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Overview on Buccal Drug Delivery Systems

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Abstract:
The buccal region of the oral cavity is an attractive target for administration of the drug of choice, particularly in overcoming deficiencies associated with the latter mode of administration. Problems such as high first-pass metabolism and drug degradation in the gastrointestinal environment can be circumvented by administering the drug via the buccal route. Moreover, rapid onset of action can be achieved relative to the oral route and the formulation can be removed if therapy is required to be discontinued. It is also possible to administer drugs to patients who unconscious and less co-operative. To prevent accidental swallowing of drugs adhesive mucosal dosage forms were suggested for oral delivery, which included adhesive tablets, adhesive gels, adhesive patches and many other dosage forms with various combinations of polymers, absorption enhancers. Natural polymers have recently gained importance in pharmaceutical field. Mucoadhesive polymers are used to improve drug delivery by enhancing the dosage form's contact time and residence time with the mucous membranes. Mucoadhesion may be defined as the process where polymers attach to biological substrate or a synthetic or natural macromolecule, to mucus or an epithelial surface. When the biological substrate is attached to a mucosal layer then this phenomenon is known as mucoadhesion. The substrate possessing bioadhesive polymer can help in drug delivery for a prolonged period of time at a specific delivery site. The studies of Mucoadhesive polymers provide a good approach of mucoadhesion and some factors which have the ability to affect the mucoadhesive properties of a polymer. Both natural and synthetic polymers are used for the preparation of mucoadhesive buccal patches. In addition to this, studies have been conducted on the development of controlled or slow release delivery systems for systemic and local therapy of diseases in the oral cavity.

Key word: *Mucoadhesive buccal patch, Natural polymer, Bioadhesive polymers, Buccal formulations, Buccal Mucosa, first-pass effect, permeation enhancers.*

INTRODUCTION:

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[1,2]. 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[3]. 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[4].

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:

1. Buccal drug delivery systems
2. Sublingual drug delivery systems
3. Rectal drug delivery systems
4. Vaginal drug delivery systems
5. Ocular drug delivery systems
6. Nasal drug delivery systems

Chitosan is one of the natural polymers, which is being widely used. Chitosan is composed of glucosamine and N-acetyl glucosamine which are also constituent of mammalian tissue. It is non toxic, biocompatible and biodegradable polymer. This polymer is considered for its film as well as matrix forming abilities. Chitosan is also used as enzyme inhibitor as well as permeation enhancer properties[5].

Table 1: Buccal dosage forms formulated using natural polymer

Sl	Natural	Drug	Dosage form
1.	Chitosan	Propranolol	Buccal film[6]
		Metoprolol tartarate	Bioadhesive bilayered
		Cetylpyridinium	Mucoadhesive buccal
		Curcumin	Mucoadhesive buccal
		Propranolol	Mucoadhesive buccal
		Resperidone	Mucoadhesive buccal
		Salbutamol sulphate	Mucoadhesive buccal
		Verapamil HCL,	Mucoadhesive buccal
2.	Gelatin	Sumatriptan succinate	Mucoadhesive bilayered
		Aceclofenac	Mucoadhesive buccal
3.	Guar gum	Diltiazem	Mucoadhesive buccal
4.	Sodium alginate	Diltiazem	Mucoadhesive buccal
		Methotrexate	Buccal mucoadhesive
5.	Xanthan	Tizanidine	Mucoadhesive buccal

Advantages of buccoadhesive drug delivery[18]:

Drug administration via the buccoadhesive drug delivery offers several advantages such as:

1. Drug is easily administered and extinction of therapy in emergency can be facilitated.
2. Drug release for prolonged period of time.
3. In unconscious and trauma patient's drug can be administered.
4. Drugs bypass first pass metabolism so increases bioavailability.
5. Some drugs that are unstable in acidic environment of stomach can be administered by buccal delivery.
6. Drug absorption by the passive diffusion.
7. Flexibility in physical state, shape, size and surface.

