2. REVIEW OF LITERATURE
Several terms have been used to describe the parts of the oral cavity by different scientific disciplines (Rathbone et al., 1994). With the current emphasis on drug delivery to specific sites within the oral cavity, some of these terms were confusing. It was referred specifically to the use of the term 'buccal' being interchangeable with the term 'oral', for example, the 'buccal cavity' and 'oral cavity'. Therefore for the sake of clarity, some common terms were defined here and the redundant terms were identified.

**Oral cavity** - The area of the mouth delineated by the lips, cheeks, hard palate, soft palate and floor of mouth.

**Oral cavity mucosa** - The membranes that line the oral cavity, which include the sublingual, buccal mucosa, the gums (gingivae), the palatal mucosa, and the labial mucosa.

**Buccal membrane** - The membrane inside the mouth that lines the cheek.

**Sublingual administration** - Systemic and local administration via or to the membrane beneath the tongue.

**Oral mucosal drug delivery** - General term describing the systemic and local delivery of drugs via or to any membrane that lines the oral cavity.

**Buccal drug delivery system** - A dosage form designed to deliver drugs systemically or locally via or to the buccal mucosa.

**Oral mucosal drug delivery system** - A delivery system designed to systemically or locally delivers drugs via or to oral cavity membranes.

Terms and their particular historical usage, which had become redundant, are:

**Buccal cavity** - The historical term for the oral cavity, the term buccal cavity should be used to describe the cavity on the inside the mouth that lines the cheeks.

**Buccal mucosa** - General descriptive term traditionally used to describe all the membranes that line the oral cavity and should be replaced by the term oral mucosa.
**Buccal drug delivery** - Traditionally used as a general term to describe systemic and local oral mucosal drug delivery. This term should be restricted in use to describe drug delivery to or via the buccal membrane.

There is good accessibility to the membranes that line the oral cavity, which makes application painless and without discomfort, precise dosage form localization possible and facilitates ease of removal without significant associated pain and discomfort. Thus patients could conceivably control the period of administration or terminate delivery in cases of emergencies. The oral mucosal route has in the past exhibited better patient compliance than either the vaginal or rectal route of drug administration. Thus it would be anticipated that novel buccal or sublingual dosage forms would be well accepted by patients. In addition, the route is not gender specific as is the case with the vaginal route.

Mucoadhesive dosage forms satisfy several features (or advantages) of the controlled release systems (Gupta et al., 1992; Anders and Merkle, 1989):

1. For the drugs with bioavailability problems, they localise the drug in a particular region, thereby improving and enhancing the bioavailability.

2. The strong interaction between the polymers and the mucosal lining of the tissues, help in increasing the contact time and permitting localization. This is an essential issue when modification of tissue permeability is important for delivery, examples are peptides, proteins, and ionised species. Co-administration of permeability enhancers will modify absorption in a well-defined area.

3. Metabolizing enzymes (proteases) in a localized area are inhibited.

4. Local delivery of agents is possible for the purpose of modulating antigenicity.

5. It bypasses hepatic first pass metabolism thereby offering a greater bioavailability and/or lowering the dose.

6. Drug is not subjected to the destructive acidic environment of the stomach. Also drugs showing poor and erratic absorption from the stomach can be given via this route.

7. It can be made unidirectional to ensure only buccal absorption.
8. The buccal mucosa is highly perfused with blood vessels and offers a greater permeability than the skin.

9. The oral mucosa lacks prominent mucus secreting goblet cells, thereby diffusion limited mucus build up over time beneath the dosage form is not possible. Thus, a mucoadhesive drug delivery device can be applied to the oral mucosa with out any problem.

10. It offers a passive system, which does not require activation.

11. It can be easily removed in cases of emergency.

12. Therapeutic serum concentrations of the drug can be achieved more rapidly.

However, related impermeability and metabolism for many compounds as well as a small surface area of the exposed tissues are realistic problems for this route of delivery. Almost all drugs intended for sublingual or buccal absorption are marketed in a tablet form and administration in this tablets form has several limitations:

1. Once placed at the absorption site, the tablet should not be disturbed.

2. Eating and drinking are restricted until complete absorption has taken place.

3. There is an ever-present possibility that the patient may swallow the tablet.

Besides these, there are other disadvantages also:

a) The drug swallowed with the saliva is lost.

b) Patient compliance is difficult to achieve.

c) Properties like unpleasant taste, odour, irritability to the mucosa, stability at the buccal pH etc, pose limitations to the choice of the drug along with their physicochemical limitations.

d) They may overhydrate to form a slippery surface and the structural integrity of multilayered formulations may be disrupted by the swelling and hydration of the bioadhesive polymers.
e) It is collectively less permeable than the small intestine, rectum and vagina and typically more permeable than skin.

f) The need to fabricate dosage forms that are "user friendly".

A local microenvironment can thus be created between the dosage form and the mucosa to enhance absorption. Although such modifications occur in a well-described area, irritation limits of the tissue, especially with chronic delivery, need to be established. However, this approach offers an advantage that the irritation or damage to the mucosa by the drug or excipients is restricted to a limited area. In addition, on long-term treatment, the application site may be varied thereby restricting the time of contact and extent of damage to allow compromised mucosa to recover before readministration to the same site, because of the size of the dosage form relative to the buccal mucosa available.

Conventional dosage forms for delivery of drugs via the oral mucosa include solutions, erodible or chewable, buccal or sublingual tablets and capsules. Unfortunately, a major portion of the drug in these systems may be unavailable due to involuntary swallowing and a very short residence time. Because of mastication, speech, etc., the administration of such a dosage form is usually restricted in terms of residence time and hence sustained release is usually not within the scope of such formulations.

In recent years, significant interest has been shown in the development of novel bioadhesive dosage forms for mucosal delivery of drugs that attempt to overcome these limitations. Bioadhesive systems have been used for many years in surgical applications, dentistry, orthopedics and ophthalmology. The use of bioadhesives has recently gained considerable attention in the area of soft tissue based mucosal delivery and several formulations are now commercially available or under-development.

Sobrero (1847) reported that nitroglycerine was absorbed from the oral cavity from solutions. The first evidence of the oral mucosa as a potential absorptive mucosa was through studies by Brunton (1877). He showed that sublingual therapy of glyceryl nitrate could significantly alleviate symptoms of angina pectoris. For over a century, nitroglycerine has been delivered sublingually to alleviate the pain of acute angina, by allowing the tablet to dissolve beneath the tongue or in the cheek pouch. More than 30 years ago, it was reported that the local use of penicillin, using sodium carboxy methyl cellulose in petrolatum, giving prolonged contact at the site of application (Rothner et al.,
1949). The first adhesive commercial product was "Orabase", consisting of finely ground pectin, gelatin and sodium carboxy methyl cellulose in a polyethylene/mineral oil gel base (Kanig and Menago-Ulgado, 1965).

The advances in bioadhesive and controlled release technology have caused a renewal of interest in the delivery of drugs via the oral cavity mucosa. More recently, a variety of compounds have been administered via the oral mucosa, ranging from calcium channel blockers to nicotine, in a variety of delivery systems. Peptides such as insulin have been studied via buccal and sublingual routes (Ishida et al, 1981). In spite of the undoubtedly higher natural permeability of other mucosae, the oral mucosa appears to be rather attractive, but should be found to increase its permeability. Various formulations suitable for oral mucosal drug delivery have been proposed for clinical use are shown in the Table 1 (Ponchel, 1994).

Table 1. Commercially Available Drug Delivery Systems for Systemic Delivery by the Oral Mucosal Route

<table>
<thead>
<tr>
<th>Mucosal site</th>
<th>Drug</th>
<th>Dosage form</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sublingual</td>
<td>Nitroglycerine</td>
<td>Tablets, sprays, bioadhesive tablets</td>
</tr>
<tr>
<td></td>
<td>Isorbide dinitrate</td>
<td>Tablets, chewable tablets and sprays</td>
</tr>
<tr>
<td></td>
<td>Erythrityle trinitrate</td>
<td>Tablets</td>
</tr>
<tr>
<td></td>
<td>Nifedipine</td>
<td>Tablets</td>
</tr>
<tr>
<td></td>
<td>Buprenorphine</td>
<td>Tablets</td>
</tr>
<tr>
<td></td>
<td>Amorphine hydrochloride</td>
<td>Tablets</td>
</tr>
<tr>
<td>Buccal</td>
<td>Prochlorperazine</td>
<td>Bioadhesive tablets and solutions</td>
</tr>
<tr>
<td></td>
<td>Phloroglucinol</td>
<td>Lyocs</td>
</tr>
<tr>
<td></td>
<td>Oxazepam</td>
<td>Lyophilised tablets</td>
</tr>
<tr>
<td></td>
<td>Lorazepam</td>
<td>Lyophilised tablets</td>
</tr>
<tr>
<td></td>
<td>Methylerstereone</td>
<td>Lyophilised tablets</td>
</tr>
<tr>
<td></td>
<td>Nicotine</td>
<td>Chewing gum</td>
</tr>
</tbody>
</table>

Numerous features of the oral cavity make it a complex and difficult area for systemic drug delivery and hence, it is useful to review the oral mucosa structure relevant to drug delivery.
2. Review of Literature

2.1. Overview of oral mucosa

2.1.1. Structure of the oral mucosa

Chen et al. (1949) have described the structure and function of human oral mucosa. The oral cavity is lined with stratified squamous epithelium, below which lies the basement membrane, supported by a connective tissue lamina propria as shown in Fig. 1 (Squire et al., 1976). Classification of epithelium into recognizable cell layers is usually difficult because well defined strata, as seen in the epidermis or keratinized oral epithelium, are absent. There is a well defined layer of basal cuboidal cells succeeded by several rows of slightly flattened cells representing the prickle cell layer. This layer is also referred to as the spinous cell layer. The prickle cell layer is further divided into the upper (superficial) and lower (basal) prickle cells. The remaining one-third of the epithelium consists of flattened nucleated cells called superficial cells. The lamina propria consists of collagen fibers, a supporting layer of connective tissues, blood vessels and smooth muscle. Drugs administered via the oral mucosa gain access to the systemic circulation through a network of arteries and capillaries. The major artery supplying the blood to the oral cavity is the external carotid artery. The venous backflow goes through branches of capillaries and veins and is finally taken up by the jugular vein.

