REVIEW ON ORAL MUCOSAL DRUG DELIVERY SYSTEM

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ABSTRACT

Oral mucosal drug delivery is an alternative method of systemic drug delivery that offers several advantages over both injectable and enteral methods and also enhances drug bioavailability because the mucosal surfaces are usually rich in blood supply, providing the means for rapid drug transport to the systemic circulation and avoiding, in most cases, degradation by first-pass hepatic metabolism. The systems contact with the absorption surface resulting in a better absorption, and also prolong residence time at the site of application to permit once or twice daily dosing. In this review, attention is focused to give regarding physiology of oral mucosal including tissue permeability, barriers to permeation and route of permeation, biopharmaceutics of buccal and sublingual absorption, factors affecting drug absorption, detailed information of penetration enhancers, design of oral mucosal drug delivery system and role of mucoadhesion and various theories of bioadhesion. Evaluation techniques and selection of animal model for In-vivo studies are also discussed.

Keywords: Oral mucosal, Buccal route, Sublingual route, Mucoadhesion, In-vitro and In-vivo model.

INTRODUCTION

The cost involved both in terms of money and time in the development of a single new chemical entity has made it mandatory for pharmaceutical companies to reconsider delivery strategies to improve the efficacy of drugs that have already been approved. However, despite the tremendous advances in drug delivery, the oral route remains the preferred route for the administration of therapeutic agents due to low cost, ease of administration and high level of patient compliance.

However, significant barriers are imposed on the per oral administration of drugs, such as hepatic first pass metabolism and drug degradation within the gastrointestinal (GI) tract prohibiting the oral administration of certain classes of drugs especially biologics e.g. peptides and proteins. Consequently, other absorptive mucosa are being considered as potential sites for drug administration including the mucosal linings of the nasal, rectal, vaginal, ocular, and oral cavity.
These transmucosal routes of drug delivery offer distinct advantages over per oral administration for systemic drug delivery such as the possible bypass of the first pass effect and avoidance of presystemic elimination within the GI tract [1]. Amongst these, delivery of drugs to the oral cavity has attracted particular attention due to its potential for high patient compliance and unique physiological features.

Within the oral mucosal cavity, the delivery of drugs is classified into two categories: (i) local delivery and (ii) systemic delivery either via the buccal or sublingual mucosa.

This review examines the physiological considerations of the oral cavity in light of systemic drug delivery and provides an insight into the advances in oral transmucosal delivery systems. Oral mucosal drug delivery system is subdivided into buccal and sublingual in which buccal cavity is widely applicable for drug administration through mucosa in case of sublingual route mostly useful for fastest onset of action as in the case of Angina pectoris.

**Advantages of Oral Mucosal Drug Delivery system:**[2]

1. Bypass of the gastrointestinal tract and hepatic portal system, increasing the bioavailability of orally administered drugs that otherwise undergo hepatic first-pass metabolism. In addition the drug is protected from degradation due to pH and digestive enzymes of the middle gastrointestinal tract.

2. Improved patient compliance due to the elimination of associated pain with injections; administration of drugs in unconscious or incapacitated patients; convenience of administration as compared to injections or oral medications.


4. 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.

5. Increased ease of drug administration.

6. 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.

7. In comparison to TDDS, mucosal surfaces do not have a stratum corneum. Thus, the major barrier layer to transdermal drug delivery is not a factor in Oral mucosal routes.
of administration. Hence Oral mucosal systems exhibit a faster initiation and decline of delivery than do transdermal patches.

8. Oral mucosal delivery occurs is less variable between patients, resulting in lower inter-subject variability as compared to transdermal patches.

9. The large contact surface of the oral cavity contributes to rapid and extensive drug absorption.

**Limitations of Oral Mucosal Drug Delivery System:**

Depending on whether local or systemic action is required the challenges faced while delivering drug via oral especially buccal drug delivery can be enumerated as follows. [2]

1. For local action the rapid elimination of drugs due to the flushing action of saliva or the ingestion of foods stuffs may lead to the requirement for frequent dosing.

2. The non-uniform distribution of drugs within saliva on release from a solid or semisolid delivery system could mean that some areas of the oral cavity may not receive effective levels.

3. For both local and systemic action, patient acceptability in terms of taste, irritancy and ‘mouth feel’ is an issue.

4. For systemic delivery the relative impermeability of oral cavity mucosa with regard to drug absorption, especially for large hydrophilic biopharmaceuticals, is a major concern.

**Flow Chart for the Development of Oral Solid Dosage Form** [3]

- Conventional oral solid dosage forms (tablets, capsules)
- Modified release tablets/capsules
- Fast action oral solid dosage form (fast dissolving tablets/capsules)
- Fast action solid dosage form (fast dissolving oral)
Physiology of the Oral Mucosa[4,5,6,7]

Structure

The cheeks, lips, hard and soft palates and tongue form the oral cavity. The main difference between the oral mucosa and skin as compared to the gastrointestinal (GI) tract lining lies in the organization of the different epithelia. While the latter has a single layer of cells forming the simple epithelium, the skin and the oral cavity have several layers of cells with various degrees of differentiation. Within the oral cavity, the masticatory mucosa has a keratinized or cornified epithelium, and covers the stress-enduring regions such as the gingival and the hard palate, providing chemical resistance and mechanical strength. It is divided into four layers: keratinized, granular, prickle-cell, and basal layer (Figure 1). The lining mucosa, which provides elasticity, in contrast, is comprised of non-cornified surface epithelium covering the rest of the regions including the lips, cheeks, floor of the mouth, and soft palate. It also can be further divided into superficial, intermediate, prickle-cell, and basal layers. The third type of mucosa is the specialized mucosa consisting of both keratinized and non-keratinized layers, and is restricted to the dorsal surface of the tongue. The intercellular spaces contain water, lipids, and proteins.

