Pharmacophore

Review Article

RECENT TREND AND APPROACHES OF BUCCAL DRUG DELIVERY SYSTEM: A REVIEW

Krishnarajan D[1]*, Jithin T.G.[1], Nikhil V[1], Archana M. Nair[1], Asmina Sherin[1], Sneha Thomas[1] and M.Purushothaman[2]

[1]JKK Munirajah College of Pharmacy, Komarapalayam-638183, Namakkal,Tamilnadu, India

[2]Vasavi Institute of Pharmaceutical Sciences, Kadapa-516247, Andrapradesh, India

ABSTRACT

The oral rout is an attractive site for the delivery of drugs. Through this route it is possible to carry mucosal (the local effect) and Transmucosal (the systemic effect) drug administration. Within the oral mucosal cavity, the buccal site offers an attractive route of administration for systemic drug delivery. The mucosa has a rich blood supply and it is relatively permeable. Environment of the oral mucosa and the experimental methods used in assessing buccal drug permeation/absorption. The main obstacles that drug meets when administered via buccal route derive from limited absorption area and the barrier properties of the mucosa. It is the objective of this article to review buccal drug delivery by discussing the advantages and limitations of buccal drug delivery, structure and design of buccal dosage forms, mechanism and factors affecting of buccal absorption Buccal dosage forms will also be reviewed with an emphasis on bioadhesive polymeric based delivery systems and methodology in evaluating buccal formulations.

Keywords: Buccal drug delivery system, Buccal dosage forms, Bioadhesion, Buccal absorption.

INDRODUCTION

Bioadhesive drug delivery formulations were introduced in 1947 when gum tragacanth was mixed with dental adhesive powder to apply penicillin to the oral mucosa. In recent years delivery of therapeutic agents via Mucoadhesive drug delivery system has become highly interesting. Certain drugs have lack of efficacy due to decreased bioavailability, GI intolerance, unpredictable and erratic absorption or pre-systemic elimination of other potential route for administration. The recent development in the drug delivery has intensified the investigation of mucosal drug delivery. Such route includes oral, buccal, ocular, nasal and pulmonary routes etc. Amongst the various routes of drug delivery, oral route is perhaps the most preferred to the patient and the clinician alike. However, peroral administration of drugs has disadvantages such as hepatic first pass metabolism and enzymatic degradation within the GI tract, that prohibit oral administration of certain classes of drugs especially peptides and proteins. Consequently, other absorptive mucosae are considered as potential sites for drug administration. Transmucosal routes of drug delivery (i.e., the mucosal linings of the nasal, rectal, vaginal, ocular, and oral cavity) offer distinct advantages over peroral administration for systemic drug delivery. These advantages include possible bypass of first pass effect, avoidance of presystemic elimination within the GI tract, and, depending on the particular drug, a better enzymatic flora for drug absorption.[1] Mucoadhesive drug delivery systems are delivery systems, which utilized the property of bioadhesion of certain polymers, which become adhesive on hydration and hence can be used for targeting a drug to particular region of the body for extended period of time.[2] The ability to maintain a delivery system at a particular location for an extended period of time has great appeal

for both local as well as systemic drug bioavailability.[3] Pharmaceutical aspects of mucoadhesion have been the subject of great interest during recent years because it provides the possibility of avoiding either destruction by gastrointestinal contents or hepatic first-pass inactivation of drug. The mucoadhesive drug delivery system includes the following[4]

- Buccal drug delivery systems
- Sublingual drug delivery systems
- Rectal drug delivery systems
- Vaginal drug delivery systems
- Ocular drug delivery systems
- Nasal drug delivery systems

ADVANTAGES OF BUCCAL DRUG DELIVERY SYSTEM[5,6]

➢ Drug is easily administered and extinction of therapy in emergency can be facilitated.
➢ Drug release for prolonged period of time.
➢ Relatively large surface area
➢ Accessibility
➢ Rich blood Supply
➢ Low metabolic activity
➢ Robust
➢ Prolonged retention
➢ Intestinal alternative
➢ Zero-order controlled release
➢ Ease of use and Low variability
➢ In unconscious and trauma patient's drug can be administered.
➢ Drugs bypass first pass metabolism so increases bioavailability.
➢ Some drugs that are unstable in acidic environment of stomach can be administered by buccal delivery.
➢ Drug absorption by the passive diffusion.
➢ Flexibility in physical state, shape, size and surface.
➢ Maximized absorption rate due to close contact with the absorbing membrane.
➢ Rapid onset of action.

LIMITATIONS OF BUCCAL DRUG DELIVERY SYSTEM[7]

➢ Drugs which are unstable at buccal pH cannot be administered.
➢ Drugs which have a bitter taste or unpleasant taste or an obnoxious odor or irritate the mucosa cannot be administered by this route.
➢ Drug required with small dose can only be administered.
➢ Those drugs which are absorbed by passive diffusion can only be administered by this route.
➢ Eating and drinking may be restricted.
➢ Possibility of the patient to swallow the tablet.
➢ Small surface area is available for absorption.

ORAL MUCOSA SITES

Within the oral mucosal cavity, delivery of drugs is classified in to three categories.

Sublingual Delivery

It is the administration of the drug via the sublingual mucosa (the membrane of the ventral surface of the tongue and the floor of the mouth to the systemic circulation.

Buccal Delivery

It is the administration of drug via the buccal mucosa (the lining of the cheek) to the systemic circulation.

Local Delivery

It is for the treatment of conditions of the oral cavity, principally ulcers, fungal conditions and periodontal disease. These oral mucosal sites differ greatly from one another in terms of anatomy, permeability to an applied drug and their ability to retain a delivery system for a desired length of time.[8,9]

ORAL MUCOSA

The oral mucosa is composed of an outermost layer of stratified squamous epithelium (about 40-50 layers thick), a lamina propria followed by the sub mucosa as the innermost layer. The oral mucosal thickness varies depending on the site: the buccal mucosa measures at 500-800μm, while the mucosal thickness of the hard and soft palates, the floor of the mouth, the ventral tongue, and the gingival measure at about 100-200μm. The mucosa of the gingival and hard palate are keratinized similar to the epidermis contain neutral lipids like ceramides and acylceramides which are relatively impermeable to water. The mucosa of the soft palate, the sublingual, and the buccal regions, however, are not keratinized contain only small amounts of ceramides. The turnover time for the buccal epithelium has been estimated at 5- 6 days, and this is probably representative of the oral mucosa as a whole.[10]
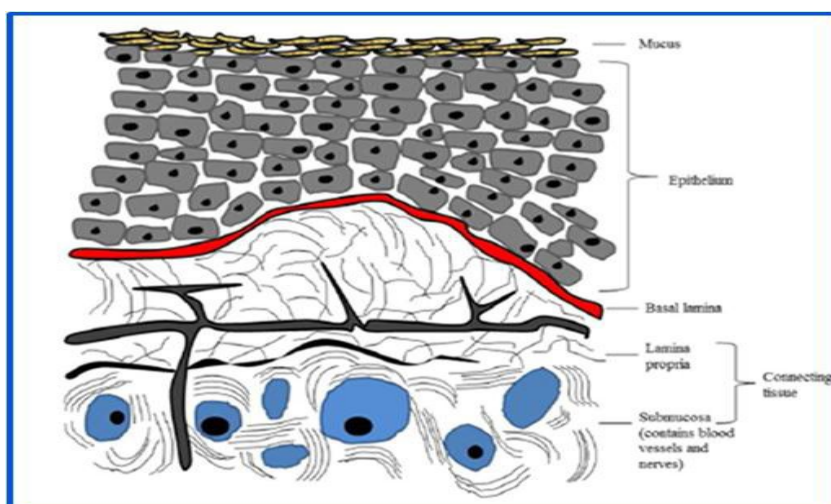

Figure 1: Oral mucosa

Role of Saliva

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

Role of Mucus

1. Made up of proteins and carbohydrates.
2. Cell –cell adhesion.
3. Lubrication.
4. Bioadhesion of mucoadhesive drug delivery system.

Permeability

The oral mucosa in general is somewhat leaky epithelia intermediate between that of the epidermis and intestinal mucosa. It is estimated that the permeability of the buccal mucosa is 4-4000 times greater than that of the skin. In general, the permeability's of the oral mucosa decrease in the order of sublingual greater than buccal and buccal greater than palatal. This rank order is based on the relative thickness and degree of

keratinization of these tissues, with the sublingual mucosa being relatively thin and non-keratinized, the buccal thicker and nonkeratinized and the palatal intermediate in thickness but keratinized.[11-13]

STRUCTURE AND DESIGN OF BUCCAL DOSAGE FORM
Matrix Type
The buccal patch designed in a matrix configuration contains drug, adhesive, and additives mixed together.

