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AN OVERVIEW ON BUCCAL DRUG DELIVERY SYSTEM

Surender Verma, Mahima Kaul*, Aruna Rawat and Sapna Saini

Institute of Pharmaceutical Sciences, Kurukshetra University, Kurukshetra, Haryana, India

ABSTRACT

Buccal drug delivery has gained significant attention and momentum since it offers remarkable advantages. Over past few decades, buccal route for systemic drug delivery using mucoadhesive polymers to significantly improve the performance of many drugs has been of profound interest. This review article is an overview of buccal drug delivery systems encompassing a review of oral mucosa, formulation considerations for buccal drug delivery system, theories and mechanism of mucoadhesion, different mucoadhesive formulations for buccal drug delivery and active ingredients delivered via the buccal route. Additionally, commercial technologies and future prospects of this route of drug delivery are discussed.

INTRODUCTION: The pharmaceutical industry has engendered considerable interest making it a major participant in the healthcare industry. The advances and progress made by pharmaceutical industry have greatly contributed in terms of treatment of disease, thereby enhancing the quality of life [1]. Over the time, scientists and researchers in the drug development industries are focusing on alternate routes of administration to add to the potential of approved drug products, or to overcome the drawbacks of the oral route. Although oral route is preferred for administration of drugs, it is associated with some restrictions for example: hepatic first pass metabolism, local GI toxicity and enzymatic degradation within the GI tract.

One strategy that has been reasonably successful to circumvent such problems is to deliver drugs systemically via an alternate route of administration such as intranasal (IN), buccal/sublingual, pulmonary,

or transdermal (TD) [2]. Transmucosal routes of drug delivery which comprise of the mucosal linings of the nasal, rectal, vaginal, ocular, and oral cavity offer excellent opportunities and potential advantages over peroral administration for systemic drug delivery. These advantages include possible bypass of first pass effect, avoidance of presystemic elimination within the GI tract and depending on the particular drug, a better enzymatic flora for drug absorption [3].

The sites of drug administration in the oral cavity include the floor of the mouth (sublingual), the inside of the cheeks (buccal) and the gums (gingival) [4]. With the advances and progress in biotechnology, hydrophilic high molecular weight therapeutic agents such as proteins and peptides are readily available for therapeutic use. However, when administered by the oral route, these agents suffer from problems such as degradation and poor absorption. To overcome these obstacles and for successful delivery of proteins and peptides, the buccal route of drug delivery has acquired significant attention [5].

In view of the systemic transmucosal drug delivery, the buccal mucosa is the preferred region as compared to the sublingual mucosa. One of the reasons is that buccal mucosa is less permeable and is thus not able to elicit a rapid onset of absorption and hence better suited for formulations that are intended for sustained release action. Further, the buccal mucosa being relatively immobile mucosa and readily accessible, it makes it more advantageous for retentive systems used for oral transmucosal drug delivery.

Over the past few decades, the concept of use of bioadhesive polymers to prolong the contact time has gained remarkable attention in transmucosal drug delivery. Adhesion as a process is simply defined as the "fixing" of two surfaces to one another. Bioadhesion may be defined as the state in which two materials, at least one of which is biological in nature, are held together for extended periods of time by interfacial forces. In the pharmaceutical sciences, when the adhesive attachment is to mucus or a mucous membrane, the phenomenon is referred to as mucoadhesion [6].

Thorough and vast research over the past few years has resulted in profound advances in understanding the concepts and aspects of mucoadhesion.

To accomplish site-specific drug delivery, a lot of interest has been turned on to the concept of mucoadhesion, which encompasses a pharmaceutical formulation incorporating mucoadhesive hydrophilic polymers along with the active pharmaceutical ingredient (API). The rationale being that the formulation will be 'held' on a biological surface for localized drug delivery and the release of API will be close to the site of action leading to enhanced bioavailability [7].

In the early 1980's, Professor Joseph R. Robinson at the University of Wisconsin pioneered the concept of mucoadhesion as a new strategy to prolong the residence time of various drugs on the ocular surface. Over the years, mucoadhesive polymers were shown to be able to adhere to various other mucosal membranes. The capability to adhere to the mucus gel layer which covers epithelial tissues makes such polymers very useful excipients in drug delivery [8].

Mucoadhesion is known to increase the intimacy and duration of contact between drug- containing polymer and a mucous surface. It is believed that the mucoadhesive nature of the device can increase the residence time of the drug in the body. The bioavailability of the drug is improved because of the combined effects of the direct drug absorption and the decrease in excretion rate. Increased residence time and adhesion may lead to lower API concentrations and lower administration frequency to achieve the desired therapeutic outcome [9].

Characteristics of an Ideal Buccoadhesive System [10-13]:
An ideal buccal adhesive system should possess the following characteristics:

1. Quick adherence to the buccal mucosa and sufficient mechanical strength.
2. Drug release in a controlled fashion.
3. Facilitates the rate and extent of drug absorption.
4. Should have good patient compliance.

5. Should not hinder normal functions such as talking, eating and drinking.

6. Should accomplish unidirectional release of drug towards the mucosa.

7. Should not aid in development of secondary infections such as dental caries.

8. Possess a wide margin of safety both locally and systemically.

9. Should have good resistance to the flushing action of saliva.

Advantages of Buccal Drug Delivery System [7, 14-19]: Drug administration via buccal mucosa offers several distinct advantages:

1. The buccal mucosa is relatively permeable with a rich blood supply, robust in comparison to the other mucosal tissues.

2. Bypass the first-pass effect and non-exposure of the drugs to the gastrointestinal fluids.

3. Easy access to the membrane sites so that the delivery system can be applied, localized and removed easily.

4. Improve the performance of many drugs, as they are having prolonged contact time with the mucosa.

5. High patient acceptance compared to other non-oral routes of drug administration.

6. Tolerance (in comparison with the nasal mucosa and skin) to potential sensitizers.

7. Increased residence time combined with controlled API release may lead to lower administration frequency.

8. Additionally significant cost reductions may be achieved and dose-related side effects may be reduced due to API localization at the disease site.

9. As a result of adhesion and intimate contact, the formulation stays longer at the delivery site improving API bioavailability using lower API concentrations for disease treatment.

10. Harsh environmental factors that exist in oral delivery of a drug are circumvented by buccal drug delivery.

11. It offers a passive system of drug absorption and does not require any activation.

12. The presence of saliva ensures relatively large amount of water for drug dissolution unlike in case of rectal or transdermal routes.

13. Provides an alternative route for the administration of various hormones, narcotic analgesics, steroids, enzymes, cardiovascular agents etc.

14. It allows the local modification of tissue permeability, inhibition of protease activity and reduction in immunogenic response. Thus, delivery of therapeutic agents like peptides, proteins and ionized species can be done easily.

