ORAL SOLID DOSAGE FORMS – BUCCAL DRUG DELIVERY SYSTEM: A REVIEW

D. PRAKASH CHANDRA, P. KHAJA, B. VINODA, S. ASMA, M. AIJAZ

2. Principal & Professor, Azad college of pharmacy, Moinabad, Hyderabad, Telengana.
3. Azad college of pharmacy, Moinabad, Hyderabad, Telengana.
5. Azad college of pharmacy, Moinabad, Hyderabad, Telengana.

Accepted Date: 18/07/2018; Published Date: 27/08/2018

Abstract: Oral drug delivery has been known for decades as the most widely utilized route of administered among all the routes that have been employed for the systemic delivery of drug via various pharmaceutical products of different dosage forms. The reasons that the oral route achieved such popularity may be in part attributed to its ease of administration belief that by oral administration of the drug is well absorbed.

Keywords: Sustain Release System, Controlled Release System

Corresponding Author: D. PRAKASH CHANDRA

Access Online On:
www.ijprbs.com

How to Cite This Article:
D. Prakash Chandra, IJPRBS, 2018; Volume 7(4): 65-87
INTRODUCTION

For many decades, treatment of an acute disease or a chronic illness has been mostly accomplished by delivering drugs using various pharmaceutical dosage forms, including tablets, capsules, pills, suppositories, creams, ointments, liquids, aerosols and injectables as carriers. Amongst various routes of drug delivery oral route is perhaps the most preferred to the patient and the clinician alike. However this route presents some problems for a few drugs. The enzymes in the GI fluids, GIT-pH conditions and the enzymes bound to GIT membranes are a few factors responsible for the bioavailability problems. The blood that drains the GIT carries the drug directly to the liver leading to first-pass metabolism resulting in poor bioavailability. The inherent problems associated with the drug in some cases can be solved by modifying the formulation or by changing the routes of administration. Parenteral, mucosal and transdermal routes circumvent hepatic first-pass metabolism and offer alternative routes for the systemic delivery of drugs.

In recent years, the interest in novel routes of drug administration occurs from their ability to enhance the bioavailability of drugs. Drug delivery via the buccal route using bioadhesive dosage forms offers such a novel route of drug administration. Extensive first-pass metabolism and drug degradation in the harsh gastrointestinal environment can be circumvented by administering the drug via buccal route. Buccal delivery involves administration of desired drug through the buccal mucosal membrane lining of oral cavity. The mucosal lining of oral cavity offers some distinct advantages. It is richly vascularized and more accessible for the administration and removal of a dosage form. Additionally, buccal drug delivery has high patient acceptability compared to other non-oral routes of drug administration. Drug absorption through buccal mucosa is mainly by passive diffusion into the lipoidal membrane. After absorption the drug is transported through facial vein which then drains into the general circulation via jugular vein bypassing the liver and thereby sparing the drug from first-pass metabolism. Buccal route provides one of the potential routes for typically large, hydrophilic and unstable proteins, oligonucleotides and polysaccharides as well as conventional small drug molecules. The oral cavity can be used for local and systemic therapy. Examples of local therapy would be the treatment of oral infections, dental caries, mouth ulcers and stomatitis. The buccal route is of particular interest with regard to the systemic delivery of small molecules that are subjected to first pass metabolism or for the administration of proteins and peptides.

1.1 BUCCAL DRUG DELIVERY SYSTEM:

Buccal delivery of drugs provides an attractive alternative to the oral route of drug administration, particularly in overcoming deficiencies associated with the latter mode of administration problems such as high first pass metabolism, drug degradation in harsh gastro
intestinal environment can be circumvented by administering a drug via buccal route. More over buccal drug absorption can be terminated promptly in case of toxicity by removing the dosage form from the buccal cavity. It is also possible to administer the drug to patients who cannot be dosed orally to prevent accidental swallowing.

Buccal delivery refers to drug release which can occur when a dosage form is placed in the outer vestibule between the buccal mucosa and gingiva. Various advantages and other aspects of this route are elucidated of the following.

1.1.1 Advantages of Buccal Drug Delivery Systems:

Drug administration via buccal mucosa offers several distinct advantages,

1. Ease of administration.

2. Permits localization of the drug in the oral cavity for a prolonged period of time.

3. Offers excellent route for systemic delivery of drugs with high first pass metabolism, thereby offering a greater bioavailability.

4. A significant reduction in dose can be achieved, thereby reducing dose dependent side effects.

5. Drugs which are unstable in acidic environment of the stomach or are destroyed by the enzymatic or alkaline environment of the intestine.