Reservoir Type
The buccal patch designed in a reservoir system contains a cavity for the drug and additives separate from the adhesive. An impermeable backing is applied to control the direction of drug delivery; to reduce patch deformation and disintegration while in the mouth; and to prevent drug loss.[14]

MECHANISM OF BUCCAL ABSORPTION
Buccal drug absorption occurs by passive diffusion of the non ionized species, a process governed primarily by a concentration gradient, through the intercellular spaces of the epithelium. The passive transport of non-ionic species across the lipid membrane of the buccal cavity is the primary transport mechanism. The buccal mucosa has been said to be a lipoidal barrier to the passage of drugs, as is the case with many other mucosal membrane and the more lipophillic the drug molecule, the more readily it is absorbed.[15] The dynamics of buccal absorption of drugs could be adequately described by first order rate process. Several potential barriers to buccal drug absorption have been identified. Dearden and Tomlison (1971) pointed out that salivary secretion alters the buccal absorption kinetics from drug solution by changing the concentration of drug in the mouth. The linear relationship between salivary secretion and time is given as follows:

$$\frac{-dm}{dt} = \frac{KC}{ViVt}$$

Where,
M - Mass of drug in mouth at time
K - Proportionality constant
C - Concentration of drug in mouth at time
Vi - The volume of solution put into mouth cavity and
Vt - Salivary secretion rate.

PHYSIOLOGICAL FACTORS AFFECTING BUCCAL BIOAVAILABILITY
- Inherent permeability of the epithelium: The permeability of the oral mucosal epithelium is intermediate between that of the skin epithelium, which is highly specialized for barrier function and the gut, which is highly specialized for an adsorptive function. Within the oral cavity, the buccal mucosa is less permeable that the sublingual mucosa.
- Thickness of epithelium: The thickness of the oral epithelium varies considerably between sites in the oral cavity. The buccal mucosa measures approximately 500-800μm in thickness.
- Blood supply: A rich blood supply and lymphatic network in the lamina propria serve the oral cavity, thus drug moieties which traverse the oral epithelium are readily absorbed into the systemic circulation.
- Metabolic activity: Drug moieties adsorbed via the oral epithelium are delivered directly into the blood, avoiding first pass metabolism effect of the liver and gut wall. Thus oral mucosal delivery may be particularly attractive for the delivery of enzymatically labile drugs such as therapeutic peptides and proteins.
- Saliva and mucous: The activity of the salivary gland means that the oral mucosal surfaces are constantly washed by a stream of saliva, approximately 0.5- 2L per day. The sublingual area in

particular, is exposed to a lot of saliva which can enhance drug dissolution and therefore increase bioavailability.

- Ability to retain delivery system: The buccal mucosa comprises an expense of smooth and relatively immobile surface and thus is ideally suited to the use of retentive delivery systems.
- Species differences: Rodents contain a highly keratinized epithelium and thus are not very suitable as animal models when studying buccal drug delivery.
- Transport routes and mechanism: Drug permeation across the epithelium barrier is via two main routes:
- ➢ The paracellular route: Between adjacent epithelial cells;
- ➢ The transcellular route: Across the epithelial cells, which can occur by any of the following mechanism: passive diffusion, carrier mediated transport and via endocytic processes.[16,17]

FACTORS AFFECTING BUCCAL ABSORPTION

The oral cavity is a complex environment for drug delivery as there are many interdependent and independent factors which reduce the absorbable concentration at the site of absorption.

Membrane Factors

This involves degree of keratinization, surface area available for absorption, mucus layer of salivary pellicle, intercellular lipids of epithelium, basement membrane and lamina propria. In addition, the absorptive membrane thickness, blood supply/ lymph drainage, cell renewal and enzyme content will all contribute to reducing the rate and amount of drug entering the systemic circulation.

Environmental Factors

Saliva

The thin film of saliva coats throughout the lining of buccal mucosa and is called salivary pellicle or film. The thickness of salivary film is 0.07 to 0.10 mm. The thickness, composition and movement of this film affect the rate of buccal absorption.

Salivary Glands

The minor salivary glands are located in epithelial or deep epithelial region of buccal mucosa. They constantly secrete mucus on surface of buccal mucosa. Although, mucus helps to retain mucoadhesive dosage forms, it is potential barrier to drug penetration.

Movement of Buccal Tissues

Buccal region of oral cavity shows less active movements. The mucoadhesive polymers are to be incorporated to keep dosage form at buccal region for long periods to withstand tissue movements during talking and if possible during eating food or swallowing.[18-19]

BIOADHESION[20]

'Bioadhesive' is defined as a substance that is capable of interacting with biological material and being retained on them or holding them together for extended period of time. Bioadhesive are classified into three types.

- Bioadhesion between biological layers without involvement of artificial materials. Cell diffusion and cell aggregation are good examples.
- Bioadhesion can be represented by cell adhesion into culture dishes or adhesion to a variety of substances including metals, woods and other synthetic materials.
- Adhesion of artificial substances to biological substrate such as adhesion of polymer to skin or other soft tissue.

MECHANISM OF BIOADHESION[21-23]

For bioadhesion to occur, three stages are involved

- An intimate contact between a bioadhesive and a membrane either from a good wetting of the bioadhesive and a membrane or from the swelling of bioadhesive.

- Penetration of the bio-adhesive into the tissue takes place.
- Inter penetration of the chains of the bioadhesive with mucous takes place. Low chemical bonds can then settle. The bonding between the mucus and the biological substance occurs chiefly through both physical and chemical interactions results from enlargement of the adhesive material and chemical bonds due to electrostatic interaction, hydrophobic interactions, hydrogen bonding and dispersion forces.
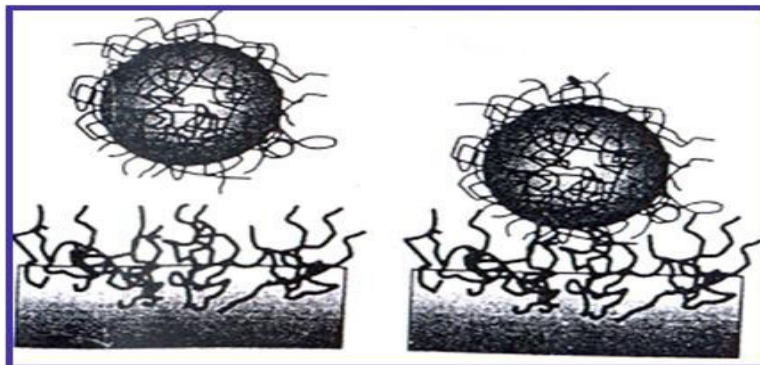

Figure 2: Inter penetration of bioadhesive and mucus polymer chain

THEORIES OF BIOADHESION OR MUCOADHESION[24-25]

Several theories have been proposed to explain the fundamental mechanism of adhesion.

Wetting Theory

Wetting theory is predominantly applicable to liquid bioadhesive systems and analyzes adhesive and contact behavior in terms of a liquid or a paste to spread over a biological system. The work of adhesion [expressed in terms of surface and interfacial tension (γ) being defined as energy per cm^2 released when an interface is formed.

According to Dupres equation, work of adhesion is given by

$WA = \gamma_A + \gamma_B - \gamma_{AB}$

Where, A and B refers to the biological membrane and the bioadhesive formulation respectively. The work of cohesion is given by

$Wc = 2\gamma_A$ or γ_B

For a bioadhesive material B spreading on a biological substrate, the spreading coefficient is given by:

$SB/A = \gamma_A - (\gamma_B + \gamma_{AB})$

SB/A should be positive for a bioadhesive material to adhere to a biological membrane. For a bioadhesive liquid B adhering to a biological membrane A, the contact angle is given by
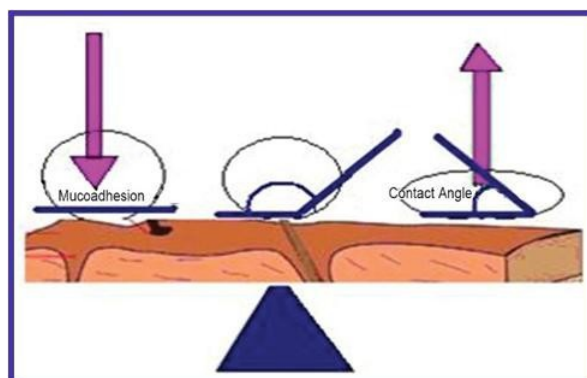
$\cos\Phi - (\Phi_A - \Phi_{AB} / \Phi_B)$.

Figure 3: mucoadhesion and contact angle

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 cross links and decreases significantly as the cross linking density decreases.
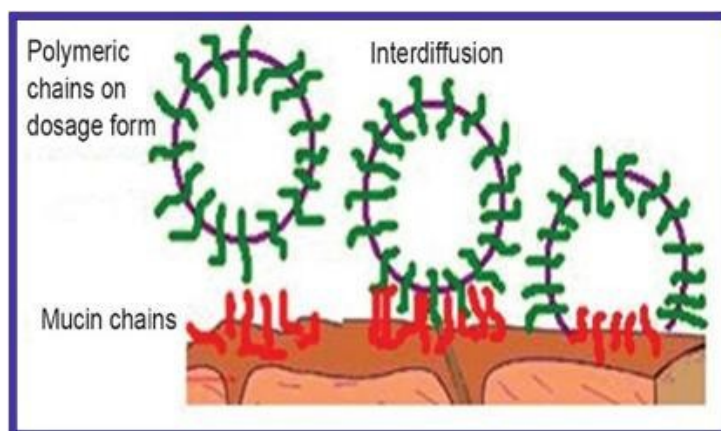

Figure 4: Secondary interaction between mucoadhesive device and mucus.