Disadvantages of Buccal Drug Delivery System [5, 20]: The main challenges of buccal administration are:

1. Limited absorption area- the total surface area of the membranes of the oral cavity available for drug absorption is 170 cm^2 of which ~50 cm^2 represents non-keratinized tissues, including buccal membrane.

2. Barrier properties of the mucosa.

3. The continuous secretion of the saliva (0.5-2 l/day) leads to subsequent dilution of the drug.

4. The hazard of choking by involuntarily swallowing the delivery system is a concern.

5. Swallowing of saliva can also potentially lead to the loss of dissolved or suspended drug and ultimately the involuntary removal of the dosage form.

Overview of the Oral Mucosa:

- **Anatomy of the oral mucosa** [20]: 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. The basement membrane is, in turn, supported by connective tissues (**Fig. 1**).
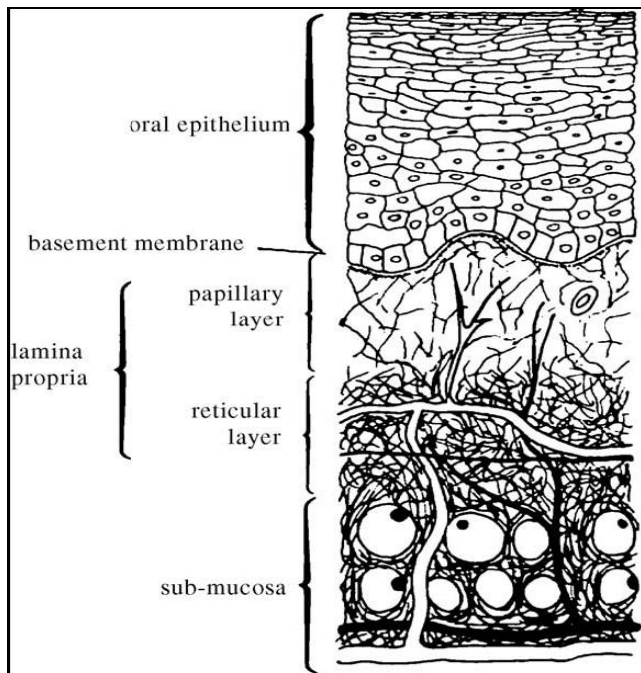
FIGURE 1: ANATOMY OF THE ORAL MUCOSA

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 shape, and increase in size while moving towards the surface. The thickness of buccal epithelium in humans, dogs, and rabbits has been determined to be approximately 500–800 μm.

The basement membrane forms a distinctive layer between the connective tissues and the epithelium. It provides the required adherence between the epithelium and the underlying connective tissues, and functions as a mechanical support for the epithelium. The underlying connective tissues provide many of the mechanical properties of oral mucosa.

The buccal epithelium is classified as a non-keratinized tissue. It is penetrated by tall and conical-shaped connective tissues. These tissues, which are also referred to as the lamina propria, consist of collagen fibers, a supporting layer of connective tissues, blood vessels, and smooth muscles. The rich arterial blood supply to the oral mucosa is derived from the external carotid artery. The buccal artery, some terminal branches of the facial artery, the posterior alveolar artery, and the infra-orbital artery are the major sources of blood supply to the lining of the cheek in the buccal cavity.

A gel-like secretion known as mucus, which contains mostly water-insoluble glycoproteins, covers the entire oral cavity. Mucus is bound to the apical cell surface and acts as a protective layer to the cells below. It is also a visco-elastic hydrogel, and primarily consists of 1-5% of the above-mentioned water insoluble glycoproteins, 95-99% water, and several other components in small quantities, such as proteins, enzymes, electrolytes, and nucleic acids. This composition can vary based on the origin of the mucus secretion in the body.

- **Drug permeability through buccal mucosa** [21]: There are two possible routes of drug absorption through the squamous stratified epithelium of the oral mucosa:

  o Transcellular (intracellular, passing through the cell) and;
  o Paracellular (intercellular, passing around the cell).

Permeation across the buccal mucosa has been reported to be mainly by the paracellular route through the intercellular lipids produced by membrane-coating granules (**fig. 2**).
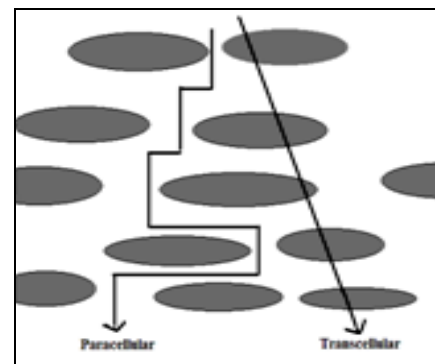

FIG. 2: **THE PARACELLULAR AND TRANSCELLULAR ROUTES OF TRANSPORT HAVE BEEN DESIGNATED TO THE BUCCAL MUCOSA**

- **Barriers to penetration across buccal mucosa** [10]: The barriers such as saliva, mucus, membrane coating granules, basement membrane etc., retard the rate and extent of drug absorption through the

buccal mucosa. The main penetration barrier exists in the outermost quarter to one third of the epithelium.

Membrane Coating Granules or Cored Granules: In non keratinized epithelia, the accumulation of lipids and cytokeratins in the keratinocytes is less evident and the change in morphology is far less marked than in keratinized epithelia. The mature cells in the outer portion of non-keratinized epithelia become large and flat retain nuclei and other organelles and the cytokeratins do not aggregate to form bundles of filaments as seen in keratinizing epithelia.

As cells reach the upper third to quarter of the epithelium, membrane-coating granules become evident at the superficial aspect of the cells and appear to fuse with the plasma membrane so as to extrude their contents into the intercellular space. The membrane-coating granules found in non-keratinizing epithelia are spherical in shape, membrane-bounded and measure about 0.2 µm in diameter. Such granules have been observed in a variety of other human non keratinized epithelia, including uterine cervix and esophagus.

However, current studies employing ruthenium tetroxide as a post-fixative indicate that in addition to cored granules, a small proportion of the granules in non-keratinized epithelium do contain lamellae, which may be the source of short stacks of lamellar lipid scattered throughout the intercellular spaces in the outer portion of the epithelium. In contrast to the intercellular spaces of stratum corneum, those of the superficial layer of non-keratinizing epithelia contain electron lucent material, which may represent non-lamellar phase lipid, with only occasional short stacks of lipid lamellae.

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. It serves as an effective delivery vehicle by acting as a lubricant allowing cells to move relative to one another and is believed to play a major role in adhesion of mucoadhesive drug delivery systems.