6. The presence of saliva ensures relatively large amount of water for drug dissolution unlike the case of rectal and transdermal routes.

7. It offers passive system for drug absorption and does not require any activation.

8. It can be made unidirectional to ensure only buccal absorption.

9. The buccal mucosa is highly perfused with blood vessels and offers greater permeability than the skin.

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


12. Buccal mucosa is less prone to damage or irritation than nasal mucosa and shows short recovery times after stress or damage.
13. Termination of therapy is easy.

14. Can be administered to unconscious patients.

15. Increased patient’s compliance.

**1.1.2 Disadvantages of buccal drug delivery system:**

Drug administration via buccal mucosa has certain limitations,

1. Drugs which irritate the oral mucosa have a bitter or unpleasant taste or odour cannot be administered by this route.

2. Drugs, which are unstable at buccal pH, cannot be administered by this route.

3. Only drugs with small dose requirements can be administered.

4. Drugs may get swallowed with saliva and loses the advantages of buccal route.

5. Only those drugs, which are absorbed by passive diffusion, can be administered by this route.

6. Over hydration may lead to the formation of slippery surface and structural integrity of the formulation may get disrupted by the swelling and hydration of the bioadhesive polymers.

7. Surface area available for absorption is less.

8. The buccal mucosa is relatively less permeable than the small intestine, rectum, etc.

**1.2 ANATOMY AND NATURE OF ORAL CAVITY:**

**1.2.1 Oral Cavity:**

Oral cavity is the foremost part of digestive system of human body due to its excellent accessibility and reasonable patient compliance, oral mucosal cavity offers attractive route of drug administration for the local and systemic therapy.

**1.2.2 Overview of oral cavity:**

Oral cavity is that area of mouth delineated by the lips, cheeks, hard palate, soft palate and floor of mouth. The oral cavity consists of two regions,

1. Outer oral vestibule, which is bounded by cheeks, lips, teeth and gingiva (gums).
2. Oral cavity proper, which extends from teeth and gums back to the faces (which lead to pharynx) with the roof comprising the hard and soft palate. The tongue projects from the floor of the cavity.

![Fig.1: structure of buccal cavity](image)

The drug 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 back flow goes through branches of capillaries and veins and finally taken up by the jugular vein. The secretion in the oral cavity includes saliva, cerviccular fluid and mucus. From that, saliva is a complex fluid containing organic and inorganic materials. It is produced by the three pairs of major glands (parotid, submandibular and sublingual) each situated outside the oral cavity and in minor salivary glands situated in the tissues lining most of the oral cavity. The total average volume of saliva produced daily in an adult is around 750 ml. The flow rates of saliva depend upon the type of stimulus used, the time of day, the length of time, glands had been stimulated, the age and sex of the individual and by their state of health. Chemically, saliva is 99.5% water and 0.5% solutes. The solutes include ions (sodium, potassium, magnesium, phosphate, bicarbonate and chloride), dissolved gases, urea, uric acid, serum albumin, globulin, mucin and enzymes [lysozyme and amylase (ptyalin)].

Second was the cerviccular fluid it is a fluid secreted from the gingival glands of oral cavity. The third type was the mucus, it is a thick secretion composed mainly of water, electrolytes and a mixture of several glycoprotein, which themselves are composed of large polysaccharides bound with smaller quantities of protein. It is secreted over many biological membranes of body for example, throughout the gastrointestinal tract walls. Mucus is secreted by special type of epithelia called mucosa. The mucus secreted in buccal cavity admixtures with saliva of
salivary glands in oral cavity to produce whole saliva. The two main glycoproteins found in buccal mucus or mucin is MG1 and MG2.

1.3 ORAL MUCOSA

1.3.1 Anatomy and physiology of the oral mucosa:

The mucosa that lines the oral cavity may be divided into three types, classified according to their function as;

1. **Masticatory mucosa**: Which includes the mucosa around the teeth and on the hard palate and these regions have keratinized epithelium.

2. **Lining mucosa**: Which covers the lips, cheeks, fornix, base of the oral cavity, lower part of tongue, buccal mucosa and the soft palate and these regions have non-keratinized epithelium.

3. **Specialized mucosa**: covering the dorsum of the tongue with highly keratinization. Light microscopy reveals several distinct patterns of maturation in the epithelium of the human oral mucosa based on various regions of the oral cavity. Three distinctive layers of the oral mucosa are the epithelium, basement membrane and connective tissues. The oral cavity is lined with the epithelium, below which lies the supporting basement membrane. The basement membrane is in turn supported by connective tissues (Fig. 2). The epithelial cells originating from the basal cells mature change their shape and increase in size while moving towards the surface.

