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# DRUG DELIVERY BASED ON BUCCAL ADHESIVE SYSTEMS - A REVIEW

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## ABSTRACT

Buccal delivery involves the administration of the desired drug through the buccal mucosal membrane lining of the oral cavity.The objective of this article is to review buccal drug delivery by discussing the structure and environment of the oral mucosa and highlighting the mechanisms of drug permeation and methodology in evaluating buccal formulations. This review also highlights a brief description of advantages, limitations of buccal drug delivery and theories involved in mucoadhesion. Additionally, we discuss on the new generation of mucoadhesive polymers such as thiolated polymers, lectins, followed by the recent mucoadhesive formulations for buccal drug delivery.

**KEYWORDS:** **Buccal drug delivery, mucoadhesion, polymers.**

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# INTRODUTION

Over the last two decades mucoadhesion has become of interest for its potential to optimise localised drug delivery, by retaining a dosage form at the site of action (e.g. within the gastrointestinal tract) or systemic delivery, by retaining a formulation in intimate contact with the absorption site (e.g. the nasal cavity)[1]. The oral route of drug administration constitutes the most convenient and preferred means of drug delivery to systemic circulation body. However oral administration of most of the drugs in conventional dosage forms has short-term limitations due to their inability to restrain and localize the system at gastrointestinal tract. In order to circumvent this problem, it has been proposed, successfully for several of them, to associate drugs to polymeric particulate systems because of their propensity to interact with the mucosal surface[2]. An advantage of using a mucoadhesive polymer carrier for drug delivery is the prevention of first pass metabolism of certain protein drugs by the liver through the introduction of the drug via a route bypassing the digestive tract. Drugs that are absorbed through the mucosal lining of tissues can enter directly into the bloodstream and not be inactivated by enzymatic degradation in the gastrointestinal tract [3]. It is generally thought that mucoadhesion occurs mainly through hydrogen bonding of the mucoadhesive polymer with mucin, a glycoprotein that is secreted locally, and which coats the mucosal surface[4]. Mucoadhesive polymers have been utilised in many different dosage forms in efforts to achieve systemic delivery of drugs through the different mucosae. These dosage forms include tablets, patches, tapes, films, semisolids and powders. Mucoadhesive polymers should possess some general physiochemical features such as predominantly anionic hydrophilicity with numerous hydrogen bond-forming groups, suitable surface property for wetting mucus/mucosal tissue surfaces and sufficient flexibility to penetrate the mucus network or tissue crevices[5]. The major barrier layer to transdermal drug delivery is not a factor in transmucosal routes of administration because mucosal surface do not have stratum corneum. Hence transmucosal systems exhibit a faster initiation and decline of delivery than do transdermal patches [6, 7]. Mucoadhesives materials could also be used as therapeutic agents in their own right, to coat and protect damaged tissues (gastric ulcers or lesions of the oral mucosa) or to act as lubricating agents (in the oral cavity, eye and vagina) [1].

### *ADVANTAGES OF DRUG DELIVERY VIA THE BUCCAL LINING [6, 7]*

- Bypass hepatic first pass metabolism.
- Improved patient compliance due to the elimination of associated pain with injections.
- Sustained drug delivery.
- A relatively rapid onset of action can be achieved relative to the oral route, and the formulation can be removed if therapy is required to be discontinued.
- Ease of drug administration can be easily accomplished.
- Though less permeable than the sublingual area, the buccal mucosa is well vascularized, and drugs can be rapidly absorbed into the venous system underneath the oral mucosa.
- Transmucosal systems exhibit a faster initiation and decline of delivery than do transdermal patches.
- Transmucosal delivery occurs is less variable between patients, resulting in lower intersubject variability as compaired to transdermal patches.
- The large contact surface of the oral cavity contributes to rapid and extensive drug absorption.

### *LIMITATIONS OF BUCCAL DRUG DELIVERY [6, 7]*

Depending on whether local or systemic action is required the challenges faced while delivering drug via buccal drug delivery can be enumerated as follows.

- The requirement for frequent dosing due to local action the rapid elimination of drugs or the flushing action of saliva or the ingestion of foods stuffs.
- The non-uniform distribution of drugs within saliva on release from a solid or semisolid delivery system.
- Patient acceptability in terms of taste, irritancy and 'mouth feel' is an issue both locally and systematically.

### *OVERVIEW OF BUCCAL MUCOSA*

The oral mucosa is comprised of squamous stratified (layered) epithelium. Below this lies a basement membrane, the lamina propria followed by submucosa[8] (figure 1).

