



# INTERNATIONAL JOURNAL OF PHARMACEUTICAL RESEARCH AND DEVELOPMENT (IJPRD)

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## A COMPREHENSIVE REVIEW ON BUCCAL DRUG DELIVERY SYSTEM

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### ABSTRACT

*Of the various routes of drug delivery, the oral route is most ancient as well as preferred by the patient being convenient to take. However, peroral administration of drugs has shortcomings such as hepatic first-pass metabolism and enzymatic degradation within the GI tract which comprehend a hindrance to the absorption of peptides and proteins group of drug. On the contrary of per oral route, mucosal layer (nasal, rectal, vaginal, ocular and oral cavity) are often considered as potential sites for drug administration and having distinct advantages for systemic drug delivery. These advantages include possible liver bypass effect, avoidance of presystemic elimination within the GI tract with improved absorption and hence better bioavailability. Although, the mucosal surface as a site for drug delivery has certain drawback too as the lack of dosage form retention at the site of absorption. Consequently, the concept of bioadhesive polymers has extensively been employed in the development of transmucosal drug delivery systems. If these polymers are then incorporated into buccal formulations, drug absorption by buccal mucosa layers may be enhanced or the drug may be released for extended period of time as per the formulation design at a particular site. This review describes historical background of mucoadhesive system, different polymers used, permeation enhancers, theory and mechanism of mucoadhesion, in vitro and in vivo methods of bioadhesion.*

**Keywords:** Mucoadhesive drug delivery system, Polymer, Mucoadhesion, Permeation enhancer, Mucin turn over.

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## INTRODUCTION

Mucoadhesive drug delivery systems are the drug delivery system which utilized the property of bioadhesion of certain polymers which become adhesive on hydration and hence can be used for targeting a drug to a particular region of the body for extended periods of time<sup>1,2</sup>.

Bioadhesion is an interfacial phenomenon in which two materials of which one is of biological nature are held together by means of interfacial forces. The attachment can be between biological substrate and an artificial material, seems like an adhesion between a biological membrane and a polymer. In the case of polymer attached to the mucous layer of a mucosal membrane of gastrointestinal tract (GI tract) the term “mucoadhesion” is used. The mucosal layer line covers a number of regions of the body including the GI tract, the urogenital tract, the airways, the ear, nose and eye. These are the potential sites for retention of any bioadhesive system and hence, the mucoadhesive drug delivery system included the following:

- i. Buccal drug delivery system
- ii. Oral drug delivery system
- iii. Vaginal drug delivery system
- iv. Rectal drug delivery system
- v. Nasal drug delivery system
- vi. Ocular drug delivery system

Oral route is the most commonly employed route for a lot number of drugs administered for the treatment of candidosis. Indeed, some drugs which are susceptible to highly acidic conditions of stomach and possesses high first pass metabolism due to degradation in liver in that circumstances this route fails to accomplish the delivery. To overcome these problems various mucoadhesive systems are designed which are given by contrasting route other than oral route like e.g., buccal, nasal, vaginal<sup>2,3</sup>.

Now a day various newer researches are carried out on mucoadhesive drug delivery system. Diverse category of drug like antihypertensive, anti-anginal, analgesic, anti-inflammatory, anti-asthmatic, anti-infective, anti-neoplastic, hormonal and

ophthalmic drugs in which mucoadhesive system are formed.

### Routes, mechanism, potential role of mucus

The ability to retain pharmacologically active agents for extended periods of time on any mucosal epithelia, including eye, nose, mouth, rectum or vagina confers a number of potential therapeutic advantages. All of these epithelial layers are coated with a layer of mucus. The most promising systems will be examined for evidence of mucoadhesives function and physiological effects in healthy volunteers. In order for a drug to be absorbed across mucosal epithelia it must first diffuse across a layer of mucus, and any associated unstirred water layer of GI tract<sup>4,5</sup>. A number of drugs like, testosterone and the tetracycline antibiotics have been shown to be highly bound to mucus and exhibit significant increased in diffusion coefficients and lag time in the mucus membrane compared to those which are not bound to the mucus layer. It is not known how many drugs are similarly affected, although the potential role of mucus in limiting absorption is likely to become important as their presence is mandate to deliver peptides and proteins therapeutically via mucosal surfaces. The selected components of important role in the absorption process are being investigated in isolation to determine the role of mucus<sup>6,7</sup>. Mucus which are collected from different regions are in partially purified state through which diffusion of drug are being examined *in vitro* in the presence and absence of known drug to reduce or promote structure in the mucus gel. The epithelium of the small intestine plays a pivotal role to regulate diverse absorptive and secretory functions. Secretions from various region of GI tract delivered into the intestinal region are synthesized and assembled within the intestinal epithelial cells. These secretions include mucus, which is formed by goblet cells of intestinal mucosa. In order for a drug (or nutrient) molecule to be absorbed it must faces the hurdle to diffuse across this layer, Turnover of mucus and other mucosal surfaces and factors by which it gets affected is not clearly understood yet in spite of

the fact that, the residence times of bioadhesives systems that attached to mucin are typically longer than the reported mucin turnover that confirms the presence of bioadhesive polymer on mucin may alter the turnover of this biopolymer. It is reported that the mucin turnover time is the direct measure of residence time of dosage forms in the buccal mucosa that ranges between 47 and 270 min in rats and 12 – 24 h in humans<sup>8</sup>.

#### **Mucoadhesive buccal drug delivery system<sup>9</sup>**

Drug delivery via the mucosal membranes of the oral cavity can be subdivided into following parts.

Sublingual delivery: Drug administration via sublingual mucosa to the systemic circulation.

Buccal delivery: Drug administration via buccal mucosa to the systemic circulation.

Local delivery: Drug administration via bioadhesive system either to the palate (the gingival) or the cheek.