Physiological Importance of Mucins and Saliva

The mucosal tissues are further covered with mucus, which is negatively charged, and contains large glycoproteins termed mucins. These are thought to contribute significantly to the visco-elastic nature of saliva, and maintain a pH of 5.8–7.4. Mucin consists of a protein core, rich in O-glycosylated serine and threonine, containing many helix-breaking proline residues. The salivary glands secreting mucus also synthesize saliva, which offers protection to the soft tissues from chemical and mechanical abrasions. The average thickness of the salivary film in the mouth varies between 0.07 and 0.10 mm. Sustained adhesion of the dosage form (tablet, patch) to the mucosa is an important first step to successful buccal delivery. The mucus plays an important role during this mucoadhesive process by buccal drug delivery systems. The interaction between the mucus and mucoadhesive polymers generally used in most dosage forms can be explained by theories summarized in Table 1.
Figure 1: Structure of the mucosa
### TABLE 1: POSTULATED MECHANISM FOR POLYMER – MUCOSAL ADHESIVE PROPERTIES

<table>
<thead>
<tr>
<th>Theory of Adhesion</th>
<th>Mechanism of Adhesion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adsorption</td>
<td>Secondary chemical bonds such as van der waal forces, hydrophobic interactions, electrostatic attraction, and hydrogen bonds between mucus and polymer.</td>
</tr>
<tr>
<td>Diffusion</td>
<td>Entanglements of the polymer chains in to mucus network.</td>
</tr>
<tr>
<td>Electronic</td>
<td>Attractive forces across electrical double layer formed due to electron transfer across polymer and mucus.</td>
</tr>
<tr>
<td>Wetting</td>
<td>Analyze the ability of past to spared over the biological surface and calculate the interfacial tension between the two. The tension is considered to proportional to $X^{1/2}$, where $X$ is the polymer –polymer interaction parameter. Low values of these parameters correspond to structural similarities between polymers and an increased miscibility.</td>
</tr>
<tr>
<td>Fracture</td>
<td>Relates to the force necessary to separate to surfaces to the adhesive bond strength and it is often used to calculate fracture strength of adhesive bonds.</td>
</tr>
</tbody>
</table>

The mean total surface area of the mouth has been calculated to be 214.7±12.9 cm$^2$. The teeth, keratinized epithelium, and non-keratinized epithelium occupy about 20%, 50%, and 30% of this surface area, respectively. Drug delivery through the oral mucosa can be achieved via different pathways: sublingual (floor of the mouth), buccal (lining of the cheeks), and gingival (gums). The sublingual mucosa is the most permeable followed by the buccal and then the palatal. This is due to the presence of neutral lipids such as ceramides and acylceramides in the keratinized epithelia present on the palatal region, which are impermeable to water.

The non-keratinized epithelia contain water-permeable ceramides and cholesterol sulfate. A comparison of the various mucosae is provided in Table 2. The thickness of the buccal epithelium varies from 10 to about 50 cell layers in different regions because of serrations in connective tissue. In fact, the thickness of buccal mucosa has been observed to be 580 micron meter, the hard palate 310 micron meter, the epidermis 120 micron meter, and the floor of mouth mucosa 190 micron meter.
TABLE 2: SUITABILITY OF VARIOUS REGIONS OF THE ORAL MUCOSA FOR THE TRANSMUCOSAL DRUG DELIVERY BASED ON VARIOUS TISSUE PROPERTIES

<table>
<thead>
<tr>
<th>Tissue</th>
<th>Structure</th>
<th>Epithelial thickness, µm</th>
<th>Permeability</th>
<th>Blood flow</th>
<th>Residence time</th>
</tr>
</thead>
<tbody>
<tr>
<td>Buccal</td>
<td>Nonkeratinized</td>
<td>500–600</td>
<td>++</td>
<td>++</td>
<td>+</td>
</tr>
<tr>
<td>Sublingual</td>
<td>Nonkeratinized</td>
<td>100–200</td>
<td>++</td>
<td>++</td>
<td>--</td>
</tr>
<tr>
<td>Gingival</td>
<td>Keratinized</td>
<td>200</td>
<td>--</td>
<td>+</td>
<td>--</td>
</tr>
<tr>
<td>Palatal</td>
<td>Keratinized</td>
<td>250</td>
<td>--</td>
<td>--</td>
<td>++</td>
</tr>
</tbody>
</table>

Note ++ means very suitable; -- means least suitable.

**Tissue Permeability**

In comparison to the skin, the buccal mucosa offers higher permeability and faster onset of drug delivery; whereas the key features which help it score over the other mucosal route, the nasal delivery system, include robustness, ease of use, and avoidance of drug metabolism and degradation. The buccal mucosa and the skin have similar structures with multiple cell layers at different degrees of maturation. The buccal mucosa, however, lacks the intercellular lamellar bilayer structure found in the stratum corneum, and hence is more permeable. An additional factor contributing to the enhanced permeability is the rich blood supply in the oral cavity.

The lamina propria, an irregular dense connective tissue, supports the oral epithelium. Though the epithelium is avascular, the lamina propria is endowed with the presence of small capillaries. These vessels drain absorbed drugs along with the blood into three major veins-lingual, facial, and retro-mandibular, which open directly into the internal jugular vein, thus avoiding first-pass metabolism. Numerous studies have been conducted comparing the blood supply of the oral cavity to the skin in animals. A thicker epithelium has been associated with a higher blood flow probably due to the greater metabolic demands of such epithelia.