At buccal pH, mucus can form a strongly cohesive gel structure that binds to the epithelial cell surface as a gelatinous layer. Mucus molecules are able to join together to make polymers or an extended three-dimensional network. Different types of mucus are produced, for example G, L, S, P and F mucus, which form different network of gels. Other substances such as ions, protein chains, and enzymes are also able to modify the interaction of the mucus molecules and, as a consequence, their biophysical properties.

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. The dense sugar coating of mucins gives them considerable water-holding capacity and also makes them resistant to proteolysis, which may be important in maintaining mucosal barriers.

K. Khanvilkar *et al.*, have studied various methods for mucous permeability. They concluded that the tertiary conformation of the glycoproteins and their resulting interactions with water and with other mucins determines the mucus gel's structural characteristics. The observed variability in experimental data regarding the barrier properties of mucus suggests that the macromolecular structure of mucus is extremely sensitive to its environment. Changes in pH, ionic strength, and the presence of other agents (i.e., drugs)

can all affect the self-association of mucin macromolecules [24].

A thorough understanding of the glycoprotein mucin component is very important with regard to understanding the properties of mucus (**Fig. 3**). Mucin glycoproteins may be described as consisting of a basic unit made from a single-chain polypeptide backbone with two distinct regions [24].
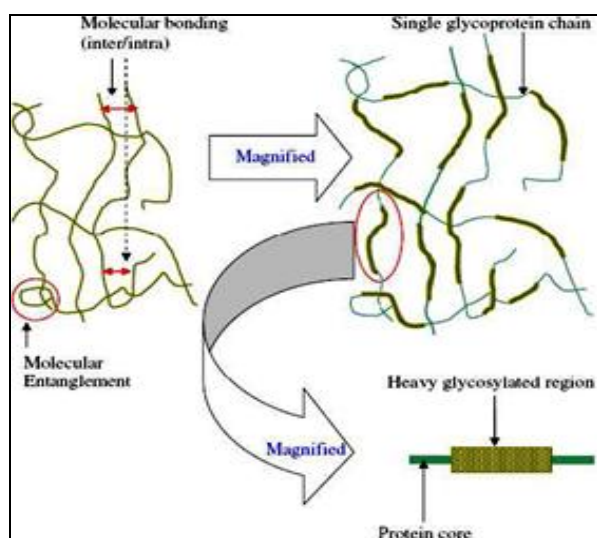

FIG. 3: THE COMPOSITION AND INTERACTION OF GLYCOPROTEIN CHAINS WITHIN MUCUS

(1) A heavy glycosylated central protein core to which many large carbohydrate side chains are attached, predominantly via O-glycosidic linkages.

(2) One or two terminal peptide regions where there is little glycosylation. These regions are often referred to as 'naked protein regions'.

Mucins are secreted as massive aggregates by prostaglandins with molecular masses of roughly 1 to 10 million Da. Within these aggregates, monomers are linked to one another mostly by non-covalent interactions, although intermolecular disulphide bonds also play a role in this process. Oligosaccharide side chains contain an average of about 8–10 monosaccharide residues of five different types namely L-fucose, D-galactose, N-acetyl-D-glucosamine, N-acetyl-D-galactosamine and sialic acid. Amino acids present are serine, threonine and proline. Because of the presence of sialic acids and ester sulfates, mucus is negatively charged at physiological salivary pH of 5.8–7.4.

Saliva: The mucosal surface has a salivary coating estimated to be 70 µm thick, which act as 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.

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. Total output from the major and minor salivary glands is termed as whole saliva, which at normal conditions has flow rate of 1–2 ml/min. Greater salivary output avoids potential harm to acid-sensitive tooth enamel by bathing the mouth in copious neutralizing fluid. With stimulation of salivary secretion, oxygen is consumed and vasodilator substances are produced; and the glandular blood flow increases, due to increased glandular metabolism.

Saliva is composed of 99.5% water in addition to proteins, glycoproteins and electrolytes. It is high in potassium (7×plasma), bicarbonate (3×plasma), calcium, phosphorous, chloride, thiocyanate and urea and low in Na (1/10×plasma). The normal pH of saliva is 5.6–7. Saliva contains enzymes namely α-amylase (breaks 1–4 glycosidic bonds), lysozyme (protective, digests bacterial cell walls) and lingual lipase (break down the fats).

Saliva serves multiple important functions:

1) It moistens the mouth, initiates digestion and protects the teeth from decay.
2) It also controls bacterial flora of the oral cavity.
3) Because saliva is high in calcium and phosphate, it plays a role in mineralization of new teeth repair and precarious enamel lesions.

4) It protects the teeth by forming "protective pellicle". This signifies a saliva protein coat on the teeth, which contains antibacterial compounds.

Thus, problems with the salivary glands generally result in rampant dental caries. Lysozyme, secretory IgA, and salivary peroxidase play important roles in saliva's antibacterial actions. Lysozyme agglutinates bacteria and activates autolysins. Ig A interferes with the adherence of microorganisms to host tissue. Peroxidase breaks down salivary thiocyanate, which in turn, oxidizes the enzymes involved in bacterial glycolysis. However, salivary flow rate may play role in oral hygiene. Intraoral complications of salivary hypofunction may cause candidiasis, oral lichen planus, burning mouth syndrome, recurrent aphthous ulcers and dental caries.

A constant flowing down of saliva within the oral cavity makes it very difficult for drugs to be retained for a significant amount of time in order to facilitate absorption in this site. The other important factor of great concern is the role of saliva in development of dental caries. Salivary enzymes act on natural polysaccharidic polymers that hasten the growth of mutants of streptococci and other plaque bacteria leading to development of dental caries.

Permeabilities between different regions of the oral cavity vary greatly because of the diverse structures and functions. In general, the permeability is based on the relative thickness and degree of keratinization of these tissues in the order of sublingual>buccal> palatal. The permeability of the buccal mucosa was estimated to be 4–4000 times greater than that of the skin.

Formulation Considerations: For buccal drug delivery, it is cardinal to prolong and augment the contact between API and mucosa to obtain the desired therapeutic effect. Buccal adhesive drug delivery systems with the size 1-3 cm^2 and a daily dose of 25 mg or less are preferable. The maximal duration of buccal delivery is approximately 4-6 h [25]. To comply with the therapeutic requirements, the excipients or functional agents used in formulation for buccal drug delivery are mentioned below as per their categories. Also the excipients used in the formulation should be GRAS-listed i.e., Generally Recognized as Safe.

