INTRODUCTION

Drug delivery systems that can precisely control the release rate of drug to specific body sites have an enormous potential in the healthcare world. The last two decades in the pharmaceutical industry have witnessed an avant-grade interaction in the field of polymers and material science, resulting in the development of various novel drug delivery systems.

Research and technological advancements in drug delivery have led to utilization of wider routes for drug administration. However, oral drug delivery for systemic and local effects still remains the route of choice for drug administration.

Peroral administration of drugs has certain limitations such as, hepatic first pass metabolism and enzymatic degradation within the GI tract, that prohibit oral administration of certain classes of drugs especially peptides and proteins. Consequently, other absorptive mucosae are considered as potential sites for drug administration.

The concept of bioadhesion involves the binding of a natural/ synthetic bioadhesive polymer to biological substrate such as mucus membranes and epithelium. Transmucosal route of drug delivery (ie. - the mucosal lining of nasal, rectal, vaginal, ocular and oral cavity ) offer distinct advantages over peroral administration. Oral mucosal drug delivery offers several advantages 1-4:

- Prolongation of the residence time of dosage form at site of absorption.
- As residence time increased, there is enhanced absorption and therapeutic efficacy of drug and improving drug bioavailability.
- Provides rapid drug transport to systemic circulation and avoids degradation by first pass hepatic metabolism.
- Accessibility is excellent and acidic degradation of drug is prevented.

These factors make the oral mucosal cavity a very attractive and feasible site for drug delivery. The oral cavity has been used as a site for local and systemic drug delivery.
Local therapy has a number of applications, including the treatment of toothaches, periodontal disease, bacterial and fungal infections etc. While, systemic delivery carries the drug into the main circulation avoiding hepatic first pass metabolism effects. Therefore, mucosal lining of the oral cavity has gained a lot of interest in drug delivery research.

The bioadhesion and mucoadhesion have been widely promoted as a way of achieving targeted drug delivery to an active site of choice through the incorporation of bioadhesive hydrophilic polymer within pharmaceutical formulations along with the drug.

The rationale being that the formulation will be ‘held’ on or at the biological surface and the drug will be released close to the absorptive membrane, with a consequent enhancement of bioavailability.

However, buccal mucosa due to low permeation has limitation on bioavailability of some drug and these issues are drug specific and have to be studied for individual molecules under evaluation.¹

Selection of polymer/s, compatibility of polymers with drug, adhesion capability and drug release modulation are parameters which are specific to polymer type and drug. These have influence on effectiveness and acceptability of this drug delivery system and need to be evaluated for system under development.

There is also a need for analyzing the viability of buccal devices on a commercial scale and the willingness of the industry to take up potential candidates so as to offer an alternative to conventional drug therapy.

The buccal mucoadhesive drug delivery offers several advantages for drug delivery for extended periods of time. However, the right dosage form design, formulation excipients Mucoadhesive polymer, permeability enhancers, methods for evaluation of system,
stability of system and ease of scalability for commercial use needs to be evaluated for
drug under consideration for effective utilization of this novel site.

OVERVIEW OF ORAL MUCOSA¹:
A] Structure:

The buccal mucosa lines the inner cheek, buccal formulations are placed in the mouth
between the upper gingivae (gums) and cheek (referred to as the buccal pouch). The
oral mucosa is composed of an outermost layer of stratified squamous epithelium. Below
this lies a basement membrane, a lamina propria followed by the submucosa as the
innermost layer.
The oral mucosal thickness varies depending on the site: the buccal mucosa measures at
500-800 µm, while the mucosal thickness of the hard and soft palates, the floor of the
mouth, the ventral tongue, and the gingivae measure are 100-200 µm in thickness.

B] Permeability:

The oral mucosae in general is a 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.

C] Environment:

The cells of the oral epithelia are surrounded by an intercellular ground substance,
mucus, the principle components of which are complexes made up of proteins and
carbohydrates. At physiological pH the mucus network carries a negative charge (due to
the sialic acid and sulfate residues) which may play a role in mucoadhesion. At this pH
mucus can form a strongly cohesive gel structure that will bind to the epithelial cell
surface as a gelatinous layer.

Another feature of the environment of the oral cavity is the presence of saliva produced
by the salivary glands. Saliva is the protective fluid for all tissues of the oral cavity. It
protects the soft tissues from abrasion by rough materials and from chemicals. The
salivary pH ranges from 5.5 to 7 depending on the flow rate. The daily salivary volume is between 0.5 to 2 liters and it is this amount of fluid that is available to hydrate oral mucosal dosage forms.