![Fig.- Structure of buccal mucosa.](image-url)
1.3.2 Biochemistry of oral mucosa:

All the layers of the oral mucosal membranes contain a large amount of protein in the form of filaments, consisting at least seven proteins called “keratins” with molecular sizes of 40-70 Kda. Both keratinized and non-Keratinized tissues of varying thickness and composition are found in oral cavity. Keratinized and non-keratinized tissues occupy about 50% and 30% respectively of the total surface area of the mouth.

Table: Composition and state of keratinization of oral mucosa

<table>
<thead>
<tr>
<th>Tissue</th>
<th>State of keratinization</th>
<th>Composition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Buccal mucosa</td>
<td>Non-Keratinized</td>
<td>Few natural, but mainly polar lipids, particularly cholesterol sulphate &amp; glucosylceramites.</td>
</tr>
<tr>
<td>Sublingual mucosa</td>
<td>Non-keratinized</td>
<td>Few natural, but mainly polar lipids, particularly cholesterol sulphate &amp; glucosylceramides.</td>
</tr>
<tr>
<td>Gingiva mucosa</td>
<td>Keratinized</td>
<td>Lipids i.e, ceramides</td>
</tr>
<tr>
<td>Palatal mucosa</td>
<td>Keratinized</td>
<td>Lipids i.e., Ceramides</td>
</tr>
</tbody>
</table>

1.3.3 Mechanisms involved in drug absorption across the oral mucosa:

The mechanisms by which drugs cross biological lipid membranes are passive diffusion, facilitated diffusion, active transport and pinocytosis. Small water-soluble molecules may pass through, small water filled pores. The main mechanism involved in drug transfer across the oral mucosa, is passive diffusion has also been shown to take place, primarily with nutrients. Passive diffusion involves the movement of a solute from a region of high concentration in the mouth to a region of low concentration within the buccal tissues. Further diffusion then takes place into the venous capillary system, with the drug eventually reaching the systemic circulation via the jugular vein. The physicochemical characteristics of a drug are very important for this diffusion process. The permeability barrier property of the oral mucosa is predominantly due to intercellular materials derived from the so-called “membrane coating granules” (MCGs). MCGs are spherical or oval organelles that are 100–300 nm in diameter and found in both keratinized and non-keratinized epithelia. These organelles have also been referred to as small spherically shaped granules “corpuscula”, small dense granules, small lamellated bodies, lamellated dense
bodies, keratinosomes, transitory dense bodies and cementsomes. MCGs are found near the upper, distal or superficial border of the cells and a few occur near the opposite border. Several hypothesis have been suggested to describe the functions of MCGs including a membrane thickening effect, cell adhesion, production of a cell surface coat, cell desquamation and permeability barrier. They discharge their contents into the intercellular space to ensure epithelial cohesion in the superficial layers and this discharge forms a barrier to the permeability of various compounds. Another barrier to drug permeability across buccal epithelium is enzymatic degradation. Saliva contains no proteases but does contain moderate levels of esterase, carbohydrates and phosphates. However, several proteolytic enzymes have been found in the buccal epithelium. Walker et al. reported that endopeptidases and carboxypeptidases were not present on the surface of porcine buccal mucosa, whereas amino peptidases appeared to be the major enzymatic barrier to the buccal delivery of peptide drugs.

2. TYPES OF BUCCAL DRUG DELIVERY SYSTEM:

For delivery of drug through buccal region several mucoadhesive dosage forms have been reported because of the presence of a smooth and relatively immobile surface for placement of a mucoadhesive dosage forms the buccal region appears to be more suitable for sustained delivery of therapeutic agents using a mucoadhesive system. The various types of buccal drug delivery system are explained as follows;
2.1 Buccal patches/films:

Patches are laminates consisting of an impermeable backing layer a drug-containing reservoir layer from which the drug is released in a controlled manner and a bioadhesive surface for mucosal attachment. Two methods used to prepare adhesive patches include solvent casting and direct milling. In the solvent casting method the intermediate sheet from which patches are punched is prepared by casting the solution of the drug and polymers onto a backing layer sheet and subsequently allowing the solvents to evaporate. In the direct milling method formulation constituents are homogenously mixed and compressed to the desired thickness and patches of predetermined size and shape are then cut or punched out. An impermeable backing layer may also be applied to control the direction of drug release, prevent drug loss and minimize deformation and disintegration of the device during the application period.