#### **Advantages of mucoadhesive buccal drug delivery system**

Mucoadhesive via buccal route offers following advantages:

- i. Ease of drug administration and termination of drug action can be easily accomplished.
- ii. Permits localization or retention of the drug to the specified area of oral cavity for extended period of time.
- iii. Bypass hepatic first pass metabolism.
- iv. Drugs with poor bioavailability owing to the high first pass metabolism can be administered conveniently.
- v. No energy is required as the mode of absorption is passive.
- vi. Ease of drug administration to unconscious patients.
- vii. Water content of saliva is being capable to ensure drug dissolution.
- viii. Some drug can be suitably delivered which are prone to degraded in acidic media.
- ix. Lack of prominent mucus secreting goblet cells and therefore there is a hindrance of a diffusion limited mucous build up, beneath the applied designed system.

- x. These system allow local modification of tissue permeability, inhibition of protease activity and reduction in immunogenic response, and hence can selectively be used for peptides, proteins and ionized species delivery<sup>10,11</sup>.

#### **Limitations of buccal drug administration**

There is certain limitation via drug administered through buccal route

- i. Drugs with ample dose are often difficult to be administered.
- ii. Possibility of the patient to swallow the tablet being forgotten.
- iii. Eating and drinking may be restricted till the end of drug release.
- iv. This route is unacceptable for those drugs, which are unstable at pH of buccal environment.
- v. This route cannot administer drugs, which irritate the mucosa or have a bitter or unpleasant taste or an obnoxious odour.
- vi. Limited surface area is available for absorption<sup>12</sup>.

#### **Literature review**

A buccal patch for systemic administration of carvedilol in the oral cavity has been developed by **Vishnu Y.V et al.**, in 2007 using two different mucoadhesive polymers<sup>13</sup>. The formulations were tested for *in vitro* drug permeation studies, buccal absorption test, *in vitro* release studies, moisture absorption studies and *in vitro* bioadhesion studies. The drug and polymers were present in an unchanged state in the patch and no evidence of interaction was reported by them. They also performed XRD and confirmed that the drug were in crystalline state in the polymer matrix. Bioavailability studies of this buccal patch in healthy pigs revealed that good buccal absorption and was found that 2.29 folds increased bioavailability compared to that of oral solution. The basic pharmacokinetic parameters like the  $C_{max}$ ,  $T_{max}$  and AUC total were calculated and showed statistically significant difference ( $P < 0.05$ ) when given by buccal route compared to that of oral solution.

**Patel J. K. and Patel M. M. 2007** formulated mucoadhesive amoxicillin microspheres for treating gastric and duodenal ulcers link with *Helicobacter pylori* and evaluated their *in vitro* and *in vivo* performances<sup>14</sup>. Amoxicillin mucoadhesive microspheres containing chitosan as mucoadhesive polymer were prepared by simple emulsification phase separation technique using glutaraldehyde as a cross-linking agent. Prepared microspheres were discrete, spherical, free flowing and also showed high percentage drug entrapment efficiency. *In vitro* mucoadhesive test showed that amoxicillin mucoadhesive microspheres adhered more strongly to gastric mucous layer and could retain in gastrointestinal tract for an extended period of time. A 32 full factorial design was employed and found that the best batch exhibited a high drug entrapment efficiency of 70 % and a swelling index of 1.39; percentage mucoadhesion after 1 h was 79 % and drug release was sustained for more than 12 h. *In vitro* release test showed that amoxicillin released slightly faster in pH 1.0 hydrochloric acid than in pH 7.8 phosphate buffer. *In vivo* *H. pylori* clearance tests were also carried out by administering amoxicillin mucoadhesive microspheres and powder, to *H. pylori* infectious Wistar rats under fed conditions at single dose or multiple dose(s) in oral administration. The results showed that amoxicillin mucoadhesive microspheres had a better clearance effect than amoxicillin powder. Finally authors concluded that the prolonged gastrointestinal residence time and enhanced amoxicillin stability resulting from the mucoadhesive microspheres of amoxicillin had a significant role in eradication of *H. pylori*.

A bioadhesive films for the buccal delivery of fentanyl was developed and *in vitro* evaluation were performed using the pig esophageal model by **Consuelo I.D and co-workers** in 2007<sup>15</sup>. Films were made with polyvinylpyrrolidone (PVP) of two different molecular weights: PVP K30 and PVP K90. Delivery of fentanyl was determined across full-thickness mucosa and influence of film pH was investigated, and found that fentanyl permeation increased with increasing pH (i.e., when a higher percentage of the unionized fraction of drug was

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present). However, at the pH values studied, fentanyl was predominantly ionized suggesting that transport pathways was hydrophilic, or polar, environment across the mucosa. The transport rates achieved from the PVP films provided the highest delivery suggested that a buccal system of only 1-2 cm<sup>2</sup> in surface area could achieve a therapeutic effect equivalent to a 10 cm<sup>2</sup> transdermal patch, with a much shorter lag-time.

**In 2008, Semalty et al.**, demonstrated using a modified disintegration apparatus that the films formulated with a combination of Carbopol 934P and HPMC E15 had the residence time *in vitro* almost double than films containing only HPMC E15<sup>16</sup>. Moreover, they had also demonstrated that the combined polymers exhibited more resistance to rupture, using the folding endurance test. In another study, **Shidhaye et al.**, described the manufacture, permeation, and mucoadhesive properties of chitosan films, containing gelatin and PVP in different proportions, for the buccal delivery of sumatriptan succinate<sup>17</sup>. It was demonstrated that an increase in the chitosan component increased the mucoadhesive strength of films. The authors imputed the increasing concentration of chitosan having the effect of increasing the number of amine groups that can interact with the negative charge groups (carboxyl, sulfate, etc.) which are present on the buccal epithelium surface.<sup>[18]</sup> **Cui et al.** reported on the manufacture of carboxylated chitosan-grafted nanoparticles (CCGNs) added to chitosan-ethylenediamine tetraacetic acid (CEDTA) films with a backing layer of ethyl cellulose (EC)<sup>19</sup>. Films loaded with CCGNs exhibited higher mucoadhesion than that of placebo films. This high mucoadhesion effect was attributed to the high number of carboxyl groups that the CCGNs have, increasing the chance of hydrogen bonding with the mucosa. Films containing propranolol hydrochloride, EudraGI tract RS100, and triethyl citrate as a plasticizer exhibited almost three times the mucoadhesion force than that of films prepared with chitosan as the mucoadhesive polymer<sup>20</sup>. The authors proposed that the plasticizer had an important role for the increase in mucoadhesion. However, since the use of a