Fig. 1. Schematic diagram showing the main tissue components of the oral mucosa.
The gingiva and the hard palate are lined with a masticatory mucosa, where the epithelium has a confined surface containing keratin. Keratin is found in the superficial cells of the epithelium, which become flattened and virtually devoid of organelles. Keratinized tissue may be subdivided into ortho- and para-keratinized. In ortho keratinized tissue cells, a predominant granular layer is present, which is not in para-keratinized tissue cells. The labial and buccal mucosa, floor of the mouth, soft palate and under side of the tongue are lined with non keratinized stratified squamous epithelium. The stratified squamous epithelia consists of a mitotically active basal cell layer, progressing through a number of differentiating intermediate layers to the superficial layer, where the cells are shed from the surface of the epithelium. These regions represent the major absorption site in the oral cavity. An important issue is the turnover of cells. Unlike the skin, which has a complete turnover period of approximately 30 days, the oral mucosa has a turnover time in the range of 3 to 8 days.

The thickness of the oral epithelium varies depending on the location and species. The buccal epithelium is composed of approximately 40 to 50 cell layers, while sublingual tissue contains considerably fewer cell layers. In humans, dogs and rabbits, the buccal mucosa measures 500-800 μm in thickness, whereas the floor of the mouth, ventral tongue and gingivae region measure 100-200 μm. The surface of the mucous membrane is continuously washed by a stream of about 0.5 to 2 liters of saliva daily, which is produced by the salivary glands comprising three pairs of parotid, submaxillary and sublingual glands. In addition, the buccal and palatal regions contain minor salivary glands.

The composition of the epithelia varies depending on location. Cells of both keratinized and non-keratinized epithelia contain large amounts of proteins, in the form of tonofilaments. Cells of non-keratinized epithelia contain low molecular weight proteins whereas those of keratinized epithelia contain higher molecular weight keratin. The keratinized epithelia contain neutral lipids like ceramides and acyl ceramides which have been associated with the barrier function. These epithelia are relatively impermeable to water. In contrast, the non-keratinized epithelia, such as the floor of the mouth and the buccal epithelia, do not contain acylceramide and possess only small amounts of ceramide. They contain few neutral but polar lipids, particularly cholesterol sulfate and glucosyl...
ceramides. These epithelia have been found to be considerably more permeable to water than keratinized epithelia.

2.1.2. Permeability and permeability barriers of the oral mucosa

One of the fundamental properties of the oral mucosa is its barrier function. It excludes potentially dangerous endogenous or exogenous substances present in the oral cavity. Like the skin, the oral mucosa consists of stratified squamous epithelium. However, unlike the skin which has a dry surface coated with sebaceous lipid the oral mucosa is always moist because of saliva that is constantly secreted by three pairs of salivary glands and it does not show the presence of keratin (buccal and sublingual). These dissimilarities with skin make the oral mucosa more permeable than skin. The buccal permeability value for water (Lesch et al., 1980) suggests the permeability coefficient \( P \) values for the oral mucosa to be greater than that for skin. This improved permeability of the oral mucosa, as compared to skin, holds for a wide of drugs. Both the gut and oral mucosa are kept moist all the time. However, the gastrointestinal tract is lined with columnar epithelia, highly specialized for its absorptive function. Hence, one might expect the oral mucosa to be less permeable than the gut and to have permeability characteristics between that of gut and the skin and closer to the gut than skin.

2.1.2.1. Experimental systems

Both \textit{in vitro} and \textit{in vivo} methods of study of oral mucosal absorption are available and discussed in the evaluating parameters of mucoadhesive drug delivery systems.

2.1.2.2. Permeability barrier

It is currently believed that the permeability barrier in the oral mucosa is a result of intercellular material derived from the so-called "membrane coating granules" (MCGs). This barrier exists in the outermost 200 \( \mu \text{m} \) of the superficial layer. Permeability studies have been performed using two tracers, namely, lanthanum nitrate and horseradish peroxidase (Squier and Hall, 1984). The two tracers differ in size and chemical properties. Horseradish peroxidase is a macromolecule \((M, 40 000)\), 5-6 nm in size, while lanthanum exists as a colloid, 2 nm in size. Even though the two tracers have different sizes, both are hydrophillic and are therefore expected to be confined to aqueous pathways through the mucosa. Topically applied tracers did not penetrate further than the top 1-3 cell layers.
However, when the same probes were introduced subepithelially, they extended through the intercellular spaces into the prickle cell layers. In both keratinized and non-keratinized epithelium, the limit of penetration coincided with the levels where the MCGs could be seen adjacent to the superficial plasma membranes of the epithelial cells. Since the pattern of penetration is similar in both keratinized and non-keratinized epithelia, it is unlikely that keratinization, per se, is a major barrier for penetration. Since the limit of penetration coincided with the levels where the MCGs are seen, it appears that MCGs are involved in formation of the major barrier for penetration. Microscopically visible tracers like horseradish peroxidase and lanthanum can provide useful information on the site and extent of the barrier in the epithelium. Autoradiography studies of small-molecular-weight peptides confirm that only outer one-third of the epithelial tissue is rate limiting and no barrier properties are found beneath this layer.

It has been shown that for some compounds the barrier to penetration is not the upper one-third of the epithelium. Alfano and his co-workers (Alfano et al., 1975) studied the penetration of endotoxins through non-keratinized oral mucosa. The results of their studies indicated that the basement membrane is a rate-limiting barrier to penetration. The structure of the lamina propria is not sufficiently dense to present a barrier to permeation of relatively large molecules. Hence with few exceptions, most studies reveal that the outer one-third of the epithelial tissue is rate limiting to permeation.

2.1.2.3. Mechanism of drug transport

Substances can be transported across various epithelial membrane by means of simple diffusion, carrier mediated diffusion, active transport or other specialized mechanisms, such as endocytosis. While cells of the oral epithelium and epidermis are capable of taking up materials by endocytosis, particularly in the basal and prickle layers, it does not seem likely to be a transport mechanism across an entire stratified epithelium. There is considerable evidence that most substances passing across the oral mucosa move by simple Fickian diffusion. The early works of Beckett and his co-workers indicated that loss of drugs from the oral cavity occurred by the process of passive diffusion of the non-ionized form in accordance with the pH-partition hypothesis (Beckett and Hossic, 1971). Some amino acids, such as glutamic acid and lysine, are reported to be transported via a carrier-mediated process. Also, certain vitamins, such as L-ascorbic acid, nicotinic acids
and thiamine, are transported via carrier-mediated transport. While both glutathione and homocitrulline are transported by a carrier-mediated process, the transport of the former is sodium independent and that of later is sodium dependent. A few monosaccharides have been proven to be transported by a carrier-mediated process.

Two potential routes across the oral mucosa can be classified as non-polar and polar. The non-polar route involves lipid elements of the mucosa by partitioning of the drug into the lipid bilayer of the plasma membrane or into the lipid of the intercellular matrix. The polar route involves the passage of hydrophilic material through aqueous pores in the plasma membrane of individual epithelial cells or ionic channels in the intercellular spaces of the epithelium.

An alternative classification involves passage through intercellular spaces between the cell, i.e., the paracellular route, and transport into and across the cells i.e., the transcellular route. The transcellular route involves partitioning, cellular channel diffusion, and carrier-mediated transport. However, the paracellular route represents diffusive convective transport occurring through the intercellular space.

Some of the electrical properties that are used to classify epithelia as leaky or tight include the measurement of resistance or potential difference. Accordingly, tissues like the rabbit gall bladder, rat duodenum and jejunum and rabbit ileum with low resistance and potential difference are classified as leaky and hence, more permeable. The gastric mucosa of the fundus of nectrus, frog skin, toad bladder epithelium and the rabbit buccal with high resistance and potential difference are classified as tight mucosae. In terms of better permeability, the nasal, rectal and vaginal mucosa appear to be preferred over the oral area (buccal and sublingual). However, because of excellent accessibility of the oral mucosa, appropriate dosage forms can be fabricated and drug action can be terminated at any time by simply removing the dosage form. For this route, patients are expected to have high compliance and the application is essentially painless. In view of the natural function of the oral mucosa, it is routinely exposed to a multitude of foreign substances and, hence, must be rather robust and less prone to irreversible damage by drug, dosage form, adjuvant like penetration enhancers, enzyme inhibitors and/or solubilizers. Thus, in spite of undoubtedly higher natural permeability of most other routes, the buccal area
appears attractive for delivery of certain drugs, particularly if bioadhesive are part of the delivery system.

2.1.2.4. Nature of permeant

The ability of a molecule to permeate through the mucosa can be related to molecular size, lipid solubility and ionization.