Gingiva and anterior and posterior dorsum of tongue have significantly higher blood flows than all other regions; skin has a lower flow than the majority of oral regions; and palate has the lowest of all regions. In fact, the mean blood flow to the buccal mucosa in
the rhesus monkey was observed to be 20.3 mL/min/100 g tissue as compared to 9.4 mL/min/100 g in the skin.

**Barriers to Permeation** [8-10]

The main resistance to drug permeation is caused by the variant patterns of differentiation exhibited by the keratinized and non-keratinized epithelia. As mucosal cells leave the basal layer, they differentiate and become flattened. Accumulation of lipids and proteins also occurs. This further culminates in a portion of the lipid that concentrates into small organelles called membrane-coating granules (MCGs). In addition, the cornified cells also synthesize and retain a number of proteins such as profilagrin and involucrin, which contribute to the formation of a thick cell envelope. The MCGs then migrate further and fuse with the intercellular spaces to release the lipid lamellae. The lamellae then fuse from end to end to form broad lipid sheets in the extracellular matrix, forming the main barrier to permeation in the keratinized regions in the oral cavity. These lamellae were first observed in porcine buccal mucosa, and have been recently identified in human buccal mucosa. Though the non-keratinized epithelia also contain a small portion of these lamellae, the random placement of these lamellae in the non-cornified tissue vis-à-vis the organized structure in the cornified tissue makes the former more permeable. Also, the non-keratinized mucosa does not contain acylceramides, but has small amounts of ceramides, glucosylceramides, and cholesterol sulfate. The lack of organized lipid lamellae and the presence of other lipids instead of acylceramides make the non-keratinized mucosa more water permeable as compared to the keratinized mucosa.

**Physicochemical properties and routes of permeation**

There are two possible routes of drug absorption through the squamous stratified epithelium of the oral mucosa:

- Transcellular (intracellular, passing through the cell)
- Paracellular (intercellular, passing around the cell)

Permeation across the buccal mucosa has been reported to be mainly by the paracellular route through the intercellular lipids produced by membrane-coating granules. Although passive diffusion is the main mechanism of drug absorption, specialized transport mechanisms have been reported to exist in other oral mucosa (that of the tongue) for a few drugs and nutrients; glucose and cefadroxil were shown to be absorbed in this way.
Figure 2 shows the two routes of permeation that can be used by drugs to pass through the buccal mucosa. The buccal mucosa is a potential site for the controlled delivery of hydrophilic macromolecular therapeutic agents (biopharmaceuticals) such as peptides, oligonucleotides and polysaccharides. However, these high molecular weight drugs usually have low permeability leading to a low bioavailability, and absorption enhancers may be required to overcome this. The buccal mucosa also contains proteases that may degrade peptide-based drugs. In addition, the salivary enzymes may also reduce stability.

**FIG. 2:** A, Ultrastructural features of oral buccal epithelium. MCGs become evident microscopically in the prickle cell layer, approximately at the midpoint of the epithelium. B, Routes of drug transport across oral epithelium.

Disease states where the mucosa is damaged would also be expected to increase permeability. This would be particularly true in conditions that result in erosion of the mucosa such as lichen planus, pemphigus, viral infections and allergic reactions.

**Biopharmaceutics of Buccal and Sublingual Absorption** [11-13]

**Principles of Drug Absorption**

The oral mucosa contains both hydrophilic and hydrophobic components and a combination of both keratinized and non-keratinized epithelia. Passive diffusion is the
most common route of permeation through the oral mucosa, and uses the Fick’s first law of diffusion given by the general equation

\[
P = \frac{DK_p}{h}
\]

The amount of drug absorbed \(A\) is given by;

\[
P = PCSt = \frac{DK_p}{h} CSt
\]

Where, \(P\) is the permeability coefficient, \(C\) is the free drug concentration in the delivery medium, \(D\) is the diffusion coefficient of the drug in the oral mucosa, \(K_p\) is the partition coefficient of the drug between the delivery medium and the oral mucosa, \(h\) is the thickness of the oral mucosa, \(S\) is the surface area of the delivery or the absorption site on the mucosa, and \(t\) is the duration of time the drug stays in contact with the mucosa. The thickness of the tissue, partition coefficient, and the diffusion coefficient are properties of the mucosa and cannot be altered. Designing appropriate formulations that need the necessary conditions can vary the surface area for delivery of the drug, time of contact, and the free drug concentration.

The partitioning of the drug into the membrane will depend on its ratio of hydrophilicity and lipophilicity. Studies performed with amines and acids showed that their absorptions were proportional to their partition coefficients, thus also establishing the fact that the transcellular route was the primary route of absorption of these drugs. Similar results were obtained for \(\beta\)-adrenoreceptor-blocking drugs. Since the drug will face different barriers through the paracellular and the transcellular routes, the flux of drug permeation through these routes will differ to some extent. The equation above can be modified to account for this difference. Hydrophilic compounds will tend to use the paracellular route and permeate through the intercellular spaces, which present a smaller surface area.
The flux of drug permeation through this pathway can be described as Where, DH is the diffusion coefficient, h is the length of the tortuous path followed in the paracellular route, CD is the concentration of the drug on the donor side is the fraction of the surface area of the paracellular route. A lipophilic drug will preferably use the transcellular route since it will be easier for it to partition into the lipophilic cell membrane. The path length here is shorter than for the paracellular route but the drug has to move through several types of barriers (cell membrane, the cytoplasm, as well as intercellular spaces).

**Factors affecting Drug Absorption**

Besides the biochemical characteristics of the buccal and sublingual membranes, which are responsible for the barrier function and permeability, various factors of the drug molecule influence the extent of permeation through the membranes. The lipid solubility, degree of ionization, pKa of the drug, pH of the drug solution, presence of saliva and the membrane characteristics, molecular weight and size of the drug, various physicochemical properties of the formulation, and the presence or absence of permeation enhancers, all affect the absorption and the permeation of drugs through the oral mucosa.