- **Mucoadhesive polymers:** Polymer is a generic term used to describe a very long molecule consisting of structural units and repeating units connected by covalent chemical bonds. The term is derived from the Greek words: polys meaning many and more meaning parts [26]. Mucoadhesives are synthetic or natural polymers that interact with the mucus layer covering the mucosal epithelial surface and main molecules constituting a major part of mucus. The concept of mucoadhesives has alerted many investigators to the possibility that these polymers can be used to overcome physiological barriers in long-term drug delivery[27]. The development of Orahesive® followed, leading to trials of Orabase® in 1959. Orabase® was formulated from natural gums and represented the first purposely developed mucoadhesive. Orabase® product (Adcortyl in Orabase®) provides local relief of mouth ulcers via a twofold mechanism: barrier function and an anti-inflammatory function (due to triamcinolone acetonide) [7].

Classification: In general, adhesive polymers can be classified as synthetic vs. natural, water-soluble vs. water insoluble, and charged vs. uncharged polymers. **Table 1** summarizes the mucoadhesive polymers used in buccal drug delivery [20].

TABLE 1: MUCOADHESIVE POLYMERS USED IN BUCCAL DELIVERY

Criteria	Categories	Examples
Source	**Semi-natural/natural**	Agarose, chitosan, gelatin, Hyaluronic acid, Various gums (guar, hakea, xanthan, gellan, carrageenan , pectin, and sodium alginate)
	Synthetic	**Cellulose derivatives** [CMC, thiolated CMC, sodium CMC, HEC, HPC, HPMC, MC, methylhydroxyethylcellulose] **Poly(acrylic acid)-based polymers** [CP, PC, PAA, polyacrylates, poly(methylvinylether-co-methacrylic acid), poly(2-hydroxyethyl methacrylate), poly(acrylic acid-co-ethylhexylacrylate), poly(methacrylate), poly(alkylcyanoacrylate), poly(isohexylcyanoacrylate), poly(isobutylcyanoacrylate), copolymer of acrylic acid and PEG]

	Others	
	Poly(N-2-hydroxypropyl methacrylamide) (PHPMAm), polyoxyethylene, PVA, PVP, thiolated polymers	
Aqueous solubility	**Water-soluble**	CP, HEC, HPC (water < 38°C), 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

The polymers most commonly used in buccal dry or partially hydrated dosage forms include polyacrylic acid (PAA), polyvinyl alcohol (PVA), sodium carboxy methylcellulose (NaCMC), hydroxypropylmethyl cellulose (HPMC), hydroxyethylcellulose (HEC), hydroxy propylcellulose (HPC) and sodium alginate [28-34].

New generation of mucoadhesive polymers (with the exception of thiolated polymers) can adhere directly to the cell surface, rather than to the mucus. They interact with the cell surface by means of specific receptors or covalent bonding instead of non-specific mechanisms, which are characteristic of the previous polymers. Examples of such are the incorporation of L-cysteine into thiolated polymers and the target-specific, lectin-mediated adhesive polymers. These classes of polymers hold promise for the delivery of a wide variety of new drug molecules, particularly macromolecules, and create new possibilities for more specific drug-receptor interactions and improved targeted drug delivery [20].

Thiolated polymers or designated thiomers are mucoadhesive basis polymers, which display thiol bearing side chains [35]. These polymers are obtained by addition of conjugated sulfidryl groups [36]. Thiolated polymers are a type of second-generation mucoadhesive polymer derived from hydrophilic polymers such as polyacrylates, chitosan or deacetylated gellan gum.

Table 2 lists typical hydrophilic polymers that have been thiolated and the subsequent effect on mucoadhesive bond strength. The presence of thiol groups allows the formation of covalent bonds with cysteine-rich sub domains of the mucus gel layer, leading to increased residence time and improved bioavailability [7].

TABLE 2: AN EXAMPLE OF THIOLATED POLYMERS AND THE EFFECT ON MEASURED MUCOADHESION

Polymer	Mucoadhesive bond strength
Chitosan iminothiolane	250-fold improved mucoadhesive properties.
Poly(acrylic acid)-cysteine	100-fold improved mucoadhesive properties.
Poly(acrylic acid)- homocysteine	Approximately 20-fold improved mucoadhesive properties
Chitosan-thioglycolic acid	Tenfold improved mucoadhesive properties
Chitosan-thioethylamidine	ninefold improved mucoadhesive properties
Alginate-cysteine	fourfold improved mucoadhesive properties
Poly(methacrylic acid)-cysteine	Improved cohesive and mucoadhesive properties
Sodium carboxymethylcellulose-cysteine	Improved mucoadhesive properties

In recent years, lectins have been studied as specific bioadhesives for drug delivery in the oral cavity [37]. Their peculiarity lies in the mucoadhesion mechanism: such substances are able to recognize and bind some specific sugar residues on mucosal surface without altering the structure of the recognized ligand [38]. Recently, lamellar and cubic liquid crystalline phases of glyceryl monooleate (GMO) have shown mucoadhesive properties and feasibility to be used as carriers for buccal drug delivery [39].

Mechanism of Mucoadhesion [40]**:** The mechanism of adhesion of certain macromolecules to the surface of a mucous tissue is not well understood yet. The mucoadhesive must spread over the substrate to initiate close contact and hence increase surface contact, promoting the diffusion of its chains within the mucus. Attraction and repulsion forces arise and, for a mucoadhesive to be successful, the attraction

forces must dominate. Each step can be facilitated by the nature of the dosage form and how it is administered.

Thus, the mechanism of mucoadhesion is generally divided in two steps:

1) The contact stage, and
2) The consolidation stage

The first stage or the contact stage (Figure 4) is characterized by the contact between the mucoadhesive and the mucous membrane, with spreading and swelling of the formulation, initiating its deep contact with the mucus layer. In the consolidation step (**Figure 4**), the mucoadhesive materials are activated by the presence of moisture. Moisture plasticizes the system, allowing the mucoadhesive molecules to break free and to link up by weak van der Waals and hydrogen bonds.
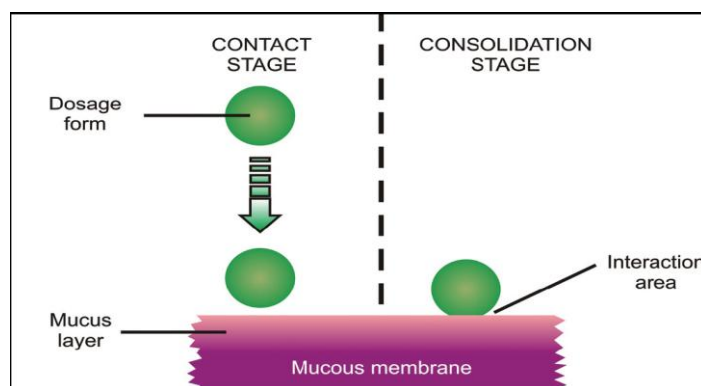

FIG. 4: THE TWO STEPS OF THE MUCOADHESION PROCESS

Theories of mucoadhesion [41]**:** Although the chemical and physical basis of mucoadhesion are not yet well understood, there are six classical theories adapted from studies on the performance of several materials and polymer-polymer adhesion which explain the phenomenon. The predominant theories on mucoadhesion are briefly described here in **table 3**.