Electronic Theory

According to this theory, electronic transfer occurs upon contact of an adhesive polymer and the mucus glycoprotein network because of differences in their electronic structure. This result in the formulation of an electronic double layer at the interface adhesion occurs due to attractive forces across the double layer.

Fracture Theory

According to Fracture theory of adhesion is related to separation of two surfaces after adhesion. The fracture strength is equivalent to adhesive strength as given by,

$$G = (E\varepsilon. /L)^{1/2}$$

Where: E= Young's module of elasticity

ε = Fracture energy

L= Critical crack length when two surfaces are separated.
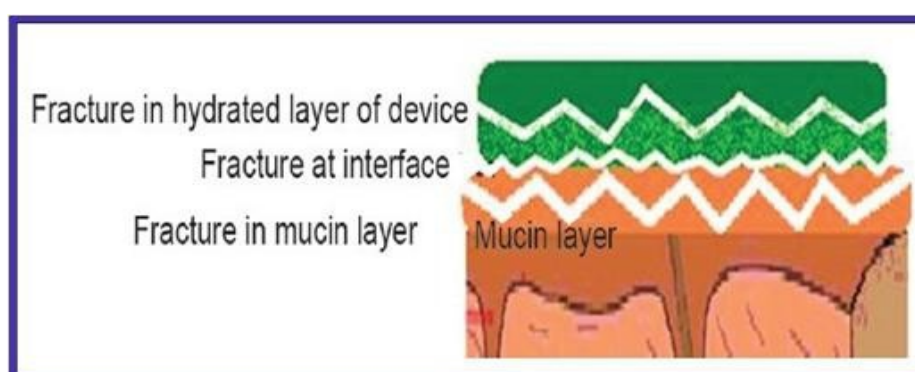

Figure 5: Fractures occurring for Mucoadhesion

Adsorption Theory

According to this theory, after an initial contact between two surfaces, the materials adhere because of surface forces acting between the atoms in the two surfaces. Two types of chemical bonds such as primary covalent (permanent) and secondary chemical bonds (including electrostatic forces, vander-waals forces and hydrogen and hydrophobic bonds) are involved in the adsorption process.
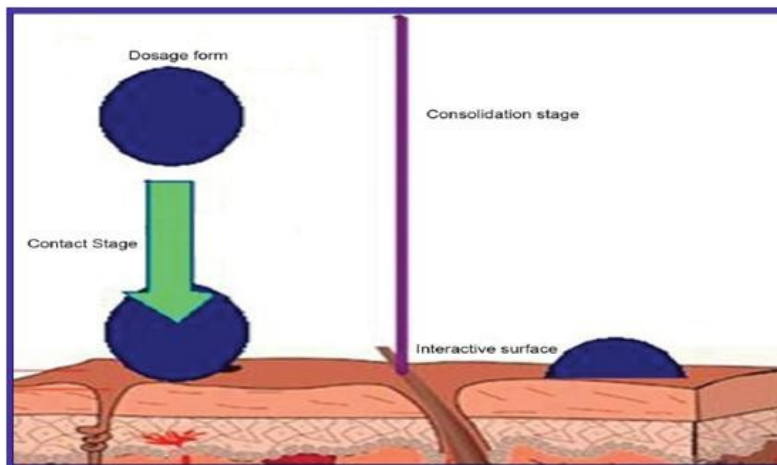
Figure 6: The process of consolidation

BASIC COMPONENTS OF BUCCAL DRUG DELIVERY SYSTEM

The basic components of buccal drug delivery system are

➢ Drug substance
➢ Bio adhesive polymers
➢ Backing membrane
➢ Permeation enhancers

Drug Substance

Before formulating mucoadhesive drug delivery systems, one has to decide whether the intended, action is for rapid release/prolonged release and for local/systemic effect. The selection of suitable drug for the design of buccoadhesive drug delivery systems should be based on pharmacokinetic properties.
The drug should have following characteristics.[26]

- The conventional single dose of the drug should be small.
- The drugs having biological half-life between 2-8 hrs are good candidates for controlled drug delivery.
- Tmax of the drug shows wider-fluctuations or higher values when given orally.
- Through oral route drug may exhibit first pass effect or presystemic drug elimination.
- The drug absorption should be passive when given orally.

Bioadhesive Polymer

The first step in the development of buccoadhesive dosage forms is the selection and Characterization of appropriate bio adhesive polymers in the formulation. Bio adhesive polymers play a major role in buccoadhesive drug delivery systems of drugs. Polymers are also used in matrix devices in which the drug is embedded in the polymer matrix, which control the duration of release of drugs. Bio adhesive polymers are from the most diverse class and they have considerable benefits upon patient health care and treatment the drug is released into the mucous membrane by means of rate controlling layer or core layer. Bio adhesive polymers which adhere to the mucin/ epithelial surface are effective and lead to significant improvement in the oral drug delivery.[27-28]

An Ideal Polymer For Buccoadhesive Drug Delivery Systems Should Have Following Characteristics29

- It should be inert and compatible with the environment
- The polymer and its degradation products should be non-toxic absorbable from the mucous layer.
- It should adhere quickly to moist tissue surface and should possess some site specificity.
- The polymer must not decompose on storage or during the shelf life of the dosage form.
- The polymer should be easily available in the market and economical.
- It should allow easy incorporation of drug in to the formulation.

Criteria Followed In Polymer Selection

- It should form a strong non covalent bond with the mucine/epithelial surface
- It must have high molecular weight and narrow distribution.
- It should be compatible with the biological membrane.

Table 2: Mucoadhesive Polymers used in the Oral Cavity[30]

Criteria	Categories	Examples
Source	Semi natural/ Natural	Agarose, chitosan, gelatin, Hyaluronic acid, Various gums (guar gum, xanthan, gellan, carragenan, pectin and sodium alginate).
	Synthetic	**Cellulose derivatives:** [CMC, thiolated CMC, NaCMC, HEC, HPC, HPMC, MC.]
		Poly(acrylic acid)-based polymers: [CP, PC, PAA, polyacrylates, poly(methyl vinyl ether-co-methacrylic acid), poly(2- hydroxy ethyl methacrylate),poly(acrylic acidco-ethyl hexyl acrylate), poly(methacrylate),poly(isobutylcyanoacrylate), copolymer of acrylic acid and PEG].
		Others: polyoxyethylene, PVA, PVP, thiolated Polymers.
Aqueous solubility	Water soluble	CP, HEC, HPC, HPMC (cold water), PAA, NaCMC, sodium alginate.
	Water insoluble	Chitosan (soluble in dilute aqueous acids), EC, PC.
Charge	Cationic	Aminodextran, Chitosan, (DEAE)- dextran, TMC
	Anionic	Chitosan-EDTA, CP, CMC, pectin, PAA, PC, sodium alginate, NaCMC, xanthan gum.
	Non-ionic	Hydroxy ethyl starch, HPC, poly(ethylene oxide), PVA,
Potential	Covalent	PVP, scleroglucan
	Hydrogen bond	Cyanoacrylate
Bioadhesive forces	Electrostatic interaction	Acrylates [hydroxylated methacrylate, poly(methacrylic acid)], CP, PC, PVA, Chitosan

Table 3: List of Investigated Bio Adhesive Polymers

Bioadhesive Polymer (s) Studied	Investigation Objectives
HPC and CP	Preferred mucoadhesive strength on CP, HPC, and HPC-CP combination Measured Bioadhesive property using mouse peritoneal Membrane Studied inter polymer complexation and its effects on bioadhesive strength.
CP, HPC, PVP, CMC	Studied inter polymer complexation and its effects on bioadhesive strength.
Polycarbophil	Design of a unidirectional buccal patch for oral mucosal delivery of peptide drugs.
Poly(acrylicacid) Poly(methacrylic acid)	Synthesized and evaluated cross-linked polymers differing in charge densities and hydrophobicity.

Number of Polymers including HPC, HPMC, CP, CMC	Measurement of bioadhesive potential and to derive meaningful information on the structural requirement for bioadhesion.
Poly(acrylic acid-coacrylamide)	Adhesion strength to the gastric mucus layer as a function of cross-linking agent, degree of swelling, and carboxyl group density
Poly(acrylic acid)	Effects of PAA molecular weight and cross-linking concentration on swelling and drug release characteristics.
HPC, HEC, PVP, and PVA	Tested mucosal adhesion on patches with two-ply laminates with an impermeable backing layer and hydrocolloid polymer layer.
HPC and CP	Used HPC-CP powder mixture as peripheral base for strong adhesion and HPC-CP freeze dried mixture as core base.
CP, PIP, and PIB	Used a two roll milling method to prepare a new bioadhesive patch formulation.
Xanthan gum and Locust bean gum, Chitosan, HPC, CMC, Pectin, Xanthan gum, and Polycarbophil.	Hydrogel formation by combination of natural gums Evaluate mucoadhesive properties by routinely measuring the detachment force form pig intestinal mucosa.
Formulation consisting of PVP, CP, and cetyl pyridinium chloride (as stabilizer)	Device for oralmucosal delivery of LHRH - device containing a fast release and a slow release layer.
Formulation consisting of PVP, CP, and cetyl pyridinium chloride (as stabilizer)	Mucoadhesive gels for intraoral delivery.