**Degree of Ionization, pH, and Lipid Solubility**

The permeability of unionizable compounds is a function of their lipid solubilities, determined by their oil–water partition coefficients demonstrated this dependence of water permeability on the lipid contents of keratinized and non-keratinized epithelia. The lipids present however contribute to this effect more in the keratinized epithelia (more total lipid content, non-polar lipids, ceramides) than in the non-keratinized epithelia where permeability seems to be related to the amount of glycosylceramides present. The absorption of drug through a membrane depends upon its lipophilicity, which in turn depends on its degree of ionization and partition coefficient. The higher the unionized fraction of a drug, the greater is its lipid solubility.

The degree of ionization in turn depends on the pH of the mucosal membrane and the pKa of the drug. Beckett and Triggs studied the buccal absorption of basic drugs over a range of concentration, pH, and the use of different drug combinations (alone and mixtures). The resultant pH–absorption curves showed that the percentage of drug absorbed increased as the concentration of drug in the unionized form increased. Also, the shapes of the absorption curves were a function of the pKa values and the lipid
solubility of their unionized form. A study conducted with fentanyl, a weak base with a pKa of 8.2, further demonstrated the relationship between the pH and the absorption across oral mucosa. When the pH of the delivery solution was increased, more of the drug was present in the unionized form, with the drug being 2.45% unionized at pH 6.6, 9.1% unionized at pH 7.2, and 24% unionized at pH 7.7. The fentanyl solutions with a pH range of 6.6 to 7.7 showed a three- to fivefold increase in peak plasma concentration, bioavailability, and permeability coefficients.

Similar studies conducted with sublingual administration of opioids such as buprenorphine, methadone, and fentanyl showed increased absorption with increase in pH, where the drug was predominantly present in the unionized form.

However, absorption of other opioids such as levorphanol, hydromorphone, oxycodone, and heroin under similar conditions did not improve. These drugs, however, were more hydrophilic as compared to the earlier set of opioids. Thus, pH modifiers can be used to adjust the pH of the saliva prior to drug administration to increase the absorption of such drugs through the mucosal membranes. However, the nature of the buccal and sublingual membrane complicates the above condition since the pH may vary depending on the area of the membrane and also on the layer of the membrane that is considered. The pH of the mucosal surface may be different from that of buccal and sublingual surfaces throughout the length of the permeation pathway. Thus, the drug in its unionized form may be well absorbed from the surface of the membrane, but the pH in the deeper layers of the membrane may change the ionization and thus the absorption. Also, the extent of ionization of a drug reflects the partitioning into the membrane, but may not reflect the permeation through the lipid layers of the mucosa.

Henry et al., studied the buccal absorption of propranolol followed by repeated rinsing of the mouth with buffer solutions and recovered much of this drug in the rinsing. In addition, the effect of lipophilicity, pH, and pKa will depend on the transport pathway used by the drug. Studies conducted with buspirone showed that the unionized form of the drug used the more lipophilic pathway, the transcellular route, but an increase in the pH increased the ionization of the drug and subsequently the absorption. It was concluded that this transport of the ionized form of the drug was through the more hydrophilic paracellular pathway. Therefore, at neutral pH the preferred pathway was found to be
transcellular, but at acidic pH, the ionized species of the drug also contributed to the absorption across the membrane.

**Molecular Size and Weight**

The permeability of a molecule through the mucosa is also related to its molecular size and weight, especially for hydrophilic substances. Molecules that are smaller in size appear to traverse the mucosa rapidly. The smaller hydrophilic molecules are thought to pass through the membrane pores, and larger molecules pass extracellularly. Increases in molar volume to greater than 80 mL/mol produced a sharp decrease in permeability. Due to the advantages offered by the buccal and the sublingual route, delivery of various proteins and peptides through this route has been investigated.

It is difficult for the peptide molecules with high molecular weights to make passage through the mucosal membrane. Also, peptides are usually hydrophilic in nature. Thus, they would be traversing the membrane by the paracellular route, between cells through the aqueous regions next to the intercellular lipids. In addition, peptides often have charges associated with their molecules, and thus their absorption would depend on the amount of charge associated with the peptide, pH of the formulation and the membrane, and their isoelectric point.

**Permeability Coefficient**

To compare the permeation of various drugs, a standard equation calculating the permeability coefficient can be used. One form of this equation is

\[
P = \frac{\% \text{ permeated} \times V_d}{A \times t \times 100}
\]

Where P is the permeability coefficient (cm/s), A is the surface area for permeation, Vd is the volume of donor compartment, and t is the time. This equation assumes that the concentration gradient of the drug passing through the membrane remains constant with time, as long as the percent of drug absorbed is small.
Formulation Factor
The permeation of drugs across mucosal membranes also depends to an extent on the formulation factors. These will determine the amount and rate of drug released from the formulation, its solubility in saliva, and thus the concentration of drug in the tissues. In addition, the formulation can also influence the time the drug remains in contact with the mucosal membrane. After release from the formulation, the drug dissolves in the surrounding saliva, and then partitions into the membrane, thus the flux of drug permeation through the oral mucosa will depend on the concentration of the drug present in the saliva. This concentration can be manipulated by changing the amount of drug in the formulation, its release rate, and its solubility in the saliva. The first two factors vary in different types of formulations, and the last can be influenced by changing the properties of the saliva that affect the solubility (e.g., pH).

Penetration Enhancers [14-16]
To increase the absorption of poorly soluble drugs especially large hydrophilic molecules, permeation enhancers have become of increasing interest in recent years.