2.1.2.5. Molecular size

For hydrophilic substances, the rate of absorption is a function of the molecular size. Small molecules (<75-100 Da) appear to cross the mucosa rapidly, but permeability falls off rapidly as molecular size increases. This relationship between size and permeability has not been demonstrated for lipophilic substances.

2.1.2.6. Lipid solubility

For any series of unionized compounds, their relative permeabilities are functions of their oil-water partition coefficients, with the more lipid-soluble compounds having higher permeabilities.

2.1.2.7. Ionization

The degree of ionization of a permeant is a function of both its pKa and the pH at the mucosal surface. For many weak acids and weak bases, only the unionized form possesses appreciable lipid solubility. The absorption of many compounds has been shown to be at the pH at which they are mostly unionized, tailing off as the degree of ionization increases.

2.1.2.8. Permeability coefficient

The experimental designs of such studies are so different that meaningful comparisons between studies are virtually impossible. However, the permeability coefficient, P (cm/s), which is shown in equation;

\[ P = \frac{\%\text{permeated} \times V_d}{A t \times 100} \]
where, $V_d$ is the volume of donor compartment, $A$ is the surface area for permeation and $t$ is time.

Only handful of investigators have determined this parameter. Table 2 gives the permeability coefficient of some compounds across the oral mucosa (Harris and Robinson, 1992).

<table>
<thead>
<tr>
<th>Probe</th>
<th>Mucosa</th>
<th>$P$, cm/s</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Tritiated water</td>
<td>Rabbit buccal</td>
<td>$3.7 \times 10^5$</td>
</tr>
<tr>
<td>2. Glycerol</td>
<td>Rabbit buccal</td>
<td>$6.0 \times 10^7$</td>
</tr>
<tr>
<td>3. Octanol</td>
<td>Rabbit buccal</td>
<td>$2.2 \times 10^5$</td>
</tr>
<tr>
<td>4. Progesterone</td>
<td>Rabbit buccal</td>
<td>$8.9 \times 10^6$</td>
</tr>
<tr>
<td>5. Glutamic acid</td>
<td>Rabbit buccal</td>
<td>$4.0 \times 10^7$</td>
</tr>
<tr>
<td>6. Lysine</td>
<td>Rabbit buccal</td>
<td>$2.3 \times 10^7$</td>
</tr>
<tr>
<td>7. Serine</td>
<td>Rabbit buccal</td>
<td>$1.3 \times 10^6$</td>
</tr>
<tr>
<td>8. Glycine</td>
<td>Rabbit buccal</td>
<td>$8.3 \times 10^7$</td>
</tr>
<tr>
<td>9. Leucine</td>
<td>Rabbit buccal</td>
<td>$1.9 \times 10^7$</td>
</tr>
<tr>
<td>10. Benzyamine</td>
<td>Rabbit buccal</td>
<td>$1.5 \times 10^5$</td>
</tr>
<tr>
<td>11. Salicylic acid</td>
<td>Rabbit buccal</td>
<td>$9.3 \times 10^7$</td>
</tr>
<tr>
<td>12. TRH</td>
<td>Rabbit buccal</td>
<td>$2.0 \times 10^7$</td>
</tr>
<tr>
<td>13. Dextran 4000</td>
<td>Rabbit buccal</td>
<td>$2.2 \times 10^9$</td>
</tr>
<tr>
<td>14. DGA VP</td>
<td>Pig buccal</td>
<td>$1.1 \times 10^8$</td>
</tr>
<tr>
<td>15. Isorpterenol</td>
<td>Pig buccal</td>
<td>$6.0 \times 10^8$</td>
</tr>
<tr>
<td>16. Tritiated water</td>
<td>Pig buccal</td>
<td>$5.0 \times 10^5$</td>
</tr>
<tr>
<td>17. Tritiated water</td>
<td>Pig buccal</td>
<td>$2.6 \times 10^5$</td>
</tr>
<tr>
<td>18. Estradiol</td>
<td>Pig buccal</td>
<td>$6.6 \times 10^6$</td>
</tr>
<tr>
<td>19. Amphetamine</td>
<td>Pig buccal</td>
<td>$1.5 \times 10^5$</td>
</tr>
<tr>
<td>20. Ouabain</td>
<td>Pig buccal</td>
<td>$6.5 \times 10^6$</td>
</tr>
<tr>
<td>21. Tritiated water</td>
<td>Hamster cheek pouch</td>
<td>$2.9 \times 10^5$</td>
</tr>
<tr>
<td>22. Butanol</td>
<td>Hamster cheek pouch</td>
<td>$4.3 \times 10^5$</td>
</tr>
<tr>
<td>23. Benzoic acid</td>
<td>Hamster cheek pouch</td>
<td>$4.6 \times 10^5$</td>
</tr>
<tr>
<td>24. Urea</td>
<td>Rat sublingual</td>
<td>$2.2 \times 10^6$</td>
</tr>
<tr>
<td>25. Glucose</td>
<td>Rat sublingual</td>
<td>$4.8 \times 10^7$</td>
</tr>
<tr>
<td>26. Glycerol</td>
<td>Rat sublingual</td>
<td>$1.1 \times 10^6$</td>
</tr>
<tr>
<td>27. Butanol</td>
<td>Rat sublingual</td>
<td>$2.9 \times 10^5$</td>
</tr>
<tr>
<td>28. Urea</td>
<td>Rabbit sublingual</td>
<td>$8.4 \times 10^6$</td>
</tr>
<tr>
<td>29. Sucrose</td>
<td>Rabbit sublingual</td>
<td>$8.0 \times 10^7$</td>
</tr>
<tr>
<td>30. Dextran 2000</td>
<td>Rabbit sublingual</td>
<td>$4.0 \times 10^7$</td>
</tr>
</tbody>
</table>
2.1.2.9. Permeation enhancers

The major efforts of scientists to improve transmucosal absorption are addressed to the use of substances acting as absorption promoters, otherwise called absorption enhancers or penetration enhancers. Categories and examples of membrane permeation enhancers are given in the Table 3 (Aungst, 1995). Absorption enhancers can be divided in many different classes: a first classification is between the chemical and physical enhancers. Generally speaking, chemical enhancers act by destroying the mucosa, very often in the irreversible way.

Table 3. Membrane Permeation Enhancers

<table>
<thead>
<tr>
<th>A. Bile salts and other steroidal detergents</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>- Sodium glycocholate</td>
<td></td>
</tr>
<tr>
<td>- Sodium taurocholate</td>
<td></td>
</tr>
<tr>
<td>- Saponins</td>
<td></td>
</tr>
<tr>
<td>- Sodium taurodihydrofusidate</td>
<td></td>
</tr>
<tr>
<td>- Sodium glycodihydrofusidate</td>
<td></td>
</tr>
<tr>
<td>B. Surfactants</td>
<td></td>
</tr>
<tr>
<td>1. Nonionics</td>
<td></td>
</tr>
<tr>
<td>- Laureth-9</td>
<td></td>
</tr>
<tr>
<td>- Polysorbate 80</td>
<td></td>
</tr>
<tr>
<td>- Sucrose esters</td>
<td></td>
</tr>
<tr>
<td>- Dodecylmaltoside</td>
<td></td>
</tr>
<tr>
<td>2. Cationic</td>
<td></td>
</tr>
<tr>
<td>- Cetyltrimethylammonium bromide</td>
<td></td>
</tr>
<tr>
<td>3. Anionic</td>
<td></td>
</tr>
<tr>
<td>- Sodium lauryl sulfate</td>
<td></td>
</tr>
<tr>
<td>- Fatty acids</td>
<td></td>
</tr>
<tr>
<td>C. Other enhancers</td>
<td></td>
</tr>
<tr>
<td>1. Azones</td>
<td></td>
</tr>
<tr>
<td>2. Salicylates</td>
<td></td>
</tr>
<tr>
<td>3. Chealating agents</td>
<td></td>
</tr>
<tr>
<td>4. Sulfoxides</td>
<td></td>
</tr>
</tbody>
</table>

The effect of bile salts, nonionic and ionic surfactants, steroidal detergents, and other absorption promoters on the transmucosal absorption of buccal insulin was studied in rats. Laureth 9, sodium fusidate, sodium laurate and sodium lauryl sulfate were among the agents studied. In the absence of an absorption promoter, buccal insulin was less than 4% as effective as *i.m* insulin. All steroidal detergents examined as absorption promoters markedly improved buccal insulin absorption, from aqueous vehicles containing 5% adjuvant. Concentrations greater than 1% were required. The nonionic surfactant, laureth 9 was also effective at lower concentrations. Ester nonionic surfactants had no effects.
The effect of pH was evaluated for sodium fusidate, laureth 9 vehicles and with both adjuvants, buccal insulin absorption was lower at pH 5.4 than at pH 3.4 or pH 7.4. Other effective adjuvants included sodium laurate and sodium lauryl sulfate. It was concluded that the absorption of insulin can be markedly increased using adjuvants which are known to enhance nasal, rectal, or transdermal absorption rates (Aungst and Rogers, 1989).

In another study, *in vitro* permeability of verapamil hydrochloride through the cheek pouch and abdominal skin of hamsters and the effects of laurocapram (azone) and (+)-limonene (d-limonene) on verapamil permeability were examined (Liu, et al., 1992). In a neutral hydrogel vehicle, permeability of the cheek pouch was 14 times higher than that of the skin. However, permeability through both cheek pouch and skin increased with increasing vehicle pH. Laurocapram and (+)-limonene enhanced verapamil permeability at both sites; yet, laurocapram was more effective than (+)-limonene as an absorption enhancer at keratinized buccal mucosa.