2.2 Buccal gels and ointments:

Such semisolid dosage forms have the advantage of easy dispersion throughout the oral mucosa. Poor retention of the gels at the site of application has been overcome by using bioadhesive formulations. Certain bioadhesive polymers undergo a phase change from a liquid to a semisolid; this change enhances the viscosity which results in sustained and controlled release of drugs. Hydrogels are also promising dosage forms which are formed from polymers that are hydrated in an aqueous environment and physically entrap drug molecules for subsequent slow release by diffusion or erosion. These dosage forms provide an extended retention time, adequate drug penetration as well as high efficacy and patient acceptability.

2.3 Buccal tablets:

Buccal tablets are small, flat, and oval shaped dosage form. Unlike conventional tablets buccal mucoadhesive tablets allow for drinking and speaking without major discomfort. They so often adhere to the mucosa and are retained in position until dissolution and/or release is complete. These tablets can be applied to different sites in the oral cavity including the palate the mucosa lining the cheek as well as between the lip and the gum.

2.4 Advances in Buccal Drug Delivery Dosage Forms:

Buccal mucoadhesive dosage forms can be categorized into three types based on their geometry (Fig 4).

Type I:

It is a single layer device with multidirectional drug release. This type of dosage form suffers from significant drug loss due to swallowing.
Type II:

It is a device in which an impermeable backing layer is superimposed on top of the drug loaded bioadhesive layer creating a double-layered device and preventing drug loss from the top surface into the oral cavity.

Type III:

It is a unidirectional drug release device, from which drug loss is minimal, since the drug is released only from the side adjacent to the buccal mucosa. This can be achieved by coating every face of the dosage form, except the one that is in contact with the buccal mucosa.

![Diagram of buccal mucoadhesive dosage forms](image)

**Fig 4: Design of buccal mucoadhesive dosage forms.**

2.5 Conventional Dosage Form:

The conventional type of buccal dosage forms are buccal tablets, troches and lozenges and mouth washers. Buccal tablets are small, flat, oval tablets and are intended to be held between the cheek and the teeth or in the cheek pouch (buccal tablets). Progesterone tablets can be administered this way. Troches and lozenges are two other types of tablets used in oral cavity where they are intended to exert a local effect in the mouth or throat. These tablet forms are commonly used to treat sore throat or to control coughing in common cold. Lozenges (pastilles or cough drops) are usually made with the drug incorporated in a flavoured, hard-candy sugar base. Lozenges may be made by compression but are usually formed by fusion or by a candy–moulding process. Troches, on the other hand, are manufactured by compression as are other tablets.
3. MUCOADHESIVE BUCCAL TABLETS:

The purpose of the buccal tablet is absorption of the drug through the lining of the mouth. Buccal tablets can be most easily held between the gum and cheek. Various drugs have been investigated for their delivery through the buccal mucosa in a mucoadhesive buccal tablet form.

Table:- List of drugs investigated for mucoadhesive buccal tablet

<table>
<thead>
<tr>
<th>Sl. No</th>
<th>Drug Name</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Carbamazepine</td>
</tr>
<tr>
<td>2</td>
<td>Cholorhexidine</td>
</tr>
<tr>
<td>3</td>
<td>Dichofenac Sodium</td>
</tr>
<tr>
<td>4</td>
<td>Ergatamine tartrate</td>
</tr>
<tr>
<td>5</td>
<td>Hydrocortesone acetate</td>
</tr>
</tbody>
</table>

3.1 MUCOADHESION

3.1.1 Definition:

Longer and Robinson defined the term “bioadhesion” as the attachment of a synthetic or natural macromolecule to mucus and/or an epithelial surface. The general definition of adherence of a polymeric material to biological surfaces (bioadhesive) or to the mucosal tissue (mucoadhesive) still holds. A bioadhesive has been defined as a synthetic or biological material which is capable of adhering to a biological substrate or tissue and when the biological substrate is mucus the term was known as mucoadhesive.

3.1.2 Mechanism of mucoadhesion:

Mucoadhesion is the attachment of the drug along with a suitable carrier to the mucous membrane. It is a complex phenomenon which involves wetting, adsorption and interpenetration of polymer chains.

- Mucoadhesion has the following mechanism

1. Intimate contact between a bioadhesive and a membrane (wetting or swelling phenomenon also called as contact stage).
2. Penetration of the bioadhesive into the tissue or into the surface of the mucous membrane (interpenetration or consolidation stage).