Properties of Penetration Enhancers:
1. Safe and effective
2. Pharmacologically inactive
3. Chemically inert
4. Reversible effect

Majority of the most widely investigated permeation enhancer have surfactant like properties and those that are water soluble seem to be most active at concentrations above the critical micelle concentration. The following have been investigated as a means of enhancing buccal permeability.

Mechanism of Absorption Enhancement:
Permeation enhancers in general act by following ways (figure 3):
1. Increasing the fluidity of the cell membrane
2. Extracting inter and intracellular lipids
3. Disrupting lipid structure e.g., solubilization by formation of micelles to create aqueous channels
4. Altering cellular proteins
5. Increasing the thermodynamic activity of the drug
6. Overcoming enzymatic barriers, particularly for peptide and protein drugs
7. Altering surface mucin rheology

![Mechanism of Absorption Enhancement Diagram]

**FIG. 3: MECHANISM OF ABSORPTION ENHANCEMENT**

**Types of Penetration Enhancers:**
- Bile salts
- Fatty acids and their salts and Esters
- Azones
- Surfactants
- Complexing Agents
- Co-solvents
- Miscellaneous

**Transmucosal drug delivery system**

**Pharmaceutical consideration and formulation design for successful transmucosal drug delivery system**

Drug selection for oral transmucosal delivery is limited by the physicochemical properties of the drugs themselves. To be delivered transmucosally, drugs must have unique physicochemical properties, i.e. a proper balance between solubility and lipophilicity. Moreover, generally only a few milligrams of drug can cross the oral
mucosa, even if the drug has a favorable profile for oral mucosal delivery. Presently, new classes of drugs are typically not developed specifically for oral transmucosal delivery.

It is also important to consider factors influencing drug release from a system. The release kinetics of a given drug from a system could be governed predominantly by the polymer morphology and excipients present in the system. Finally, ideal formulation and its degradation products should be non-toxic, non-irritant and free from leachable impurities. It should not aid in development of secondary infections and prevent the effects of local drug irritation at the site of application.

An ideal transmucosal drug delivery system must meet several prerequisites to be successful. The first prerequisite for a transmucosal drug delivery system is that it should rapidly attach to the mucosal surface and maintain a strong interaction to prevent displacement. Spontaneous adhesion of the system at the target site is critical and can be achieved through bioadhesion promoters that use tethered polymers. Contact time should also be sufficiently long at the target site, normally longer than that needed for complete drug release. The second prerequisite for a successful and effective transmucosal drug delivery system is that the bioadhesion performance should not be impacted by surrounding environmental pH.

Other desirable characteristics of a transmucosal drug delivery system include high drug loading, complete drug release, and convenient administration. Drug release from a
polymeric material takes place either by the diffusion or by polymer degradation or by their combination. Polymer degradation usually takes place by the enzymes or hydrolysis. This may happen in the form of bulk erosion or surface erosion\textsuperscript{[17, 18]}. It is also important to consider factors influencing drug release from a polymer. The release kinetics of a given drug from a polymeric matrix could be governed predominantly by the polymer morphology and excipients present in the system\textsuperscript{[19]}

**Oral transmucosal dosage forms**

To improve oral transmucosal delivery of drugs, several new dosage forms have been developed: solutions, tablets/lozenges (including lyophilized and bioadhesive), chewing gum, solution sprays, laminated systems and patches, hydrogels, adhesive films, hollow fibres and microspheres\textsuperscript{[20]}. Advances in oral mucosal drug delivery have focused on the development of drug delivery systems that not only achieve the therapeutic aims of delivery but also overcome the unfavorable environmental conditions found in the oral cavity. Modern formulations have used creative approaches that incorporate a combination of these strategies to create a balance between patient convenience and clinical benefits. Mucoadhesive carrier is a viable option to develop a non-invasive carrier platform for the controlled release of bioactive.

**Solid forms**

Several solid lozenges formulations have been developed and are commercially available, including nitroglycerin sublingual tablet, fentanyl lozenge on a handle and prochlorperazine buccal tablets. Although these formulations vary in shape and size, they share many common characteristics. This method of delivery is simple for patients to use. The solid formulations dissolve in the oral cavity. The drugs are released and exposed to the entire mucosa and the top third of the esophageal mucosa. The limitation of this delivery form is the short residence time. Depending on the size and formulation, the lozenge or tablet is usually dissolved within 30 min, thus limiting the total amount of drug that can be delivered. The dissolution or disintegration is usually controlled by the patient, i.e. how hard they suck the unit. Increased sucking and saliva production causes swallowing and loss of drug down the esophagus and the gastrointestinal tract. Thus, solid dosage forms generally have a much higher inter- and intraindividual variation in absorption and bioavailability. In addition,
since these formulations are open systems, the delivery medium is not well controlled. Although the formulation offers some control, it is difficult to control drug or other ingredient concentrations because the media is constantly diluted by saliva. This makes it difficult to effectively use permeation enhancers in this type of system. Taste of the drug is another hurdle for this delivery system. Unless the drug is tasteless or the taste can be masked by sweetening and flavorings agents, it is difficult to achieve high patient acceptability of this type of product.

Gum

Chewing gum is one of the modern approaches to oral transmucosal drug delivery and is a useful means for systemic drug delivery. The advantages of chewing gum over other oral mucosal drug delivery systems are the possibility of controlled drug release over an extended time and the potential to improve the variability in drug release and retention times. One of the advantages of chewing gum convenience. Furthermore, an individual may be able to control the drug intake by simply changing the rate and vigour of chewing, or expelling the gum altogether. Since chewing gum is also an open system, it shares many of the same limitations of the other solid formulations.