**TRANSMUCOSAL DRUG ABSORPTION**¹,²:

**A] Principles of absorption via oral transmucosa:**

The oral mucosa is highly vascularized, and therefore any drug diffusing into the oral mucosa membranes has direct access to the systemic circulation via capillaries and venous drainage. In order for a drug to pass through the oral mucosa, it must first diffuse through the lipophilic cell membrane, and then pass through the hydrophilic interior of the cells of the oral epithelium. Thus the oral mucosa provides both hydrophilic and hydrophobic barriers that must be overcome for efficient mucosal delivery. An enzymatic barrier also exists at the mucosa which causes rapid degradation of peptides and proteins, limiting their transport across the oral mucosa.

**B] Transmucosal drug absorption mechanism:**

Drug absorption via the oral mucosa is a passive diffusion process. Parameters such as, diffusion coefficient, partition coefficient and thickness of tissue are inherent properties that determine the interaction between the drug and the mucosa.

In general, lipophilic compounds have much higher permeability coefficients than hydrophillic compounds. However, the aqueous solubility of lipophilic compound is usually much lower than those of hydrophilic compounds. Thus, the amount of drug absorbed may not be high for lipophilic compounds if their hydrophobicity is too high. There is a fine balance between partition coefficient and solubility for a drug to be suitable for oral mucosal delivery.

Due to these constraints, the potency of the drug is important for selecting appropriate candidates. Occasionally, permeation enhancers are used to promote drug absorption, especially for hydrophilic drugs.
C) Basic steps for drug absorption:

- **Step 1 - Contact stage:** An intimate contact is formed between the adhesive and mucous membrane.
- **Step 2 – Consolidation stage:** Various physicochemical interactions occur to consolidate and strengthen the adhesive joint, leading to prolonged adhesion.

THEORIES OF BIOADHESION:

Several theories have been proposed to explain the fundamental mechanisms of bioadhesion:

A) **Electronic theory:** When the bioadhesive material and target biological material comes in contact with each other, causing the formation of a double layer of electrical charge at the bioadhesive-biologic material interface.

B) **Adsorption theory:** The bioadhesive bond formed between an adhesive substrate and tissue or mucosa is due to van der Waals interactions, hydrogen bonds and related forces.

C) **Wetting theory:** This theory uses interfacial tensions to predict spreading and in turn adhesion. Using this theory, it is possible to calculate spreading coefficients for various bioadhesives over biological tissues and predict the intensity of the bioadhesive bond.

D) **Diffusion theory:** The diffusion theory states that interpenetration and entanglement of polymer chains are responsible for bioadhesion. Bond strength increases with the degree of penetration of the polymer chains into the mucous layer.

E) **Fracture theory:** This theory analyzes the forces required to separate two surfaces after adhesion.

FACTORS AFFECTING PERMEABILITY OF ORAL MUCOSA:

A) **Aging and permeability of oral mucosa:**
Skin shows well-documented changes in structure and function with age, most of which arise from chronic exposure to ultraviolet radiation (i.e., Photoaging). The oral mucosa, being protected from such environmental effects, shows few changes that can be unambiguously ascribed to aging. In some regions there is a slight thinning of epithelium with a concomitant flattening of epithelial-connective tissue interface.
B) Reactive changes in the oral mucosa:

- **Inflammation**: The mild degree of inflammation stimulates epithelial proliferation, leading to hyperplastic changes, whereas severe inflammation suppresses proliferation so that epithelium may become thinner or even be lost (i.e., Ulcerated). The accumulation of bacteria in plaque around the teeth gives rise to toxins and antigens that produce chronic inflammation in the periodontal tissues. Also, infection of mucosal surface with fungus candida is widespread and if untreated lead to chronic inflammation.

- **Extrinsic factors**: A variety of extrinsic factors can bring about changes in the oral mucosa that have a potential for altering permeability. The most frequent of these is irritation from physical damage, such as cheek biting, rough dental fillings or toothbrushing, or from chemical irritants such as tobacco and tobacco smoke, alcohol, toothpastes and mouth rinses.

C) Special mucosal disease:

Mucosal diseases results in thinning (atrophy) or breakdown (ulceration) of the oral epithelium. The most common of these is aphthous ulceration (aphthous stomatitis), affecting 20-60% of the population.

**BUCCAL ADHESIVE DOSAGE FORMS:**

To improve buccal delivery of drugs, several new dosage forms have been developed: solutions, tablet/lozenges (including lyophilized and bioadhesive), chewing gum, solution sprays, laminated systems and patches, hydrogels, adhesive films, microspheres etc.