plasticizer is necessary in EudraGI tract RS100 films, such film formulations may then be suitable for the manufacture of mucoadhesive dosage forms. Salts of soluble polymethacrylate derivatives, namely EudraGI tract S100 and L100, have been reported to increase mucoadhesion<sup>21</sup>. BioDelivery Sciences International have used their BioErodible MucoAdhesive (BEMA™) technology platform to develop Onsolis™, a fentanyl buccal soluble film intended to be delivered in the buccal mucosa for the management of pain in cancerous patients<sup>22</sup>. The formulation contained the mucoadhesive polymers carboxymethyl cellulose, hydroxyethyl cellulose, and polycarbophil, along with a backing layer to direct drug release towards the buccal mucosa. Using the same technology platform, BioDelivery Sciences International have completed a phase II clinical study for BEMA™ Buprenorphine with a significant improvement in the primary efficacy endpoint, SPID-8 (sum of pain intensity differences at 8 h), compared to that exhibited by the placebo. The other commercialized film product is Suboxone™ Film, a buprenorphine and naloxone sublingual film. Using a polymeric matrix based on polyethylene oxide and hydroxypropylmethyl cellulose, rapid dissolution and absorption are achieved<sup>23</sup>.

**Balamurugan and coworkers in 2001** prepared a drug loaded buccoadhesive films of propranolol hydrochloride to the rabbit oral mucosa & achieved inhibition of isoprenaline induced tachycardia. *In vitro* drug release followed zero order kinetics<sup>24</sup>. In another work in **2002 Raghuraman et al.**, prepared propranolol hydrochloride buccal films using different polymers in different proportion. The physical parameters like thickness, weight variation, drug content, % moisture absorption and % moisture loss were evaluated. These studies were conducted in rabbits & *in vitro* drug release was evaluated and found to be followed first order kinetics<sup>25</sup>. **Lalla et al., 2002** studied the permeability coefficient of diclofenac potassium on to the guinea pig buccal mucosa at pH 6.8 and 8. Keratinised buccal pouch showed poor permeation. They exhibited pH independent effect. Use of 5% polysorbate 80 enhanced the permeation of

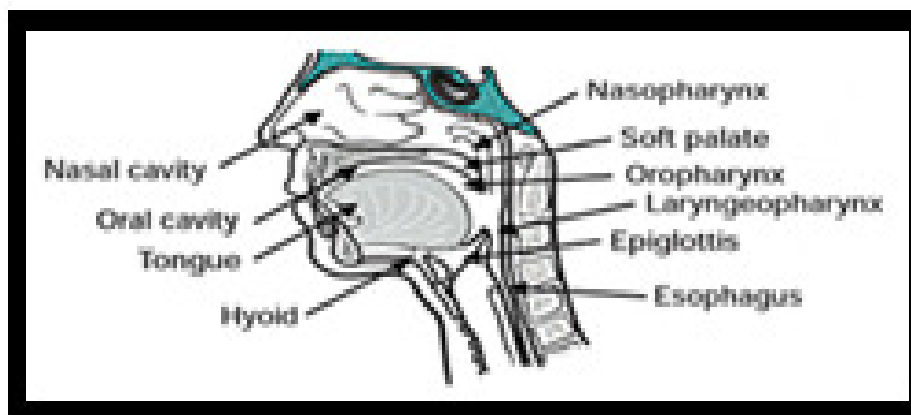
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diclofenac potassium<sup>26</sup>. **Parvez et al., 2002** formulated lignocaine hydrochloride buccal tablet using mucoadhesive polymer carbopol 934P. Adhesion time was greater than 6 h. Surface pH was found to be 7. Bioadhesive strength was found to be 31.96 g. Dissolution study showed 86.66% release of drug in 360 min.<sup>[27]</sup> A multilayered mucoadhesive buccal tablets of hydralazine hydrochloride were developed using polymers carbopol-934 & carboxymethyl cellulose by **Dinsheet and co-authors, in 1994**. Release enhancers as citric acid, D-mannitol and PEG-4000 and techniques like lyophilization were used. A milipore membrane filter (0.22 µm) was used for drug permeation study<sup>28</sup>. **Ilango et al., 1997** prepared chitosan based buccal strips of glibenclamide to prevent first pass metabolism. Buccal strips of glibenclamide are more efficient in the treatment of diabetes<sup>29</sup>. A mucoadhesive buccal films of clotrimazole prepared by **Khanna et al., 1997** using carbopol-934P and hydroxypropyl methyl cellulose in the ratio of 1:5 and using ethanol (95 %) as the solvent. The film exhibited *in vitro* adhesion time of 4 h and maintained the concentration of clotrimazole in the dissolution medium (phosphate buffer pH 6.6) above the minimum inhibitory concentration (MIC) of candida albicans for up to 4 h. A  $C_{max}$  of 21.1µg/ml was obtained in 2 h ( $t_{max}$ ) i.e., the time taken to attain the peak plasma concentration<sup>30</sup>. **Ali et al., 1998** prepared buccoadhesive films of triamcinolone acetonide, for the treatment of oral lesions using propylene glycol as plasticizer & different bioadhesive polymers. The films were evaluated on the basis of their physical characteristics, bioadhesive performance, release characteristic, surface pH, folding endurance and stretchability. The optimized film exhibited an *in vitro* adhesion time of 3.24 h and drug release of 89.98% in 3.5 h<sup>31</sup>. A new oral mucosal dosage form of insulin developed by **Nagai and his colleagues in 1990** in view to solve the problem of administration by injection using HPC-H and carbopol-934 (1:2) and sodium glycocholate. Absorption of insulin was about 0.5% compared with amount absorbed on intramuscular injection