Patches

Flexible adhesive patches have been developed in an effort to overcome some of the drawbacks of other dosage forms. Transmucosal delivery patches have unique characteristics, including relatively rapid onset of drug delivery, sustained drug release and rapid decline in the serum drug concentration when the patch is removed. Also, a buccal patch is confined to the buccal area over which it is attached and therefore the absorption profile may have less inter- and intraindividual variability. In general, oral mucosal patches can be classified into three categories: patches with a dissolvable matrix, patches with a non-dissolvable backing, and patches with a dissolvable backing. Patches with a dissolvable matrix are designed to release drug into the oral cavity. They work similarly to, and share many of the limitations of, the solid dosage form. The mucoadhesive layer, either in the drug matrix or attached to drug matrix as an additional layer, prolongs the duration of drug matrix in the oral cavity. Therefore, compared with other open dosage forms, these types of patches are longer acting and can potentially deliver more drug. They also use the entire oral cavity mucosa as compared with other closed systems.
that typically use smaller areas. These types of patches are also suitable for treating local
diseases such as candidiasis or mucositis. Patches with non-dissolvable backing are
usually designed for systemic delivery. Since they are closed systems and the
formulations are protected from saliva, the drug concentrations are controlled and drug is
continuously delivered for 10 to 15 h. The disadvantages of these systems are that they
use only a small mucosal area and the backings have to be removed by the patient after
drug administration. Patches with dissolvable backing share many characteristics of
patches with non-dissolvable backing,
but they have the advantage of the entire patch dissolving in the oral cavity. Patches with
dissolvable backings are shorter acting than patches with non-dissolvable backing. Oral
mucosal dosage forms are convenient, easy to use, and have the potential to offer a low-
cost and painless alternative to more invasive routes of administration. Each delivery
form offers very distinct delivery characteristics that can be used in a broad range of
therapies. The majority of patches provide a longer period over which to deliver the
formulated as either solvent cast mucoadhesive polymer discs or drug to and through the
buccal mucosa.

Solution, suspension, and gel-forming liquids
Viscous liquids have been investigated primarily to coat the mucosa to act as a protectant
or a vehicle for drug delivery for the treatment of local disorders, including motility
dysfunction, fungal infections. Using sodium alginate suspension as a novel bioadhesive
liquid, researchers showed that the esophageal surface can be coated to protect against
reflux and can deliver therapeutic agents to the damaged mucosa\textsuperscript{[20, 21]}. The retention
behavior of various bioadhesive formulations was evaluated on the esophageal surface
under conditions mimicking the salivary flow. Both polycarbophil and xanthum gum
demonstrated excellent bioadhesive potential, and carmellose sodium and thermo
sensitive poloxamer (Lutrol 407) demonstrated poor retention. A thermo sensitive
hydrogel of poloxamer covalently linked to polyacrylic acid and carbopol. This
“esophageal bandage”, upon oral administration, demonstrated significant retention
within the esophagus.

Multiparticulates, microparticles, and nanoparticles
Oral delivery systems based on multiparticulates, microparticles, and nanoparticles often exhibit improved performance in comparison with monolithic matrix tablets.\(^{22}\) By diffusing into the mucous gel layer by virtue of their relatively small size, these small immobilized carriers show a prolonged gastrointestinal residence time. Recent work has shown that, in addition to size and chemistry, shape is also a critical feature of transmucosal drug delivery particles and can dictate particle velocity, diffusion and adhesion to the mucus surface in a complex manner \(^{23-24}\).

**In-vitro and in-vivo Study Methods** \(^{25-28}\)

**Animal Models for Studies**

The limited available tissue area in the human buccal cavity has encouraged the use of animal models that may mimic human oral mucosal absorption. Rats, hamsters, dogs, rabbits, guinea pigs, and rhesus monkeys have all been used in buccal studies. As with any animal model, these all have their advantages and disadvantages. Almost all animals have a completely keratinized epithelium. The hamster cheek pouch offers a large surface area but is not flushed with saliva. The oral mucosa of the monkey, a primate, has been widely used but the high cost of procurement as well as challenging handling are disadvantages when it comes to selecting these animals. Rabbit mucosa is similar to human mucosa since it has regions of non-keratinized tissue. However, the small surface area and difficulty in accessing the required tissue make it an impractical choice. The animal of choice remains the pig because of comparable permeability to human buccal mucosa and a large surface area enabling reduced variability in the data. The methods used for measuring the amount of drug absorbed have to be designed in such a way as to account for local delivery of the drug to the mucosa as well as systemic delivery through the mucosa into the circulation. A selection of in vivo and in vitro techniques has been developed and tested over the years.

**In-vivo Methods**

Both human and animal models have been used for in-vivo testing of oral mucosal drug delivery. Choices of animal models depend on how closely the mucosal membrane reflects the structure and properties of human mucosa. An important in vivo technique using human test subjects, the ‘‘buccal absorption test’’ was developed and established by Beckett and Triggs. They adjusted solutions of several basic drugs to various pH
values with buffer, and placed the solution in the subject’s mouth. The solution was circulated about 300–400 times by the movement of the cheeks and tongue for a contact time of 5 min. The solution was then expelled, and the subject’s mouth was rinsed with 10 mL distilled water for 10 s.

The rinsing was collected, and combined with the earlier expelled solution, and the fraction of the drug remaining in this solution was measured by gas–liquid chromatography. It was observed that the absorption of drug from the oral cavity was dependent on pH. Though this technique is easy to perform, noninvasive, and gives relatively consistent results with little intra and inter subject variation, limitations for the method do exist. It does not provide information concerning the varying permeabilities of different regions in the oral cavity. Also, the continuous flow of saliva affects the pH of the applied solution as well as the overall volume. In addition, the test analyzes the amount of drug that has been transported from the sample into the oral cavity and does not provide information on the actual systemic absorption of the drugs.

