BUCCAL DRUG DELIVERY SYSTEM

INTRODUCTION:

1. **Sublingual** delivery, consisting of administration through the membrane of the ventral surface of the tongue and the floor of the mouth.
2. **Buccal delivery** , consisting of administration through the buccal mucosa, mainly composed of the lining of the cheeks and
3. **Local delivery** , consisting of administration through all areas other than former two region.

These sites differ anatomically in their permeability to drugs, rate of drug delivery, and ability to maintain a delivery system for the time required for drug release out of the delivery apparatus and into the mucosa.

Buccal Drug Delivery

The buccal mucosa lines the inner cheek, and buccal formulations are placed in the mouth between the upper gingivae (gums) and cheek to treat local and systemic conditions. The buccal route provides one of the potential route for typically large, hydrophilic and unstable proteins, oligonucleotides and polysaccharides, as well as conventional small drug molecules. The oral cavity has been used as a site for local and systemic drug delivery.

Advantages of Drug Delivery Via The Buccal Lining :

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.
3. Sustained drug delivery.
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 transmucosal routes of administration. Hence transmucosal systems exhibit a faster initiation and decline of delivery than do transdermal patches.
8. Transmucosal delivery occurs is **less variable** between patients, resulting in lower intersubject variability as compaired to transdermal patches.
9. The large contact surface of the oral cavity contributes to **rapid and extensive drug absorption**

Limitations of Buccal Drug Delivery :

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

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.

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

Structure and Design of Buccal Dosage Form

Buccal Dosage form can be of

1. **Matrix type:** The buccal patch designed in a matrix configuration contains drug, adhesive, and additives mixed together.

2. **Reserviour type:** The buccal patch designed in a reservoir system contains a cavity for the drug and additives separate from the adhesive. An impermeable backing is applied to control the direction of drug delivery; to reduce patch deformation and disintegration while in the mouth; and to prevent drug loss.

Additionally, the patch can be constructed to undergo minimal degradation in the mouth, or can be designed to dissolve almost immediately.

Transmucosal drug delivery systems can be bi-directional or unidirectional. Bi-directional (Figure 1) patches release drug in both the mucosa and the mouth while, Unidirectional (Figure 2) patches release the drug only into the mucosa

Figure 2 : Buccal Patch designed for Bidirectional drug release

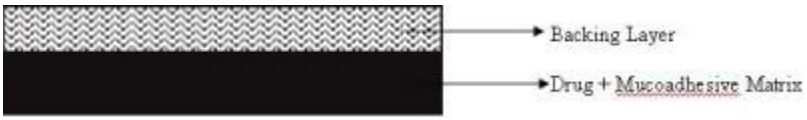

Figure 3: Buccal Patch designed for Unidirectional drug release

Structure of Oral Mucosa

The oral mucosa is comprised of squamous stratified (layered) **epithelium, basement membrane** , the **lamina propria** and **submucosa**. It also contains many sensory receptors including the taste receptors of the tongue.

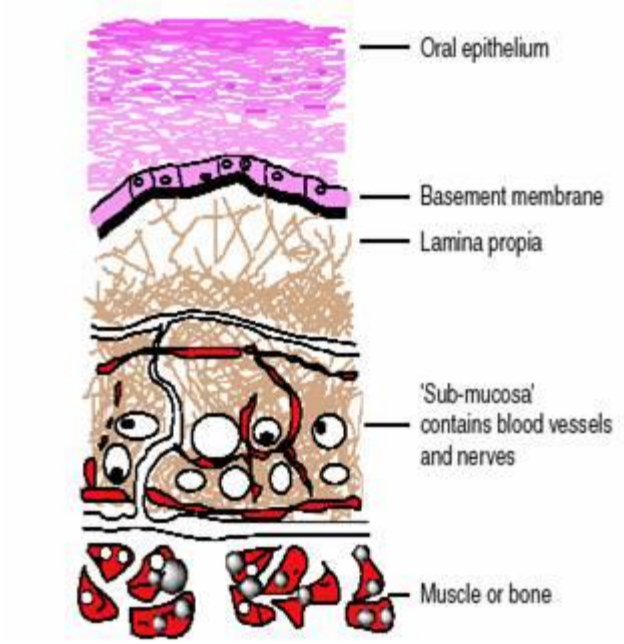

Figure 1: Cross section of Oral Mucosa

Buccal Mucosa: Environment

The oral cavity is marked by the presence of saliva produced by the salivary glands and mucus which is secreted by the major and minor salivary glands as part of saliva.