when tested in beagle dogs<sup>32</sup>. In the year of 1981 **Anders and Merkle.**, developed and evaluated laminated mucoadhesive patches of protirelin for buccal drug delivery. The patches consisted of laminates of an impermeable backing layer and a hydrocolloid polymer layer containing the drug. The duration of mucosal adhesion *in vivo* was found to be dependent on the type of polymer used, its viscosity grade, the polymer load per patch and drying procedure for the preparation<sup>33</sup>. **Bottenburg et al., 1991** developed a bioadhesive fluoride containing slow release tablet from modified starch, polyacrylic acid, polyethylene glycol and sodium carboxymethyl cellulose (Na CMC). The fluoride release from the tablet was evaluated in healthy human volunteers and found that fluoride levels sustained significantly longer

than those obtained with the administration of toothpaste having four times the fluoride content<sup>34</sup>. **Nafee N. A. et al., 2003** prepared mucoadhesive patches containing 10 mg miconazole nitrate with ionic polymers, sodium carboxymethyl cellulose (SCMC) and chitosan, or non-ionic polymers, polyvinyl alcohol (PVA), hydroxyethyl cellulose (HEC) and hydroxypropylmethyl cellulose (HPMC) were evaluated and found that sustained release over more than 5 h<sup>35</sup>. **Ahuja and coworkers** studied the release of diltiazem HCl from a carbopol 934 and PVP K-30 (1:4) matrix containing 6% citric acid and 12% PEG 4000 in 1997. *In vitro* release of 86% and a 7% release across bovine cheek pouch were observed<sup>36</sup>.

### Anatomy of the Oral Cavity



**Fig 1:** Schematic diagram of anatomy of oral cavity depicting the posterior view of nasal cavity, oral cavity and pharynx

The anatomical and physiological properties of the oral mucosa have been extensively cited in the literature by several authors. The oral cavity comprises the lips, cheek, tongue, hard palate, soft palate and floor of the mouth. The oral cavity is lined by a relatively thick, dense and multilayered mucous membrane of a highly vascularized nature (Fig 1). Drug penetrating into the membrane can find access to the systemic circulation via net of capillaries and arteries lying underneath.

The mucus secreting region comprising of the soft palate, the floor of the mouth, the underside of the tongue, and the labial and buccal mucosa, which have a normally non-keratinized epithelium.

The hard palate and the gingiva are the regions of the masticatory mucosa and have a normally keratinized epidermis. Specialized zone consists of the borders of the lips and the dorsal surface of the tongue with its highly selective keratinization.

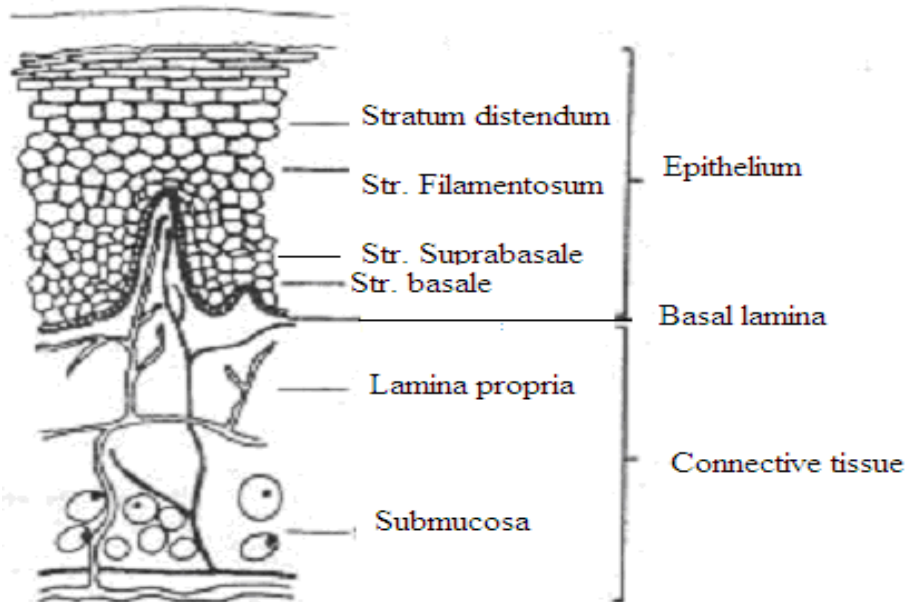
Vascular drainage from the oral mucosa is principally by the lingual, facial, and retromandibular veins. These veins open into the internal jugular vein and thus avoid just-pass metabolism. As the stratum corneum may be a potential barrier to mucosal penetrations, drugs are traditionally placed at the nonkeratinized sites like the buccal and sublingual regions<sup>37</sup>.

### The mucus layer

Mucus is a translucent and viscid secretion which forms a thin, continuous gel blanket adhered to the mucosal epithelial surface. The mean thickness of this layer varies from about 50 to 450  $\mu\text{m}$  in humans. It is secreted by the goblet cells lining the epithelia or by special exocrine glands with mucus cells acini<sup>38</sup>. The exact composition of the mucus layer varies substantially depending on the species, the anatomical location and the pathophysiological

state. The mucous comprised of water (50%), glycolipid (0.5-5%), mineral salts (0.5-1%) and free proteins (0.5-1%)<sup>39</sup>.

At physiological pH, the mucus network may carry a significant negative charge because of the presence of sialic acid and sulfate residues and this high charge density due to negative charge contributes significantly to bioadhesion.



**Fig 2:** Schematic diagram showing the anatomical components of oral mucosa

### Functions of Mucus layer<sup>40</sup>

The Primary functions of the mucus layer are:

- They are protective in nature because of their hydrophobicity.
- Mucus layer acts as a barrier in tissue absorption of drugs and other substrates is well known as it influences the bioavailability of drug.
- Mucus has strong adhesion properties and firmly binds to the epithelial cell surface as a continuous gel layer.
- An important role of the mucus layer is to lubricate the mucosal membrane and keep it moist. Continuous secretion of mucus from the goblet cell is necessary to compensate for the removal of the mucus layer due to digestion, bacterial

degradation and volatilization of mucin molecules.

### Permeability barriers across buccal mucosa

The permeability of buccal mucosa is intermediate between that of the skin epidermis and intestinal mucosa.