Some of the drugs could be swallowed or accumulated, and redistributed into the epithelium or biotransformed in the mucosa. Simultaneous measurement of appearance of the drug in the systemic circulation could further validate this test. ‘‘Disk methods’’ for assessing absorption have also been studied where the drug-loaded disk is kept in contact with certain area of the mucosal membrane to allow for absorption. One such polytef disk was used by Anders et al., for the buccal absorption of protirelin. The disk had an area of ~10 cm² and a central circular depression containing the drug. It was removed after 30 min of contact with the buccal mucosa, and blood samples were taken to determine the amount of drug absorbed from the mucosa.

The disk method provides information about absorption from a specific area of the mucosa. Interference from salivary secretions, difficulties in keeping the disk adhered, and loss of drug permeating due to leakage of the drug from the disk is some disadvantages with this method. Another method has been the use of perfusion cells. These cells have certain specific area and can contain a drug solution that is stirred continuously. The closed cell isolates the solution from the surroundings, thus negating the effects of the environmental factors such as saliva and pH. Solution under test can be passed through the mucosal membrane once or it can be re-circulated. The solution in the
cells is then analyzed for drug content. However, the surface area for absorption is low, and the tissue has a tendency to become erythematous.

This method, like the buccal absorption test, measures the loss of drug from the cell, but not the actual absorption of the drug through the buccal mucosa. These methods have been used to analyze different types of dosage forms (composite films, patches, and bioadhesive tablets) and their mucosal drug absorption and have been used to assess both buccal and sublingual absorptions across the respective mucosa. A glass perfusion cell was developed and used by Yamahara et al., for the measurement of drug absorption through mucosal membranes of anesthetized male beagle dogs. The cell contained a biocompatible bioadhesive polymer O-ring that adhere the cell to the oral mucosal membrane. This type of cell can be used to measure buccal and sublingual absorption as well as perfusion through the surface of the tongue.

**In-vitro Methods**

These methods have proven to be important tools in the study of Oral mucosal absorption, since they can facilitate studies of drug permeation under controlled experimental conditions. Oral mucosal tissue can be surgically removed from the oral cavity of animals. These tissues contain a fair amount of connective tissue, which is separated from the mucosal membrane. This connective tissue, if not removed, may contribute to the permeability barrier. This separation can be carried out with the aid of heat where tissues are separated at 60oC, or chemically by the use of various enzymes or EDTA. These tissues are then stored in buffer solution (usually Krebs). This storage step is important in preserving the viability and integrity of the tissue. The tissue is then placed in a side-by-side diffusion cell, where the placement of the tissue is in between the donor and the receptor chambers. The donor contains the drug solution, whereas the receptor usually contains a buffer solution to emulate the body fluids. The chambers can be stirred continuously to ensure even distribution of the drug and are maintained at a desired temperature. The epithelial side of the tissue faces the donor chamber, allowing the drug to pass from the donor chamber through the tissue into the receptor chamber from where samples can be withdrawn at specific time intervals and replaced with fresh receptor solution.
Cell and Tissue Culture Systems

The advantages of the in vitro approaches described above also apply to buccal cell culture systems. In addition, other aspects such as cell growth and differentiation can be studied in these systems in detail. Also, once the source is established, a continuous supply of cell lines can be obtained, which obviates the need for expensive animal or human tissues that are often difficult to obtain in large quantities. On the other hand, the established cell line must simulate, as closely as possible, the physical and biochemical properties of the buccal or sublingual tissues in vivo. These properties such as the growth, differentiation, biological barrier effectiveness, permeability levels, and metabolic pathways are crucial to the permeation studies.

**Current and future development of transmucosal drug delivery**

Many dosage forms have been developed and include toothpastes, mouthwashes, lozenges, gels, chewing gums, lollipops, films, patches, tablets and some specialized devices [29]. Conventional dosage forms, however, exhibit some drawbacks, for example, low bioavailability, because of the washing effect of saliva and mechanical stresses. Formulations that prolong the drug release in the mouth offer great advantages in preventing and treating local diseases or in promoting transmucosal delivery of drugs for systemic therapies [30]. Despite these obstacles for transmucosal drug delivery mentioned above, the buccal mucosa remains an attractive site for the delivery of systemic drugs, in particular for those who are prone to a high level of degradation inside the gastrointestinal tract. Various buccal delivery applications have thus been marketed or proposed in treatment of systemic and chronic diseases among them are trigeminal neuralgia, Meiniere's disease, diabetes, addiction and so on [31-37].

Similar to the treatment of diseases affecting the oral cavity, intraoral systemic drug delivery would benefit from sustained drug release, without the need for the patient to intervene. This would raise the patient's compliance particularly of chronically ill. Acharya et al. patented a device and method for oral transmucosal delivery of drugs or any other constituents via the inner buccal cavity. The device is applied and adheres to the mucosa of the oral cavity without causing adverse effects. It consists of a bilayer tablet: a mucoadhesive layer and an overlying active substance containing layer. The mucoadhesive layer can contain polyvinylpyrrolidone (PVP) as the only adhesive or can
be combined with other hydrophilic polymeric substances. It was claimed that this non-plasticized PVP mucoadhesive has sufficient adhesion not only for mucosal membranes but also to a variety of materials, such as polyacrylic denture material. The active layer also contains a hydrophilic polymer carrier. The layers in the device dissolve and release the active substance into the oral cavity and are particularly suitable for delivering substances active in the oral cavity such as breath fresheners and substances to combat dry mouth. It is also useful for the delivery of ionic drugs such as peptides. Krumme et al. patented a device and a method of multi-layer transmucosal therapeutic film, comprising at least two layers connected with each other, for transmucosal administration of active substances \[38\]. The therapeutic systems which are suitable, in particular, for transmucosal administration (entering through or across the mucous membrane) of active substances have a structure of at least two layers that are connected with each other. The mucoadhesive layer is capable of swelling in an aqueous medium, although it is insoluble or only poorly soluble in such media. One of the two sides of the inventive system is limited by a mucoadhesive layer which optionally contains active substance or is free of active substance. The mucoadhesive layer of the system is connected with a backing layer that is monolayered or double-layered and which may serve as an active substance reservoir.