Residence time for most mucosal routes is less than an hour and typically in minutes, it can be increased by the addition of an adhesive agent in the delivery system which is useful to localize the delivery system and increases the contact time at the site of absorption. The exact mechanism of mucoadhesion is not known but an accepted theory states that a close contact between the mucoadhesive polymer and mucin occurs which is followed by the interpenetration of polymer and Mucin is shown in figure 4. The adhesion is prolonged due to the formation of vandervaals forces, hydrogen bonds and electrostatic bonds.

![Image of the two steps of the process of mucoadhesion](image)

**Fig.: The two steps of the process of mucoadhesion**

### 3.1.3 THEORIES OF MUCOADHESION

There are five theories explain the processes of mucoadhesion which are given as, electronic theory, absorption theory, wetting theory, diffusion theory and fracture theory.

#### 3.1.3.1 The electronic theory:

This theory is based on the assumption that the bioadhesive material and the glycoprotein mucin network have different electronic structures. When the two materials come in contact with each other electron transfer will occur causing the formation of a double layer of electrical charge at the interface. The bioadhesive force is due to attractive forces across this electrical double layer. The system is charged when the adhesive and the substrate are in contact and discharged when they are separated. However, this theory has caused some controversy
regarding whether the electrostatic forces are an important cause or the result of the contact between the bioadhesive and the biological tissue.

3.1.3.2 The absorption theory:

According to this theory, after an initial contact between two surfaces, the material adheres because of surface forces acting between the atoms in the two surfaces. Two types of chemical bonds resulting from these forces can be distinguished

- Primary chemical bonds of covalent nature, which are undesirable in bioadhesion because their high strength may result in permanent bonds.

- Secondary chemical bonds having many different forces of attraction, including electrostatic forces, Vander walls forces and hydrogen and hydrophobic bonds.

3.1.3.3 The wetting theory:

According to this theory the ability of bioadhesive polymer or mucus to spread and develop intimate contact with their corresponding substrate or bond formation. The contact angle (θ) which should be zero or near zero for proper spreading is related to interfacial tensions (γ) through young’s equations,

\[ γ_{tg} = γ_{bt} + γ_{bg} \cos φ \]

Where the t, g and b stand for tissue, gastro intestinal contents and bioadhesive polymers respectively (φ) must equal to zero for spontaneous wetting to occur. Using wetting theory, it is possible to calculate spreading coefficients for various bioadhesive over biological tissues and
predict the intensity of the bioadhesive bond. Hence, it provides essential information for development of bio-adhesive drug delivery system.

3.1.3.4 Diffusion theory:

According to this theory, the polymer chains and the mucus mix to a sufficient depth to create a semi-permanent adhesive bond. The exact depth to which the polymer chains penetrate the mucus depends on the diffusion coefficient and the time of contact. This diffusion coefficient, in turn, depends on the value of molecular weight between crosslink's and decreases significantly as the cross linking density increases. This theory suggests that interpenetration and entanglements of bio-adhesive polymer chain and mucus polymer chains produce semi-permanent adhesive bonds, and bond strength is believed to increase with the depth of penetration of the polymer chains.

![Diffusion theory](image)

**Fig.-:** Diffusion theory

3.1.3.5 Fracture theory:

This theory analyses the force that is required to separate two surfaces after adhesion. The maximum tensile stress produced during detachment can be determined by dividing the maximum force of detachment, \( F_m \), by the total surface area \( A_0 \) involved in the adhesive interaction.

\[
\text{Tensile strength} = \frac{F_m}{A_0}
\]

The above equation can be used for calculating fracture strengths of adhesive bonds involving hard, bioadhesive material in which the polymer chains may not penetrate the mucus layer.

3.1.4 FACTORS AFFECTING MUCOADHESION:

The mucoadhesion of a drug carrier system to the mucous membrane depends on the below mentioned factors.

1. Polymer based factors:
Molecular weight of the polymer

Concentration of polymer used

Flexibility of polymer chains

Swelling factor

Stereochemistry of polymer

2. Environment related factors:

pH at polymer substrate interface

Applied strength

Contact time

3. Physiological factors:

Mucin turnover rate

Diseased state

3.1.4.1. Polymer based Factors

(a) Molecular Weight: The optimum molecular weight for most bioadhesion depends on the type of bioadhesive polymer at issue. It is usually implicit that the threshold required for successful bioadhesion is at least 100,000 molecular weight. For example, polyethylene glycol (PEG), with a molecular weight of 20,000, has little adhesive character, whereas PEG with 200,000 molecular weight has enhanced, and a PEG with 400,000 has superior adhesive properties. The fact that bioadhesiveness improves with increasing molecular weight for linear polymers imply two things:

- Interpretation is more critical for lower molecular weight polymers to be a excellent bioadhesive,
- Entanglement is important for higher molecular weight polymers.