Backing Membrane

Backing membrane plays a major role in the attachment of bioadhesive devices to the mucus membrane. The materials used as backing membrane should be inert, and impermeable to the drug and penetration enhancer. Such impermeable membrane on buccal bioadhesive patches prevents the drug loss and offers better patient compliance. The commonly used materials in backing membrane include carbopol, magnesium stearate, HPMC, HPC, CMC, polycarbophil etc.

Permeation Enhancers

Substances that facilitate the permeation through buccal mucosa are referred as permeation enhancers. Selection of enhancer and its efficacy depends on the physicochemical properties of the drug, site of administration, nature of the vehicle and other Excipients.[31]

MECHANISMS OF ACTION OF PERMEATION

- Changing mucus rheology:
  - ➢ By reducing the viscosity of the mucus and saliva overcomes this barrier.
- Increasing the fluidity of lipid bilayer membrane:
  - ➢ Disturb the intracellular lipid packing by interaction with either lipid packing by interaction with either lipid or protein components.
- Acting on the components at tight junctions:
  - ➢ By inhibiting the various peptidases and proteases present within buccal mucosa, thereby overcoming the enzymatic barrier. In addition, changes in membrane fluidity also alter the enzymatic activity indirectly.
- Increasing the thermodynamic activity of drugs:
  - ➢ Some enhancers increase the solubility of drug there by alters the partition coefficient.[32]

Table 4: Examples of permeation enhancers with mechanism

Category	Examples	Mechanism(s)
Surfactants and Bile Salts	Surfactants and Bile Salts Sodium dodecyl sulphate Sodium lauryl sulphate Polysorbate 80	Acting on the components at tight junctions Increasing the fluidity of lipid bilayer membrane;
Fatty Acids	Oleic acid, Cod liver oil, Capric acid, Lauric acid	Increasing the fluidity of lipid bilayer membrane.
Polymers and Polymer Derivatives	Chitosan Trimethyl chitosan Chitosan-4- thiobutylamide	Increasing the fluidity of lipid bilayer membrane; Increased retention of drug at mucosal surface
Others	Ethanol, Azone, Octisalate, Padimate, Menthol	Acting on the components at tight junctions; Increasing the fluidity of lipid bilayer membrane

BUCCOADHESIVE POLYMERS USED IN THE ORAL CAVITY

The major advantages of bioadhesive systems are increase in the residence time of the drug containing device in the oral cavity and localization of drugs in a particular region. The bioadhesion process has been explained by electronic, adsorption, wetting, diffusion, and fracture theories. Generally, some of the necessary structural characteristics for bioadhesive polymers include strong hydrogen bonding groups, strong anionic or cationic charges, high molecular weight, chain flexibility, and surface energy properties which favor spreading on mucus layer. In general, adhesive polymers sources should be natural or synthetic, water-soluble and water insoluble, charged and uncharged polymers. Examples of the recent bioadhesive buccal polymers are listed in table. The polymers classified in table 2 are represented as nonspecific bioadhesive and are considered as first-generation bioadhesive. The duration of bioadhesion is largely determined by the fast turnover of mucus layer. Factors such as saliva secretion, food intake, local pH, and compositions of delivery systems also strongly affect bioadhesion.[33]

NOVEL SECOND-GENERATION MUCOADHESIVE POLYMERS

Lectins, bacterial adhesions and thiolated polymers are classified and considered as second-generation mucoadhesive polymers.

Lectins

Lectins are naturally occurring proteins that play a fundamental role in biological recognition phenomena involving cells and proteins. These are proteins/glycoproteins that possess high specific affinity for carbohydrates. After initial mucosal cell binding, lectins can either remain on the cell surface or in the case of receptor-mediated adhesion possibly become internalized via endocytosis. Although lectins offer significant advantages in relation to site targeting, many are toxic or immunogenic, and the effects of repeated lectin exposure are largely unknown. It is also feasible that lectin induced antibodies could block subsequent adhesive interactions between mucosal epithelial cell surfaces and lectin delivery vehicles. Moreover, such antibodies may also render individuals susceptible to systemic anaphylaxis on subsequent exposure. Recently, lectin-based second-generation bioadhesives have attracted considerable interests for oral drug delivery. It has been found that lectin binding on human buccal cells occurred within 20 second and was not detached by saliva flushing.[34]
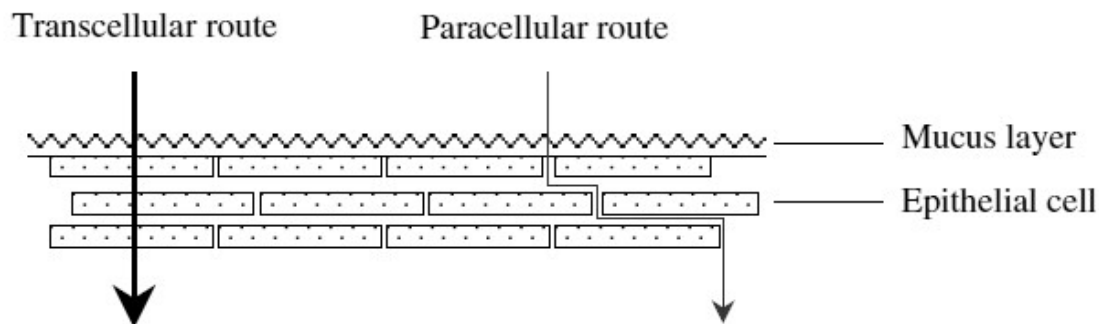
Figure 7 : Schematic representation of penetration routes in buccal drug delivery,

BACTERIAL ADHESIONS

The adhesive properties of bacterial cells have been investigated recently. The ability of bacteria to adhere to a specific target is rooted from particular cell-surface components or appendages, known as fimbriae that facilitate adhesion to other cells or inanimate surfaces. These are extracellular, long threadlike protein polymers of bacteria that play a major role in many diseases. Bacterial fimbriae adhere to the binding moiety of the specific receptors. A significant correlation has been found between the presence of fimbriae on the surface of bacteria and their pathogenicities.[35] The attractiveness of this approach lies in the potential increase in the residence time of the drug on the mucus and its receptor-specific interaction, similar to those of the plant lectins. *Escherichia coli* (E.coli) has been reported to specifically adhere to the lymphoid follicle epithelium of the ileal Peyer's patch in rabbits.[36] Additionally, different staphylococci possess the ability to adhere to the surface of mucus gel layers and not to the mucus-free surface.[37] Thus, it appears that drug delivery based on bacterial adhesion could be an efficient method to improve the delivery of particular drugs or carrier systems. Antigen K99-fimbriae, an attachment protein derived from E. coli, has been covalently attached to polyacrylic acid networks.[38] The formulated polymer–fimbriae platform exhibited a significant increase in adhesion in vitro in comparison to the control (unmodified polymer these).

THIOLATED POLYMERS

Thiolated polymers (thiomers) are of the second-generation mucoadhesive derived from hydrophilic polymers such as polyacrylates, chitosan or deacetylated gellan gum. The presence of thiol groups allows the formation of covalent bonds with cysteine- rich sub-domains of the mucus gel layer, leading to increase in the residence time and improvement of the bioavailability]. Thiomers mimic the natural mechanism of secreted mucus glycoproteins that are also covalently anchored in the mucus layer by the formation of disulphide bonds]. While first-generation mucoadhesive polymers are involved in non-covalent secondary interactions, the covalent bonding mechanisms involved in second-generation systems lead to interactions that are less susceptible to changes in ionic strength and/or the pH. Moreover the presence of disulphide bonds may significantly alter the mechanism of drug release from the delivery system due to increase in rigidity and cross-linking. In such platforms a diffusion-controlled drug release mechanism is more typical, whereas in the first-generation polymers anomalous transport of API into bulk solution is more common.[39,40]

INVESTIGATIONS ON THE BUCCAL DRUG DELIVERY SYSTEMS

Several buccal drug delivery devices have been developed at the laboratory scale by many researchers either for local or systemic actions. They are broadly classified into (i) Solid buccal adhesive dosage forms (ii) Semi-solid buccal adhesive dosage forms (iii) Liquid buccal adhesive dosage forms. Buccal mucoadhesive dosage forms can also be categorized into three types on the basis of geometry. Type I is a single layer device with multidirectional drug release. This type of dosage form suffers from significant drug loss due to swallowing. In the type II devices, an impermeable backing layer is superimposed on top

of the drug-loaded bioadhesive layer, creating a double-layered device, preventing drug loss from the top surface of the dosage form into the oral cavity. Type III is a unidirectional release device, from which drug loss is minimal, since the drug is released 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. The device should be fabricated so that the swelling rate of bioadhesive polymer is optimized to ensure a prolonged period of bioadhesion as well as a controlled or sustained drug release.[41]
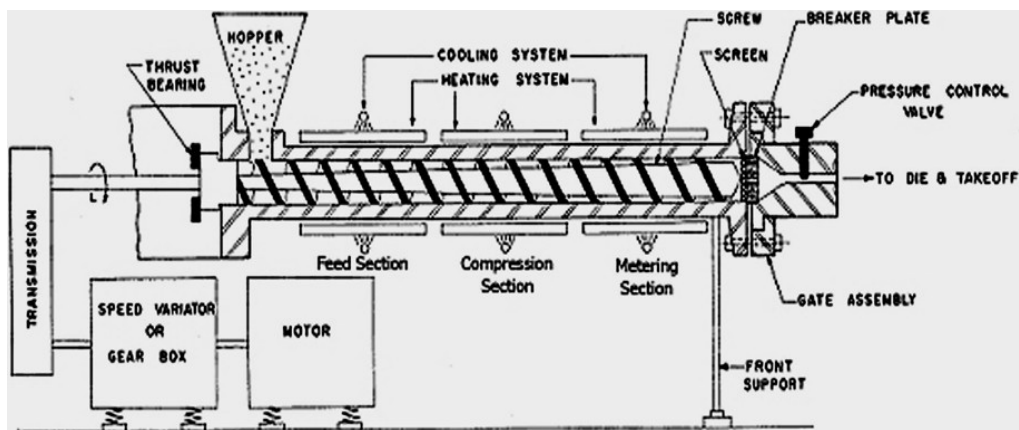

Figure 8: Schematic representation of penetration routes in buccal drug delivery.