Role of Saliva

- Protective fluid for all tissues of the oral cavity.
- Continuous mineralization / demineralization of the tooth enamel .
- To hydrate oral mucosal dosage forms.

Role of Mucus

- Made up of proteins and carbohydrates.
- Cell-cell adhesion
- Lubrication
- Bioadhesion of mucoadhesive drug delivery systems

Permeability of Drugs Through Buccal Mucosa :

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

i.Transcellular (intracellular, passing through the cell) and

ii.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, specialised 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.
- 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.
- 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.

Buccal Drug Delivery and Mucoadhesivity

In the development of these Buccal drug delivery systems, mucoadhesion of the device is a key element. The term ‘mucoadhesive’ is commonly used for materials that bind to the mucin layer of a biological membrane. Mucoadhesive polymers have been utilized in many different dosage forms in efforts to achieve systemic delivery of drugs through the different mucosae. These dosage forms include tablets, patches, tapes, films, semisolids and powders. To serve as mucoadhesive polymers, the polymers should possess some general physiochemical features such as

i Predominantly anionic hydrophilicity with numerous hydrogen bond-forming groups

ii Suitable surface property for wetting mucus/mucosal tissue surfaces and

iii Sufficient flexibility to penetrate the mucus network or tissue crevices.

The polymers which have been tried and tested over the years include Carboxymethyl cellulose, Carbopol, Polycarbophil, Poly(acrylicacid/ divinyl benzene), Sodium Alginate, Hydroxyethyl cellulose, Hydroxypropyl methylcellulose, Hyaluronic acid, Gelatin, Guar Gum, Thermally modified Starch, Pectin, Polyvinyl pyrrolidone, Acacia, Polyethylene glycol, Psyllium

Amberlite-200 resin, Hydroxypropyl cellulose, Chitosan, Hydroxyethyl methacrylate.

There are some Novel Mucoadhesive Polymers under development **,** these include Copolymer of PAA and PEG monoethylether monomethacrylate, PAA complexed with PEGylated drug conjugate, Hydrophilic pressure-sensitive adhesives (PSAs), AB block copolymer of oligo(methyl methacrylate) and PAA , Polymers with thiol groups (cysteine was attached covalently to polycarbophil by using carbodiimide as a mediator.

Factors affecting Drug Delivery via Buccal Route

- The rate of absorption of hydrophilic compounds is a function of the molecular size. Smaller molecules (75-100 Da) generally exhibit rapid transport across the mucosa, with permeability decreasing as molecular size increases. For hydrophilic macromolecules such as peptides, absorption enhancers have been used to successfully alter the permeability of the buccal epithelium, causing this route to be more suitable for the delivery of larger molecules.
- Only the nonionized forms of molecules have the ability to cross-lipoidal membranes in significant amounts. The more lipid soluble a compound is, the higher its permeability. The permeabilities for these compounds are direct functions of their oil-water partition coefficients. The partition coefficient is a useful tool to determine the absorption potential of a drug. In general, increasing a drug's polarity by ionization or the addition of hydroxyl, carboxyl, or amino groups, will increase the water solubility of any particular drug and cause a decrease in the lipid-water partition coefficient. Conversely, decreasing the polarity of a drug (e.g. adding methyl or methylene groups) results in an increased partition coefficient and decreased water solubility. The

partition coefficient is also affected by pH at the site of drug absorption. With increasing pH, the partition coefficient of acidic drugs decreases, while that of basic drugs increases. The partition coefficient is also an important indicator of drug storage in fat deposits. Obese individuals can store large amounts of lipid-soluble drug in fat stores. These drugs are dissolved in the lipid and are a reservoir of slow release from these fat deposits.

- The ionization of a drug is directly related to both its pKa and pH at the mucosal surface. Only the nonionized form of many weak acids and weak bases exhibit appreciable lipid solubility, and thus the ability to cross lipoidal membranes. As a result, maximal absorption of these compounds has been shown to occur at the pH at which they are unionized, with absorbability diminishing as ionization increases.
- In short one can say that the lipid solubility of drugs is an important factor in Transmucosal Drug Delivery system. Along with lipid solubility, drugs selected for Transmucosal Drug Delivery system must have physiochemical properties, including size and pKa that facilitate drug movement through the mucosa at a rate capable of producing therapeutic blood concentrations. The drug must resist, or be protected by salivary and tissue enzymes that could cause inactivation. Additionally, the drug and adhesive materials must not damage the teeth, oral cavity, or surrounding tissues (e.g. by keratinolysis, discoloration, and irritation).