(b) Concentration of active polymers: There is an optimum concentration of a bioadhesive polymer to produce maximum bioadhesion. In extremely concentrated systems, beyond the optimum level, however, the adhesive strength drops significantly because the coiled molecules become separated from the medium so that the chains available for interpenetration become limited.
(c) **Flexibility of polymer chains**: It is critical for interpenetration and entanglement. As water-soluble polymers become crosslinked, mobility of character polymer chains decrease and thus the valuable length of the chain that can penetrate into the mucus layer decreases, which reduces bioadhesive strength.

(d) **Spatial conformation**:

Besides molecular weight or chain length, spatial conformation of a molecule is also main. In spite of a high molecular weight of 19,500,000 for dextrans, they have related adhesive strength to the polyethylene glycol with a molecular weight of 200,000. The helical conformation of dextran may shield many adhesively active groups, primarily dependable for adhesion, unlike PEG polymers which have a linear conformation.

### 3.1.4.2. Environment Related Factors

(a) **Applied strength**: To place a solid bioadhesive system, it is required to concern a defined strength. Whatever the polymer, poly(acrylic acid / vinyl benzene poly (HEMA) or carbopol 934, the adhesion strength increases with the applied strength or with the period of its application, up to an optimum. The pressure initially applied to the mucoadhesive tissue contact site can influence the depth of interpenetration. If high pressure is applied for a sufficiently long period of time, polymers become mucoadhesive even though they do not have attractive interaction with mucin.

(b) **pH**: It can manipulate the formal charge on the surface of mucus as well as certain ions capable bioadhesive polymers. Mucus will have a different charge density depending on pH due to difference in dissociation of efficient groups on the carbohydrate moiety and the amino acids of the polypeptide backbone. pH of the medium is important for the degree of hydration of crosslinked polyacrylic acid, showing consistently increased hydration from pH 4 to 7 and then a reduce as alkalinity and ionic strength increases.

(c) **Initial Contact Time**: Contact time between the bioadhesive and mucus layer determines the extent of swelling and interpenetration of the bioadhesive polymer chains. Bioadhesive strength increases as the initial contact time increases.

(d) **Swelling**: It depends on the polymer concentration, ionic concentration, as well as the presence of water. Over hydration results in the formation of a slippery mucilage without adhesion.
3.1.4.3. Physiological Variables

**a) Mucin Turnover:** The natural turnover of mucin molecules is important for a minimum two reasons. First, the mucin turnover is expected to limit the residence time of the mucoadhesive on the mucus layer. No matter, how high the adhesive strength, mucoadhesive are detached from the surface due to mucin turn over. Second, mucin turnover results in substantial amounts of soluble mucin molecules. These molecules interact with the mucoadhesive before they have a chance to act together with the mucus layer. Mucin turnover may depend on other factors such as presence of food.

**b) Disease States:**

The physiochemical properties of mucus are known to adjust during disease conditions such as common cold, gastric ulcers, and ulcerative colitis, bacterial and fungal infections of the female reproductive tract.

3.1.5 Mucoadhesive Polymers:

Mucoadhesive polymers are water-soluble and water insoluble polymers which are swellable networks jointed by cross-linking agents. These polymers possess optimal polarity to make sure that they permit the mutual adsorption and interpenetration of polymer and mucus to take place. Two classes of polymers are currently used for mucoadhesion which include hydrophilic polymer and hydrogels. It has been found recently that hydrophilic polymers that adhere to the mucin epithelial surface can be conveniently divided into three broad categories.

1. Polymers that become sticky when placed in water and owe their mucoadhesion to stickiness.

2. Polymers that adhere through nonspecific, no covalent interactions those are primarily electrostatic in nature (although hydrogen and hydrophobic bonding may be significant).

3. Polymers that bind to specific receptor site on title self surface. The promising mucoadhesive polymers include sodium alginate, hydroxypropyl methylcellulose, hydroxyethyl cellulose and cationic hydrogels such as chitosanetc.