SOLID BUCCAL ADHESIVE DOSAGE FORMS

They are dry formulations which achieve bioadhesion via dehydration of the local mucosal surface.

Buccal Tablets

Tablets have been the most commonly investigated dosage forms for buccal drug delivery. Several bioadhesive buccal tablet formulations have been developed by direct compression method in recent years either for local or systemic drug delivery. They are designed to release the drug either unidirectionally by targeting buccal mucosa or multi-directionally into the saliva. Alternatively, the dosage form can contain an impermeable backing layer to ensure that drug is delivered unidirectionally. Disadvantages of buccal tablets may be patient acceptability (mouth feel, taste and irritation) and the nonubiquitous distribution of drug within saliva for local therapy. It is important to point out the possible problems those children and the elderly may experience by the use of adhesive tablets such as possible discomfort provoked by the material applied to the mucosa and the possibility of the separation of dosage form the mucosa, swallowing, and then adherence to the wall of the esophagus. A typical bioadhesive formulation of this type consists of a bioadhesive polymer (such as polyacrylic acids or a cellulose derivative), alone or in combination, incorporated into a matrix containing the active agent and excipients, and perhaps a second impermeable layer to allow unidirectional drug delivery.[42-43]

Bioadhesive Micro/Nanoparticles

Bioadhesive micro/nanoparticles offer the same advantages as tablets but their physical properties enable them to make intimate contact with a lager mucosal surface area. These are typically delivered as an aqueous suspension or are incorporated into a paste or ointment or applied in the form of aerosols. Particulates have the advantage of being relatively small and more likely to be acceptable by the patients. Bioadhesive polymeric microparticles of carbopol, polycarbophil, chitosan or Gantrez are to adhere to porcine esophageal mucosa, with particles prepared from the polyacrylic acids exhibiting greater mucoadhesive strength during tensile testing studies. However in elution studies, particles of chitosan or Gantrez were found to persist on mucosal tissue for longer periods of time. It has been reported. The use of nanoparticles for local delivery to the oral mucosa has been reported]. Two types of nanoparticles, solid lipid nanoparticles incorporating either idarubicin or BODIPY®FL C12 as model fluorescent probes and polystyrene nanoparticles (Fluo-Spheres®) were investigated using monolayer-cultured human oral

squamous cell carcinoma (OSCC) cell lines and normal human oral mucosal explants in a proof of concept study. The results demonstrated that OSCC cells internalized solid lipid nanoparticles. The observed penetration of nanoparticles through the epithelium and basement membranes into the underlying connective tissue suggested the possibility of oral transmucosal nanoparticle delivery for systemic therapy. Monti and co-workers produced an atenolol containing microsphere using Poloxamer 407 and evaluated the formulation in vivo in rabbits against a marketed tablet formulation as a reference. After administration of the microsphere formulations, the atenolol concentration remained higher than the reference tablet during the entire elimination phase showing a sustained release profile from the microspheres. Moreover, the absolute bioavailability of microsphere formulations was higher than that of reference tablets in spite of a lower drug dose, suggesting a possible dose reduction by atenolol microparticles via oral transmucosal administration. Liposomes are one of the alternatives for drugs which are poorly soluble and hence are not efficiently delivered from a solid dosage form. For example, silamyrin liposomal buccal delivery showed steady state permeation through a chicken buccal pouch for 6 hrs and which was higher than free drug powder.[44] The small size of microparticles compared to tablets means that they are less likely to cause local irritation at the site of adhesion and the uncomfortable sensation of a foreign object within the oral cavity is reduce.

Bioadhesive Wafers

The delivery system is a composite wafer with surface layers possessing adhesive properties, while the bulk layer consists of antimicrobial agents, biodegradable polymers and matrix polymers. A conceptually novel periodontal drug delivery system intended for the treatment of microbial infections associated with periodontitis has been reported.

Bioadhesive Lozenges

A slow release bioadhesive lozenge offers the potential for prolonged drug release with improved patient compliance. Bioadhesive lozenges may be used for the delivery of drugs that act within the mouth including antimicrobials, corticosteroids, local anaesthetics, antibiotics and antifungals. A Bioadhesive lozenge has been reported as a means to deliver antifungal agents to the oral cavity. The limitation of these bioadhesive lozenzes is the short residence time at the site of absorption which depends to the size and type of formulation and since dissolve within 30min, the total amount of the drug that can be delivered is limited. The dissolution or disintegration of lozenges is usually controlled by the patient, i.e. how hard they suck the unit. Increased sucking and saliva production causes uncontrolled swallowing and loss of drug down the GI tract. Thus, solid dosage forms generally have a much higher inter- and intra-individual variations in absorption and bioavailability. Also these types of system are not able to provide unidirectional release of drugs. Continuous secretion of saliva is another major hurdle to the performance of such dosage forms.[45]

Semi-Solid Dosage Forms
Medicated chewing gums

Although medicated chewing gums pose difficulties in regulation of the administered dose, they still have some advantages as drug delivery devices, particularly in the treatment of diseases of the oral cavity and in nicotine replacement therapy. Some commercial products are available in the market. Caffeine chewing gum, Stay Alert®, was developed recently for alleviation of sleepiness. It is absorbed at a significantly faster rate and its bioavailability was comparable to the capsule formulation. Nicotine chewing gums (e.g., Nicorette® and Nicotinell®) have been marketed for smoking cessation.

Adhesive gels

Various adhesive gels may be used to deliver drugs via the buccal mucosa and allow sustained release. Gel forming bioadhesive polymers include cross-linked polyacrylic acid that has been used to adhere to the mucosal surfaces for extended periods of time and provide controlled release of drug at the site of

absorption. Designed of a novel, hydrogel based, bioadhesive, intelligent response system for controlled drug release has been reported. This system combined several desirable facets into a single formulation; a poly (hydroxyethyl methacrylate) layer as barrier, poly (methacrylic acid-g-ethylene glycol) as a biosensor and poly (ethylene oxide) to promote mucoadhesion. The limitations for gel formulations are inability to deliver a measured dose of drug to the site and as a result have limited uses for drugs with narrow therapeutic window.

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. Flexible films/patches have been prepared either by solvent casting or hot melt extrusion technique to deliver drugs directly to a mucosal membrane. Compared to creams and ointments they offer advantages in delivering a measured dose of drug to the site.[46]

Solvent Casting Technique

In this technique the required quantity of mucoadhesive polymer is treated with required volume of solvent system and vortexed to allow polymer to swell. After swelling, mixture was treated with, measured quantity of plasticizer (propylene glycol or glycerin or dibutyl phthalate) and vortexed. Finally the required quantity of drug was dissolved in small volume of solvent system and added to the polymer solution and mixed well. It was set aside for some time to remove any entrapped air and transferred into a previously cleaned anumbra petri plate. Drying of these patches was carried out in an oven at 400C. The formed patches were stored in a desiccator till the evaluation tests were performed.[47]

Hot Melt Extrusion Technique

The Hot-melt extrusion (HME) technique is an attractive alternative to traditional processing methods and offers many advantages over the other pharmaceutical processing techniques. Molten polymers during the extrusion process can function as thermal binders and act as drug depots and/or drug release retardants upon cooling and solidification. Since solvents and water are not necessary, the numbers of processing and time-consuming drying steps are reduced. A matrix can be massed into a larger unit independent of compression properties. The intense mixing and agitation imposed by the rotating screw cause de-aggregation of suspended particles in the molten polymer resulting in a more uniform dispersion and the process is continuous and efficient. Bioavailability of the drug substance may be improved when it is solubilized or dispersed at the molecular level in HME dosage forms. Pharmaceutical Hot-Melt Extrusion processes can be categorized as either ram extrusion or screw extrusion.[48]

Ram extrusion

It operates with a positive displacement ram capable of generating high pressures to push materials through the die. During ram extrusion, materials are introduced into a heated cylinder. After an induction period for softening of the materials, a ram (or a piston) pressurizes the soft materials through the die and transforms them into the desired shape. High-pressure is the operating principle of ram extrusion. This technique is well suited for the precision extrusion of highly valuable materials. The ram exerts modest and repeatable pressure as well as a very consistent extrudate diameter. The major drawback of ram extrusion in comparison with extrudates processed by screw extrusion is limited melting capacity that causes poor temperature uniformity in the extrudate and resulting in lower homogeneity.