The permeation of salicylic acid across rabbit buccal mucosa was studied *in vitro* and the effects of penetration enhancers on drug flux were examined using differential scanning calorimetry (DSC), flux, electrophysiology and microscopy techniques (Gandhi and Robinson, 1992). It was concluded that the superficial layers and protein domain of the epithelium appear to be the primary barriers of rabbit buccal mucosa to salicylic acid.

The effects of absorption enhancers on the buccal absorption of hybrid (BDBB) alpha-interferon were studied in rats and found that the sodium taurocholate increases the permeability with a dose related response (Steward et al., 1994).

The effect of some penetration enhancers on epithelial membrane lipids was examined using human buccal cell membranes labeled with fluorophores as a model for epithelial lipid bilayer (Turunen et al., 1994). Bile salts can enhance the buccal penetration of a model compound, fluorescein isothiocyanate, *in vitro* across buccal mucosa (Senel et al., 1994).

Zhang et al (1994) has investigated the possibility of effective permeability enhancement without tissue damage, the effectiveness of sodium cholate, sodium taurocholate and lysolecithin (lyosphophatidylcholine) as enhancers in the buccal administration of insulin in anesthetized dogs. The results shown that sodium taurocholate
and lyssolecithin transiently alter the mucosal barrier function, while sodium cholate alters the mucosal barrier function for prolonged times which may be the result of either extended enhancer stay in the mucosa or mucosa damage.

Sodium glycodeoxycholate as an absorption enhancer on the buccal delivery of fluorescein isothiocyanate labeled dextran 4400 and buserelin (Hoogstraate et al., 1996a; Hoogstraate et al., 1996b; Hoogstraate et al., 1996c) and on morphine sulfate (Senel et al., 1997) was studied.

2.1.2.10. Mathematical and physical models of buccal absorption

Beckett et al (1968) studied the kinetics of buccal absorption of amphetamine using an analog computer. The results indicated that kinetic constants may be useful to assign numerical values to the relative partitioning properties of drugs into the oral mucosa. A five minute cumulative absorption data showed the most important criteria for the rapid absorption of drugs, which should have large partition coefficient (Beckett and Moffat, 1968; Beckett and Moffat, 1969). They have suggested useful compartment model for the buccal absorption of some carboxylic acids and mathematical equations were used to describe the transfer.

The application of a diffusion model to additional in vivo buccal absorption data involving p-n-alkyl phenylacetic acids, p-halogen phenylacetic acids and toluic acids was reported. The model underscores the importance of the diffusion layer and its effect on the transport of nonionized drug molecules in the buccal absorption situation (Vora et al., 1972). A review on biophysical models described the buccal absorption of drugs, including barrier properties of the human buccal epithelium, methods for studying absorption and mechanisms (Ho, 1993).

2.2. Bioadhesion

Bioadhesion has been the subject of growing interest. From a theoretical standpoint, bioadhesion may lead to the solution of bioavailability problems resulting from a too short stay of the dosage form at the absorption site (Duchene et al., 1988). This technique can be applied to almost any kind of dosage form and is particularly studied with microparticles and nanoparticles administered by the nose, with the object of finding
an alternative to the parenteral administration of drugs. However, most of the dosage forms presently marketed are classic tablets for either local or systemic use.

Bioadhesion may be defined as the ability of a material (synthetic or biological) to adhere to a biological tissue for an extended period of time. Formation of an adhesive bond between a polymer and biological membrane or its coating can be visualized as a two-step process. The first step involves initial contact between the two surfaces. The second step involves formation of secondary bonds due to non-covalent interactions. The surface of the biological membrane and the surface of the adhesive form an interfacial layer and causes bond formation. In most cases, the adhesive interaction would initially be between the bioadhesive polymer and the mucous layer and would not directly involve the epithelial surface. Molecular events that take place in the interfacial layer depend on various characteristics of both the polymer and the membrane. In order to gain a thorough understanding of interfacial events, a brief discussion of the characteristics of the two surfaces will be presented.

2.2.1. Biological membrane

The oral cavity is covered with a gel-like structure known as mucus. Hence, during the process of attachment, all bioadhesive materials must interact with the mucous layer. Mucus serves as a link between the adhesive and the membrane. The composition of the mucus varies widely, depending on animal species, anatomical location, and whether the tissue is in a normal or pathological state. There is considerable variation in thickness and composition of the mucous layer within the oral mucosa.

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 negative charge density contributes significantly to bioadhesion. The concentration of the mucus in solution may be the most important parameter in determining its rheological properties. Involvement of the epithelial cell layer, the structure and density of the cell surface oligosaccharide side chains and their interaction with lipids and proteins must be considered in developing an accurate mechanism of bioadhesion.
2.2.2. Bioadhesive polymers

Currently, a variety of polymers can be used in bioadhesive systems including many water-soluble and insoluble hyrdocolloid polymers, both ionic and non-ionic, as well as insoluble hydrogels (Park and Robinson, 1986; Peppas and Buri, 1986; Nagai, 1986). Drug release from soluble polymers typically occurs by bulk erosion. However, drug release from insoluble hydrogels follows either Fickian or non-Fickian diffusion kinetics. The bioadhesive properties of a polymer is affected by the following factors.

2.2.2.1. Molecular weight and polymer conformation

The optimum molecular weight for maximum bioadhesion depends on the type of bioadhesive polymer at issue. It is generally understood that the threshold required for successful bioadhesion is at least 100,000 molecular weight, as seen in the case of PEG polymer and increases with molecular weight for linear polymers. It is obvious that the polymer molecule must have an adequate length to allow chain interpenetration. It is also necessary to consider the size and configuration of the polymer molecule. For example, there is a critical molecular weight of 78,600 for sodium carboxy methyl cellulose that is required to produce interpenetration and entanglement. The molecular weight differs depending on polymer conformation. Thus, with polyethylene oxide, the adhesive strength increases even up to a molecular weight of 4,000,000, since the molecule has a highly linear configuration, contributing to interpenetration. In sharp contrast, dextrans of molecular weight as high as 19,500,000 show similar bioadhesive strength as those with molecular weight of 200,000. Since the molecules in dextran exhibit a coiled conformation, many of the active adhesive groups are "shielded" inside the coils and are unavailable for the adhesion process.

2.2.2.2. Cross-linking density

An increase in cross-linking is found to decrease the strength of mucoadhesion, due to decreasing diffusion coefficient, chain segment flexibility and mobility. Therefore, the extent of interpenetration was reduced.
2.2.2.3. Charge and ionization

Using a cell culture-fluorescent probe technique, polymers were studied for their bioadhesive potential. It appears that charge density is an important element for bioadhesion and polyanions are preferred over polycations when one considers toxicity in addition to bioadhesion. Carboxylated polyanions are good potential bioadhesives for drug delivery (Park and Robinson, 1984).

2.2.2.4. Concentration of the polymer

In order to achieve optimal bioadhesion, there exist a critical concentration of polymer (Duchene et al., 1988). When the concentration of polymer increases, the adhesive strength decreases significantly. In a concentrated solution of a polymer, the coiled molecules become solvent-poor. As a result, the macromolecules approach the dimension of an unperturbed state and the available chain length for penetration decreases.

2.2.2.5. pH

pH can influence the formal charge on the surface of the mucus as well as certain ionizable bioadhesive polymers. It was found to have a significant effect on mucoadhesion as observed in studies of polyacrylic acid polymers cross-linked with carboxyl groups (Park and Robinson, 1984). Mucus will have a different charge density on the surface depending on pH, depending on the dissociation of functional groups (carbohydrate moiety and amino acid moiety) of the polypeptide backbone. pH of the medium is critical for hydration of the lightly cross-linked polyacrylic acid copolymers. The apparent $pK_a$ for the polymer is approximately 4.7 (Ch'ng et al., 1985). Maximum adhesion was observed at pH 5 and 6 and a minimum at pH 7, which was attributed to difference in charge density. Hence, the charge density of both mucin and the polymer are influenced by pH, which in turn effects the bioadhesion.

2.2.2.6. Hydration

Swelling characteristics are related to the bioadhesive itself and its environment. Swelling depends on the polymer concentration, ionic strength as well as the presence of water. Excess water results in an abrupt drop in adhesive strength. Thus, adhesive strength is optimum at a certain degree of hydration. Sufficient water is necessary
2. Review of Literature.

- to hydrate the mucoadhesive
- to expose the adhesive site for secondary bond formation
- expand the gel to create pores of sufficient size
- mobilize all the flexible polymer chains for interpenetration

When the degree of hydration is high, adhesiveness is lost, probably due to formation of a slippery, nonadhesive mucilage in an environment of a large amount of water at or near the surface. Such a phenomenon must not occur too early to detach the dosage form. However, its appearance allows easy detachment of the bioadhesive system after release of the active ingredient has ceased.

2.2.3. Theories of bioadhesion

The surface characteristic and composition of the mucoadhesive material, as well as, the substrate and the associated applied force to bring the substrate in contact are important parameters in assessing mucoadhesion. Bonding occurs chiefly through both physical and weak chemical means. Physical or mechanical bonds result from entanglement of the adhesive material with the extended mucus chains. Chemical bonding may be of primary or secondary type. Primary bonds are due to covalent bonding and secondary bonds may be due to electrostatic, hydrophobic or hydrogen bonds. Electrostatic interactions and hydrogen bonding appear to be important as a result of the large number of charged species. Hydrophobic bonding occurs when non-polar groups associated with each other in aqueous solution due to a tendency of water molecules to exclude non-polar molecules. The van der Waals attractions between hydrophobic groups have binding energies between 1-10 kcal/mol, where as hydrogen bonds between hydrophillic groups have an energy of about 6 kcal/mol. Hydrophobic bonding is generally considered to be the most important in bioadhesion.