**Epithelium:** The predominant barrier to drug diffusion resides approximately within the outermost 1/3<sup>rd</sup> to the epithelium. In general, the permeabilities of the oral mucosae decrease in the order of sublingual greater than buccal and buccal greater than palatal<sup>41</sup>. This rank order is based on the relative thickness and degree of keratinization of these tissues, with the sublingual mucosa being relatively thin and non-keratinized, the buccal thicker and non-keratinized, and the palatal intermediate in thickness but keratinized.

The oral mucosae in general is somewhat leaky epithelia intermediate between that of the epidermis and intestinal mucosa. It is estimated that the permeability of the buccal mucosa is 4-4000 times greater than that of the skin<sup>42</sup>.

**Membrane coating granules (MCGs):** The MCGs are spherical or oval organelles (100-300 nm in diameter) found in the intermediate cell layer of many stratified epithelia<sup>43</sup>. The granules are found both in keratinized as well as non-keratinized epithelia, but are different with regard to composition<sup>44</sup>. The MCGs discharge their contents into the intercellular space forming the permeability barrier. This barrier exists in the outermost 200µm of the superficial layer. Permeation studies have been performed using a number of very large molecular weight tracers, such as horseradish peroxidase<sup>[45]</sup> and lanthanum nitrate<sup>46</sup>.

#### **Permeant Factors**

The permeation of a drug molecule across the buccal mucosa is dependent on the:

**Molecular size:** Molecular weight, size and radius are more important for hydrophilic substances, as it increases corresponding to decrease in permeability. Small molecular weight permeant (MW<100 Da) are rapidly transported through the buccal mucosa.

**Lipid solubility:** For non-ionizable compounds on increasing lipophilicity the drug permeability typically increases. To maximize the absorption rate, a drug should be available in the salivary film at its solubility limit.

**pH:** The work on pH-solubility profile reported by Kramer and Flynn showed that it is possible to saturate unionized and ionized drug species at particular pH simultaneously called  $pH_{max}$  which should lead to an increased transbuccal permeability compared to any other pH<sup>47</sup>.

**Ionization:** For ionizable drugs, maximum permeation occurs at particular pH where ionization is minimum. Where the drug is predominantly in the unionized form<sup>48</sup>. evaluated the influence of the degree of quaternization of *N*-trimethyl chitosans (TMCs) on the mucoadhesive and penetration enhancement properties towards

buccal mucosa. Fluorescein isothiocyanate dextran (MW 4400 Da) was used as model molecule. The trimethylation of chitosan allows improvement of the mucoadhesive properties by enhancing their penetration effect. In particular, the mucoadhesive properties increase on increasing degree of quaternization.

TMC derived from the lower molecular weight chitosan and characterized by the highest degree of quaternization shows the best mucoadhesive and penetration enhancement properties and is the most promising TMC to improve the bioavailability of hydrophilic and large molecular weight molecules (like peptides and proteins) when administered via buccal route.

#### **Buccal mucosal permeation enhancers<sup>49</sup>**

Permeants enhancer diffuses across oral mucosa via passive transport through paracellular and transcellular routes depending on the physicochemical properties of the diffusible molecule. Since the intercellular spaces and cytoplasm are hydrophilic in character, lipophilic compounds would have low solubilities in this environment. The cell membrane, however, is rather lipophilic in nature and hydrophilic solutes will have difficulty permeating through the cell membrane due to a low partition coefficient. Thus, the intercellular spaces more prone to a barrier to the permeation of lipophilic compounds and the cell membrane act as the major transport barrier for hydrophilic compounds.

A number of drugs are investigated for buccal delivery using various permeation/ absorption enhancers range in both molecular weight and physicochemical properties. Small molecules such as butyric acid and butanol<sup>50</sup>, ionizable low molecular weight drugs such as acyclovir<sup>51</sup>, propranolol<sup>52</sup>, and salicylic acid<sup>53</sup>, and a variety of peptides including octreotide<sup>54</sup>, leutinizing hormone releasing hormone (LHRH)<sup>55</sup>, insulin<sup>56</sup>, and  $\alpha$ -interferon<sup>57</sup>, have all been studied.

#### **Mucoadhesive polymers**

The focus of pharmaceutical research is being steadily shifted from the development of new chemical entities to the development of novel drug delivery system (NDDS)

of existing drug molecule to maximize their effective in terms of therapeutic action and patent protection<sup>58,59</sup>. Moreover, the development of NDDS are going to be the utmost need of pharmaceutical industry especially after enforcement of Product Patent<sup>60,61</sup>.

The development of NDDS has been made possible by the various compatible polymers to modify the release pattern of drug<sup>62,63</sup>. In the recent years the interest is growing to develop a drug delivery system with the use of a mucoadhesive polymer that will adhered to related tissue or to the surface coating of the tissue for the targeting various absorptive mucosa such as ocular, nasal, pulmonary, buccal and vaginal etc. This system of drug delivery is called as mucoadhesive drug delivery system<sup>64, 65</sup>.

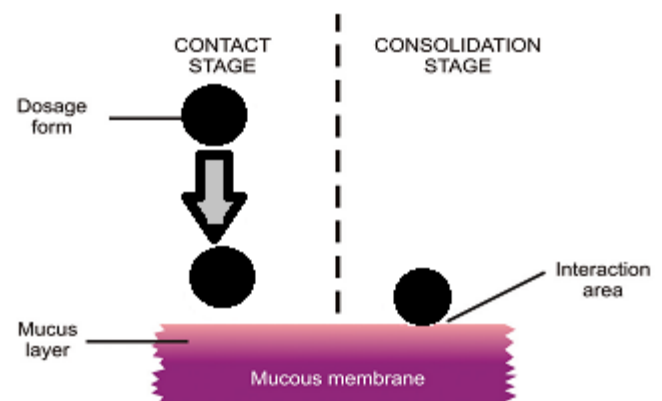
Transmucosal delivery of therapeutic agents is a popular method because membranes are relatively permeable, allowing for the rapid uptake of a drug into the systemic circulation and avoiding the first pass metabolism<sup>66,67</sup>. The efficient uptake offers several benefits over other methods of delivery and allows drugs to circumvent some of the body's natural defense mechanism<sup>68-70</sup>. The market share of transmucosal drug delivery system has been increasing, with an estimated US market share of US\$179 million in year 2000<sup>71</sup>.