**BUCCAL ADHESIVE POLYMERS**: 2-4

Bucladhesive formulations use polymers as the adhesive component. The term buccal adhesive polymer covers a large, diverse group of molecules, including substances from natural origin to biodegradable grafted copolymers and thiolated polymers. Some examples of polymer study in buccal adhesive are as tabulated below.
<table>
<thead>
<tr>
<th><strong>Bioadhesive Polymer(s) Studied</strong></th>
<th><strong>Investigation Objectives</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>HPC and CP</td>
<td>Preferred mucoadhesive strength on CP, HPC, and HPC-CP combination</td>
</tr>
<tr>
<td>CP, PIP, and PIB</td>
<td>Used a two roll milling method to prepare a new bioadhesive patch formulation</td>
</tr>
<tr>
<td>Xanthum gum and Locust bean gum</td>
<td>Hydrogel formation by combination of natural gums</td>
</tr>
<tr>
<td>Chitosan, HPC, CMC, Pectin, Xanthum gum, and Polycarbophil</td>
<td>Evaluate mucoadhesive properties by routinely measuring the detachment force from pig intestinal mucosa</td>
</tr>
<tr>
<td>Poly(acrylic acid-co-acrylamide)</td>
<td>Adhesion strength to the gastric mucus layer as a function of crosslinking agent, degree of swelling, and carboxyl group density</td>
</tr>
<tr>
<td>Poly(acrylic acid)</td>
<td>Effects of PAA molecular weight and crosslinking concentration on swelling and drug release characteristics</td>
</tr>
<tr>
<td>Poly(acrylic acid-co-methyl methacrylate)</td>
<td>Effects of polymer structural features on mucoadhesion</td>
</tr>
<tr>
<td>Poly(acrylic acid-co-butylacrylate)</td>
<td>Relationships between structure and adhesion for mucoadhesive polymers</td>
</tr>
<tr>
<td>HEMA copolymerized with Polymeg® (polytetramethylene glycol)</td>
<td>Bioadhesive buccal hydrogel for controlled release delivery of buprenorphine</td>
</tr>
<tr>
<td>Cydot® by 3M (bioadhesive polymeric blend of CP and PIB)</td>
<td>Patch system for buccal mucoadhesive drug delivery</td>
</tr>
<tr>
<td>Formulation consisting of PVP, CP, and cetylpyridinium chloride (as stabilizer)</td>
<td>Device for oramucosal delivery of LHRH - device containing a fast release and a slow release layer</td>
</tr>
<tr>
<td>CMC, Carbopol 974P, Carbopol EX-55, Pectin (low viscosity), Chitosan chloride,</td>
<td>Mucoadhesive gels for intraoral delivery</td>
</tr>
<tr>
<td>CMC, CP, Polyethylene oxide, Polymethylvinylether/Maleic anhydride (PME/MA), and Tragacanth</td>
<td>Buccal mucoadhesive device for controlled release antifungal device - CMC tablets yielded the highest adhesive force</td>
</tr>
<tr>
<td>HPMC and Polycarbophil (PC)</td>
<td>Buccal mucoadhesive tablets with optimum blend ratio of 80:20 PC to HPMC yielding the highest force of adhesion</td>
</tr>
<tr>
<td>PVP, Poly(acrylic acid)</td>
<td>Transmucosal controlled delivery of isosorbide dinitrate</td>
</tr>
<tr>
<td>Poly(acrylic acid-co-poly ethyleneglycol) copolymer of acrylic acid and poly ethyleneglycol monomethylether monomethacrylate</td>
<td>To enhance the mucoadhesive properties of PAA for buccal mucoadhesive drug delivery</td>
</tr>
<tr>
<td>Poly acryl acid and poly ethylene glycol</td>
<td>To enhance mucoadhesive properties of PAA by interpolymer complexation through template polymerization</td>
</tr>
<tr>
<td>Drum dried waxy maize starch (DDWM), Carbopol 974P, and sodium stearyl fumarate</td>
<td>Bioadhesive erodible buccal tablet for progesterone delivery</td>
</tr>
</tbody>
</table>

**Abbreviations:** CP = Carbopol 934P, HPC = Hydroxy propyl cellulose, PVP = Poly(vinyl pyrrolidone), CMC = Sodium carboxymethyl cellulose, HPMC = Hydroxy propyl methyl cellulose, HEC = Hydroxy ethyl cellulose, PVA = Poly(vinyl alcohol), PIB = Poly(isobutylene), PIP = Poly(isoprene).