TABLE 3: THEORIES OF MUCOADHESION

Theory	Mechanism of bioadhesion	Comments
Electronic theory	Attractive electrostatic forces between glycoprotein mucin network and the bioadhesive material.	Electrons transfer occurs between the two forming a double layer of electric charge at the Surface.
Wetting theory	Ability of bioadhesive polymer to spread and develop intimate contact with the mucous membrane.	Spreading coefficient of polymers must be positive. Contact angle between polymer and cells must be near to zero.
Adsorption theory	Surface force resulting in chemical bonding.	Strong primary force: covalent bonds. Weak secondary forces: hydrogen bonds and van der Waal's forces.
Diffusion theory	Physical entanglement of mucin strands and flexible polymer chains.	For maximum diffusion and best adhesive strength, solubility parameters of the bioadhesive polymer and the mucus glycoproteins must be similar.
Mechanical theory	Adhesion arises from an interlocking of liquid adhesive into irregularities on the rough surface.	Rough surfaces provide an increased surface area available for interaction along with an enhanced viscoelastic and plastic dissipation of energy during joint failure, which are more important in the adhesion process than a mechanical effect.
Fracture theory	Analyses the maximum tensile stress developed during attachment of the transmucosal DDS from the mucosal surface.	Does not require physical entanglement of bioadhesive polymer chains and mucous strands, hence it is appropriate to study the bioadhesion of hard polymers which lack flexible chains.

Penetration enhancers: Penetration enhancers are the substances, which increase the buccal mucosal membrane permeation rate. Although most penetration enhancers were originally designed for purposes other than absorption enhancement, a systemic search for safe and effective penetration enhancers must be a priority in drug delivery [42]. With the rapid development of biotechnology, more and more protein, peptide, and nucleotide drugs are becoming available, most of which have low membrane-absorption characteristics including:

- A large size with high molecular weight,
- Domains of different hydrophobicity,
- Irregular shapes, and
- Delicate structures easily inactivated.

These drugs are unable to cross membrane barriers in therapeutic amounts and thus research into penetration enhancers becomes ever more important [43].

Classification [43]:

TABLE 4: CLASSIFICATION OF PENETRATION ENHANCERS

Surfactants	**a) Ionic**
	Sodium lauryl sulfate
	Sodium laurate
	Polyoxyethylene-20-cetyl ether
	Laureth-9
	Sodium dodecyl sulfate(SDS)
	Dioctyl Sodium sulfosuccinate
	b) Nonionic
	Polyoxyethylene-9-lauryl ether (PLE) (nonionic)
	Tween 80(nonionic)
	Nonylphenoxypolyoxyethylene(NP-POE)(nonionic)
	Polysorbates
	Sodium glycocholate
Bile salts and derivatives	Sodium deoxycholate
	Sodium taurocholate
	Sodium taurodihydrofusidate(STDHF)
	Sodium glycodihydrofusidate
	Sodium glycocholate
	Sodium deoxycholate
Fatty acids and derivatives	Oleic acid
	Caprylic acid
	Mono(di)glycerides
	Lauric acid
	Linoleic acid
	Acylcholines
	Acylcarnitine
	Sodium caprate
	Oleic acid
Chelating agents	EDTA
	Citric acid
	Salicylates
Sulfoxides	Dimethyl sulfoxide(DMSO)
	Decylmethyl sulfoxide
Polyols	Propylene glycol
	Polyethylene glycol
	Glycerol
	Propanediol
Monohydric alcohols	Ethanol
	Isopropanol
Others (non-surfactants)	Urea and derivative
	Unsaturated cyclic urea
	Azone(1-dodecylazacycloheptan-2-one) (laurocapram)
	Cyclodextrin
	Enamine derivatives
	Terpenes
	Liposomes
	Acyl carnitines and cholines

A new absorption promoter for buccal delivery named lysalbinic acid has been studied using hamster cheek mucosa as a simple animal model for the initial evaluation of absorption promoters. It was shown that co-administration of lysalbinic acid with relatively small proteins (6-16 kDa), such as α-inteferon and insulin, can significantly increase their absorption via the buccal epithelium. Thus, lysalbinic acid has been shown to increase significantly permeability of the hamster oral mucosa for peptide compounds of low-to middle-molecular weight [44].

Mechanism of buccal permeation enhancers [45]: Table 5 provides an overview of some of the proposed mechanisms of action of penetration enhancers.

TABLE 5: MUCOSAL PENETRATION ENHANCERS AND MECHANISMS OF ACTION

Classification	Examples	Mechanism
Surfactants	**Anionic**: sodium lauryl sulfate, Sodium laurate **Cationic**: cetylpyridinium chloride **Nonionic**: poloxamer, Brij, Span, Myrj, Tween **Bile salts**: sodium glycodeoxy cholate, sodium glycocholate, sodium taurodeoxycholate, sodium taurocholate, Azone®	Perturbation of intercellular lipids, protein domain integrity
Fatty acids	Oleic acid, caprylic acid	Increase fluidity of phospholipids domains
Cyclodextrins	α-, β, γ-cyclodextrin, methylated β-cyclodextrins	Inclusion of membrane compounds
Chelators	EDTA, sodium citrate Polyacrylates	Interfere with Ca^{2+}
Positively charged polymers, Cationic compounds	Chitosan, trimethyl chitosan, Poly-L-arginine, L-lysine	Ionic interaction with negative charge on the mucosal surface

Enzyme Inhibitors: The co-administration of a drug with enzyme inhibitors is another strategy for improving 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 affecting the activities of the enzymes, altering the conformation of the peptides or proteins and/or

rendering the drug less accessible to enzymatic degradation [25, 46, 47].

It has been shown that some mucoadhesive polymers can act as an enzyme inhibitor. The particular importance of this finding lies in delivering therapeutic compounds that are specifically prone to extensive enzymatic degradation, such as proteins and polypeptide drugs. Investigations have demonstrated that polymers, such as poly(acrylic acid), operate through a competitive mechanism with proteolytic enzymes.

This stems from their strong affinity to divalent cations (Ca^{2+}, Zn^{2+}). These cations are essential cofactors for the metalloproteinases, such as trypsin. Circular dichroism studies suggest that Ca^{2+} depletion, mediated by the presence of some mucoadhesive polymers, causes the secondary structure of trypsin to change, and initiates a further autodegradation of the enzyme[48, 49].

Buccal Dosage Forms: Over the past few years, different dosage forms intended for buccal drug delivery have been developed. **Table 6** lists the active ingredients delivered via the buccal route [21].