8. Maximized absorption rate due to close contact with the absorbing membrane.
9. Rapid onset of action.

Limitations of buccoadhesive drug delivery [19]:

There are some limitations of buccal drug delivery system such as

1. Drugs which are unstable at buccal pH cannot be administered.
2. Drugs which have a bitter taste or unpleasant taste or an obnoxious odor or irritate the mucosa cannot be administered by this route.
3. Drug required with small dose can only be administered.
4. Those drugs which are absorbed by passive diffusion can only be administered by this route.
5. Eating and drinking may become restricted.

Various mucoadhesive polymers can broadly be categorized as follow[20]:

(I) Synthetic polymers:

1. Cellulose derivatives (Methylcellulose (MC), Ethyl cellulose (EC), Hydroxy ethyl cellulose (HEC), Hydroxyl propyl cellulose (HPC), Hydroxy propyl methylcellulose (HPMC), Sodium carboxy methylcellulose (NaCMC).
2. Poly (Acrylic acid) polymers (Carbomers, Polycarbophil).
3. Poly hydroxyl ethyl methylacrylate.
4. Poly ethylene oxide.
5. Poly vinyl pyrrolidone.
6. Poly vinyl alcohol.

(II) Natural polymers:

1. Tragacanth
2. Sodium alginate
3. Guar gum
4. Xanthan gum
5. Soluble starch
6. Gelatin
7. Chitosan

Oral mucosal sites:

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

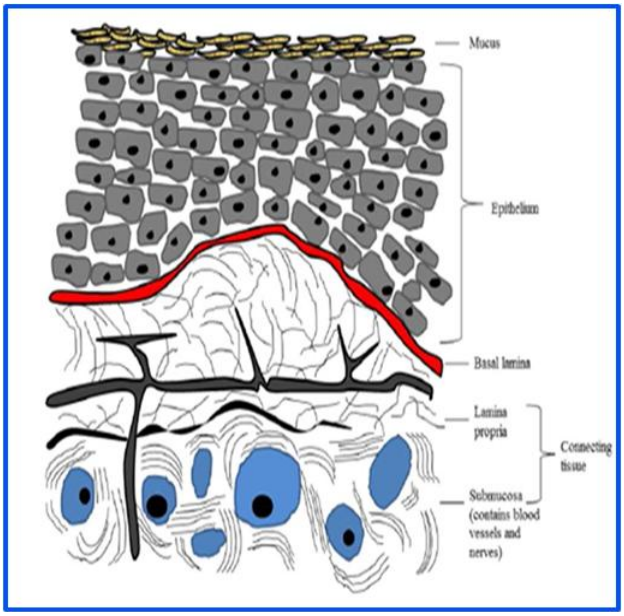
1. Sublingual delivery: is the administration of the drug via the sublingual mucosa (the membrane of the ventral surface of the tongue and the floor of the mouth to the systemic circulation.

2. Buccal delivery: is the administration of drug via the buccal mucosa(the lining of the cheek)to the systemic circulation.

3. Local delivery: 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 [21,22].

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 composition of the epithelium varies depending on the site in the oral cavity. 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.



Structure of buccal mucosa

Novel buccal dosage forms:

The novel type buccal dosage forms include buccal adhesive tablets, patches, films, semisolids (ointments and gels) and powders.

A. Buccal mucoadhesive tablets: Buccal mucoadhesive tablets are dry dosage forms that have to be moistened prior to placing in contact with buccal mucosa. Example: a double layer tablet, consisting of adhesive matrix layer of HPC and polyacrylic acid with an inner core of cocoa butter containing insulin and a penetration enhancer (sodium glycocholate).

B. Patches and Films: Buccal patches consists of two laminates, with an aqueous solution of the adhesive polymer being cast onto an impermeable backing sheet, which is then cut into the required oval shape. A novel mucosal adhesive film called "Zilactin" - consisting of an alcoholic solution of HPC and three organic acids. The film which is applied to the oral mucosal can be retained in place for at least 12 hrs even when it is challenged with fluids.

C. Semisolid Preparations (Ointments and Gels): Bioadhesive gels or ointments have less patient acceptability than solid bioadhesive dosage forms, and most of the dosage forms are used only for localized drug therapy within the oral cavity. One of the original oral mucoadhesive delivery systems -"orabase"- consists of finely ground pectin, gelatin and NaCMC dispersed in a poly (ethylene) and a mineral oil gel base, which can be maintained at its site of application for 15-150 mins.

