agar gel plates, incubated at 37 °C±1 °C, and examined for any physical changes. At regular time intervals until 3 h, patches are removed from the gel plates and excess surface water is removed carefully using the filter paper. The swollen patches are then reweighed (W2) and the swelling index (SI) were calculated using the following formula.[57]

\[SI = \left( \frac{W2-W1}{W1} \right) \times 100\]

**Folding endurance**

Folding endurance can be done by folding the patches upto200 times with our breaking.[58]

**Thermal analysis study**

Thermal analysis study is performed using differential scanning calorimeter (DSC).

**Morphological characterization**

Morphological characters are studied by using scanning electron microscope (SEM).[59]
Water absorption capacity test
Circular Patches, with a surface area of 2.3 cm² are allowed to swell on the surface of agar plates prepared in simulated saliva (2.38 g Na₂HPO₄, 0.19 g KH₂PO₄, and 8 g NaCl per liter of distilled water adjusted with phosphoric acid to pH 6.7), and kept in an incubator maintained at 37 °C ± 0.5 °C. At various time intervals (0.25, 0.5, 1, 2, 3, and 4 h), samples are weighed (wet weight) and then left to dry for 7 d in a desiccators over anhydrous calcium chloride at room temperature then the final constant weights are recorded.

Ex-vivo bioadhesion test
A piece of gingival mucosa is tied in the open mouth of a glass vial, filled with phosphate buffer (pH 6.8). This glass vial is tightly fitted into a glass beaker filled with phosphate buffer (pH 6.8, 37 °C ± 1 °C) so it just touched the mucosal surface. The patch is stuck to the lower side of a rubber stopper with cyanoacrylate adhesive. Two pans of the balance are balanced with a 5 g weight. The 5 g weight is removed from the left-hand side pan, which loaded the pan attached with the patch over the mucosa. The balance is kept in this position for 5 min of contact time. The water is added slowly at 100 drops/min to the right-hand side pan until the patch detached from the mucosal surface.

In vitro drug release
The dissolution medium consisted of phosphate buffer pH 6.8 maintaining a temperature at 37 °C ± 0.5 °C, with a rotation speed of 50 rpm. The backing layer of the buccal patch is attached to the glass disk with the instant adhesive material. The disk is allocated to the bottom of the dissolution vessel. Samples (5 ml) are withdrawn at predetermined time intervals and replaced with fresh medium. The samples filtered through whatman filter paper and analyzed for drug content after appropriate dilution in a UV spectrophotometer. The in vitro buccal permeation through the buccal mucosa (sheep and rabbit) is performed using Keshary Chien/Franz-type glass diffusion cell at 37 °C ± 0.2 °C. Fresh buccal mucosa is mounted between the donor and receptor compartments. The buccal patch is placed with the core facing the mucosa and the compartments clamped together. The donor compartment is filled with suitable buffer.

Permeation study of buccal patch
The receptor compartment is filled with phosphate buffer pH 6.8, and the hydrodynamics in the receptor compartment is maintained by stirring with a magnetic bead at 50 rpm. Samples are withdrawn at predetermined time intervals and analyzed for drug content.

Ex-vivo mucoadhesion time
The ex-vivo mucoadhesion time performed after application of the buccal patch on freshly cut buccal mucosa (sheep and rabbit). The fresh buccal mucosa is tied on the glass slide, and a mucoadhesive patch is wetted with 1 drop of phosphate buffer pH 6.8 and pasted to the buccal mucosa by applying a light force with a fingertip for 30 seconds. The glass slide is then put in the beaker, which is filled with 200 ml of the phosphate buffer pH 6.8, is kept at 37 °C ± 1 °C. After 2 min, a 50-rpm stirring rate is applied to simulate the buccal cavity environment, and patch adhesion is monitored for 12 h. The time for changes in color, shape, collapsing of the patch and drug content is noted.

Measurement of mechanical properties
Mechanical properties of the films (patches) include tensile strength and elongation at break is evaluated using a tensile tester. Film strip with the dimensions of 60 x 10 mm and without any visual defects cut and positioned between two clamps separated by a distance of 3 cm. Clamps designed to secure the patch without crushing it during the test, the lower clamp held stationary and the strips are pulled apart by the upper clamp moving at a rate of 2 mm/sec until the strip break. Force and elongation of the film at the point when the strip break is recorded. The tensile strength and elongation at break values are calculated using the formula. Where, M is the mass in gm, g is the acceleration due to gravity 980 cm/sec², B is the breadth of the specimen in cm, T is the thickness of specimen in cm. Tensile strength (kg/mm²) is the force at break (kg) per initial cross-sectional area of the specimen (mm²).

Stability study in human saliva
The stability study of optimized bilayered and multilayered patches is performed in human saliva. The human saliva is collected from humans (age 18-50 y). Buccal patches are placed in separate Petri dishes containing 5 ml of human saliva and placed in a temperature controlled oven at 37 °C ± 0.2 °C for 6 h. At regular time intervals (0, 1, 2, 3, and 6 h), the dose formulations with better bioavailability are needed.

Animal models for permeability measurement
The most commonly used animal models are dogs, rabbits, and pigs. A general criterion for selecting an in vivo animal model is the resemblance of the animal mucosa to the oral mucosa of human beings in both ultrastructure and enzyme activity, which represent the physical and metabolic barriers of the oral mucosa.

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 enhancers 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.

REFERENCES

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