Buccal mucoadhesive dosage forms can be categorized into three types based on their geometry illustrated in the following **fig. 5**.

TABLE 6: ACTIVE INGREDIENTS DELIVERED VIA THE BUCCAL ROUTE

| Active Ingredients	Active Ingredients
Acitretin	Metronidazole
Acyclovir	Melatonin
Arecoline	Metoprolol tartrate
Buprenorpine	Morphine sulphate
Carbamazepine	Nalbuphine
Cetyl Pyridinium chloride	Nicotine
Chlorhexidine diacetate	Nifedipine
Chitosan	Omeprazole
Chlorpheniramine maleate	Oxytocin
Cyanocobalamin	Pentazocine
Danazol	Protirelin
Denbufylline	Pindolol
Diclofenac sodium	Piroxicam
Diltiazem Hydrochloride	Propranolol
Ergotamine tartrate	Propolis
Fluride	Recombinant human epidermal growth factor (Rh EFG)
Flurbiprofen	Salmon calcitonin
Glucagon-like peptide (GLP)-1	Sodium fluoride
Hydrocortisone acetate	Testosterone
Insulin	Terbutaline sulphate
Lactoferrin	Theophylline
Lignocaine	Thyotropin releasing hormone
Leu-enkephalin	Triamcinolone acetate
Luteinizing hormone releasing Hormone (LHRH)	Zinc sulphate
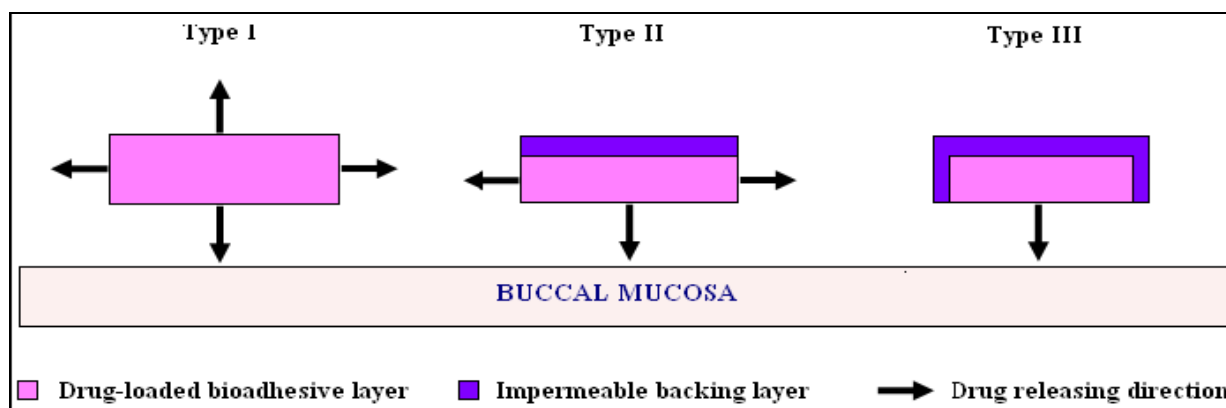
FIGURE 5: DESIGN OF BUCCAL MUCOADHESIVE DOSAGE FORMS

Buccal Mucoadhesive Dosage: 3 types;

Type I: It is a single layer device with multidirectional drug release. This type of dosage form suffers from significant drug loss due to swallowing.

Type II: In this type, an impermeable backing layer is superimposed on top of the drug loaded bioadhesive layer, creating a double-layered device and preventing drug loss from the top surface of the dosage form into the oral cavity.

Type III: This is a unidirectional release device, from which drug loss is minimal, since the drug is released only 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.

Buccal dosage forms can also be classified as either a "reservoir" or "matrix" type. In the reservoir type, an excessive amount of the drug is present in the reservoir surrounded by a polymeric membrane, which controls the drug's release rate. In the matrix type systems, the drug is uniformly dispersed in the polymer matrix, and drug release is controlled by diffusion through the polymer network.

A number of relevant buccal mucoadhesive dosage forms have been developed for a variety of drugs. Several peptides, including thyrotropin-releasing hormone (TRH), insulin, protirelin, buserelin and oxytocin, have been delivered via the buccal route, albeit with relatively low bioavailability (0.1–5%)[47]

owing to their hydrophilicity and large molecular weight, as well as the inherent permeation and enzymatic barriers of the buccal mucosa.

Buccal dosage forms can be used to treat both local and systemic conditions. A promising example of buccal mucoadhesive formulations for systemic use is the buccal delivery of salmon calcitonin (sCT) using thin-film composite containing 40 µg of sCT (200 IU)[50].

The *in vivo* studies in female New Zealand white rabbits demonstrated a relative bioavailability of 43.8±10.9%, and the reduction in plasma calcium level after the buccal administration of sCT was comparable to that observed when sCT was administered by the intravenous route. These results indicate that therapeutically effective amounts of salmon calcitonin can be delivered to the systemic circulation via the buccal mucosa.

Table 7 summarizes various buccal dosage forms described in the literature[5].

Table 7: Summary of the different buccal dosage forms described in the literature

Dosage forms	Structures	Release	Effect	Active ingredients
Matrix tablets	Monolithic matrix	Sustained/bidirectional	Local/systemic	**Local administration**: metronidazole. **Systemic administration**: propanolol, timolol, metoclopramide, morphine sulphate, nitroglycerin, codein, insulin, calcitonin, glucagone-like peptide
	Coating matrix (coated on the outer side or on all but one faces)	Monodirectional	Systemic	
	Two-layer matrix,	Bidirectional	Local (mainly)	
	Two-layer matrix coated with impermeable layer	Monodirectional	Systemic	
Patches	Laminated film with coating layer	Monodirectional	Local/systemic	**Local administration**: diclofenac, tannic acid, boric acid. **Systemic administration**: thyrotropin-releasing hormone, octreotide, oxytocin, buserelin, calcitonin, leuenkephalin
Lipophilic gels	Cubic and lamellar liquid crystalline phases of glyceryl monooleate	–	Systemic	**Systemic administration**: (D-Ala2, D-Leu5) enkephalin
Transfersomes	Phospholipid deformable vesicles	–	Systemic	**Systemic administration**: insulin

Buccal Tablets: Tablets have been the most commonly investigated dosage form for buccal drug delivery. Buccal tablets are small, flat, and oval shaped dosage form and unlike conventional tablets allow for drinking

and speaking without major discomfort. They soften, adhere to the mucosa and are retained in position until dissolution and/or release is complete[17]. List of investigated buccal mucoadhesive tablets is given in the following **table 8**.