3.1.5.1 Characteristics of ideal mucoadhesive polymers:

There are various characteristics of an ideal mucoadhesive polymer which are explained as, the polymer and its degradation products should be non-toxic, non-irritant and free from leachable impurities, it should have good spreadability wetting, swelling and solubility and biodegradability properties, the pH should be biocompatible and should possess good viscoelastic properties, it should adhere quickly to buccal mucosa and should possess sufficient
mechanical strength, it should possess peel, tensile and shear strengths at the bioadhesive range, the polymer must be easily available and its cost should not be high, it should show bioadhesive properties in both dry and liquid state, the polymer demonstrate local enzyme inhibition and penetration enhancement properties, the polymer demonstrate acceptable shelf life and have optimum molecular weight.

3.1.5.2 Classification:

In general, adhesive polymers can be classified as synthetic vs. natural, water-soluble vs. water insoluble and charged vs. uncharged polymers.

<table>
<thead>
<tr>
<th>Table: Classification of mucoadhesive polymers in buccal drug delivery</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Source</strong></td>
</tr>
<tr>
<td>Semi-natural / natural</td>
</tr>
<tr>
<td>Synthetic</td>
</tr>
<tr>
<td><strong>Solubility</strong></td>
</tr>
<tr>
<td>Water-insoluble</td>
</tr>
<tr>
<td><strong>Charges</strong></td>
</tr>
<tr>
<td>Anionic</td>
</tr>
<tr>
<td>Non-ionic</td>
</tr>
<tr>
<td>covalent</td>
</tr>
</tbody>
</table>
3.2 METHOD OF PREPARATION OF MUCOADHESIVE BUCCAL TABLETS:

The design of mucoadhesive was mainly done by three processes namely wet granulation process, dry granulation process and direct compression process. From this the wet granulation process was the most widely used and most general method of tablet preparation. Its popularity is due to the greater probability that the granulation will meet all physical requirements for the compression of good tablets. The dry granulation process explained as when the tablet ingredients are sensitive to moisture and are unable to withstand elevated temperatures during drying and when the tablet ingredients have sufficient inherent binding or cohesive properties, slugging may be used to form granules. This method is known as dry granulation or pre-compression method or the double compression method. Finally the third method was direct compression method in this method of tablet manufacturing the all ingredients such as drug, diluents, binders, lubricants and other required excipients and chemicals are weighed individually then mixed and blended together for some time period and then directly compressed into a compact mass. This process was the most preferred method of tablet manufacturing because of it is the cheapest and fastest direct method of tablet production.

3.3 EVALUATION OF MUCOADHESIVE BUCCAL TABLETS:

The prepared mucoadhesive buccal tablets should be evaluated for various physical and chemical evaluation parameters. The physical evaluation parameters mainly involves tablet appearance, hardness test which provide a measure tablet strength to the tablet, friability gives an indication of the tablets ability to resist abrasion on handling during packaging, thickness gives size of the tablet, weight variation also carried out for similarity in weight of same tablets. After doing these physical evaluation tests the chemical evaluation comes which are explained as drug content for demonstrating actual amount of drug present in individual tablet, swelling index and surface pH of tablet also checked, in vitro release study demonstrate the release pattern of drug in the medium. Ex vivo permeation of buccal tablets through the excised sheep buccal mucosal membrane was studied using modified Keshary Chien (K-C) type of diffusion cell, the ex vivo residence time for buccal tablet was determined using a locally modified USP disintegration apparatus, the FTIR interpretation checks the drug excipients interaction for suitable dosage form and the stability study also done for long time storage of the tablets. The important evaluation factor for the buccal tablet was the in vitro mucoadhesive strength of the tablet was measured on a modified physical balance employing the method.
described by Gupta et al using sheep buccal mucosa as model mucosal membrane and the results are obtained in grams.

3.4 RELEASE KINETICS OF DRUG RELEASE FROM TABLETS:

3.4.1 Zero-order release kinetics:

\[(Q_t) = k_0 t\]

Where \(Q(t)\) is the percent of drug dissolved as a function of time \(t\) in minutes and \(k_0\) describes the dissolution rate constant for zero-order release. A plot of the percent of drug released against time will be linear if the release obeys zero-order release kinetics. Values of release rate constant \(k_0\) were obtained in each case from the slope of percent drug released versus time plots.

3.4.2 First-order release kinetics:

\[\log Q_t = \log Q_0 + k_1 t/2.303\]

The first-order equation describes the release from systems where release rate is concentration dependent. Where \(Q_0\) is the initial amount of the drug, \(t\) is in minutes and \(k_1\) describes the dissolution rate constant for first-order release kinetics. A plot of the logarithm of the percent drug remained against time will be linear if the release obeys first-order release kinetics. Values of release rate constant \(k_t\) were obtained in each case from the slope of the log percent drug remained versus time plots.