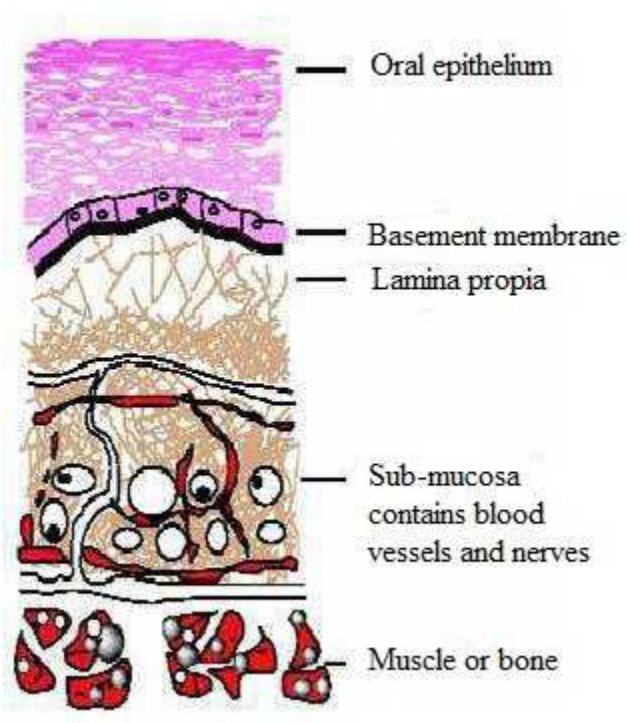


**Figure 1**
***Cross section of oral mucosa[9]***

### *Epithelium[10]*

The epithelium of the oral mucosa serves as a protective covering for the tissues and a barrier to the entry of foreign materials. These functions are reflected in the organization of the epithelium in which individual epithelial cells are closely opposed and stratified so there are a number of layers that show a sequence of differentiation. The uppermost layers form a surface that is resistant to physical insult and to penetration by foreign substances.

### *Buccal Mucosa: Environment [11]*

The oral cavity is marked by the presence of saliva produced by the salivary glands. The cells of the oral epithelia are surrounded by an intercellular ground substance, mucus, the main components of which are complexes made up of proteins and carbohydrates. Saliva is an aqueous fluid with 1% organic and inorganic materials. The role of saliva is to protect fluid for all tissues of the oral cavity. It allows continuous mineralization / demineralization of the tooth enamel and hydrate oral mucosal dosage forms. Whereas the role of mucus - made up of proteins and carbohydrates, bioadhesion of mucoadhesive drug delivery systems and cell-cell adhesion.

### *PERMEABILITY OF DRUGS THROUGH BUCCAL MUCOSA* [12]

There are two possible routes of drug absorption through the squamous stratified epithelium of the oral mucosa: Transcellular and Paracellular (figure2). Transcellular transport involves the transportation of solutes by a cell through a cell. Paracellular transport involves the transfer of substances across an epithelium by passing through the intercellular space between the cells. Permeation across the buccal mucosa has been reported to be mainly by the paracellular route through the intercellular lipids produced by membrane-coating granules. Thus the buccal mucosa is more suitable for sustained delivery applications, delivery of less permeable molecules, peptide drugs and polysaccharides.

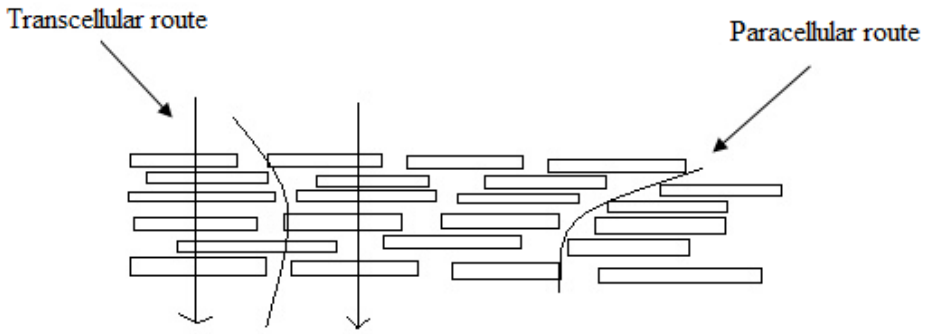


**Figure 2**
***Schematic representation of different route of drug permeation*** [13]

### *FACTORS AFFECTING DRUG DELIVERY VIA BUCCAL ROUTE*

The rate of absorption of hydrophilic compounds is a function of the molecular size. Smaller molecules (<75-100 Da) generally exhibit rapid transport across the mucosa, with permeability decreasing as molecular size increases. For hydrophilic macromolecules such as peptides, absorption enhancers have been used to successfully alter the permeability of the buccal epithelium, causing this route to be more suitable for the delivery of larger molecules[14].

The lipid solubility of drugs is an important factor in transmucosal drug delivery system. Along with lipid solubility, drugs selected for transmucosal drug delivery system must have physiochemical properties, including size and pKa that facilitate drug movement through the mucosa at a rate capable of producing therapeutic blood concentrations. Only the nonionized forms of molecules have the ability to cross-lipoidal membranes in significant amounts. The more lipid soluble a compound is, the higher its permeability. The permeabilities for these compounds are direct functions of their oil-water partition coefficients[14].

The partition coefficient is a useful tool to determine the absorption potential of a drug. In general, increasing a drug's polarity by ionization or the addition of hydroxyl, carboxyl, or amino groups, will increase the water solubility of any particular drug and cause a decrease in the lipid-water partition coefficient. Conversely, decreasing the polarity of a drug (e.g. adding methyl or methylene groups) results in an increased partition coefficient and decreased water solubility. The partition coefficient is also affected by pH at the site of drug absorption. With increasing pH, the partition coefficient of acidic drugs decreases, while that of basic drugs increases. The partition coefficient is also an important indicator of drug storage in fat deposits[14]. The ionization of a drug is directly related to both its pKa and pH at the mucosal surface. Only the nonionized form of many weak acids and weak bases exhibit appreciable lipid solubility, and thus the ability to cross lipoidal membranes[14].