TABLE 8: LIST OF INVESTIGATED BUCCAL MUCOADHESIVE TABLETS

Active ingredient	Polymers used	Investigators [Ref.]
Baclofen	NaMC, Na alginate and Methocel K15M	Basani et al.[51]
Carvedilol	HPMC K4M and CP 934P	Pandey et al.[52]
Carvedilol	HPMC K4M, HPMC K15M and CP 934	Yamsani et al.[53]
Chlorhexidine diacetate	Chitosan and Na alginate	Giunchedi et al.[54]
Chlorpheniramine maleate	Hakea gum from *Hakea gibbosa*	Alur et al.[55]
Diltiazem	NaCMC, HPMC, Na alginate and guar gum.	Manivannan et al.[56]
Flurbiprofen	HPMC K15M, HEC, CP971 and Carbomer 940	Perioli et al.[57]
Itraconazole	Eudragit 100M, HPMC K4M and CP 934P	Madgulkar et al.[58]
Miconazole nitrate	CP 934, HPMC K4M and PVP K30	Madgulkar et al.[59]
Morphine sulfate	HPMC K100M, CP 910 and Eudragit RSPM	Anlar et al.[60]
Nicotine	CP 934 and HPC	Park and Munday [61]
Nifedipine	CMC, CP 934P, HPMC, PVP K30 and PVA	Varshosaz et al.[62]
Omeprazole	Na alginate, HPMC	Choi and Kim[63]
Ondansetron	HPMC 15 cps, CP 934, Na alginate and NaCMC.	Hassan et al.[64]
Oxytocin	Mucilage of *Diospyros peregrina* fruit	Metia et al.[65]
Piroxicam	HPMC K4M and CP934	Velmurugan et al.[66]
Pravastatin Na	PVP K-30 and Pluronic F127and EC	Shidhaye et al.[67]
Prednisolone	HPMC, CP 934 and NaCMC	Samani et al.[68]
Propranolol HCl	Na alginate, CP 971P and PVP K30	Derle et al.[69]
Propranolol HCl	HPMC K4M, Xanthan gum, EC and acrypol 934P	Shukla et al.[70]
Salbutamol sulphate	HPMC K4M and EC	Arya et al.[71]
Tizanidine HCl	CP 934, HPMC K4M, HPMC K15M and NaCMC and EC	Shivanand et al.[72]
Verapamil HCl	CP934 P, HPMC K4M, HEC and NaCMC	Chandira et al.[73]

Monolithic and two-layered matrix tablets have been designed for buccal drug delivery. In **Fig. 6**, a schematic representation of several kinds of matrix tablets is given [5].

Bioadhesive tablets may be prepared using different methods such as direct compression or wet granulation technique. For buccal drug delivery, the tablets which are inserted into the buccal pouch may dissolve or erode; therefore, they must be formulated and compressed with sufficient pressure only to give a hard tablet. To enable or to achieve unidirectional release of drug, water impermeable materials, such as ethylcellulose, hydrogenated castor oil, etc. may be used either by compression or by spray coating to coat every face of the tablet except the one that is in contact with the buccal mucosa.

If necessary, the drug may be formulated in certain physical states, such as microspheres, prior to direct compression in order to achieve some desirable properties, e.g. enhanced activity and prolonged drug release [54].

Buccal patches: Buccal patches are described as laminates which comprise of an impermeable backing layer, a drug-containing reservoir layer which releases the drug in a controlled manner, and a bioadhesive surface for mucosal attachment. Two methods, namely, solvent casting method and direct milling are used to prepare adhesive patches. In the solvent casting method, the intermediate sheet from which patches are punched is prepared by casting the solution of the drug and polymer(s) onto a backing layer sheet, and subsequently allowing the solvent(s) to evaporate.

desired thickness, and patches of predetermined size and shape are then cut or punched out.

Also to control the direction of drug release, prevent drug loss, and minimize deformation and disintegration of the device during the application period, an impermeable backing layer may be applied. The drugs and polymers that have been used to develop buccal patches are listed in **table 9** as given below.

Buccal films: In recent times, a number of mucoadhesive dosage forms for buccal drug delivery have been developed such as tablet, films, patches, discs, ointments and gels [74-75 and 90-97]. However, buccal films are preferable over mucoadhesive discs and tablets in terms of patient comfort and flexibility and they ensure more accurate drug dosing and longer residence time compared to gels and ointments. Buccal films also reduce pain by protecting the wound surface and hence increase the treatment effectiveness [98].

An ideal buccal film should be flexible, elastic, and soft yet strong enough to withstand breakage due to stress from activities in the mouth. Moreover, it should also possess good mucoadhesive strength so that it is retained in the mouth for the desired duration [99].

FIG. 6: SCHEMATIC REPRESENTATION OF DIFFERENT MATRIX TABLETS FOR BUCCAL DELIVERY. ARROWS INDICATE THE DIRECTION OF DRUG RELEASE

In the direct milling method, formulation constituents are homogeneously mixed and compressed to the

The drugs and polymers that have been used to develop buccal mucoadhesive films are listed in **table 10**.

TABLE 9: LIST OF INVESTIGATED BUCCAL MUCOADHESIVE PATCHES

Active ingredient	Polymers used	Investigators [Ref.]
Aceclofenac	Gelatin, Poly Na CMC and PVA.	Khairnar *et al.*[74]
Atenolol	CP 934P, HPMC and NaCMC	Adhikari *et al.*[75]
Carvedilol	HPMC, CP934, Eudragit RS 100, and EC	Thimmasetty *et al.*[76]
Carvedilol	HPMC E15 and HPC JF	Vishnu *et al.*[77]
Cetylpyridium chloride	PVA, HEC, or chitosan	Nafee *et al.*[30]
Hydrochlorothiazide	EC and HPMC	Attama *et al.*[78]
Ibuprofen	NaCMC and PVP	Perioli *et al.*[79]
Insulin	NaCMC-DVP	Sahni *et al.*[80]
Methotrexate	HPMC K4M, Na alginate, NaCMC, CP 934, PVA and PVP K-30	Bhanja *et al.*[81]
Metoprolol tartrate	Eudragit NE40D with HPMC, Na CMC or CP	Wong *et al.*[82]
Miconazole	HPMC, NaCMC, Chitosan, HECand PVA.	Nafee *et al.*[31]

Pentazocine	CMC, HPMC K4M, CP 974P and PVA	Agarwal *et al.*[83]
Prochlorperazine	HPMC E15	Kolli *et al.*[84]
Propranolol HCl	Chitosan and PVP K-30	Patel *et al.*[85]
Salbutamol sulphate	Chitosan,PVA and PVPK30	Patel et al.[86]
Tizanidine HCl	NaCMC and CP 934	Giradkar et al.[87]
Triamcinolone acetonide	HPMC, Polaxamer 407 and CP971	Chun et al.[88]
Verapamil HCl	Chitosan and PVP K-30	Deshmane et al.[89]