D. Powders: HPC and beclomethasone in powder form when sprayed on to the oral mucosa of rats, a significant increase in the residence time relative to an oral solution is

seen, and 2.5% of beclomethasone is retained on buccal mucosa for over 4 hrs[23].

Structure and Design of Buccal Dosage Form:

Buccal Dosage form can be of;

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

2. 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.

Buccal absorption: Buccal absorption leads systemic or local action via buccal mucosa.

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[24].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.

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 [25].

1. 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.

2. Environmental Factors:

a. 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.

b. 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.

c. **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.

Composition of buccal patches:

A. Active ingredient.

B. Polymers (adhesive layer): HEC, HPC, polyvinyl pyrrolidone(PVP), polyvinyl alcohol (PVA), carbopol and other mucoadhesive polymers.

C. Diluents: Lactose DC is selected as diluents for its high aqueous solubility, its flavoring characteristics, and its physico-mechanical properties, which make it suitable for direct compression. other example : microcrystalline starch and starch.

D. Sweetening agents: Sucralose, aspartame, Mannitol, etc.

E. Flavoring agents: Menthol, vanillin, clove oil, etc.

F. Backing layer: EC etc.

G. Penetration enhancer: Cyano acrylate, etc

H. Plasticizers: PEG-100, 400, propylene glycol, etc

METHODS TO INCREASE DRUG DELIVERY VIA BUCCAL ROUTE

Absorption enhancers [26]: Absorption enhancers have demonstrated their effectiveness in delivering high molecular weight compounds, such as peptides, that generally exhibit low buccal absorption rates. These may act by a number of mechanisms, such as increasing the fluidity of the cell membrane, extracting inters/intracellular lipids, altering cellular proteins or altering surface mucine. The most common absorption enhancers are azone, fatty acids, bile salts and surfactants such as sodium dodecyl sulfate. Solutions/gels of chitosan were also found to promote the transport of mannitol and fluorescent-labelled dextrans across a tissue culture model of the buccal epithelium while Glyceryl mono oleates were reported to enhance peptide absorption by a co-transport mechanism.

Prodrugs [26]: Hussain et al delivered opioid agonists and antagonists in bitterless prodrug forms and found that the drug exhibited low bioavailability as prodrug. Nalbuphine and naloxone bitter drugs when administered to dogs via the buccal mucosa, the caused excess salivation and swallowing. As a result, the drug exhibited low bioavailability. Administration of nalbuphine and naloxone in prodrug form caused no adverse effects, with bioavailability ranging from 35 to 50% showing marked improvement over the oral bioavailability of these compounds, which is generally 5% or less.

pH [26]: Shojaei et al evaluated permeability of acyclovir at pH ranges of 3.3 to 8.8, and in the presence of the absorption enhancer, sodium glycocholate. The in vitro permeability of acyclovir was found to be pH dependent with an increase in flux and permeability coefficient at both pH extremes (pH 3.3 and 8.8), as compared to the mid-range values (pH 4.1, 5.8, and 7.0).

Patch Design[26]: Several in vitro studies have been conducted regarding on the type and amount of backing materials and the drug release profile and it showed that both are interrelated. Also, the drug release pattern was different between single-layered and multi-layered patches.

BIOADHESION [27-29]:

'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.

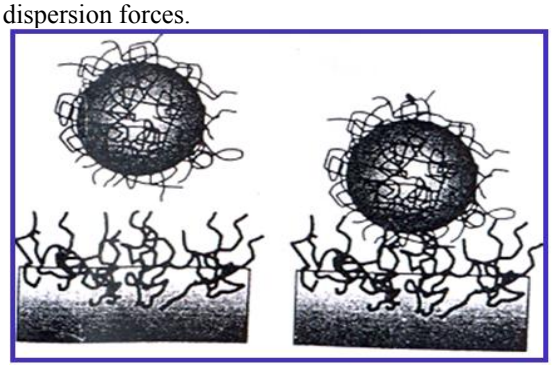
1. Bioadhesion between biological layers without involvement of artificial materials. Cell diffusion and cell aggregation are good examples.
2. Bioadhesion can be represented by cell adhesion into culture dishes or adhesion to a variety of substances including metals, woods and other synthetic materials.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

Mechanism of bioadhesion [30-32, 29]:

For bioadhesion to occur, three stages are involved:

1. 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.
2. Penetration of the bio-adhesive into the tissue takes place.
3. 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.