Mucin turnover rate is another important factor.Estimation of mucin turnover varies widely, depending on location and method of measurement.The residence times of bioadhesives that are thought to attach to mucin are typically longer than the reported mucin turnover, suggesting that the presence of bioadhesive polymer on mucin may alter the turnover of this biopolymer. The residence time of dosage forms is limited by the mucin turnover time, which has been calculated to range between 47 and 270 min in rats and 12 – 24 h in humans [9]. Saliva, as a dissolution medium, affects the behavior of the polymer. Depending on both the saliva flow rate and method of determination, the pH of this medium has been estimated to be between 6.5 and 7.5.[9]

## *STRUCTURE AND DESIGN OF BUCCAL DOSAGE FORM* [15]

Buccal Dosage form can be of Matrix type: The buccal patch designed in a matrix configuration contains drug, adhesive, and additives mixed together. Reserviour type: The buccal patch designed in a reservoir system contains a cavity for the drug and additives separate from the adhesive. An impermeable backing is applied to control the direction of drug delivery; to reduce patch deformation and disintegration while in the mouth; and to prevent drug loss.

## *METHODS TO PROMOTE BUCCAL ABSORPTION*

### *Prodrugs* [15]

Hussain et al delivered opioid agonists and antagonists in bitterless prodrug forms and found that the drug exhibited low bioavailability as prodrug. Nalbuphine and naloxone bitter drugs when administered to dogs via the buccal mucosa, the caused excess salivation and swallowing. As a result, the drug exhibited low bioavailability. Administration of nalbuphine and naloxone in prodrug form caused no adverse effects, with bioavailability ranging from 35 to 50% showing marked improvement over the oral bioavailability of these compounds, which is generally 5% or less.

### *pH* [15]

Shojaei et al evaluated permeability of acyclovir at pH ranges of 3.3 to 8.8, and in the presence of the absorption enhancer, sodium glycocholate. The in vitro permeability of acyclovir was found to be pH dependent with an increase in flux and permeability coefficient at both pH extremes (pH 3.3 and 8.8), as compared to the mid-range values (pH 4.1, 5.8, and 7.0).

### *Absorption enhancers*[16]

Absorption enhancers have demonstrated their effectiveness in delivering high molecular weight compounds, such as peptides, that generally exhibit low buccal absorption rates. These may act by a number of mechanisms, such as increasing the fluidity of the cell membrane, extracting inter/intracellular lipids, altering cellular proteins or altering surface mucin. The most common absorption enhancers are azone, fatty acids, bile salts and surfactants such as sodium dodecyl sulfate. Solutions/gels of chitosan were also found to promote the transport of mannitol and fluorescent-labeled dextrans across a tissue culture model of the buccal epithelium while Glyceryl monooleates were reported to enhance peptide absorption by a co-transport mechanism.

**Table 1**
***List of investigated Permeation Enhancers***

| Permeation Enhancers | References |
|---|---|
| 2,3-Lauryl ether | 12 |
| Aprotinin | 12 |
| Benzalkonium chloride | 12 |
| Cetyltrimethyl ammonium bromide | 12 |
| Glycol | 12 |

| | |
|---|---|
| Sodium taurocholate | 12 |
| Sodium taurodeoxycholate | 12 |
| Sodium lauryl sulfate | 12 |
| Sodium EDTA | 12 |
| Sodium glycocholate | 12 |
| Sodium glycodeoxycholate | 12 |
| Azone | 17, 18 |
| Cetylpyridinium chloride | 19 |
| Cyclodextrin | 20 |
| Polysorbate 80 | 19, 20 |
| Phosphatidylcholine | 21 |
| Lauric acid | 21 |
| Sodium salicylate | 21 |
| Sulfoxides | 22 |
| Lauric acid/Propylene | 22 |
| Lysophosphatidylcholine | 23 |
| Menthol | 21, 24 |

***Patch design*** [25]

Several in vitro studies have been conducted regarding on the type and amount of backing materials and the drug release profile and it showed that both are interrelated. The drug release pattern was different between single-layered and multi-layered patches. The adhesion characteristics of buccal patches depends on the type and amount of backing materials.

***MECHANISM OF MUCOADESION***

Many theories have been proposed to describe mucoadhesion, namely adsorption theory, electronic theory, fracture theory, wetting theory, diffusion theory and mechanical theory. Mucoadhesion is believed to occur in three stages: wetting, interpenetration and mechanical interlocking between mucin and polymer[26]. The mechanism by which mucoadhesion takes place has been said to have two step, intimate contact between a bioadhesive and a membrane (wetting or swelling phenomenon) step followed by penetration of the bioadhesive into the tissue or into the surface of the mucous membrane (interpenetration) [27].