3.4.3 The simplified Higuchi model:

\[Q(t) = K_h t^{1/2}\]

Where \(Q(t)\) is the percent of drug dissolved, time \(t\) in minutes, \(k_h\) is a dissolution rate constant for square root of time kinetics in percent dissolved min–½. A plot of the fraction of drug released against square root of time will be linear if the release obeys Higuchi equation. Values of release of rate constant \(k_h\) were obtained in each case from the slope of the percent drug released versus square root of time plots.

3.4.4 The Hixson-Crowell cube root model:

\[W_0^{1/3} - W_t^{1/3} = K_{HC} t\]

Where \(W_0\) is the initial amount of drug in the dosage form, \(W_t\) is the remaining amount of drug at time \(t\). Hixson-Crowell cube root law describes the release from systems where there is a change in surface area and diameter of the particles. \(k_{HC}\) is the release rate constant for Hixson-
Crowell rate equation. Then a graphic of the cubic root of the unreleased percent of drug versus time will be linear if the equilibrium conditions are not reached and if the geometrical shape of the dosage forms diminish proportionally over time. The release rate constant \( K_{HC} \) corresponds to the slope. This model has been used to describe the release profile from the diminishing surface of the drug particles during the dissolution.

### 3.4.5 Release from spherical matrix system:

The rate of the release of the drug from a spherical matrix controlled by diffusion, proposed by Baker-Lonsdale and its empirical form is,

\[
\frac{3}{2} \left[ 1 - \left(1 - \frac{M_t}{M_\infty}\right)^{2/3} \right]
\]

Where \( M_\infty \) is the amount of drug released at an infinite time and \( M_t \) is the amount of drug released after time \( t \), \( K_{BL} \) is the release rate constant. The graphic relating the left side of the equation and time will be linear if the established conditions of this model were fulfilled and the slope corresponds to the release rate constant \( K_{BL} \).

### 3.4.6 Erosion controlled release from matrix system:

The rate of release of the drug from a dosage form controlled by erosion is constantly proportional to the actual area of the surface of the dosage form and its simplified form is,

\[
\frac{M_t}{M_\infty} = 1 - (1 - k_{er} t)^3
\]

Where \( M \) is the amount of drug released at an infinite time and \( M_t \) is the amount of drug released after time \( t \). The model assumes that the rate limiting step of drug release is the erosion of the matrix itself and that time dependent diffusional resistance internal or external to the eroding matrix do not influence it. \( k_{er} \) is the rate constant of erosion which takes into account the rate of erosion and obtained from the slope of the plot between \((1 - M_t/M_\infty)^{1/3}\) versus time ‘\( t \’\).  

### 3.4.7 The Fickian and non-Fickian drug release model:

In order to define a model, which will represent a better fit for the release from the tablet formulations, dissolution data up to 60% can be further analyzed using Peppas and Korsemeyer equation (power law). To evaluate the contribution of the release mechanisms other than diffusion, other models of the release kinetics were employed. Since erosion of the matrix will contribute to the release, a model describing general solute release from hydrophilic polymers as employed by the Korsemeyer et al (1983) was used. Applied to the hydrophilic polymers it has the simplified empirical form (Ford et al, 1991).

\[
\frac{M_t}{M_0} = K t^n
\]
Where \( k \) is the release rate and \( n \) is the release exponent. Values of the release exponent (\( n \)) and the kinetic constant (\( k \)) obtained in each case from the slope and y-intercept of a logarithmic plot of percent released versus time respectively. Peppas (1985) used this \( n \) value in order to characterize different release mechanisms.

**Table 4: Interpretation of Korsmeyer-Peppas power law release exponent**

<table>
<thead>
<tr>
<th>Release exponent((n))</th>
<th>Drug transport mechanism</th>
<th>Rate as a function of time</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.50</td>
<td>Fickian diffusion</td>
<td>( t^{-0.5} )</td>
</tr>
<tr>
<td>0.50 &lt; ( n &lt; 1.0 )</td>
<td>Anomalous transport</td>
<td>( t^{n-1} )</td>
</tr>
<tr>
<td>1.0</td>
<td>Case II transport</td>
<td>Zero order release</td>
</tr>
<tr>
<td>Higher than 1.0</td>
<td>Super case II transport</td>
<td>( t^{n-1} )</td>
</tr>
</tbody>
</table>

**REFERENCES**