Screw Extruders are of two types

- *Single Screw Extruder*
- *Twin-Screw Extruders*

Single Screw Extruder

The single screw extruder is the most widely used extrusion system in the world. One screw rotates inside the barrel and is used for feeding, melting, devolatilizing, and pumping. Mixing is also accomplished for less demanding applications. Single screw extruders can be either flood or starve fed, depending upon the intended manufacturing process. Single screw extruders are continuous, high-pressure pumps for viscous materials that can generate thousands of pounds of pressure while melting and mixing. Most extruder screws are driven from the hopper end. However, when screws are reduced to less than 18 mm, they become weak and solids transportation is far less reliable. To overcome these shortcomings, a vertical screw, driven from the discharge end, may be used. The strength of discharge of such screws is 24- times higher than solids transport. There are three basic functions of a single screw extruder: solids conveying, melting and pumping. The forwarding of the solid particles in the early portion of the screw is a result of friction between the material and the feed section's bore. After solids conveying the flight depth begins to taper down and the heated barrel causes formation of a melt. The energy from the heaters and shearing contribute to melting. Ideally, the melt pool will increase as the solid bed reduces in size until all is molten at the end of the compression zone. Finally, the molten materials are pumped against the die resistance to form the extrudate.

Twin-Screw Extruders

Twin-screw extruders have several advantages over single screw extruders, such as easier material feeding, high kneading, and dispersing capacities, less tendency to over-heat and shorter transit time. The first twin-screw extruders were developed in the late 1930's in Italy, with the concept of combination of the machine actions of several available devices into a single unit. As the name implies, twin-screw extruders utilize two screws usually arranged side by side. The use of two screws allows a number of different configurations and imposes different conditions on all zones of the extruder, from the transfer of material from the hopper to the screw, all the way to the metered pumping zone. In a twin-screw extruder, the screws can either rotate in the same (co-rotating extruder) or the opposite (counter-rotating extruder) direction. The counter-rotating designs are utilized when very high shear regions are needed since they subject materials to very high shear forces as the material is squeezed through the gap between the two screws when they come together. Also, the extruder layout is good for dispersing particles in a blend. Generally, counter-rotating twin-screw extruders suffer from disadvantages of potential air entrapment, high-pressure generation, and low maximum screw speeds and output. Co-rotating twin-screw extruders on the other hand are generally of the intermeshing design, and are thus self-wiping. Industrially they are the most important type of extruders and can be operated at high screw speeds to achieve high outputs, while maintaining good mixing and conveying characteristics. Unlike counter-rotating extruders, they generally experience lower screw and barrel wear as they do not experience the outward "pushing" effect due to screw rotation. These two primary types can be further classified as non-intermeshing and fully intermeshing. The fully intermeshing type of screw design is the most popular type used for twin-screw extruders. This design is self-wiping by itself, where it minimizes the non-motion and prevents localized overheating of materials within the extruder. The extruder operates by a first in/first out principle since the material does not rotate along with the screw. Non-intermeshing extruders, on the other hand, are often used for processing when large amounts of volatiles need to be removed and when processing highly viscous materials. Non-intermeshing extruders allow large volume de-volatization via a vent opening since the screws are positioned apart from one another. Non-intermeshing extruders are not susceptible to high torques generated while processing highly viscous materials for the same reasons.[48-49]

Liquid Dosage Forms

They are solutions or suspensions of drugs in suitable aqueous vehicles. Such types of dosage forms are usually employed to exert local action into the oral cavity and several antibacterial mouthwashes and mouth-freshener are commercially available for this purpose. The limitation associated with these liquid

dosage forms are that they are not readily retained or targeted to buccal mucosa and can deliver relatively uncontrolled amounts of drug throughout oral cavity. From the wide range of polymer solutions, chitosan represents the greatest binding, followed by methylcellulose, gelatin, carbopol and polycarbophil. Viscous liquids may be used to coat buccal surface either as protectants or as drug delivery vehicles to the mucosal surface. Dry mouth is treated with artificial saliva solutions that are retained on mucosal surfaces to provide lubrication. These solutions contain sodium CMC as bioadhesive polymer.[50]

Evaluation of Buccal Delivery Systems

Buccal adhesive drug delivery devices are subjected to the routine evaluation tests such as weight variation, thickness variation, friability, hardness, content uniformity, in vitro dissolution for tablets; tensile strength, film endurance, hygroscopicity etc. for films and patches; viscosity, effect of aging etc. for gels and ointments. They should also to be evaluated specifically for their bioadhesive strengths and permeabilities. Moisture absorption studies for buccal patches: The moisture absorption studies for the buccal patches give an indication about the relative moisture absorption capacities of polymers and an idea whether the buccal patches maintain their integrity after absorption of moisture. Moisture absorption studies have been performed in 5 % w/v agar in distilled water, which while hot was transferred to petri plates and allowed to solidify. Then six buccal patches from each formulation were selected and weighed. Buccal patches were placed in desiccator overnight prior to the study to remove moisture if any and laminated on one side with water impermeable backing membrane. Placed on the surface of the agar plate and incubated at 37° C for 2 hrs in incubator. The patches were weighed again and the percentage of the absorbed moisture was calculated using the formula:

$$\% \text{ Moisture absorbed} = \frac{\text{Final weight} - \text{Initial weight}}{\text{Initial weight}} \times 100$$

Swelling and erosion studies for buccal tablets: Swelling and erosion studies for buccal tablets were determined gravimetrically in phosphate buffer, of pH 6.6. The tablets were attached to pre-weighed glass supports using a cyanoacrylate adhesive sealant. The supports with tablets were immersed into the phosphate buffer at 37 °C. At pre-determined time intervals, the devices were removed from the media, blotted with tissue paper to remove excess water, and weighed. After determination of the wet weight, the tablets were dried at 40°C until constant mass. Swelling index (S.I) and erosion were determined gravimetrically according to the following equations.

$$\text{Swelling index (\%)} = \frac{ws - wd}{wd}$$

$$\text{Erosion (\% mass loss)} = \frac{\text{Original weight} - \text{remaining dry weight}}{\text{Original weight}} \times 100$$

Where W_d and W_s are the weights of dry and swollen devices, respectively.

Study of the surface pH : The bioadhesive buccal tablets were covered with 1ml of distilled water and allowed to swell for 1-2h at room temperature. The surface pH of the tablets or patches was measured by bringing the pH meter electrode in contact with the surface of the patch or tablet and allowing it to equilibrate for one minute.[51] Measurement of Mechanical Properties: Mechanical properties of the films has been reported and has been performed by using a microprocessor based advanced force gauze equipped with a motorized test stand (Ultra Test, Mecmesin, West Sussex, UK), equipped with a 25 kg load cell. Film strips with the dimensions of 60 x 10 mm were held between two clamps positioned at a distance of 3 cm. A cardboard has been attached on the surface of the clamp to prevent the film from being cut by the grooves of the clamp. During Published by "Tehran University of Medical Sciences" Measurement, the strips were pulled by the top clamp at a rate of 2.0 mm/s to a distance till the film broke. The force and elongation were measured when the films were broken. Results from film samples, which were broken at

end and not being present between the clamps were not included in observations. Measurements were run in six replicates for each formulation. The following equations were used to calculate the mechanical properties of the films.

$$\text{Tensile strength (kg.mm-2)} = \frac{\text{Force at break (kg)}}{\text{Initial cross sectional area of the sample (mm2)}}$$

$$\text{Elongation at break (\%.mm-2)} = \frac{\text{Increase in the length (mm)}}{\text{Original length}} \times \frac{100}{\text{Cross sectional area (mm2)}}$$

Bioadhesion measurement: Methods available for the measurement of bioadhesion are limited, and their selections depend on applicability, reproducibility, and providing useful information. It is unnecessary to compare the absolute values of different methods and is more meaningful to examine the relative bioadhesive performance using each technique. In addition, some factors, including saliva secretion, mastication, and mucus turnover that can markedly affect the adhesion strength and duration of in vivo adhesion are not present in in-vitro testing.[52]

In vitro bioadhesion measurement: In vitro bioadhesion measurement method was first reported in evaluation of the adhesive properties of patches using a microprocessor based on advanced force gauze equipment with porcine buccal membrane as a model tissue under simulated buccal conditions. Data collection and calculations were performed using the Data Plot software package of the instrument. Two parameters, namely the work of adhesion and peak detachment force were used to study the buccal adhesiveness of patches. The work of adhesion was determined from the area under force-distance curve while the peak detachment force was the maximum force required to detach the film from the tissue.