### Mechanism of mucoadhesion

The mechanism of bioadhesion of large number of macromolecules over the surface of a mucous membrane is not well understood yet. In order to make a good contact, mucoadhesive must spread over the substrate to trigger contact and increase contact surface, induce the diffusion of macromolecular chains within the mucus membrane. For a successful bioadhesion, attraction forces must predominate over the repulsion force being both the forces are insisted during the adhesion. Each steps involved during the bioadhesion can be facilitated by the nature of the dosage form and routes via which it is administered. e.g., a partially hydrated polymer can be adsorbed by the substrate because of the attraction by the surface water<sup>83,73</sup>.

Thus, the mechanism of mucoadhesion is commonly involved in two steps, the contact stage and the consolidation stage (Fig 3).

The first stage involves an intimate contact between a bioadhesive and a membrane either from a good wetting of the bioadhesive surface or forms the swelling of the bioadhesive.<sup>[74]</sup> There are some factor that may be responsible for the bioadhesion are peristaltic movement of GI TRACT, Brownian movement. When the particle approaches towards the mucous membrane, it will come into contact with repulsive forces (osmotic pressure, electrostatic repulsion, etc.) and attractive forces (Vander waals forces and electrostatic attraction). Therefore, the particle must encounter this repulsive barrier in order to make a good contact<sup>75</sup>.



**Fig 3:** Two stages (contact stage and consolidation stage) depicting the process of mucoadhesion. In the second stage as the contact is established bioadhesive material penetrates into the crevices of the tissue surface or chemical bonds/bridge is formed owing to interpenetration of the chains of the bioadhesive to the mucus membrane.

### Theoretical consideration of mucoadhesion

There are several classical theories have been studied on the basis of physicochemical properties of bioadhesive material and polymer-polymer interaction although, basis of mucoadhesion are still not well understood<sup>2,74,75</sup>.

### Electronic theory

It is based on the electronic charges on mucoadhesive and biological materials being possessing opposite electrical charges. When these

materials come into contact, they transfer electrons and finally formed the double electronic layer at the interface, mucoadhesive strength determined by attractive forces within this layer<sup>1</sup>.

#### **Adsorption theory**

Vander Waals forces hydrogen bonds, electrostatic attraction or hydrophobic interactions play an important role as far concern with this theory. By this forces mucoadhesive material adheres to the mucus layer<sup>74,75,83</sup>.

#### **Wetting theory**

The wetting theory applies to liquid systems which present affinity to the surface in order to spread over it. This theory based on measuring contact angle between two surfaces. In general, lower the contact angle greater is the affinity. The contact angle should approximately to provide adequate spreadability<sup>1</sup>.

#### **Diffusion theory**

Diffusion theory explained that both polymer and mucin chains penetrates each other to a sufficient depth to create a semi-permanent adhesive bond. The degree of penetration depends on diffusion coefficient, flexibility and nature of the mucoadhesive chains, mobility and contact time of the polymer chains<sup>1</sup>.

#### **Fracture theory**

This is perhaps the most accepted theory on the mechanical measurement of mucoadhesion<sup>1</sup>. It is based on the force required to separate two surfaces after bioadhesion is established<sup>2,74</sup>.

#### **Mechanical theory**

Mechanical theory considers adhesion to be 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 process<sup>2,76</sup>.

None of these mechanisms or theories alone could explain the basic phenomena of mucoadhesion which can vary in different situations. However, the understanding of these mechanisms somewhat can help toward the development of new mucoadhesive products<sup>2</sup>.

#### **Factor influencing bioadhesion<sup>76-79</sup>**

Structural, physiochemical and environmental factors affecting bioadhesion are discussed below:

##### **Polymer related factors**

The bioadhesive force depends upon the molecular weight of polymer. As the molecular weight increases up to 100,000 and beyond this level no significant change is observed.

Size and configuration of the polymers are of main concern, as in case of polyethylene oxide adhesive strength increases even up to molecular weights of 4,000,000 because of highly linear configuration of molecules.

##### **Concentration of active polymer**

In highly concentrated systems, the adhesive strength drops drastically. In fact in concentrated solutions, the coiled molecules become solvent repellant and the available chains of polymer are not enough to penetrate the membrane. For solid dosage forms such as tablets, having higher the polymer concentration shows stronger bioadhesion.

##### **Flexibility of polymer chains**

Cross linking in the water-soluble polymers, reduces the mobility of the individual polymer chain. As the polymer density increases due to the cross linking of molecules, the effective length of the chain of which they would penetrate into the mucus layer, decreases furthermore, mucoadhesive strength is liable to be decreased.

##### **Spatial conformation**

In spite of a high molecular weight of 19,500,000 for dextrans, they have similar adhesive strength to that of polyethylene glycol with a molecular weight of 200,000. This is attributed to helical conformation of dextran in contrary of a linear conformation of PEG.

##### **Environment related factors**

###### **pH**

pH was found to exert a significant effect on mucoadhesion as observed in studies of polyacrylic polymers cross linked with -COOH group. It has been reported that the pH of medium are the determinant factor for the degree of hydration of highly cross linked polyacrylic acid polymers and it

will be increases between pH 4 and pH 5 and decreases more at alkaline pH.

#### Applied strength

Adhesive strength depend upon the force by which is applied to a bioadhesive system. If high pressure is applied for a prolong period of time, polymers poly (acrylic acid /divinyl benzene poly (HEMA) or carbopol 934P become mucoadhesive.

#### Contact time

The mucoadhesive strength increases as the initial contact time increases. For the application of mucoadhesive to the GI tract, the initial contact time cannot be controlled.

#### Selection of the model substrate surface

Since physical and biological alteration may occur in the mucus gels or tissues under the experimental conditions. The viability of biological substrate should be confirmed by examining properties like permeability, electrophysiology or histology.

#### Swelling

Swelling depends both on polymer concentration and on presence of water. Excessive swelling may lead to loss of bioadhesive property.