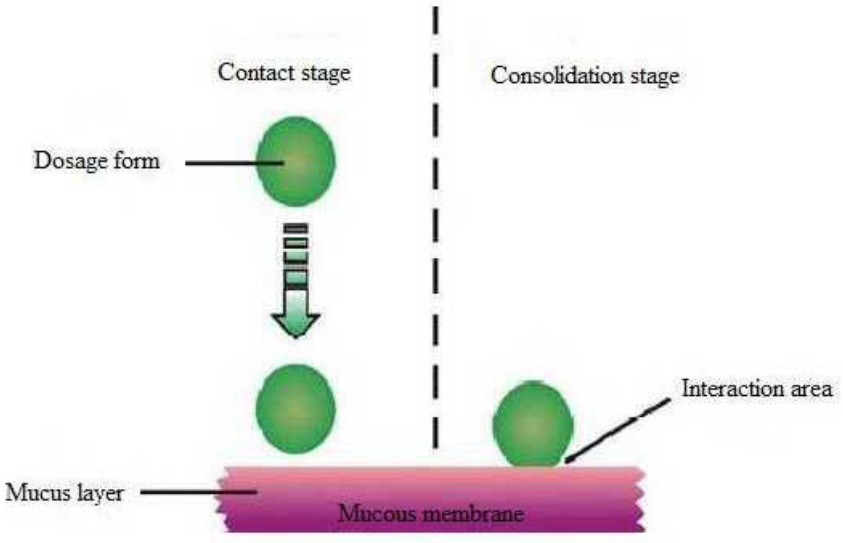


**Figure 3**
***Mechanism of mucoadhesion*** [16]

***Adsorption theory***[28]

Adhesion is the result of various surface interactions between the adhesive polymer and mucus substrate. Primary bonds due to chemisorptions result in adhesion due to ionic, covalent and metallic bonding, which is generally undesirable due to their permanency. Secondary bonds arise mainly due to Van der Waals forces, hydrophobic interactions and hydrogen bonding.The theory states that there is initial wetting of the mucin, and then diffusion of the polymer occurs into mucin layer, thus causing the fracture in the layers to effect the adhesion or electronic transfer or simple adsorption phenomenon that finally leads to the perfect mucoadhesion.

***Electronic theory***[29]

This theory describes adhesion occurring by means of electron transfer between the mucus and the mucoadhesive system, arising through differences in their electronic structures. The electron
transfer between the mucus and the mucoadhesive results in the formation of double layer of electrical charges at the mucus and mucoadhesive interface. Thus the formation of attractive forces within this double layer occurs.

***Fracture theory***[2]

This theory is based on mechanical measurement of mucoadhesion. It analyzes the force required to separate two surfaces after adhesion is established. This force, Sm, is calculated in tests of resistance to rupture by the ratio of the maximal detachment force $F_{m,}$ and the total surface area, $A_{0,}$ involved in the adhesive interaction.

$Sm = F_m / A_0$

***Wetting theory***[30]

The wetting theory applies to liquid systems which present affinity to the surface in order to spread over it. This affinity can be found by using measuring techniques such as the contact angle. The general rule states that the lower the contact angle then the greater the affinity (figure 4). The contact angle should be equal or close to zero to provide adequate spreadability.

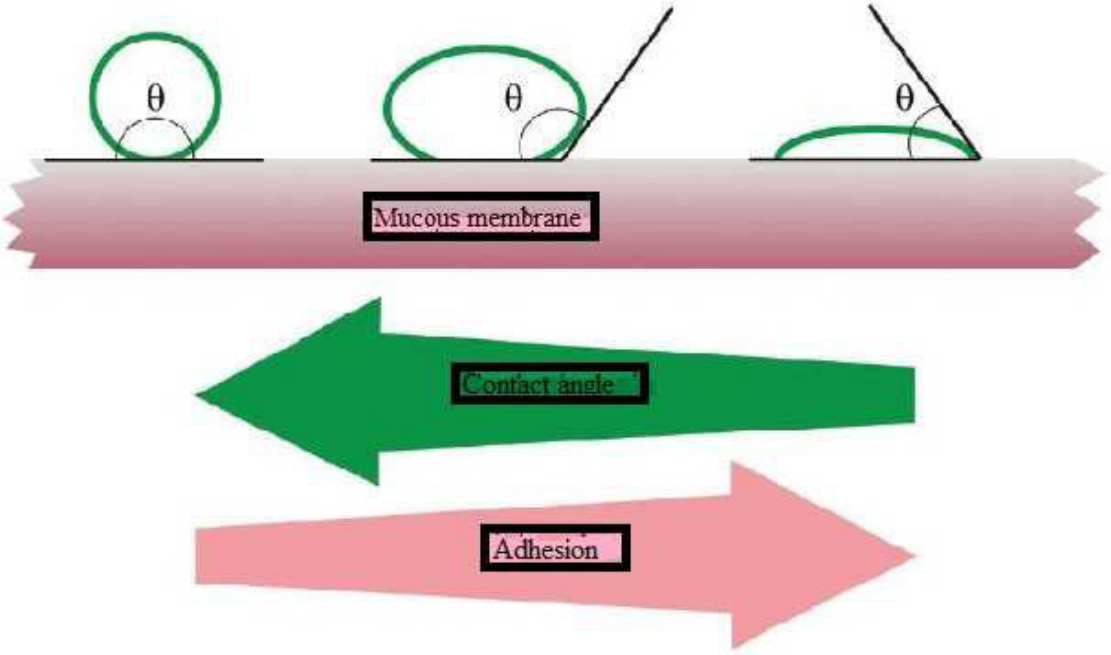


**Figure 4**
***Schematic diagram showing influence of contact angle between device and mucous membrane on bioadhesion.***