Inter penetration of bioadhesive and mucus polymer chain.

Theories of Bioadhesion or Mucoadhesion [1,27, 28, 30, 31]:

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

a) Wetting Theory: Wetting theory is predominantly applicable to liquid bioadhesive systems and analyzes adhesive and contact behaviour 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 $W_A = \gamma_A + \gamma_B - \gamma_{AB}$

Where, A and B refers to the biological membrane and the bioadhesive formulation respectively.

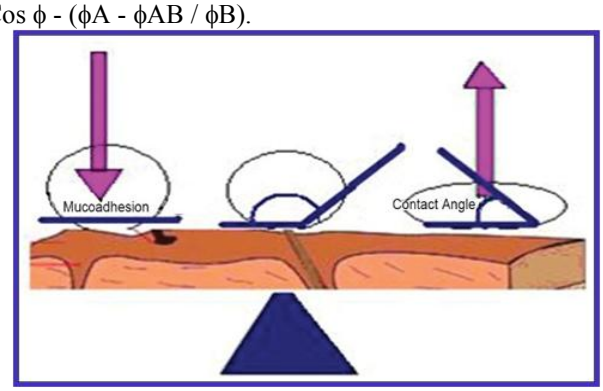
The work of cohesion is given by $Wc = 2\gamma_A$ or γ_B

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

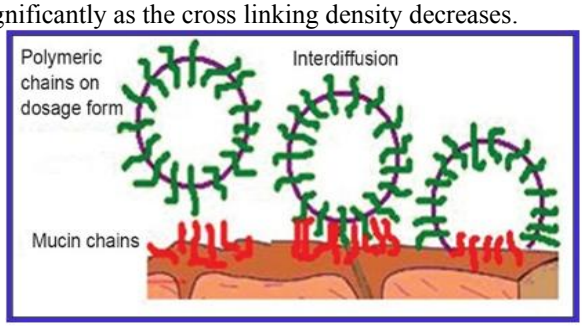
$S_{B/A} = \gamma_A - (\gamma_B + \gamma_{AB})$

$S_{B/A}$ 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 ϕ - (ϕA - ϕAB / ϕB).



b) 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.



Secondary interaction between mucoadhesive device and mucus.

c)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.

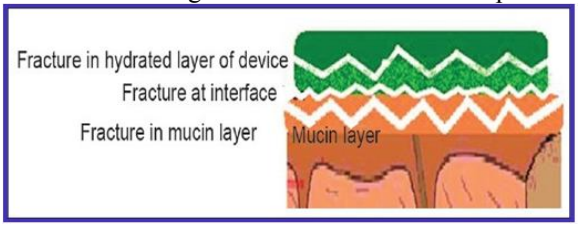
d) Fracture Theory: According to Fracture theory of adhesion is related to separation of two surfaces after adhesion. The fracture strength is equivalent to adhesive strength as given by,

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

Where: E= Young's module of elasticity

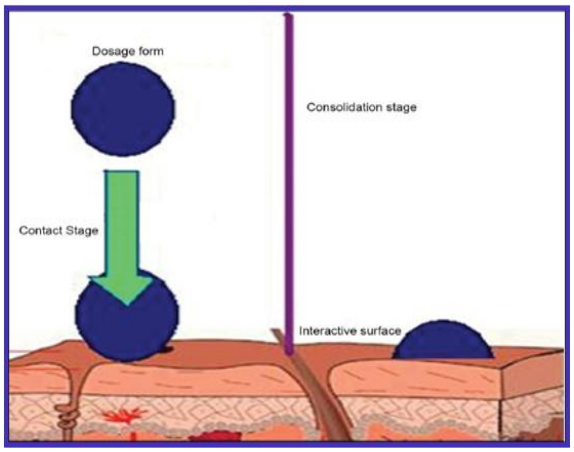
ε = Fracture energy

L= Critical crack length when two surfaces are separated.