Several theories of mucoadhesion are proposed to explain the fundamental mechanism(s) of attachment. In a particular system, one or more theories can equally explain or contribute to the formation of bioadhesive bonds. Proposed theories of bioadhesion include wetting, diffusion, electronic, adsorption and fracture (Gandhi and Robinson, 1994; Lee et al., 2000).
2.2.3.1. Wetting

Wetting theory best describes the adhesion of liquid or paste to a biological surface. The wetting theory emphasizes the intimate contact between the adhesive and mucus. The work of adhesion can be expressed in terms of surface and interfacial tension (γ) being defined as the energy per cm² released when an interface is formed. A wetted surface is controlled by structural similarity, degree of cross-linking of the adhesive polymer or use of a surfactant.

Wachem et al (1985) studied the in vitro interaction of human endothelial cells with polymeric substances possessing different degree of wetting in a culture medium containing serum. Their results suggest that moderately wettable polymers showed optimal adhesion, spreading and proliferation of the cells. Adhesion was decreased or disappeared with very hydrophilic or hydrophobic polymers. In a homologous series of cellulosic polymers, the authors observed an increase in bioadhesive strength when the contact angle increased. Hence, the surface characteristic of the bioadhesive material is an important parameter that needs to be considered.

2.2.3.2. Diffusion

The essence of diffusion theory is that the polymer chains and the mucus co-mingle to a sufficient depth to create a semi permanent adhesive bond. Additional insight with respect to the mechanism of interpenetration was explained by Prager and Tirrel (1981). The penetration rate is known as diffusion coefficient, which depends on molecular weight and cross-linking density. In addition, chain segment mobility, flexibility of the bioadhesive polymer, mucus glycoprotein and the nature of both networks are important parameters that need to be considered.

These general theories are not particularly useful in establishing a mechanistic base to modern bioadhesives, but they do identify variables that are important to the bioadhesive process.

2.2.3.3. Electronic

The adhesive polymer and mucus typically have different electronic characteristics. When these two surfaces come in contact, a double layer of electrical
charge forms at the interface. Then adhesion develops due to the attractive force from electron transfer across the electrical double layer (Deryaguin et al., 1997).

2.2.3.4. Fracture

The fracture theory of adhesion is related to separation of two surfaces after adhesion. The fracture strength is equivalent to adhesive strength.

2.2.3.5. Adsorption

In the adsorption theory, a bioadhesive polymer adheres to mucus because of secondary surface forces such as van der Waals forces, hydrogen bonds or hydrophobic interactions (Kaelble, 1997).

From a drug delivery point of view, our interest is primarily in understanding the mechanism of bioadhesion, which appears best explained by a combination of wetting, diffusion and electronic theory, although other mechanisms may be operative for a given system.

2.2.4. Methods of determination of bioadhesion

During the design and development of novel bioadhesive controlled systems, various types of experimental tests must be carried out to assure thermodynamic compatibility, physical and mechanical stability, solute diffusion, release studies, surface analysis and bioadhesive bond strength. Though methods and devices for testing the bioadhesive bond strength have been discussed in various publications, accurate methods to determine the adhesive bond strength internally are still in their infancy.

An ex vivo apparatus was described for the measurement of the adhesiveness of an insulin solid dosage form for oral mucosa. In this method, insulin dosage form is fixed on mouse peritoneal membrane on which an for 10 min and then wrenched with a spring balance (Ishida et al., 1981).

The first in vitro method consists of an investigation of the modification of cultured epithelial cells on account of interpenetration by polymer molecules (Park and Robinson, 1984). A fluorescent liposoluble pyrene probe is used to record changes in fluorescence which is proportional to polymer binding.
A method similar to the measurement of the surface tension was developed. In this method, a glass plate suspended from a microbalance is dipped in the mucous sample. After a fixed contact time, the force required for detaching the plate is recorded (Smart et al., 1984).

A new *in vitro* measurement system using a stainless steel sieve as an adhesive surface is described for assessing the adhesivity of mucoadhesive tablets containing 60% of carbomer 941 (Forget et al., 1988). Gandhi and Robinson (1988) discussed the equipment and methods for measuring mucoadhesion of several controlled-release mucoadhesive dosage forms.

The use of a mucin-gold staining technique to study the mucoadhesive properties of acrylic hydrogels was investigated. The technique employs red colloidal gold particles, which are stabilized by the adsorbed mucin molecules (mucin-gold conjugates). Upon interaction with mucin-gold conjugates, mucoadhesive hydrogels develop a red color on the surface (Park, 1989).

The applicability of a tensile testing machine for measuring mucoadhesive strength was examined. By standardizing the time of sample equilibration and the run rate before measurement, it was possible to get good reproducibility of tensile values. Based on maximum nominal breaking force and work consumed, the tensile strength was found to depend on the concentration and type of polymer used. The same rank order in adhesive properties of the polymers was achieved as with modified surface tensiometers (Dyvik and Graffner, 1992).

Various artificial biological medium have been used for bioadhesion. Usually animal tissue excised and conserved in an appropriate fluid with nutrients at appropriate temperature can also be used. *An in vitro* method for the measurement of the strength of the bond formed between mucoadhesive tablets and the mucus membrane by simulating the amount of shear, pH, temperature, mucosal surface and the wetness of the contact surface, using hamster cheek pouch as a model mucous membrane was presented (Gupta et al., 1993).
A novel in vitro method was used to measure the duration of mucoadhesion of discs containing various putative mucoadhesive materials using rat small intestine as the model for mucosal surface (Mortazavi and Smart, 1994).

To develop an in vitro model that allows the prediction of in vivo performance of mucoadhesive drug delivery systems, a modified Dia-Stron rheometer was used to measure the maximum force required as well as the total work necessary to detach 11 mucoadhesive discs that were left in contact with a model mucosal surface for 2 min at 37 °C and pH 6. The methods of measuring the adhesive strength, the nature of the mucosal surface and the means of applying stress to the adhesive joint were also evaluated (Mortazavi and Smart, 1995).

2.3. Formulation factors

The drug may be incorporated in the bioadhesive dosage form either by:

1. Synthesizing the polymer with the drug in the reaction mixture, thereby incorporating the drug in the matrix, or

2. Incorporating the drug during swelling of the polymer in a saturated drug solution.

One of the disadvantages of method 1 may be decomposition of the drug during polymer synthesis, particularly at high temperatures. However, with method 2, a major problem can be loading yield.

One or more adjuvants may be added to the bioadhesive dosage form depending upon the nature of the drug. One of the common disadvantages of delivery via the oral mucosa is low bioavailability because of poor membrane permeability or metabolism at the absorption site. For less permeable drugs, it may possible to add penetration enhancers to the bioadhesive system. However, relatively few studies have been done on the absorption in the oral cavity. In order to optimize absorption of drug, the local environment may need to be modified using solubiliser or pH-modifying agents.

Obviously, including of a single additive to the dosage form increases the complexity of the formulation. All additives released into the oral cavity should be critically evaluated, since the oral cavity is a site of complex bacterial microflora, whose
composition and viability is essential for health. Any eventual irritation of the mucosa by these adjuvants or drugs will likely be restricted to the area of application site. Considering the risk versus benefit, one may tolerate minor local, rather than general, irritation, since the site of application may be changed to allow for the tissue to regenerate.

2.4. Residence time

For a successful drug delivery system, one of the most important factors is retention time or the duration of mucosal adhesion of a mucoadhesive system. The residence time depend on the degree of binding of the polymer to the mucus surface, which in-turn depends on several factors such as the nature, viscosity and concentration of the polymer. In general, an increase in the viscosity of the polymer will provide better adhesion and hence longer retention time.

2.5. Correlation between in vitro and in vivo

The degree of binding is generally assessed by a number of in vitro tests. Although a number of test methods are already available, there is no single standard test method. Each method measures only a particular property of bioadhesive. It is not clear what parameters are more meaningful and would truly reflect in vivo performance. There is a rough correlation between the adhesion time as measured by an in vitro technique and the residence time in vivo. The general belief is that the greater the bioadhesive strength, as measured by in vitro methods, the greater will be the adhesion, and hence longer residence time, is not true. One must consider several factors that may contribute significantly to adhesion strength and adhesion time, which are not apparent in vitro. Inter-subject variation due to degree of hydration, salivary secretion, mastication, speech, and mucin turnover may significantly affect in vivo performance. In contrast, the in vitro system is a clean system providing a defined degree of water content. Hence, a predictable and reproducible degree of swelling, adhesion time and release of the drug can be obtained. Therefore, the conflicting data between iv vivo and in vitro studies remains an open question and needs further investigation. However, performance of the final dosage form is the best test for bioadhesion.
2.6. Bioadhesive dosage forms

With a better understanding of the mechanism(s) of bioadhesion, several bioadhesive dosage forms have been reported. Within the oral cavity, the buccal region has been extensively explored and appear promising for certain drugs. Hence, this region will be discussed in more depth.

2.6.1. Buccal

The presence of a smooth and relatively immobile surface for placement of a bioadhesive dosage form, the buccal region appears to be more suitable for sustained delivery of therapeutic agents using a bioadhesive system.

Since there is a limit to the size of the bioadhesive dosage form, only a limited amount of drug can be used in this system. In general, any drug with a daily requirement of 25 mg or less would be a candidate for buccal delivery. Drugs with short biological half-lives requiring a sustained effect, poor permeability, sensitivity to enzymatic degradation and poor solubility may be successfully delivered via a bioadhesive buccal mucosal delivery system. Relevant bioadhesive dosage forms in the buccal cavity include adhesive tablets, adhesive gels, adhesive patches, and adhesive ointments.