The insolubility or reduced solubility of the adhesive layer increases the period of adhesion to the mucosa, thereby enabling an active substance release that lasts for a prolonged period. Since the inventive systems are film-shaped and may have a thickness of less than 1 mm, they do not cause a foreign body sensation and are not unpleasant for patients thus contributing to improved compliance.

**Clinical application of oral transmucosal drug delivery**

Oral transmucosal delivery of analgesics has received considerable attention. Oral transmucosal fentanyl is designed to deliver rapid analgesia for breakthrough pain, providing patients with a noninvasive, easy to use and non-intimidating option. For analgesics that are used to treat mild to moderate pain, rapid onset has relatively little benefit and oral mucosal delivery is a poor option. Oral mucosal deliveries of sedatives such as midazolam, triazolam and etomidate have shown favorable results with clinical advantages over other routes of administration. Oral mucosal delivery of the antinausea
drugs scopolamine and prochlorperazine has received some attention, as has oral mucosal
delivery of drugs for erectile dysfunction.

Oral transmucosal formulations of testosterone and estrogen have been developed. In
clinical studies, sublingual testosterone has been shown to result in increase in the lean
muscle mass and muscle strength, improvement in positive mood parameters, and
increases in genital responsiveness in women. Short-term administration of estrogen to
menopausal women with cardiovascular disease has been shown to produce coronary and
peripheral vasodilatation, reduction of vascular resistance and improvement in
endothelial function. Studies of sublingual administration of estrogen are needed to
clarify the most beneficial regimen. Although many drugs have been evaluated for oral
transmucosal delivery, few are commercially available.

The clinical need for oral transmucosal delivery of a drug must be high enough to offset
the high costs associated with developing this type of product. Several cardiovascular
drugs administered transmucosally have been studied extensively. Nitroglycerin is one of
the most common drugs delivered through the oral mucosa. Transmucosal absorption of
nitroglycerin from solutions through the oral cavity was demonstrated in the mid-
nineteenth century. Research on other cardiovascular drugs, such as captopril, verapamil
and propafenone, has proven promising. Oral transmucosal delivery of analgesics has
received considerable attention. These drugs include potent analgesics such as oral
transmucosal fentanyl citrate and buprenorphine.

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such as midazolam, triazolam and etomidate has shown favorable results with clinical
advantages over other routes of administration. Oral mucosal drug delivery offers several
advantages over both injectable and enteral delivery.

Drugs absorbed via the oral mucosa to avoid the fate of enterically administered drugs:
low gastric pH and proteases, and first-pass hepatic degradation. One early study of the
hypoglycaemic effects of sublingual insulin indicated that absorption of human insulin
through the oral mucosa is possible \[^{39}\]. Oral transmucosal fentanyl is one such example.
The initial use of fentanyl was primarily in operating rooms as an anaesthetic agent and as a transdermal patch form to control chronic baseline pain. The use of fentanyl to treat breakthrough cancer pain is a new indication for which there are no other approved alternatives that offer the advantages of oral transmucosal delivery. The unique characteristics of oral transmucosal delivery combined with the pharmacokinetic and pharmacodynamic properties of fentanyl make OTFC a favorable option for pain management in cancer patients. Recently, an oral aerosol rectal, system (Oralin), was developed [41].

This system delivers accurate insulin doses into the mouth by use of a metered-dose aerosol. Mouth deposition is dramatically increased compared with that of conventional technology. This oral aerosol formulation is rapidly absorbed through the Buccal mucosal lining and in the oropharynx regions, and it provides the plasma insulin levels necessary to control postprandial glucose rise in patients with diabetes mellitus [40]. The challenge now is to synthesize drug moieties that exhibit increased absorption across the oral mucosa and are more potent in their action [42].

Recent advances in transmucosal drug delivery systems

Vaccination against debilitating infectious diseases has proven remarkable in prevention of these diseases and has contributed significantly to an increase in life expectancy, especially in children, in many parts of the world. In order to have adequate mucosal protection, there are several factors that can influence the effectiveness of vaccines. The most critical factor in mucosal vaccine effectiveness is the route of administration and potential for the antigen to be processed by the antigen-presenting immune cells, such as macrophages and dendritic cells. Presently, most vaccines are administered via the parenteral route or via other invasive routes. Invasive mode of vaccine administration can trigger the systemic immune response, but may not essentially provide adequate mucosal immune protection. On the other hand, effective mucosal vaccines will not only elicit superior local immune protection, but has been shown to trigger systemic response analogous as that of parenterally-delivered vaccine. As such, it is critically important to examine the development of mucosal vaccination strategies that can effectively trigger systemic as well as mucosal immunity [42]. Mucosal vaccines have currently been investigated using a broad spectrum of nanocarrier systems such as multiple emulsions,
liposomes, polymeric nanoparticles, dendrimers, ISCOMs etc. More importantly, mucosal delivery of nanocarrier antigens and vaccines can trigger immunization at different mucosal barriers which is body's imperative first line defense in addition to systemic immune response. From the future perspective, development of vaccines using combined strategic approach like nanocarriers delivered by mucosal route of delivery can play a major role in the treatment of infectious diseases.

REFERENCES

7. Collins LM and Dawes C. The surface area of the adult human mouth and thickness of the salivary film covering the teeth and oral mucosa. 1987; 45:2-10.


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