#### Physiological variables

##### Mucin Turnover

The natural turnover of mucin molecules from the mucus layer is important for at least two reasons. First, the mucin turnover is expected to limit the residence time of the mucoadhesive on the mucus layer. Second, mucin turnover results in substantial amounts of soluble mucin molecules. These

**Table 1:** Different polymers and respective sensitivity towards bioadhesion at well defined pH being observed from pH 5 to 6<sup>81</sup>

Polymer	Sensitivity towards bioadhesion
Carboxymethyl cellulose	+++
Poly (acrylic acid/divinyl benzene)	+++
Hydroxy ethyl cellulose	+++
Tragacanth	+++
Caropol 934	+++
Sodium alginate	+++
Polycarbophil	+++
Gum Karaya	++
Gelatin	++
Guar gum	++
Thermally modified starch	+

molecules interact with mucoadhesive before they interact with mucus layer.

#### Disease states

The physiochemical properties of the mucus are known to change during disease conditions such as common cold, ulcerative colitis, gastric ulcers, cystic fibrosis, bacterial and fungal infections of the female reproductive tract and inflammatory conditions of the eye. Mucoadhesive properties of delivery system are needed to be checked under these conditions.

#### Characteristics feature of ideal mucoadhesive polymer<sup>80</sup>

An ideal polymer has the following characteristics:

- Polymer should be nondegradable, non-toxic, non-irritant and non-absorbable from the GI tract.
- Preferably form a strong non-covalent bond with the mucin layer of epithelial cell surfaces.
- It should adhere quickly to moist tissue and possess some site specificity.
- Drug can be easily incorporated and provide no hindrance to their release.
- The polymer should not decompose on storage or during the shelf life of the dosage form.
- The cost of the polymer should not too high so that the prepared dosage form becomes inconvenient to be marketed.

Sensitivity of polymers towards bioadhesion as indicated by sign is given in Table 1.

Polyvinyl pyrrolidone	+
Pectin	+
Polyethylene glycol	+
Acacia	+
Amberlite-200 resin	+
Psyllium	+
Hydroxy propyl cellulose	+
Hydroxy ethyl methacrylate	+
Chitosan	+

Note: +++ excellent; ++ fair; + poor

### Oral mucosal permeation enhancers

Stratum corneum is the potential barrier to mucosal penetration, so in these formulation various types permeation enhancers are incorporated to ensure better bioavailability<sup>82</sup>.

### Different mechanisms of absorption enhancement

A different mechanism has been proposed for absorption by using permeation enhancers. Most permeation enhancers are seems to disrupt the lipid bilayer, which increases membrane fluidity. Enhancers may interact with the polar head of a group of the proteins in the lipid bilayer. It was observed that this interaction causes the proteins to absorb additional water and separate, whereby increasing paracellular transport. Some enhancers (nonionic/ionic surfactants) may solubilize and extract lipids. Nevertheless, extraction of membrane lipids is much more disruptive to membrane integrity than increasing membrane lipid fluidity. Hence, membrane lipids and their integrity are restored slowly with these types of permeation enhancers.

Bile salt enhances absorption, stabilize enzyme-labile drugs, and potentially inhibit proteolytic degradation and aggregation of therapeutic proteins by formation of micelles.

Permeation enhancers that open tight junctions are of little benefit for oral mucosal drug delivery since tight junctions are rarely present in these tissues. Structure/absorption enhancement activity

relationship has been completely characterized for permeation enhancers.

Nonetheless, for surfactants the structure of the polar head groups strongly influences the permeability. It was reported that ether based surfactants increases permeability and therefore absorption comparatively more than esters based with similar structure.

### Method of enhancement of buccal absorption

Despite the bypass of the hepatic first pass metabolism and degradation in stomach and intestine, the bioavailability of buccally administered drug is relatively small. Particularly for peptides (e.g., insulin) the co-administration of compounds that improve absorption seems to be inevitable. In order to obtain enhanced absorption, different techniques can be applied:

A. Improvement of drug absorption via tissue by co-administration of penetration enhancers. These compounds may alter the drug properties (e.g., by complex formation) or reduce the barrier across the mucosa layer (e.g., by pretending the desmosomes fluidization of intracellular liquids).

B. By minimizing the degradation of the drug during transport across the tissue (e.g., by co-administration of enzymes inhibitors or the use of less susceptible prodrugs). Some permeation enhancers are listed in (Table 2).

**Table 2:** Some permeation enhancers through buccal route

Aprotinin <sup>83</sup>	Sodium salicylate <sup>83</sup>	Phosphatidylcholine <sup>84</sup>
Sodium taurocholate <sup>83</sup>	Polyoxyethylene <sup>83</sup>	Azone <sup>87</sup>
Benzalkonium chloride <sup>90</sup>	Lysophosphotidyl choline <sup>89</sup>	Sodium EDTA <sup>72</sup>
Cetylpyridinium chloride <sup>87</sup>	Menthol <sup>84</sup>	Sodium glycocholate <sup>72</sup>
Cetyl trimethyl ammonium bromide <sup>85</sup>	Methoxysalicylate <sup>83</sup>	Sodium glycodeoxycholate <sup>83</sup>
Cyclodextrin <sup>88</sup>	Sulphoxide <sup>86</sup>	Sodium lauryl sulphate <sup>72</sup>
Lauric acid <sup>84</sup>	Dextran sulphate <sup>83</sup>	Sodium taurodeoxycholate <sup>89</sup>

### Methods of bioadhesion study

Testing methods are important during the design and development of a bioadhesive controlled release system as they ensure compatibility, physical and mechanical stability, surface analysis and bioadhesive bonding strength<sup>91</sup>.

The methods for bioadhesive study are as follows:

#### 1. *In vitro* methods

- a. Based on measurement of tensile strength.
- b. Based on measurement of shear strength
- c. Adhesion weight method
- d. Fluorescent probe method
- e. Flow channel method
- f. Mechanical spectroscopic method
- g. Falling liquid method
- h. Colloidal gold staining method
- i. Viscometric method
- j. Thumb test
- k. Adhesion number
- l. Electrical conductance

#### *In vitro* Release Studies<sup>92</sup>

No standard *in vitro* method has been developed for the dissolution study of buccoadhesive dosage form yet. Different workers have used apparatus of various designs and under different conditions, depending on the shape and application of the dosage form developed.