Several extensive reviews have been presented on the bioadhesive drug delivery systems. The advantages of drug absorption through the oral are compared with drug delivery via the gastrointestinal tract. The dosage forms that may be considered for buccal or sublingual administration are tablets, sprays, chewing gum and adhesive patches (Livingstone and Livingstone, 1989). The structure and composition of the mucosa at different sites in the oral cavity, mucosal permeability, absorption enhancement, experimental systems for studying mucosal permeability and formulation factors were discussed (Harris and Robinson, 1992). The advantages, disadvantages, release and bioadhesive strength of mucoadhesive buccal drug delivery systems may be referred to the reviews presented (Gupta et al., 1992; Rathbone and Tucker, 1992; Smart, 1993; Jimenez-Castellanos et al., 1993; Chidambaram and Srivatsava, 1995; Ahuja et al., 1997; Lee et al., 2000; Banaker, 1994). These dosage forms will be discussed briefly.
2.6.1.1. Adhesive tablets

Unlike conventional tablets, bioadhesive tablets allow drinking and speaking without major discomfort.

Synotocinon (oxytocin) buccal tablets have been tested for induction of labor (Grabensberger, 1969; Thummel and Stubbe, 1969). Induction was successful up to 74% of the cases. It was felt that oxytocin buccal tablets have a useful place in clinical practice, but they will not completely replace oxytocin infusions (Warm, 1970).

Schor et al (1983) developed nitroglycerin bioadhesive tablets. Various other studies also have been reported on the use of nitroglycerin, 5 mg buccal tablet (Lahiri et al., 1986), in sublingual (Nitromex) and buccal (Suscard) dosage forms in angina pectoris (Ryden, 1987; Grasso et al., 1988).

The absorption and pharmacokinetics of verapamil hydrochloride (Isoptin) were evaluated in healthy subjects who received 20 mg buccal tablets, 80-120 mg capsules and a 5 mg IV injection. The rate of absorption and terminal elimination half-life of the buccal tablet was not significantly different from that of the capsule. The absolute bioavailability of the buccal tablet (37%) was slightly greater than that of the capsule (33%) (Asthana et al., 1984).

The availability of prochlorperazine following i.m., buccal and oral administration was studied. It was reported that a 3 mg twice daily buccal dose is equivalent to a 5 mg 3 times daily oral dose (Hessell et al., 1989).

Buccal route has been studied for the administration of the morphine as premedication in surgery (Fisher et al., 1987; Hoskin et al., 1989).

Several other drugs have been investigated for the administration by this route. Examples are: nifedipine (Save and Venkitachalam, 1994; Save et al., 1994); propranolol hydrochloride (Taylan et al., 1996); triamcinolone acetonide (Mumtaz and Ch'ng, 1995); clotrimazole (Khanna et al., 1996; Khanna et al., 1997); miconazole nitrate (Bouckaert et al., 1996).
Bitterness and failure to dissolve are the common problems that were encountered with buccal formulations are (Simpson et al., 1989).

2.6.1.2. Adhesive gels

Various adhesive gels may be used to deliver drugs via the buccal mucosa and show sustained release. In comparison to solutions, gels can significantly prolong residence time and hence improve bioavailability. A highly viscous gel containing carbopol and hydroxypropyl cellulose maintained the drug upto 8 hr (Ishida et al., 1983). A buccal mucoadhesive gel formulation containing ergotamine tartrate was prepared using polyvinyl alcohol and the gels were studied in vitro to determine the adhesive force, physical strength and drug release (Tsutsumi et al., 1994).

2.6.1.3. Adhesive patches

These are the most extensively studied dosage forms for oral drug delivery. Patches may range from simple erodible and nonerodible adhesive disks to laminated systems. The size of the patches can be vary from 1 to 15 cm². The smaller the size, the more convenient and comfortable are the patches. Patches may be formulated with a backing layer providing unidirectional release of the drug into the mucus layer. Thus loss of drug to the saliva was minimized and concentration gradient of the drug to the mucosa was maximized. On the other hand, the adhesive polymer may be used for local drug release, with no backing layer. Such patches will provide a bi-directional release of drug, resulting in significant loss during swallowing of saliva.

Adhesive patches of two poly-laminates with an impermeable backing layer and a hydrocolloid polymer layer containing drug are described for buccal administration (Anders and Merkle 1989). Oral mucoadhesive films prepared by the casting procedure were described for metronidazole (Smid Korbar et al., 1991), buprenorphine (Guo and Cooklock, 1995) and protirelin (thyrotropin-releasing hormone) (Li et al., 1997).

2.6.1.4. Adhesive ointments

Bioadhesive ointments have not been investigated as extensively as tablets and patches (Ishida et al., 1983). A case of prompt and dramatic improvement following buccal application of half an inch of 2% nitroglycerin ointment was reported in a woman
with acute myocardial infarction (Shah, 1985). Mucoadhesive liposomal ointment containing triamcinolone acetonide was also tested (Sveinson and Holbrook, 1993).

### 2.6.2. Sublingual

The sublingual region generally shows higher drug permeability than the buccal region. However, unlike the buccal region, the sublingual region does not appear promising for attachment of a bioadhesive system, primarily because of the physical structure and mobility of tissue in this area. This route has been used extensively for delivery of drugs which require a rapid onset of action, example is nitroglycerin. Sublingual administration of nifedipine has been found safe and effective in the treatment of moderate to severe hypertension (Erbel et al., 1983).

### 2.6.3. Dental/gingival

Work on adhesive materials and evaluation, relative to denture adhesives, has been extensively reviewed. Both natural and synthetic hydrocolloids have been used as denture adhesives. The excipients of denture adhesives include swellable polymers, gel, antibacterial/antiseptic agents, preservatives, fillers, wetting and flavoring agents. Bioadhesive dosage form containing lidocaine was developed. This was an adhesive tablet containing magnesium stearate in the cap layer and HPC and carbopol (CP) as a base. These tablets were tested in humans. The dosage form affords a prolonged anesthetic action in the treatment of toothache. Very rapid onset of action and lasting approximately for 4 hours without anesthetizing other parts of the oral cavity was observed (Ishida et al., 1982).

In terms of protein and peptide permeability, other mucosal epithelia appear to be more efficient than the oral mucosa, examples are nasal, vaginal and rectal mucosae. On the other hand, what makes the oral mucosa rather attractive for peptide delivery is a combination of several aspects:

1. The oral mucosa is easily accessible, so dosage forms can be easily administered and even removed from the site of application.

2. Since patients are well adapted to the oral administration of drugs, patient acceptance and compliance are expected to be good.
3. According to its natural function the oral mucosa is routinely exposed to a multitude of different external compounds. Therefore, it is supposed to be rather robust and less prone to irreversible irritation or damage by a dosage form, its drug, excipients or other additives.

So in spite of the undoubtedly higher permeability of other mucosal sites, the oral mucosa appears to be an attractive alternative, providing appropriate dosage forms can be devised. The oral delivery of the protein and peptide drugs has been reviewed extensively (Merkle and Wolany, 1992).

2.7. Evaluations

The empirical evaluating parameters of mucoadhesive drug delivery systems include bioadhesive strength, release studies in vitro and in vivo.

2.7.1. In vitro methods

In vitro permeability or diffusion methods enable anatomically well defined areas of mucosa to be studied under controlled conditions, usually by clamping between diffusion compartments. A known concentration of the penetrant under study can be introduced into one compartment and the rate at which it appears in the receptor compartment is determined. If necessary, the temperature can be controlled by circulating water from a thermostat. The fluid in the chambers is agitated to prevent stagnation and continually replaced to maintain an adequate concentration gradient across the tissue. The disadvantage of the diffusion chamber is that considerable mechanical manifestation of the tissue is required. In any in vitro system, the tissue is removed from animal body and placed in a highly artificial environment. The extrapolation of results to the in vivo situation requires caution. Despite the variety of techniques used to study permeability, no one method can identify the ideal mucosal region for the penetration of drug, the pathway of entry and the kinetics of penetration. At best only two of these factors may be determined in one experiment. However, most results provide only crude information as to whether penetration occurs or does not occur.

Another approach to study the permeability of drug molecules across the area of interest in the oral cavity is the use of in vitro diffusion cells (Tanaka, et al., 1980).
major limitation of this method is that permeability studies can be run only for a limited time due to tissue viability.

The *in vitro* diffusion of a series of substituted acetanilides across the hamster cheek pouch was studied. Comparison of *in vitro* data with *in vivo* data in humans showed good correlation (Garren and Repta, 1989). The transport of protirelin (thyrotropin releasing hormone) was studies in excised rabbit buccal mucosa (Dowty et al., 1992) and beta-adrenergic blocking drugs in porcine buccal mucosa (Le Brun et al., 1989).

No standard *in vitro* release or dissolution method has yet been developed for the buccal formulations. Apparatus of varying designs were used, depending on the shape and application of the dosage form. There were reports that J.P. IX disintegration tester without the attached disc was also used. Dissolution rate was measured using 800 ml of dissolution medium for directly compressed tablets of di-isoprotenol hydrochloride meant for controlled release. Nagai et al., in 1978, prepared disc like dosage forms for the treatment of uterine cancer and measured the dissolution rate using Toyamo-Sangyo TR-553, dissolution tester. For this purpose, 900 ml of purified water as dissolution medium and rotating the basket at 100 rpm were used. This apparatus was used for the evaluation of oral mucosal dosage forms of insulin.