TABLE 10: LIST OF INVESTIGATED BUCCAL MUCOADHESIVE FILMS

Active ingredient	Polymers used	Investigators [Ref.]
Atenolol	Na alginate, CP 934P and EC	Satishbabu *et al.*[100]
Carvedilol	HPMC K15,Eudragit RL100, CP-934P, NaCMC and PVP	Viram J *et al.*[101]
Chlorhexidine diacetate	Chitosan, HPMC, Na alginate	Juliano *et al.*[102]
Ciprofloxacin HCl	HPMC K4M, PVA	Choudhury *et al.*[103]
Famotidine	HPMC, NaCMC and PVA	Kumar *et al.*[104]
Fentanyl	Eudragit RS, PVP K30 and PVP K90	Consuelo *et al.*[105]
Flufenamic acid	Chitosan and KollicoatIR®	Mura *et al.*[106]
Glibenclamide	HPC, PVP and EC	Goudanavar *et al.*[107]
Glipizide	HPMC E-15, NaCMC, Eudrait RL-100 and CP 934P	Semalty *et al.* [108]
Isosorbide Dinitrate	Eudragit RL 100, CP 93P and PVP	Doijad *et al.*[109]
Isoxsuprine HCl	HPMC, PVP K-30 and HEC	Pillai *et al.*[110]
Ketorolac	HPMC, CP 934P, NaCMC, HPC and EC	Alanazi *et al.*[111]
Lycopene	HPMC E15, PVP K30 and CP 934	Shah *et al.*[112]
Metoprolol tartrate	CP934 P, Eudragit RL100, PVP, HPMC K15M and Na CMC	Nagaich *et al.*[113]
Montelukast	HPMC K4M, HPMC 50cps, HPMC 5cps, Eudragit RL-100 and PVP K30	Rao *et al.*[114]
Ranitidine	HPMC 15 cps and PVP	Alagusundaram *et al.*[115]
Terbutaline sulphate	HPMC K4M, HPMCP, Chitosan, CP 934P	Kumar *et al.*[116]

Buccal gels and ointments: These are semisolid dosage forms having the advantage of easy dispersion throughout the oral mucosa. The problem of poor retention of gels at the application site has been overcome by using bioadhesive formulations. Certain bioadhesive polymers for example, sodium carboxymethylcellulose[82] undergo a phase change from a liquid to a semisolid. This change enhances or improves the viscosity, resulting in sustained or controlled release of drugs.

The drugs and polymers used for buccal mucoadhesive gels are listed in **table 11**.

TABLE 11: LIST OF INVESTIGATED BUCCAL MUCOADHESIVE GELS

Active ingredient	Polymers used	Investigators [Ref.]
Insulin	Pluronic F-127gel, oleic acid, eicosapentaenoic acid and docosahexaenoic acid.	Morishita *et al.* [96]
Itraconazole	2-ethylmethyl-2 pyrrolidone, Polaxamer 188 and CP 934	Kumar.K *et al.*[117]
Nystatin	Chitosan	Rasool *et al.*[118]
Triamcinolone acetonide	Polaxamer 407 and CP 934	Shin *et al.* [97]

Innovative Drug Delivery Systems: Innovative drug delivery systems comprise use of lipophilic gel, buccal spray and phospholipid vesicles to deliver peptides via the buccal route. The use of cubic and lamellar liquid crystalline phases of glyceryl monooleate as buccal drug carrier for peptide drugs has also been proposed.

A novel liquid aerosol formulation (Oralin, Generex Biotechnology) [119] has been recently developed, and it is now in clinical phase III trials. This system allows precise insulin dose delivery via a metered dose inhaler in the form of fine aerosolized droplets directed into the mouth. Levels of drug in the mouth are dramatically increased compared with conventional technology. This oral aerosol formulation is rapidly absorbed through the buccal mucosal epithelium, and it provides the plasma insulin levels necessary to control postprandial glucose rise in diabetic patients. This novel, pain-free, oral insulin formulation has a number of advantages including rapid absorption, a simple (user-friendly) administration technique, precise dosing control (comparable to injection within one unit) and bolus delivery of drug.

Phospholipid deformable vesicles, transfersomes, have been recently devised for the delivery of insulin in the buccal cavity [120]. They are morphologically similar to liposomes but differ on account of function. Transferomes respond to external stresses by rapid shape transformations requiring low energy. This high deformability allows them to deliver drugs across epithelial barriers. To prepare these vesicles, surfactants, such as sodium cholate or sodium dehoxycholate are incorporated into the vesicular membrane. The insulin administration in rabbits surpasses that seen with traditional liposomes: compared with subcutaneous administration of insulin solution, the bioavailability of deformable vesicles was significantly greater than that of the conventional vesicles.

Commercial Technologies and Marketed Products: Marketed formulations or formulations under research in clinical trials for buccal drug delivery are listed in **table 12** [5].

TABLE 12: MARKETED AND UNDER RESEARCH FORMULATIONS

Brand name	Active ingredient	Bioadhesive polymer	Dosage form	Company
Aphtach	Triamcinolone acetonide	HPC, PAA	Tablet	Teijin Ltd
Buccastem	Prochlorperazine	Xanthan gum, Povidone, Locust bean gum	Tablet	Reckitt Benkiser Plc
Oralin–Generex	Insulin	Unknown	solution	Generex Biotechnology (Phase III trials)
Lauriad	Miconazole	Unknown	Tablet	BioAlliance Pharma (Phase III trials)
Striant SR	Testosterone	Carbomer 934P, Hypromellose, PC	Tablet	Ardana Bioscience Ltd
Suscard	Glyceryl trinitrate	Hypromellose	Tablet	Forest Laboratories

CONCLUSION: In the past few decades, research in buccal drug delivery has revealed remarkable growth and advances. The transmucosal route is becoming more and more popular because it does have significant advantages like avoidance of first pass metabolism in the liver and pre-systemic elimination in the gastrointestinal tract. Buccal drug delivery holds a great promise for systemic delivery of orally inefficient drugs as well as a feasible and attractive alternative for non-invasive delivery of potent peptide and protein drug molecules.

Despite the advantages of delivering drugs through buccal mucosa, this route is still very challenging, with the main obstacles being the limited absorption area and the barrier properties of the mucosa. The strategies studied to overcome such obstacles include use of materials that combine mucoadhesive, enzyme inhibitory and penetration enhancer properties and the design of novel formulations, which besides improving patient compliance favor an intimate and prolonged contact of the drug with the absorption mucosa.

New and unforeseen challenges are expected in the use of mucoadhesives for the delivery of new drugs and in the search of ideal mucoadhesives. Efforts have to be made to develop standardized *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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