The spreadability coefficient, $S_{AB}$, can be calculated from the difference between the surface energies $\gamma_B$ and $\gamma_A$ and the interfacial energy $\gamma_{AB}$, as indicated in equation (1)

$$S_{AB} = \gamma_B - \gamma_A - \gamma_{AB} \quad (1)$$

The greater the individual surface energy of mucus and device in relation to the interfacial energy, the greater the adhesion work, $W_A$.

$$W_A = \gamma_A + \gamma_B - \gamma_{AB} \quad (2)$$

***Diffusion theory***[30]

Diffusion theory describes the interpenetration of both polymer and mucin chains to a sufficient depth to create a semi-permanent adhesive bond (figure 5). It is believed that the adhesion force increases with the degree of penetration of the polymer chains. This penetration rate depends on the diffusion coefficient, flexibility and nature of the mucoadhesive chains, mobility and contact time.

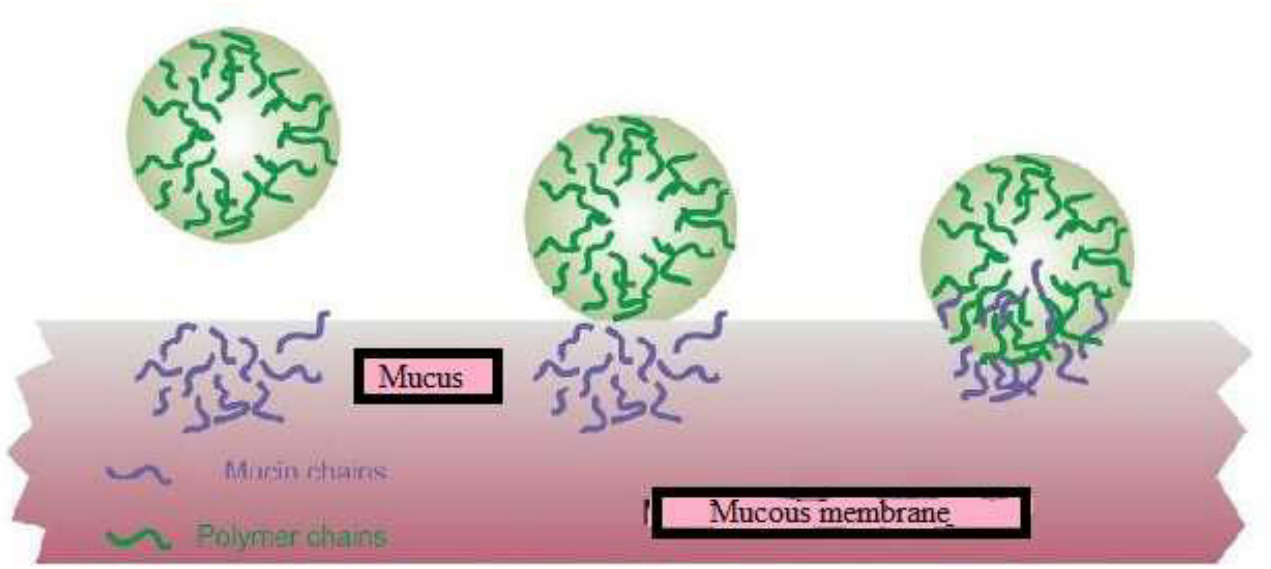


**Figure 5**
***Secondary interactions resulting from interdiffusion of polymer chains of bioadhesive device and of mucus.***

***Mechanical theory***[31, 32]

The mechanical theory explains the diffusion of the liquid adhesives into the micro-cracks and irregularities present on the substrate surface thereby forming an interlocked structure which gives rise to adhesion. Adhesion occurs due to the filling of the irregularities on a rough surface by a mucoadhesive liquid. Moreover, such roughness increases the interfacial area available to interactions thereby aiding dissipating energy and can be considered the most important phenomenon of the processs.

***MUCOADHESIVE POLYMER CHARACTERISTICS OF IDEAL MUCOADHESIVE POLYMER***[33, 34]

An ideal polymer for buccoadhesive drug delivery system should have the following characteristics.

- The polymer and its degradation products should be non-toxic and non-absorbable from the GIT
- It should be non-irritant to the mucous membrane.
- It should preferably form a strong non-covalent bond with the mucin epithelial cell surfaces.

- It should adhere quickly to moist tissue and should possess some site specificity.
- It should allow easy incorporation of the drug and offer no hindrance to its release.
- The polymer must not decompose on storage or during the shelf life of the dosage form.
- The cost of the polymer should not be high.