Methods to Increase Drug Delivery via Buccal Route

1. Absorption Enhancers

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

Table 1: List of Permeation Enhancers

Sr. no	Permeation Enhancers	Sr. no	Permeation Enhancers
1	2,3-Lauryl ether	14	Phosphatidylcholine
2	Aprotinin	15	Polyoxyethylene
3	Azone	16	Polysorbate 80
4	Benzalkonium chloride	17	Polyoxyethylene
5	Cetylpyridinium chloride	18	Phosphatidylcholine
6	Cetyltrimethyl ammonium bromide	19	Sodium EDTA
7	Cyclodextrin	20	Sodium glycocholate
8	Dextran sulfate	21	Sodium glycodeoxycholate
9	Glycol	22	Sodium lauryl sulfate
10	Lauric acid	23	Sodium salicylate
11	Lauric acid/Propylene	24	Sodium taurocholate
12	Lysophosphatidylcholine	25	Sodium taurodeoxycholate
13	Menthol	26	Sulfoxides

2. Prodrugs

Hussain et al delivered opioid agonists and antagonists in bitterless prodrug forms and found that the drug exhibited low bioavailability as prodrug.

Nalbuphine and naloxone bitter drugs when administered to dogs via the buccal mucosa, the caused excess salivation and swallowing. As a result, the drug exhibited low bioavailability. Administration of nalbuphine and naloxone in prodrug form caused no

adverse effects, with bioavailability ranging from 35 to 50% showing marked improvement over the oral bioavailability of these compounds, which is generally 5% or less

3. **pH**

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

4. **Patch design**

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

Toxicity and Irritancy associated with Buccal Drug Delivery:

Formulations that produce local damage at the site of application, such as ulceration of the mucosa, would preclude their widespread usage as a result of the associated pain and discomfort. This is articularly important in buccal drug delivery where the formulation is in contact with the mucosa for extended periods. Toxic effects can arise from the drug itself, the bioadhesive or from other components of the formulation. For example, carbomers have been reported to produce mucosal irritation believed to result from a localised low pH, whereas lectins have been shown to be cytotoxic. Excipients such as absorption enhancers (e.g., sodium dodecyl sulfate) have also been reported to be irritant.

List of Drugs Delivered via Buccal Route

In an effort to determine the feasibility of BUCCAL **ROUTE** as a novel route of drug delivery, several drugs (Table 2) have been studied. The variation in class of compounds illustrates that the pharmaceutical industries have an alternative and novel routes of administration for existing drugs.

Table 2 : List of Active Ingredients delivered via a BUCCAL ROUTE

Sr. No.	Active Ingredients	Sr. No.	Active Ingredients
1.	Acitretin	26	Metronidazole
2.	Acyclovir	26	Melatonin
3.	Arecoline	28	Metoprolol tartrate
4.	Buprenorpine	29	Morphine sulphate
5.	Carbamazepine	30	Nalbuphine
6.	Cetyl Pyridinium chloride	31	Nicotine
7.	Chlorhexidine diacetate	32	Nifedipine
8.	Chitosan	33	Omeprazole
9.	Chlorpheniramine maleate	34	Oxytocin
10.	Cyanocobalamin	35	Pentazocine
11.	Danazol	36	Protirelin
12.	Denbufylline	37	Pindolol
13.	Diclofenac sodium	38	Piroxicam
14.	Diltiazem Hydrochloride	39	Propranolol
15.	Ergotamine tartrate	40	Propolis
16.	Fluride	41	Recombinant human epidermal growth

			factor (Rh EFG)
17.	Flurbiprofen	42	Salmon calcitonin
18.	Glucagon-like peptide (GLP)-1	43	Sodium fluoride
19.	Hydrocortisone acetate	44	Testosterone
20.	Insulin	45	Terbutaline sulphate
21.	Lactoferrin	46	Theophylline
22.	Lignocaine	47	Thyotropin releasing hormone
23.	Leu-enkephalin	48	Triamcinolone acetate
24.	Luteinizing hormone releasing Hormone (LHRH)	49	Zinc sulphate