Fractures occurring for Mucoadhesion.

e) 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.



The process of consolidation.

BASIC COMPONENTS OF BUCCAL DRUG DELIVERY SYSTEM

The basic components of buccal drug delivery system are

1. Drug substance
2. Bio adhesive polymers
3. Backing membrane
4. Permeation enhancers

1. 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 [33].

- 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.

2. 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 [34]. Bio adhesive polymers are from the most diverse class and they have considerable benefits upon patient health care and treatment [35]. 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 [36].

An ideal polymer for buccoadhesive drug delivery systems should have following Characteristics [37,38].

- 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.

The commonly used as Bio adhesive polymers in pharmaceutical applications are in Table 2.

Table 2: Mucoadhesive Polymers used in the Oral Cavity [39]

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-co-acrylamide)	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 oramucosal delivery of LHRH - device containing a fast release and a slow release layer.
CMC, Carbopol 974P, Carbopol EX-55, Pectin (low viscosity), Chitosan chloride	Mucoadhesive gels for intraoral delivery.

3. 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 [40].

4. 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.

Mechanisms of action of permeation:

1) Changing mucus rheology:

- By reducing the viscosity of the mucus and saliva overcomes this barrier.

2) 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.

3) 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.

4) Increasing the thermodynamic activity of drugs:

- Some enhancers increase the solubility of drug there by alters the partition coefficient.

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

Manufacturing methods of buccal patches/ films:

Manufacturing processes involved in making mucoadhesive buccal patches/films, namely solvent casting, hot melt extrusion and direct milling.

1. Solvent casting: In this method, all patch excipients including the drug co-dispersed in an organic solvent and coated onto a sheet of release liner. After solvent evaporation a thin layer of the protective backing material is laminated onto the sheet of coated release liner to form a laminate that is die-cut to form patches of the desired size and geometry[41].

2. Direct milling: In this, patches are manufactured without the use of solvents. Drug and excipients are mechanically mixed by direct milling or by kneading, usually without the presence of any liquids. After the mixing process, the resultant material is rolled on a release liner until the desired thickness is achieved. The backing material is then laminated as previously described[42]. While there are only minor or even no differences in patch performance between patches fabricated by the two processes, the solvent-free process is preferred because there is no possibility of residual solvents and no associated solvent-related health issues[43].

Hot melt extrusion of films*:* In hot melt extrusion blend of pharmaceutical ingredients is molten and then forced through an orifice to yield a more homogeneous material in different shapes such as granules, tablets, or films. Hot melt extrusion has been used for the manufacture of controlled release matrix tablets, pellets and granules, as well as oral disintegrating films. However, only a hand full articles

have reported the use of hot melt extrusion for manufacturing mucoadhesive buccal films. **Table 3** gives suitable polymers and drugs for buccal delivery.

EVALUATIONS OF BUCCAL PATCH:

1. Surface pH: Buccal patches are left to swell for 2 hrs on the surface of an agar plate. The surface pH is measured by means of a pH paper placed on the surface of the swollen patch.[44]

2. Thickness measurements: The thickness of each film is measured at five different locations (centre and four corners) using an electronic digital micrometer [45].

3. Swelling study: Buccal patches are weighed individually (designated as W1), and placed separately in 2% agar gel plates, incubated at 37°C ± 1°C, and examined for any physical changes. At regular 1- hr time intervals until 3 hours, patches are removed from the gel plates and excess surface water is removed carefully using the filter paper[46] . The swollen patches are then reweighed (W2) and the swelling index (SI) is calculated using the following formula.

$$SI = \frac{(W2-W1)}{W1} \times 100$$

4. Folding endurance: The folding endurance of patches is determined by repeatedly folding 1 patch at the times without breaking[47].