## *CLASSIFICATION OF MUCOADHESIVE POLYMERS* [35]

**Table 2**
***List of classification of mucoadhesive polymers***

| Basis | Categories | Examples |
|---|---|---|
| Source | Natural | Agarose, chitosan, gelatin, hyaluronic acid, gums (guar, xanthan etc) |
| | Synthetic | Cellulose derivatives [Carboxymethylcellulose (CMC), thiolated CMC, sodium CMC etc], Poly (acrylic acid) -based polymers [Carbopol, polyacrylates, Poly ethylene glycol etc]. |
| Aqueous solubility | Watersoluble | Carbopol, sodium CMC, sodium alginate. |
| | Water insoluble | Chitosan (soluble in dilute aqueous acids), ethylcellulose, polycarbophil. |
| Charge | Cationic | Aminodextran, chitosan, (DEAE)-dextran, |
| | Anionic | Chitosan-EDTA, Carbopol, CMC, pectin, polycarbophil, sodium alginate, sodium CMC, xanthan gum. |
| | Nonionic | Hydroxyethyl starch, polyvinylalcohol, polyvinylpyrrolidone, scleroglucan |
| Potential mucoadhesive forces | Covalent | Cyanoacrylate. |
| | Hydrogen bond | Carbopol, polycarbophil , polyvinylalcohol |
| | Electrostatic interaction | Chitosan |

## *NOVEL MUCOADHESIVE POLYMERS UNDER DEVELOPMENT*

### *Thiolated polymers*[36]

Thiolated polymers or designated thiomers are mucoadhesive basis polymers, which display thiol bearing side chains.Based on thiol/disulfide exchange reactions and/or a simple oxidation process disulfide bonds are formed between such polymers and cysteine-rich subdomains of mucus glycoproteins building up the mucus gel layer. Thiomers mimic the natural mechanism of secreted mucus glycoproteins, which are also covalently anchored in the mucus layer by the formation of disulfide bonds—the bridging structure most commonly encountered in biological systems. This new generation novel mucoadhesive polymers are capable of forming covalent bonds. So far the cationic thiomers chitosan–cysteine, chitosan–thiobutylamidine as well as chitosan–thioglycolic acid and the anionic thiomers poly(acylic acid)–cysteine, poly(acrylic acid)–cysteamine, carboxy-methylcellulose–cysteine and alginate–cysteine have been generated.

### *Lectins* [37]

Lectins are naturally occurring proteins that play a fundamental role in biological recognition phenomena involving cells and proteins. Lectins belong to a group of structurally diverse proteins and glycoproteins that can bind reversibly to specific carbohydrate residues. 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 a process of endocytosis. Such systems could offer duality of function in that lectin based platforms could not only allow targeted specific attachment but additionally offer a method of controlled drug delivery of macromolecular pharmaceuticals via active cell-mediated drug uptake. Due to premature

inactivation by shed off mucus, it provides an initial yet fully reversible binding site followed by distribution of lectin mediated drug deli-very systems to the cell layer.

Lectins can be defined as proteins of nonimmune origin that bind to carbohydrates specifically and non-covalently. According to the molecular structure, three groups of lectins can be distinguished: Merolectins (lectins having only one carbohydraterecognising domain), Hololectins(lectins with two or more carbohydraterecognising domains) and Chimerolectins (lectins with additional unrelated domains).Lectins can increase the adherence of microparticles to the intestinal epithelium and enhance penetration of drugs. They may be used to target therapeutic agents for different gut components or even for different cells (e.g. complex-specific lectins for parietal cells or fucosespecific lectins for M cells).

***PAA and PEG monoethylether monomethacrylate***

Shojaei and Li, 1997 have designed, synthesized and characterized a mucoadhesive copolymer of PAA and PEG monoethylether monomethacrylate (PAA-co-PEG) (PEGMM). By adding PEG to these polymers, many of the shortcomings of PAA for mucoadhesion were eliminated. Hydration studies, glass transition temperature, mucoadhesive force, surface energy analysis and effect of chain length and molecular weight on mucoadhesive force were studied. The resulting polymer has a lower glass transition temperature than PAA and exists as a rubbery polymer at room temperature. Copolymers of 12 and 16-mole% PEGMM showed higher mucoadhesion than PAA. The 16-mole% PEGMM had the most favourable thermodynamic profile and the highest mucoadhesive forces[38]. Novel polymers of PAA complexed with PEGylated drug conjugate were investigated by Lele, et al. Only a carboxyl group containing drugs such as indomethacin could be loaded into the devices made from these polymers. An increase in the molecular weight of PEG in these copolymers resulted in a decrease in the release of free indomethacin, indicating that drug release can be manipulated by choosing different molecular weights of PEG[39].

***Bacterial adhesion***

The adhesive properties of bacterial cells, as a more complicated adhesion system, have recently been investigated. 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 specific receptors. A significant correlation has been found between the presence of fimbriae on the surface of bacteria and their pathogenicity [9]. Their presence has been correlated with pathogenicity, e.g. adherence of *Escherichia coli* to the brush border of epithelial cells mediated by K99 fimbriae is a prerequisite for subsequent production and cellular uptake of *E. coli* enterotoxin. Thus, the DDS based on bacterial adhesion factors could be an efficient mechanism to increase adhesion of bioadhesive microspheres to epithelial surfaces. Another study envisaging the importance of bacterial adhesions has been carried out using “invasin”, which is a membrane protein from *Yersinia pseudotuberculosis*. Cellular uptake of polymeric nanospheres functionalized with invasion has been observed using confocal laser scanning microscopy [40].