Ishida et al. (1981) used an apparatus similar to that used for the evaluation of insulin dosage forms with a slight modification of providing a water jacket for the maintenance of temperature. This apparatus was used for the dissolution rate measurement of mucosal adhesive dosage forms of lidocaine for toothache.

With the development of tissue culture techniques, it appears that this technique may be, by far, the most useful technique to study transport phenomena at the cellular and subcellular levels. Such techniques have been reported (Tavakoli Saberi and Audus, 1989). Filter-grown TR146 cells, a continued cell line of human buccal epithelial origin, is a valuable model for studying the transport of drugs across the human buccal epithelium (Jacobsen et al., 1995).

### 2.7.2. *In vivo* methods

*In vivo* assessment of the absorption characteristics of a drug is the most desirable approach and is performed in human volunteers or patients. However, because of
difficulties in cost, time, toxicity and ethical considerations, it is usually impracticable to begin with this approach. Therefore, animal models can be used and their ability to predict the results in human counterparts is verified. Very few and certainly no extensive in vivo (animal) in vivo (human) correlations have been reported. The methods are absorption cells and perfusion cells.

Various in vivo testing methods have been reported to quantitatively evaluate drug absorption through oral mucosal membrane. One of the simplest and direct measurement of penetration through the oral mucosa is the so called "buccal absorption" test. In this method, the uptake of the compound is derived from the difference between its concentration in a solution before and after rinsing around the mouth and expelling it (Beckett and Triggs, 1967). Several modifications have been proposed to the buccal absorption test and they are discussed here.

An improvement over this traditional buccal absorption test is the one which enabled to collect kinetic data in a single 15 min. trial (Tucker, 1988). The method involves multiple samples being withdrawn from the mouth using a positive displacement pipettes.

In another method, an airtight sampling chamber comprised of a standardized disc of dry and ash free-filter paper is overlaid with a disc of porous membrane material (Kaaber, 1974). Even though this technique can define the oral cavity area, it suffers from inherent disadvantages such as adherence of the disc to the membrane, leakage of drug from the disc and interference from salivary secretions.

Some of limitations described in the above methods can be overcome by using in situ perfusion cells or a similar device that are either clamped or attached to oral mucosa. The buccal absorption of flurbiprofen administered as an oral solution of pH 5.5 and pH 7 was studied in 8 normal men aged 23-49 year, using the perfusion cells. These are used to quantify the transport from the oral cavity in humans. Closed-perfusion cell apparatus is used as a means for studying drug transport across externally accessible biologic membranes. Flurbiprofen was buccally absorbed by passive diffusion and the rate of absorption was pH dependent. Absorption was greater at pH 5.5 than at pH 7. It was concluded that the buccal membranes of the human and dog are essentially lipoidal
membranes with equivalent permeabilities and no evident aqueous pore pathways (Barsuhn et al., 1988).

A buccal perfusion cell was developed and studied the kinetics of drug loss from the oral cavity were estimated (Rathbone, 1991a). The buccal perfusion cell method provides a simple and reproducible technique for estimating the rate of drug loss from the oral cavity over a fixed area of known membrane under closely controlled conditions (Rathbone, 1991b). Several pre- and post-test modifications of these methods exist in the literature and have been reviewed (Rathbone and Hadgraft, 1991; Harris and Robinson, 1992).

2.8. Drug Profile


Chlorpheniramine maleate is a histamine H1-receptor antagonist. It is given orally for the symptomatic relief of hypersensitivity reactions and in pruritic skin disorders. It is a common ingredient of cough and cold preparations. Chlorpheniramine maleate is also administered parenterally. Adverse effects include sedation and antimuscaranic effects.

Chlorpheniramine maleate: Chlorprophenpyridamine maleate. (±)-3-(4-Chlorophenyl)-NN-dimethyl-3-(2-pyridyl)propylamine hydrogen maleate.

\[ \text{C}_{16}\text{H}_{19}\text{ClN}_2 \cdot \text{C}_4\text{H}_4\text{O}_4 = 390.87 \text{ (Molecular weight).} \]

\[
\text{Cl}
\]
\[
\text{N}
\]
\[
\text{H}
\]
\[
\text{CH}_2\text{CH}_2\text{N} \cdot \text{HCCOOH}
\]
\[
\text{CH}_3
\]

Dose: Orally, 4 to 16 mg daily, in divided doses. By subcutaneous or intramuscular injection, 10 to 20 mg, repeated if required to a maximum of 40 mg in 24 hours.

Description: White, crystalline powder; odourless.
**Solubility:** 1 in 4 of water and 1 in 10 of alcohol and of chloroform; slightly soluble in ether.

**Storage:** Store in tightly-closed, light-resistant containers.

**Melting range:** Between 132 °C and 135 °C

**pH:** Between 4.0 and 5.0, determined in 1.0% w/v solution.

**Clarity and colour of solution:** A 10% w/v solution is clear, and not more intensively coloured.

**Absorption and fate:** Chlorpheniramine maleate is absorbed relatively slowly from the gastro-intestinal tract, peak plasma concentrations occurring about 2.5 to 6 hours after administration by mouth. Bioavailability is low, values of 25 to 50% have been reported. Chlorpheniramine appears to undergo considerable first-pass metabolism. About 70% of chlorpheniramine in the circulation is bound to plasma proteins. There is a wide interindividual variation in the pharmacokinetics of chlorpheniramine; values ranging from 2 to 43 hours have been reported for the half-life. Chlorpheniramine is widely distributed in the body including passage into the CNS.

Chlorpheniramine maleate is extensively metabolised. Metabolites include desmethyl- and didesmethylchlorpheniramine. Unchanged drug and metabolites are excreted primarily in the urine; excretion is dependent on urinary pH and flow-rate. Only trace amounts have been found in the faeces. A duration of action of 4 to 6 hours has been reported; this is shorter than may be predicted from pharmacokinetic parameters.

More rapid and extensive absorption, faster clearance and a shorter half-life have been reported in children.

**Uses and administration:** Chlorpheniramine maleate is an alkylamine derivative with the actions and uses of the histamine H₁-receptor antagonists. It is a potent antihistamine and causes a moderate degree of sedation; it also has antimuscarinic activity.

Chlorpheniramine maleate is given by mouth in doses of 4 mg every 4 to 6 hours up to a maximum of 24 mg daily. Sustained-release preparations are given in a dose of 8 to 12 mg twice daily.

Astemizole is a long acting non-sedative antihistamine, which has a major clinical implications for the treatment of allergic diseases such as hay fever, perennial allergic rhinitis and allergic skin conditions in adults as well as in children.

The physicochemical properties of astemizole are not well documented. A personal communication from Janseen Pharmaceuticals gave the necessary physicochemical data.

*Chemical names:* 2-(p-Fluorobenzyl)-2-[(1-(p-methoxyphenethyl)-4-piperidylamino]benzimidazole.

1-[4-Fluorophenyl)methyl]-N-[1-[2-(4-methoxyphenyl)ethyl]-4-piperidinyl]-1H-benzimidazole-2-amine.

*Empirical formula:* C_{28}H_{31}FN_{4}O.

*Structure:*

![Structure of Astemizole](attachment:image.png)

*Molecular weight:* 458.25

*Appearance, colour and odor:* White fluffy odorless powder.

*Melting range:* Astemizole melts at 149.1 °C. The base melts at 174.9 °C-176.8 °C.
### Solubility in different solvents:

<table>
<thead>
<tr>
<th>Solvent</th>
<th>Solubility in g/100 ml solution</th>
</tr>
</thead>
<tbody>
<tr>
<td>Water (pH 7.3)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Methanol</td>
<td>12</td>
</tr>
<tr>
<td>Ethanol</td>
<td>3.4</td>
</tr>
<tr>
<td>Propylene glycol</td>
<td>0.58</td>
</tr>
<tr>
<td>Poly ethylene glycol 400</td>
<td>3.9</td>
</tr>
<tr>
<td>Acetonitrile</td>
<td>0.84</td>
</tr>
</tbody>
</table>

### Solubility in aqueous medium as a function of pH:

<table>
<thead>
<tr>
<th>Solvent</th>
<th>pH of solution</th>
<th>Solubility in g/100 ml solution</th>
</tr>
</thead>
<tbody>
<tr>
<td>HCl 0.1 N</td>
<td>1.2</td>
<td>0.33</td>
</tr>
<tr>
<td>HCl 0.01 N</td>
<td>4.8</td>
<td>0.17</td>
</tr>
<tr>
<td>Citrate-HCl buffer pH 4.0</td>
<td>4.6</td>
<td>0.032</td>
</tr>
<tr>
<td>Borate-HCl buffer pH 8.0</td>
<td>8.0</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>NaOH 0.1 N</td>
<td>12.5</td>
<td>&lt; 0.001</td>
</tr>
</tbody>
</table>

### Ionization constant:

A. **Procedure:** The ionization constant is determined by potentiometric titration of an aqueous solution of astemizole, $pK_{a2} = 5.6$.

B. **Procedure:** The ionization constant is determined by potentiometric titration's of solutions of astemizole in water-methanol mixtures. The $pK_a$ is the result of a linear extrapolation of the result in a 50, 60 and 70% methanol mixture to pure water. The result $pK_{a1} = 8.4$.

### Partition coefficient:

**Procedure:** The partition coefficient is determined between n-octanol and an aqueous buffer of pH = 11.6. A double extraction method is used. The result, $log P$, is 5.36.
Storage and stability: Astemizole tablets should be stored in a tightly closed container in a cool, dry place at room temperature (15 °C to 30 °C) and away from light.