5. Thermal analysis study: Thermal analysis study is performed using differential scanning calorimeter (DSC).

6. Morphological characterization: Morphological characters are studied by using scanning electron microscope (SEM).

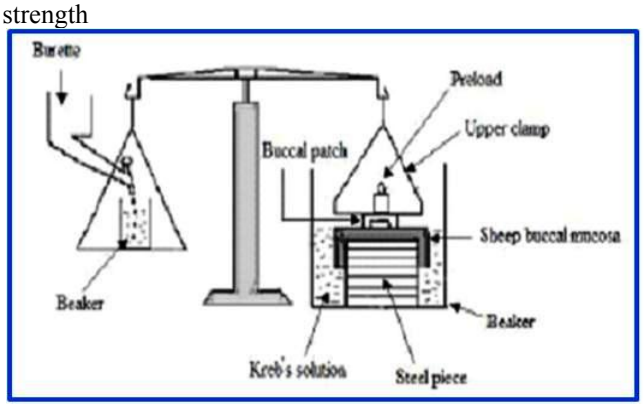
7. Water absorption capacity test: Circular Patches, with a surface area of 2.3 cm^2 are allowed to swell on the surface of agar plates prepared in simulated saliva (2.38 g Na2HPO4, 0.19 gKH2PO4, and 8 g NaCl per litter of distilled water adjusted with phosphoric acid to pH 6.7), and kept in an incubator maintained at 37°C ± 0.5°C. At various time intervals (0.25, 0.5, 1, 2, 3, and 4 hours), samples are weighed (wet weight) and then left to dry for 7 days in a desiccators over anhydrous calcium chloride at room temperature then the final constant weights are recorded. Water uptake (%) is calculated using the following equation.

Water uptake (%)= (Ww – Wi)/Wf x 100

Where,

Ww is the wet weight and Wf is the final weight. The swelling of each film is measured [48]

8. Ex-vivo bioadhesion test: The fresh sheep mouth separated and washed with phosphate buffer (pH 6.8). A piece of gingival mucosa is tied in the open mouth of a glass vial, filled with phosphate buffer (pH 6.8). This glass vial is tightly fitted into a glass beaker filled with phosphate buffer (pH 6.8, 37°C ± 1°C) so it just touched the mucosal surface. The patch is stuck to the lower side of a rubber stopper with cyano acrylate adhesive. Two pans of the balance are balanced with a 5-g weight. The 5-g weight is removed from the left hand side pan, which loaded the pan attached with the patch over the mucosa. The balance is kept in this position for 5 min of contact time. The water is added slowly at 100 drops/min to the right-hand side pan until the patch detached from the mucosal surface.[49] The weight, in grams, required to detach the patch from the mucosal surface provided the measure of mucoadhesive strength



9. In vitro drug release: The United States Pharmacopeia (USP) XXIII-B rotating paddle method is used to study the drug release from the bilayered and multilayered patches. The dissolution medium consisted of phosphate buffer pH 6.8. The release is performed at 37°C ± 0.5°C, with a rotation speed of 50 rpm. The backing layer of buccal patch is attached to the glass disk with instant adhesive material. The disk is allocated to the bottom of the dissolution vessel. Samples (5 ml) are withdrawn at predetermined time intervals and replaced with fresh medium. The samples filtered through whatman filter paper and analyzed for drug content after appropriate dilution. The in-vitro buccal permeation through the buccal mucosa (sheep and rabbit) is performed using Keshary-Chien /Franz type glass diffusion cell at 37°C± 0.2°C. Fresh buccal mucosa is mounted between the donor and receptor compartments. The buccal patch is placed with the core facing the mucosa and the compartments clamped together.

10. Permeation study of buccal patch: The receptor compartment is filled with phosphate buffer pH 6.8, and the hydrodynamics in the receptor compartment is maintained by stirring with a magnetic bead at 50 rpm. Samples are withdrawn at predetermined time intervals and analyzed for drug content [50].