***Antibodies[37]***

Antibodies can be produced against selected molecules present on mucosal surfaces. Due to their high specificity, antibody can be a rational choice as a polymeric ligand for designing site specific mucoadhesives. This approach can be useful for targeting drugs to tumor tissues.

***EXPERIMENTAL METHODOLOGY FOR BUCCAL PERMEATION STUDIES [12]***

Before a buccal drug delivery system can be formulated, buccal absorption/permeation studies must be conducted to determine the feasibility of this route of administration for the

candidate drug. These studies involve methods that would examine in vitro and/or in vivo buccal permeation profile and absorption kinetics of the drug.

***In vitro Methods***

At the present time, most of the *in vitro* studies examining drug transport across buccal mucosa have used buccal tissues from animal models. Animals are sacrificed immediately before the start of an experiment. Buccal mucosa with underlying connective tissue is surgically removed from the oral cavity, the connective tissue is then carefully removed and the buccal mucosal membrane is isolated. The membranes are then placed and stored in ice-cold (4°C) buffers until mounted between side-by-side diffusion cells for the *in vitro* permeation experiments. Buccal cell cultures have also been suggested as useful in vitro models for buccal drug permeation and metabolism. However, to utilize these culture cells for buccal drug transport, the number of differentiated cell layers and the lipid composition of the barrier layers must be well characterized and controlled. This has not yet been achieved with the buccal cell cultures used thus far.

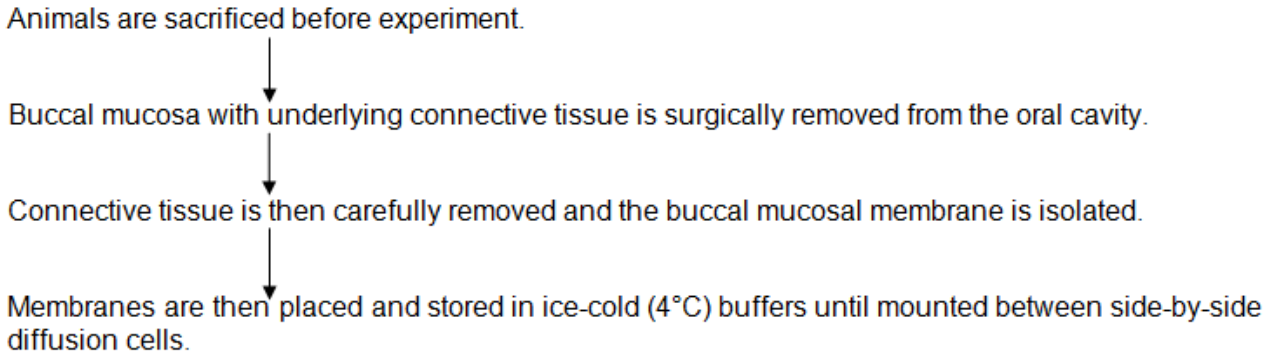


**Figure6**
***Schematic representation of in vitro buccal permeation studies.***

***In vivo Methods***

In vivo methods were first originated by Beckett and Triggs with the so-called buccal absorption test. Using this method, the kinetics of drug absorption was measured. The methodology involves the swirling of a 25 ml sample of the test solution for up to 15 minutes by human volunteers followed by the expulsion of the solution. The amount of drug remaining in the expelled volume is then determined in order to assess the amount of drug absorbed. The drawbacks of this method include salivary dilution of the drug, accidental swallowing of a portion of the sample solution, and the inability to localize the drug solution within a specific site (buccal, sublingual, or gingival) of the oral cavity. Pharmacokinetic parameters such as bioavailability can then be calculated from the plasma concentration vs. time profile. Other in vivo methods include those carried out using a small perfusion chamber attached to the upper lip of anesthetized dogs. The perfusion chamber is attached to the tissue by cyanoacrylate cement. The drug solution is circulated through the device for a predetermined period of time and sample fractions are then collected from the perfusion chamber and blood samples are drawn after 0 and 30 minutes.

***Experimental Animal Species***

For *in vivo* investigations, many researchers have used small animals including rats and hamsters for permeability studies. However, such choices seriously limit the value of the data obtained since, unlike humans, most laboratory animals have an oral lining that is totally keratinized. The rat has a buccal mucosa with a very thick, keratinized surface layer. The rabbit is the only laboratory rodent that has non-keratinized mucosal lining similar to human

tissue and has been extensively utilized in experimental studies. The difficulty in using rabbit oral mucosa, however, is the sudden transition to keratinized tissue at the mucosal margins making it hard to isolate the desired non-keratinized region. The oral mucosa of larger experimental animals that has been used for permeability and drug delivery studies include monkeys, dogs and pigs. Due to the difficulties associated with maintenance of monkeys, they are not very practical models for buccal drug delivery applications. Instead, dogs are much easier to maintain and considerably less expensive than monkeys and their buccal mucosa is non-keratinized and has a close similarity to that of the human buccal mucosa. Pigs also have non-keratinized buccal mucosa similar to that of human and their inexpensive handling and maintenance costs make them an equally attractive animal model for buccal drug delivery studies. In fact, the oral mucosa of pigs resembles that of human more closely than any other animal in terms of structure and composition. However, for use in *in vivo* studies pigs are not as ideal as dogs due to their rapid growth which renders the animal handling rather difficult. Miniature breeds of pigs can be used but their high cost is a deterrent.