Ultraviolet spectrum: The UV spectrum of astemizole in ethanol and 0.1 N hydrochloric acid were scanned from 200 to 400 nm and astemizole exhibits the following UV data.

<table>
<thead>
<tr>
<th>$\lambda_{\text{max}}$ (nm)</th>
<th>Absorbance</th>
<th>Molar absorptivity</th>
</tr>
</thead>
<tbody>
<tr>
<td>In ethanol</td>
<td></td>
<td></td>
</tr>
<tr>
<td>219</td>
<td>2.973</td>
<td>27250.229</td>
</tr>
<tr>
<td>249</td>
<td>0.707</td>
<td>6480.293</td>
</tr>
<tr>
<td>286</td>
<td>0.942</td>
<td>8634.280</td>
</tr>
<tr>
<td>In 0.1 N HCl</td>
<td></td>
<td></td>
</tr>
<tr>
<td>209</td>
<td>0.631</td>
<td>57889.908</td>
</tr>
<tr>
<td>277</td>
<td>0.197</td>
<td>18073.394</td>
</tr>
</tbody>
</table>

Pharmacokinetics: The pharmacokinetics of astemizole have been extensively studied in animals, human volunteers and patients. Radioimmunoassay methods were used for detection of the drug in such studies. The pharmacokinetic profile of astemizole features two components, the unchanged drug and its active metabolite, desmethylastemizole.

Onset and duration: The precise onset of action of astemizole in either loading or single doses have not been established. In one controlled study of hay fever patients the onset of action of astemizole was reported slow with relief to allergic symptoms not occurring for two days. Because of its delayed onset of action, astemizole is not as effective for treatment of acute allergic symptoms. The slower action of desmethylastemizole provides sustained antihistaminic protection.

Absorption: Astemizole is subject to rapid and extensive absorption with plasma peak concentrations over a range of doses occurring between 1 and 4 hours and appeared to be linearly related to dose. Astemizole undergoes and extensive first-pass metabolism and a considerable tissue distribution. This is attributed to the finding that peak concentrations of astemizole plus metabolites were several fold greater than those of unchanged astemizole.
Regarding bioavailability of astemizole, it was found that peak plasma concentration, time to peak and area under the plasma concentration-time curve are not significantly different following administration of astemizole tablets and suspension. However, concomitant administration of oral astemizole and food significantly decreased the bioavailability of astemizole and its metabolites.

**Distribution:** Astemizole has rapid and extensive distribution. The highest tissue concentrations of astemizole and its active metabolites were found in the pancreas, adrenal glands, liver, lung, salivary glands, kidney tissue and testes. The lowest tissue concentrations, on the other hand were found in subcutaneous fat, skin, muscle, thymus, heart and brain. The plasma protein binding of astemizole was reported to be 96.7%. Following a single-oral administration of astemizole (300 mg, PO) the apparent volume of distribution ($V_d$) was 250 l/kg.

**Metabolism:** Astemizole undergoes extensive first-pass metabolism via three major metabolic pathways: oxidative O-demetylation, aromatic hydroxylation at the benzimidazole moiety, and oxidative N-dealkylation at the piperidine nitrogen. Hydroxylated metabolites resulting from the two former pathways were excreted as the glucuronides. The metabolic products of astemizole are: desmetylyastemizole, which has similar antihistaminic potency to the parent compound, norastemizole, and 6-hydroxydesmethylastemizole, which are less potent and shorter acting. The prolonged duration of therapeutic effect of astemizole may be attributed to the enterohepatic recirculation of desmethylastemizole and conjugated metabolites.

**Excretion:** Following oral administration unchanged astemizole was not recovered in the urine or faeces. Fifty four to 73% of a dose of astemizole is excreted in faeces within 14 days.

**Half-life:** Estimation of plasma concentrations of half-life of astemizole was difficult because could not be followed for long enough periods of time. Following a single dose of astemizole 10 mg, 20 mg or 30 mg orally, the terminal half-life of unchanged astemizole is about 24 hours. The elimination half lives of desmethylastemizole is 18-20 days following long-term administration of 10 mg daily.
Contraindications: Patients who are hypersensitive to astemizole or any of the inactive ingredients should not receive the drug.

Precautions: Astemizole should be cautiously used in pregnant women since there are inadequate data to determine teratogenic effects (potential for harm to the developing fetus) of astemizole. In women of child-bearing potential, it is highly recommended that astemizole should not be used unless adequate contraceptive precautions are taken.

2.9. Other materials

2.9.1. Hydroxypropylmethylcellulose (HPMC 15 cps) (Hypromellose) (Reynolds, 1993; Wade and Weller, 1994)

Functional categories: Suspending agent, viscosity increasing agent, binder, coating agent, film former, and emulsion stabilizer.

Solubility: Soluble in cold water, soluble in alcohol, ether and chloroform but soluble in mixtures of methyl alcohol and methylene chloride.


Incompatibilities: At extreme pH conditions and with oxidizing materials it is incompatible.

Applications

Film former: Lower viscosity grades are used in aqueous film coating. High viscosity grades are used in solvent film coating with concentrations ranging from 2 to 10%.

Binder: 2-5% high viscosity grades are used to retard the release of water soluble drugs.

Thickening agent: For eye drops and for artificial tear solutions 0.45-1% concentrations is used.

2.9.2. Hydroxypropylcellulose (HPC) (Hyprolose) (Reynolds, 1993)

A partially substituted 2-hydroxypropyl ether of cellulose. Various grades are available and may be distinguished by appending a number indicative of the apparent
viscosity in millipascal seconds of a 2% solution measured at 20 °C. A white or yellowish white, practically odourless, hygroscopic granular solid or powder.

**Solubility:** In cold water, alcohol, chloroform, methyl alcohol, and propylene glycol, forming colloidal solutions; practically insoluble in hot water; it dissolves in glacial acetic acid forming colloidal solutions; sparingly soluble or slightly soluble in acetone. A 1% solution in water has a pH of 5.0 to 8.5.

**Adverse effects:** Hydroxypropylcellulose used as a solid ocular insert may result in blurred vision or ocular discomfort or irritation including hypersensitivity and edema of the eyelids.

**Uses and administration:** Hydroxypropylcellulose is used in the coating of tablets, as a tablet excipient, as a thickener, and in microencapsulation. It is used as an emulsifier and stabiliser in the food industry. Hydroxypropylcellulose is also used as a slow-release solid ophthalmic insert in the management of dry eye.

An acceptable daily intake for hydroxypropylcellulose as a food additive was not specified as the total daily intake arising from its use at the levels necessary to achieve the desired effect and from its acceptable background in food, was not considered to represent a hazard to health. The ability of modified cellulosics to produce laxative effects should, however, be taken into account (WHO Report, 1990).

2.9.3. **Carbopol (carbomer)** (Carboxypolymethylene; Carboxyvinylpolymer) (Reynolds, 1993)

A synthetic high molecular weight polymer of acrylic acid cross-linked with allyl sucrose or with allyl ester of pentaerythritol.

A white, fluffy, acidic, hygroscopic powder with a slight characteristic odour. After neutralisation with alkali hydroxides or amines, it is soluble in water, alcohol and glycerol.

**Uses:** Carbopol is used as a suspending agent, a gel basis, an emulsifier and a binding agents in tablets.
2. Review of Literature

2.9.4. Eudragit RL 100

*Molecular weight* > 100,000

*Functional category:* Film former.

*Description:* Eudragit RL 100 is referred to as an aminomethacrylic acid copolymer in *U.S.P.N.F.* monograph. They are synthesized from acrylic acid and methacrylic acid esters. They are insoluble in water. The films prepared are freely permeable to water.

*Solubility:* Freely soluble in methanol, ethanol and isopropanol.

2.9.5. Ethylcellulose (Reynolds, 1993)

*Properties of common ethylcellulose:* 9-11 cps (5% solution in 18/20 Toluene/Ethanol at 25 °C).

*Molecular weight:* 100,000.

*Ethoxyl content:* 48%-49%.

*Solubility:* Freely soluble in chloroform, ethanol and acetone.

*Hygroscopicity:* Ethylcellulose absorbs very little water at high relative humidities or during immersion, any absorbed water evaporates readily.

*Stability:* Ethylcellulose is a stable slightly hygroscopic material.

*Uses:* The main use of ethylcellulose in oral formulation is as a hydrophobic coating agent for tablets and granules. Ethylcellulose when dissolved in organic solvent produce water insoluble films. In tablet formulation it can be used as a binder.

2.9.6. Microcrystallinecellulose (MCC) (Cellulose Microgranulare; Cellulose gel; Crystalline Cellulose) (Reynolds, 1993; Wade and Weller, 1994)

A fine, white or almost white, odourless, crystalline powder consisting of purified, partially depolymerised cellulose, prepared by treating alpha-cellulose obtained as a pulp from fibrous plant material with mineral acids.
Partially insoluble in water, dilute acids, sodium hydroxide solution (1 in 20), and most organic solvents.

Microcrystalline cellulose is widely used in pharmaceuticals primarily as a diluent in oral tablet and capsule formulations where it is used in both wet granulation and direct compression. In addition to its use as a diluent, microcrystalline cellulose also has some lubricant and disintegrant properties.

An attempt was made to review the topics relevant to the present investigations. Based on this review, the requirements for the design and evaluation were identified for the buccal mucosal drug delivery systems. Such methods and materials were discussed in the next chapter.