Determination of the residence time

Ex vivo residence time: Ex vivo residence time was determined using a modified USP disintegration apparatus. Nakamura et al. applied this method by taking the disintegration medium composed of 800 ml phosphate buffer of pH 6.6 maintained at 37 °C. The porcine buccal tissue was tied to the surface of a glass slab, vertically attached to the apparatus. The time which was taken for complete erosion or detachment of the tablet from the mucosal surface was recorded and considered as ex vivo residence time. In vivo residence time: The experiment was performed in eight healthy adult male volunteers, aged between 22 and 28 years. The volunteers were asked to record the residence time of the film on buccal mucosa in the oral cavity, which was taken as the time for the patch to dislodge completely from the buccal mucosa by continual sensation of the patch as well as the backing membrane. In vivo residence time was recorded in each case. Permeation studies: Buccal absorption/permeation studies must be conducted to determine the feasibility of this route of administration for a drug candidate and to determine the type of enhancer and its concentration which were to control the rate of permeation of drugs during the pre-formulation studies. Similar to an in vitro permeation study in transdermal drug delivery, different types of diffusion cells with certain modifications are suitable to conduct permeation studies, except that the buccal mucosa dissected from model animals are used as diffusion barriers for buccal delivery. Despite the careful endeavor in tissue preparation to maintain viability and integrity of oral mucosa, the loss of mucus layer on the surface of the oral mucosal membrane is unavoidable since the mucus network is extremely sensitive to environmental changes. These studies involve methods that would examine in vitro, ex vivo and/or in vivo buccal permeation profile and kinetics of absorption of the drug. Porcine buccal mucosa has been extensively used as an in vitro model to study the permeability of various diffusants and to assess their potentials to be delivered through the buccal route by using Franz diffusion cell. A mucosal tissue thickness of about 500 μm is recommended for in vitro transbuccal permeation studies since the epithelium remained the major permeability barrier for all diffusants at this thickness.[53] Buccal absorption test: A method for the measurement of the developed a method to measure the kinetics of the drug absorption by swirling a 25 ml sample of the test solution for 15 min by human volunteers followed by the expulsion of the solution. The amount of the drug remaining in the expelled volume is then determined to assess the amount of drug absorbed. The drawbacks of this method are inability to localize the drug solution within a specific site of

the oral cavity, accidental swallowing of a portion of the sample solution and the salivary dilution of the drug. Modified Beckett's test: The test has been modified by addition of phenol red as a marker for drug dilution by saliva secretion as well as for accidental swallowing of the drug solution. The 'Schurmann and Turner Test' has also been modified by taking a small sample of the solution in the oral cavity every few minutes, without removal of the residual solution. In this way he was able to study kinetics of the absorption in a single test for 15-20 minutes. Advantages of this type of test over the original absorption test are; corrections for saliva secretion, accidental swallowing and changes in pH can be made and that a complete absorption curve can be measured in one single test. Still, the disadvantage is the uncertainty with respect to the amount of drug that actually reaches the systemic circulation.[54-55]

Recent Developments In Buccal Drug Delivery Systems

Recent developments in buccal drug delivery systems, such as lipophilic gel, buccal spray and phospholipid vesicles have been recently proposed to deliver peptides via the buccal route. In particular, some authors proposed the use of cubic and lamellar liquid crystalline phases of glyceryl monooleate as buccal drug carrier for peptide drugs. A novel liquid aerosol formulation (Oralin, Generex Biotechnology) has been developed recently. Phospholipid deformable vesicles, transfersomes, have been recently devised for the delivery of insulin in the buccal cavity.[56]

Commercial Buccal Adhesive Drug Delivery Systems

Commercial formulations or formulations in clinical trials, intended for buccal delivery are presented in table. Only few formulations are available on market or under clinical evaluations which indicate the difficulty to develop drug delivery systems with clear efficacy and safety profiles.

Manufacturer	Product Present Status	Status
Generex Biotechnology Corporation	Insulin Buccal Spray ORALGEN (US) ORALIN (Canada) Heparin Buccal Delivery System Fentanyl Buccal Delivery Systems	Commercially available Clinical Trials Completed Clinical Trials Completed
Columbia Laboratories Inc.	Testosterone Buccal Tablet (Straint) Desmopressin Buccal Tablet	Commercially available Commercially available
Ergo Pharm	Androdiol Buccal Tablets (Cyclo-Diol SR) Norandrodiol Buccal Tablets (Cyclo-Nordiol SR)	Commercially available Commercially available
Cytokine Pharma Sciences Inc.	Pilocarpine Buccal Tablet (PIOLOBUC)	Commercially available
Britannia Pharmaceuticals Ltd	Prochlorperazine Buccal Tablet (Buccastem)	Commercially available
Pharmax Limited	Glyceryl Trinitrate (Suscard Buccal Tablet)	Commercially available
Cephalon, Inc.	Oral Transmucosal Fentanyl Citrate Solid Dosage Form (ACTIQ	Commercially available
Wyeth Pharma Ceuticals	Lorazepam Buccal Tablets (Temesta Expidet) Oxazepam Buccal Tablets (Seresta Expidet)	Commercially available Commercially available
IVAX Corporation	Estrogen Buccal Tablet	Under Phase III clinical trials
Regency Medical research	Vitamins Trans Buccal Spray	Commercially available
Leo Pharmaceuticals	Nicotine Mucoadhesive Tablet (Nicorette) Nicotine Chewing Gum (Nicotinell)	Commercially available Commercially available
Teijin Ltd.	Triamcinolone acetonide(Aftach)	Commercially available
Rhone-Poulenc Rorer	Prochlorperazine Bioadhesive Buccal Tablet (Tementil)	Commercially available

Reckitt Benckiser	Prochlorperazine Bioadhesive Buccal controlled release Tablet (Buccastem)	Commercially available
Reckitt Benckiser	Buprenorphine HCl Tablets (Subutex)	Commercially available
Reckitt Benckiser	Buprenorphine HCl & Naloxone HCl (Suboxane)	Commercially available
Ciba-Geigy	Methyltestosterone Buccal Tablets (Metandren)	Commercially available

CONCLUSION

Buccal adhesive systems offering numerable advantages in terms of accessibility, administration and withdrawal, retentivity, low enzymatic activity, economy and high patient compliance. Mucoadhesive buccal patches have been recently gained importance in drug delivery. The use of natural polymers is increasing in buccal patches formulation. A lot of work is still going on all around the world on mucoadhesive buccal patches using various natural polymers. This review is an effort to summarize the work done till date and to show the future pathway of mucoadhesive buccal patches preparation using natural polymer. The buccal mucosa offers several advantages over controlled drug delivery for extended periods of time. The mucosa is well supplied with both vascular and lymphatic drainage and first-pass metabolism in the liver and pre-systemic elimination in the gastrointestinal tract are avoided. The area is well suited for a retentive device and appears to be acceptable to the patient. With the right dosage form design and formulation, the permeability and the local environment of the mucosa can be controlled and manipulated in order to accommodate drug permeation. Mucoadhesive buccal patches have applications from different angles includes avoiding first-pass metabolism in the liver and pre-systemic elimination in the gastrointestinal tract. Buccal drug delivery is a promising area for continued research with the aim of systemic delivery of orally inefficient drugs as well as a feasible and attractive alternative for noninvasive delivery of potent peptide and protein drug molecules. However, the need for safe and effective buccal permeation absorption enhancers is a crucial component for a prospective future in the area of buccal drug delivery. With the great influx of new molecules stemming from drug research, mucoadhesive systems may play an increasing role in the development of new pharmaceuticals.

ACKNOWLEDGEMENT

REFERENCE

1. Tengamnuay, P. and Mitra, A.K., Bile salt-fatty acid mixed micelles as nasal absorption promoters of peptides. I. Effects of ionic strength. adjuvant composition, and lipid structure on the nasal absorption of [D-Arg2]Kyotorphin, Pharm. Res., 7:127-133, 1990.

2. Vyas K, Shiv G.K. Buccal patches: Novel advancement in mucoadhesive drug delivery system. Indo American J. Pharm. Res. 2015; 5(2): 727-740.

3. Shao, Z. and Mitra, A.K., Bile salt fatty acid mixed micelles as nasal absorption promoters. III. Effects on nasal transport and enzymatic degradation of acyclovir prodrugs, Pharm. Res., 11:243-250, 1994.

4. Soyani, A.P. and Chien, Y.W., Systemic delivery of peptides and proteins across absorptive mucosae, Crit. Rev. Therap. Drug Carrier Systems, 13:85-184, 1996.

5. Shojaei AH. A systemic drug delivery via the buccal mucosal route. Pharm. Tech. 2001: 70-81.

6. Verma S, Kaul M, Rawat A, Saini S. An overview on buccal drug delivery system Ind. J .Pharm. Sci. Res. 2011; 2(6): 1303-1321.

7. Patel RS, and Poddar SS. Development and characterization of mucoadhesive buccal patches of salbutamol sulphate, Curr. Drug Deliv., 2009, 6, 140-144.

8. Satyabrata B, Ellaiah P, Choudhury R, Murthy KVR, Bibhutibhusan P and Kumar MS, Design and evaluation of Methotrexate buccal mucoadhesive patches, Inter. J. Pharm. Biomed.Sci., 2010, 1(2), 3136.

9. S .C. Chattarajee, R.B. Walker, (1995), Penetration enhancer classification, in: E.W. Smith, H.I. Maibach (Eds.), Percutaneous Penetration Enhancement, CRC Press, Boca Raton, FL, pp. 1–4.

10. Aungst, (1994), Permeability and metabolism as barriers to transmucosal delivery of peptides and proteins. In: D.S.Hsieh (Ed.), Drug Permeation Enhancement. Theory and Applications, Marcel Dekker, New York, 323-343.