11. Ex-vivo mucoadhesion time: The ex-vivo mucoadhesion time performed after application of the buccal patch on freshly cut buccal mucosa (sheep and rabbit). The fresh buccal mucosa is tied on the glass slide, and a mucoadhesive patch is wetted with 1 drop of phosphate buffer pH 6.8 and pasted to the buccal mucosa by applying a light force with a fingertip for 30 secs. The glass slide is then put in the beaker, which is filled with 200 ml of the phosphate buffer pH 6.8, is kept at 37°C ± 1°C. After 2 minutes, a 50-rpm stirring rate is applied to simulate the buccal cavity environment, and patch adhesion is monitored for 12 hrs. The time for changes in color, shape, collapsing of the patch, and drug content is noted[51, 52].

12. Measurement of mechanical properties: Mechanical properties of the films (patches) include tensile strength and elongation at break is evaluated using a tensile tester. Film strip with the dimensions of 60 x 10 mm and without any visual defects cut and positioned between two clamps separated by a distance of 3 cm. Clamps designed to secure the patch without crushing it during the test, the lower clamp held stationary and the strips are pulled apart by the

upper clamp moving at a rate of 2 mm/sec until the strip break. The force and elongation of the film at the point when the strip break is recorded.

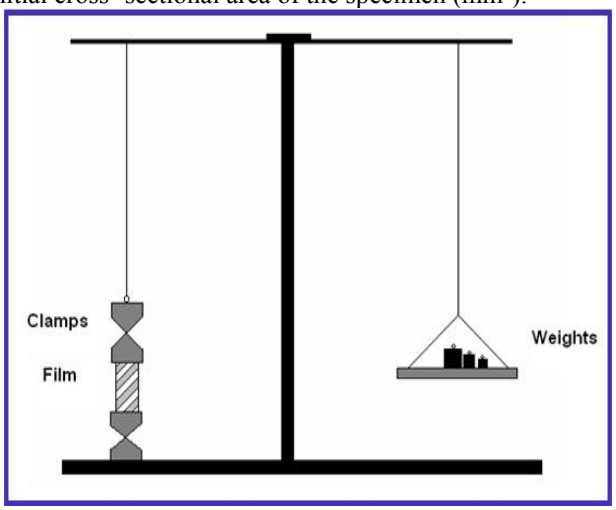
The tensile strength and elongation at break values are calculated using the formula.

$T = m \times g / b \times t$ Kg/mm^2

Where,

M - is the mass in gm, g - is the acceleration due to gravity 980 cm/sec ^{2}, B - is the breadth of the specimen in cm, T - is the thickness of specimen in cm

Tensile strength (kg/mm^2) is the force at break (kg) per initial cross- sectional area of the specimen (mm^2).



Modified tensile strength tester.

It measures the strength of patches as diametric tension or tearing force. It is measured in g or N/m^2. It shows the strength of patches to various stresses and can be measured by using simple calibrated vertical spring balance.

13. Stability study in human saliva [53, 54]: The stability study of optimized bilayered and multilayered patches is performed in human saliva. The human saliva is collected from humans (age 18-50years). Buccal patches are placed in separate petridishes containing 5ml of human saliva and placed in a temperature controlled oven at 37°C ± 0.2°C for 6 hours. At regular time intervals (0, 1, 2, 3, and 6 hrs), the dose formulations with better bioavailability are needed. Improved methods of drug release through transmucosal and transdermal methods would be of great significance, as by such routes, the pain factor associated with parenteral routes of drug administration can be totally eliminated. Buccal adhesive systems offer innumerable advantages in terms of accessibility, administration and withdrawal, retentively, low enzymatic activity, economy and high patient compliance. Adhesion of buccal adhesive drug delivery devices to mucosal membranes leads to an increased drug concentration gradient at the absorption site and therefore improved bioavailability of systemically delivered drugs. In addition, buccal adhesive dosage forms have been used to target local disorders at the mucosal surface (e.g., mouth ulcers) to reduce the overall dose required and minimize side effects that may be due to systemic administration of drugs. Researchers are now looking beyond traditional polymer networks to find other innovative drug transport systems. Currently solid dosage forms, liquids and gels applied to oral cavity are commercially successful. The future direction of buccal adhesive drug delivery lies in vaccine formulations and delivery of small proteins/peptide.

CONCLUSION:

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 polymer. 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.

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