## *DOSAGE FORMS*

### *Buccal tablets*[41]

These are solid dosage forms prepared by the compression of powder mixes that can be placed into contact with the oral mucosa and allowed to dissolve or adhere depending on the type of excipients incorporated into the dosage form. They can deliver drug multidirectionally into the oral cavity or to the mucosal surface. Alternatively, the dosage form can contain an impermeable backing layer to ensure that drug is delivered unidirectionally.

**Table 3**
***List of investigated buccal mucoadhesive tablets***

| Formulation components | Active ingredient | Ref. |
|---|---|---|
| Carbopol934p and hydroxypropylmethylcellulose | Acitretin | 42 |
| Sodiumcarboxymethylcellulose and hydroxypropylmethylcellulose | Cetylpyridinium chloride | 43 |
| Carbopol 934 with hydroxypropylmethylcellulose | Diltiazem HCl | 44 |
| Hydroxyethylcellulose, hydroxypropylcellulose and hydroxypropylmethylcellulose | Metronidazole | 45 |
| Carbopol 934 and HPC | Nicotine | 46 |
| Carbopol 974P, sodium alginate and hydroxypropylmethylcellulose | Nicotine | 47 |
| Carboxymethylcellulose and carbopol | Nifedipine | 48 |
| Hydroxypropylmethylcellulose and carbopol940 | Piroxicam | 49 |
| Hydroxypropylmethylcellulose and polycarbophil | Propranolol HCl | 50 |

### *Buccal gels and ointments*

Semisolid dosage forms usually include gels, creams and ointments, which are applied topically into the mucosal surface for either local or systemic effects. These typically contain a polymer and drug plus any required excipient dissolved or suspended as a fine powder in an aqueous or non-aqueous base. Hydrogels can also be used in semi-solids for drug delivery to the oral cavity. These are formed from polymers and can be hydrated in an aqueous environment without dissolution, acting as drug delivery systems by physically entrapping molecules, which are then slowly released by diffusion or erosion after gel hydration [51]. Semi-solid formulations can be applied using the finger (or syringe) to a target region and tend to be more acceptable in terms of mouth feel to patients relative to a solid dosage form[41]

.

**Table 4**
***List of investigated buccal mucoadhesive gels***

| Formulation components | Active ingredient | Ref. |
|---|---|---|
| Carbopol 934P | Arecoline | 52 |
| Chitosan | Chlorhexidine digluconate | 53 |
| Hydroxyethyl methacrylate | Diclofenac sodium | 54 |
| Hydroxyethylcellulos , polyvinylpyrrolidone and polycarbophil | Flurbiprofen | 55 |
| Hydroxyethylcellulose , polyvinylpyrrolidone and polycarbophil | Tetracycline | 56,57 |

***Buccal Patches/Films*** [41]

These dosage forms are usually prepared by casting a solution of the polymer, drug and any excipients (such as a plasticiser) on to a surface and allowing it to dry. Patches can be made 10-15 $cm^2$ in size but are more usually 1-3 $cm^2$ with perhaps an ellipsoid shape to fit comfortably into the centre of the buccal mucosa. There have many of the advantages and disadvantages of dosage forms, but by being thin and flexible, tend be less obtrusive and more acceptable to the patient. The relative thinness of the films, however, means that they are more susceptible to overhydration and loss of the adhesive properties.

**Table 5**
***List of investigated buccal mucoadhesive patches***

| Formulation components | Active ingredient | Ref. |
|---|---|---|
| Poly vinyl alcohol, hydroxyethylcellulose or chitosan | Cetylpyridinium chloride | 58 |
| Eudragitr NE40D withhydroxypropylmethylcellulose, or carbopol | Metoprolol tartrate | 59 |
| Sodium carboxymethylcellulose, chitosan, poly vinyl alcohol , hydroxyethylcellulose, hydroxypropylmethylcellulose | Miconazole nitrate | 60 |
| Carbopol 974p | Oxytocin | 61,62 |

**Table 6**
***List of investigated buccal mucoadhesive films***

| Formulation components | Active ingredient | Ref. |
|---|---|---|
| Chitosan hcl and poly acrylic acid sodium salt | Acyclovir | 63 |
| Chitosan | Chitosan | 64 |
| Chitosan | Chlorhexidine digluconate | 53 |
| Chitosan and polyvinylpyrrolidone | Glibenclamide | 65 |
| Atelocollagen | Tetracycline | 66 |

# CONCLUSION

The use of buccal adhesive dosage forms provides an opportunity for optimizing the delivery of drugs both locally and systemically. Buccal administration of drugs which exhibit a low oral bioavailability is a useful method to achieve higher bioavailability. Mucoadhesive polymers may provide an important tool to improve the bioavailability of the active agent by improving the residence time at the delivery site.With the development of new molecules from research, mucoadhesive systems may play an increasing role in the development of new pharmaceuticals.

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