#### *In vivo* method

*In vivo* methods are off course more significant than *in vitro* tests because such methods

presumably provide a more realistic picture of expected behaviour.

#### 2. *In vivo* method

- i. Use of radio isotopes
- ii. Use of gamma ancitigraphy

Several methods for measuring mucoadhesive strength are available. Shear stress measurement method, in which weight required to break the adhesion recorded for various polymers with different contact time. Increasing the contact time for adhesion increased the force required to slide in terms of weights in all polymers. Adhesion strength increases on increase of contact time<sup>93,94</sup>.

#### Bioadhesive buccal dosage forms

Buccal mucosa presents a relatively smooth and immobile surface suitable for the position of a bioadhesive dosage form. The amount of drug that can be incorporated is limited by the size limitation of the buccal dosage form. Those drugs having short biological half-lives requiring sustained, prolong and controlled delivery with poor aqueous solubility which are sensitive to enzymatic degradation may be fruitfully delivered across the buccal mucosa. In general, a drug with a daily requirement of 25 mg or less is more appropriate for buccal delivery. The dosage forms designed for these intended uses are includes tablets, adhesive patches, adhesive gels, and adhesive ointment. Adhesive tablets and patches can be formulated to release the drug unidirectionally or multidirectionally by varying the extent and permeability of the backing<sup>95</sup>.

Buccal dosage forms can be of reservoir or the matrix type. Formulations of the reservoir type are surrounded by a polymeric membrane, which controls the drug release rate. Reservoir systems gives a constant release profile provided the condition (a) that the polymeric membrane is rate limiting, may be achieved with providing appropriate thickness and lower diffusivity in this case the rate of drug release depends upon the polymer solubility and membrane diffusivity as well as membrane thickness and (b) an excess amount of drug is incorporated within the reservoir which may be achieved if the intrinsic thermodynamic activity of the drug is very low and the device has a thick hydrodynamic diffusion layer. In this

circumstance, the drug release profile would be affected directly upon alteration of solubility of drug in solution as well as thickness of the hydrodynamic diffusion layer.

In a matrix type system, the drug is uniformly dispersed in the polymeric matrix and which controls drug release rate. Drug molecules dispersed in the polymer have to dissolve in the medium and which diffuses through the polymer network in contact with the given media. Therefore, drug dispersion and drug depletion zone always exists in the matrix. A thin hydrodynamic diffusion layer also exists at the interface of the drug and their matrix.

**Table 3:** Some commercially available oral transmucosal drug delivery systems<sup>96</sup>

Drug Dosage	Dosage form	Type of release	Product name	Manufacturer
Fentanyl citrate	Lozenge Tablet Film	Immediate Immediate Immediate	Actiq Fentora Onsolis	Cephalon Cephalon Meda Pharmaceutical Inc.
Buprenorphine HCl	Tablet	Immediate	Subutex	Reckitt Benckiser
Buprenorphine HCl and naloxone HCl	Tablet	Immediate	Suboxone	Reckitt Benckiser
Prochlorperazine	Tablet	Controlled	Buccastem	Reckitt Benckiser
Testosterone	Tablet	Controlled	Striant SR	Columbia Pharmaceuticals
Nitroglycerine	Tablet, Spray	Immediate	Nitrostat	W Lambert–P Davis– Pfizer Pharmaceuticals
Glyceryl trinitrate	Spray	Immediate	Nitromist	NovaDel
Zolpidem	Spray Tablet	Immediate	Zolpimist Suscard	NovaDel Forest Laboratories
Nicotine	Chewing gum Lozenges	Immediate	Nicorette Nicotinine	GSK Consumer Health Novartis Consumer Health
Miconazole	Tablet	Immediate	Loramyc	BioAlliance Pharma SA
Cannabis-derived	Spray	Immediate	Sativex	GW Pharmaceuticals,
Insulin	Spray	Immediate	Oral-lyn	Generex Biotechnology

#### Future prospect

Nowadays much research work has been done on mucoadhesive drug delivery systems for various routes of drug administration. The primary aim of mucoadhesive dosage forms are to provide an intimacy of the dosage form with the absorbing surface and to increase the residence time of the

dosage form and overall absorption and bioavailability would get enhanced<sup>97</sup>.

Whilst, there are only a few mucoadhesive formulations available currently, it can be concluded that drug delivery using mucoadhesive formulation offers a great potential both for systemic and local use in the near future.

Information on the buccal absorption of peptides is still rather scarce, except for oxytocin. Other peptides includes vasopressin analogues, insulin, protirelin, buserelin, and calcitonin. Although it has been found that peptide drugs like insulin, oxytocin, protirelin, a vasopressin analogue, and octreotide can effectively permeate the buccal mucosa to provide therapeutic level drug concentration in the blood however, the overall permeability is fairly low. The bioavailability of buccally delivered peptides turned out to be more or less disappointing. In order to resolve these problems many strategies are being designed to achieve oral absorption of peptides.

These strategies include alteration of the formulation (e.g., inclusion of penetration enhancers or protease inhibitors), increasing the retention of the delivery system at the site of absorption, and alteration of the peptide so as to optimize affinity for endogenous transport systems, build in chemical and metabolic stability, minimize the size and optimize the balance between lipophilicity and hydrogen bonding potential<sup>81</sup>.

Thus, increasing the absorption rate and minimizing metabolism at the site of delivery are the major stumbling blocks in the administration of peptide drugs through the oral mucosa. As a result formulating scientists continue to seek improved delivery system via mucosal route<sup>98</sup>.

## CONCLUSION

Due to the ease of application and avoidance of the hepatic metabolism, oral transmucosal (buccal, sublingual) drug delivery offers a promising alternative to overcome the limitations of conventional oral drug delivery and parental administration. The buccal routes, in particular, presents ample opportunities and many formulation approaches have been explored, although the current commercially available formulations are mostly limited to tablets and films.

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