11. Pokhariyal T., Singh V. K., Tiwari A. K., "Formulation And Evaluation Of Buccal Patch Of Selective A1-Receptor Blocker Prazosin HCL" Indo American Journal of Pharm. Research.2013:3(2). 4293-4303

12. Pramodkumar T.M., Shivakumar H.G., Desai K.G., Oral Transmucosal Drug Delivery Systems, Indian Drugs, 2004, 41(2).

13. Lalla J.K. and Gurnancy R.A., Polymers for mucosal Delivery-Swelling and Mucoadhesive Evaluation, Indian Drugs, 2002, 39(5).

14. Gandhi SD, Pandya PR, Umbarkar R, Tambawala T and Shah MA. Mucoadhesive drug delivery system- an unusual maneuver for site specific drug delivery system, Inter. J. Pharm. Sci., 2011, 851- 872.

15. Patil SB, Murthy RSR, Mahajan HS, Wagh RD and Gattani SG. Mucoadhesive polymers: means of improving drug delivery, Pharm. Times, 2006, 38 (4), 25-28.

16. Shojaei Amir H, Buccal Mucosa As A Route For Systemic Drug Delivery: A Review;J Pharm Pharmaceut Sci (www.ualberta.ca/~csps) 1998;1 (1):15-30.

17. Amir H Shojaei, Buccal Mucosa As A Route For Systemic Drug Delivery, Journal of Pharmacy and Pharmaceutical Sciences, 1998,1(1), 15-30.

18. Salamat-Miller N, Chittchang M, Johnston TP, The use of mucoadhesive polymers in buccal drug delivery, Advance Drug Delivery Review, Nov 2005, 57(11), 16661691.

19. Sevda Senel, Mary Kremer, Katalin Nagy and Christopher Squier, Delivery of Bioactive Peptides and Proteins Across Oral (Buccal) Mucosa, Current Pharmaceutical Biotechnology, 2001; 2: 175-186.

20. Patel KV, Patel ND, Dodiya HD, Shelat PK. Buccal bioadhesive drug delivery system: An Overview. Int J Pharm Bio Arch 2011;2(2): 600-9.

21. Amir H, et al, Systemic drug delivery via the buccal mucosal route, Pharmaceutical technology, 2001, 1-27. 4.

22. Pramod Kumar TM et al, Oral transmucosal drug delivery systems, Indian drug, 2004, 41(2), 63-1.

23. Nazila SM, Montakarn C, Thomas PJ. The use of mucoadhesive polymers in buccal drug delivery. Advanced Drug Delivery Reviews. 2005; 57:1666– 1691.

24. Gandhi BR, and Robinson JR. (1988). Bioadhesion in drug delivery. Ind. J. Pharm. Sci. 1988; 50:145−152.

25. Boddupalli BM, Mohammad ZNK, Nath RA, Banji D. mucoadhesive drug delivery system an overview. J. Adv. Pharm. Tech. Res. 2010; 1(4): 381-387.

26. Gandhi SD, Priyanka RP, Rahul U, Tambawala T, Shah MA. Mucoadhesive drug delivery systems-An unusual maneuver for site specific drug delivery system. An Int. J .Pharm. Sci. ISSN: 09767908: 851-871.

27. Satheesh Madhav NV, Ashok KS, Pragati S, Kuldeep S. Orotransmucosal drug delivery systems: A review. Journal of Controlled Release. 2009; 140: 2–11.

28. Pharmaceutics the science of dosage form Design 2nd edition edited by M. E. Aulton. Published by Harcourt publishers Limited. 2002; 198-200.

29. Edsman K, et al, Pharmaceutical applications of mucoadhesion for the non-oral routes, Journal of pharmacy & pharmacology, 2005, 57, 3-19.

30. Steward A et al, The Effect of Enhancers on the Buccal Absorption of Hybrid (BDBB) Alpha Interferon, Int. J. Pharm, 104, 1994, 145– 149.

31. Deirdre Faye Vaughan, Pharmacokinetics of Albuterol and Butorphanol Administered Intravenously and via a Buccal Patch, A Thesis Submitted to the office of Graduate Studies of Texas A&M University In Partial Fulfillment of the requirements for the Degree of Master of Science, May 2003.

32. Wise Donald L, Handbook of Pharmaceutical controlled release technology: 255-265.

33. Yajaman S., Bandyopadhyay A.K., Buccal bioadhesive drug delivery- A promising option for orally less efficient drugs, Journal of Controlled Release, 2006;114:15–40.

34. Jain N.K., Controlled and novel drug delivery; 65-75; 371-377.

35. Edgar W.M., Saliva: its secretion, composition and functions, Br. Dent. J, 1992; 172:305-312,

36. Indian Journal of Pharmaceutical Science, July-Aug. 2004; 66 (4): 371-536:556-562.

37. www.controlled drugdelivery.com

38. Ahuja RP, Khar JA. Mucoadhesive drug delivery systems. Drug Dev. Ind. Pharm. 1997; 23:489-515

39. Gu JM, Robinson JR, Leung SHS. Binding of acrylic polymers to mucin/epithelial surfaces: structureproperty relationships. Crit. Rev. Ther. Drug Carr. Syst. 1998; 5:21-67.

40. Khanvilkar K, Donovan MD, Flanagan DR. Drug transfer through mucus. Adv. Drug Del. Rev. 2001; 48 (2-3):173-193.

41. Clark MA, Hirst B, Jepson M. Lectin-mediated mucosal delivery of drugs and microparticles. Adv. Drug Deliv. Rev. 2000; 43:207-223.

42. Ponchel G, Irache JM. Specific and nonspecific bioadhesive particular systems for oral delivery to the gastrointestinal tract. Adv. Drug Del. Rev. 1998; 34 (2-3):191-219.

43. Clark MA, Hirst BH, Jepson MA. Lectin mediated mucosal delivery of drugs and microparticles. Adv. Drug Del. Rev. 2000; 43 (2-3):207-223.

44. Inman LR, Cantey JR. Specific adherence of Escherichia coli (strain RDEC-1) to membranous (M) cells of the Peyer's patch in Escherichia coli diarrhea in the rabbit, J. Clin. Invest. 1983; 71:1-8.

45. Sanford BA, Thomas VL, Ramsay MA. Binding of staphylococci to mucus in vivo and in vitro. Infect. Immun. 1989; 57:3735-3742.

46. Bernkop-Schnürch A, Gabor F, Szostak M and Lubitz W. An adhesive drug delivery system based on K99-fimbriae. Eur. J. Pharm Sci. 1995; 3:293-299.

47. Leitner V, Walker GA, Bernkop-Schnürch. Thiolated polymers: evidence for the formation of disulphide bonds with mucus glycoproteins. Eur. J. Pharm. Biopharm, 2003; 56:207-214.

48. Farheen F, Bharadwaj S, Jat R.C, Arjariya P, Sharma G, Ratnak D, Khan I, Tiwari R, Rathore S.A. Buccal Patches: A Review. Indo American J. Pharm. Res. 2013; 3(4):3324-3335.

49. Bernkop-Schnürch A. Thiomers: a new generation of mucoadhesive polymers, Adv. Drug Deliv. Rev. 2005; 57:1569-1582.

50. Lee J, Kellaway IW. Buccal permeation of (D-Ala2, DLeu5) enkephalin from liquid crystalline phases of glyceryl monooleate. Int. J. Pharm. 2000; 195:35-38.

51. Bottenberg P, Cleymaet R, Muynek CD, Remon JP, Coomans D, Slop D. Development and testing of bioadhesive, fluoride containing slow-release tablets for oral use. J. Pharm. Pharmacol. 1991; 43:457-464.

52. Mortazavi SA, Aboofazeli R. Preparation and in vitro assessment of various mucosa-adhesive films for buccal delivery. DARU J. Pharm. Sci. 2000; 8(1-2):9-18.

53. Upendra K, Ravichandran M, Indiran PS, Xiaoling L, Bhaskara J. Porcine buccal mucosa as an in vitro model: relative contribution of epithelium and connective tissue as permeability barriers. J.Pharm.Sci. 2009; 98:471-483.

54. Lee J, Kellaway IW. Buccal permeation of (D-Ala2, DLeu5) enkephalin from liquid crystalline phases of glyceryl monooleate. Int. J. Pharm. 2000; 195:35-38.

55. Modi G. Evolving role of oral insulin in the treatment of diabetes using a novel rapidmist system. Diabetes Metab. Res. Rev. 2002; 18:38-42.

56. Pakhariyal T, Singh V.M, Tiwari A.J. Drug delivery via the buccal patch- A Novel Approach. Indo American J. Pharm. Res. 2013; 3(5): 3466-3483.

Correspondence Author:

Krishnarajan D[*]

JKK Munirajah College of Pharmacy, Komarapalayam-638183, Namakkal, Tamilnadu, India

Cite This Article: Krishnarajan D, Jithin TG; Nikhi, V; Archana, M Nair1; Asmina, Sherin; Sneha, Thomas and M, Purushothaman (2016), "Recent trend and approaches of buccal drug delivery system – A review", *Pharmacophore*, Vol. 7 (5), 374-396.