

DEVELOPMENT OF BUCCAL DRUG DELIVERY SYSTEM BASED ON MUCOADHESIVE POLYMERS

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ABSTRACT: This review highlights the development of mucoadhesive polymers in buccal drug delivery. Buccal delivery of the desired drug using mucoadhesive polymers has been the subject of interest since the early 1980s. Advantages associated with buccal drug delivery have rendered this route of administration useful for a variety of drugs. This article covers the anatomy of oral mucosa, mechanism of drug permeation, characteristics and properties of the desired polymers, new generation of the mucoadhesive polymers.

KEYWORDS: Bioadhesion, Mucoadhesion, Buccal drug delivery, Thiolated polymers.

INTRODUCTION

Mucoadhesive polymers are synthetic or natural macromolecules which are capable of attaching to mucosal surfaces. The concept of mucoadhesive polymers has been introduced into the pharmaceutical literature more than 40 years ago and nowadays it has been accepted as a promising strategy to prolong the residence time and to improve the specific localization of drug delivery systems on various membranes.

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.

Within the oral mucosal cavity, delivery of drugs is classified into three categories [1]

1) Sublingual delivery: which is systemic delivery of drugs through the mucosal membranes lining the floor of the mouth?

2) Buccal delivery: which is drug administration through the mucosal membranes lining the cheeks (buccal mucosa), and

3) Local delivery: which is drug delivery into the oral cavity

ADVANTAGES OF BUCCAL DRUG DELIVERY SYSTEM [2]

- 1) It is richly vascularized and more accessible for the administration and removal of a dosage form.
- 2) Buccal drug delivery has a high patient acceptability compared to other non-oral routes of drug administration.
- 3) Harsh environmental factors that exist in oral delivery of a drug are circumvented by buccal delivery.
- 4) Avoids acid hydrolysis in the gastrointestinal (GI) tract and by passing the first-pass effect.
- 5) Moreover, rapid cellular recovery and achievement of a localized site on the smooth surface of the buccal mucosa.

DISADVANTAGES OF BUCCAL DRUG DELIVERY SYSTEM [2]

- 1) Low permeability of the buccal membrane: specifically when compared to the sublingual membrane.
 - 2) Smaller surface area. The total surface area of the membranes of the oral cavity available for drug absorption is 170 cm² of which ~50 cm² represents non-keratinized tissues, including the buccal membrane.
 - 3) The continuous secretion of saliva (0.5–2 l/day) leads to subsequent dilution of the drug.
 - 4) Swallowing of saliva can also potentially lead to the loss of dissolved or suspended drug and, ultimately, the involuntary removal of the dosage form.
- These are some of the problems that are associated with buccal drug delivery.

MUCUS:

The adherent mucus gel lining the alimentary tract has a minimum thickness of $\approx 40\text{--}50\ \mu\text{m}$ and a maximum thickness of $\approx 300\ \mu\text{m}$ [3] depending on the individual and the region of the alimentary tract. Although most of mucus is water ($\approx 95\text{--}99\%$ by weight) the key macromolecular components are a class of glycoprotein known as mucins (1–5%). Mucins are large molecules with molecular masses ranging from 0.5 to over 20 MDa. They contain large amounts of carbohydrate (for gastrointestinal mucins 70–80% carbohydrate, 12–25% protein and up to $\approx 5\%$ ester sulphate). Undegraded mucins from a variety of sources are made up of multiples of a basic unit ($\approx 400\text{--}500\ \text{kDa}$), linked together into linear arrays [4] to give the macroscopic mucins with molecular masses claimed to be as high as $\approx 50\ \text{MDa}$. The basic units are linked together by regions of low or no glycosylation which are subject to trypsin digestion: the $\approx 400\ \text{kDa}$ digestion products are thus commonly referred to as domains [5]. Every third or fourth T-domain is linked by a disulphide bridge and these are susceptible to reductive disruption by thiols.

ANATOMY OF MUCOUS MEMBRANE:

Mucous membranes (mucosae) are the moist surfaces lining the walls of various body cavities such as the gastrointestinal and respiratory tracts. They consist of a connective tissue layer (the lamina propria) above which is an epithelial layer, the surface of which is made moist usually by the presence of a mucus layer. The epithelia may be either single layered (e.g. the stomach, small and large intestine and bronchi) or multilayered/stratified (e.g. in the oesophagus, vagina and cornea). The former contain goblet cells which secrete mucus directly onto the epithelial surfaces, the latter contain, or are adjacent to tissues containing, specialized glands such as salivary glands that secrete mucus onto the epithelial surface. Mucus is present as either a gel

layer adherent to the mucosal surface or as a luminal soluble or suspended form. The major components of all mucus gels are mucin glycoproteins, lipids, inorganic salts and water, the latter accounting for more than 95% of its weight, making it a highly hydrated system. The mucin glycoproteins are the most important structure-forming component of the mucus gel, resulting in its characteristic gel-like, cohesive and adhesive properties. The thickness of this mucus layer varies on different mucosal surfaces, from 50 to 450 \AA in the stomach [6,7] to less than 1 \AA in the oral cavity. The major functions of mucus are that of protection and lubrication (they could be said to act as antiadherents) **fig (1) anatomy of oral mucosa**

ORAL MUCOSAL PERMEATION

ENHANCERS:

Similar to any other mucosal membrane, the buccal mucosa as a site for drug delivery has limitations as well. One of the major disadvantages associated with buccal drug delivery is the low flux which results in low drug bioavailability [1]. Various compounds have been investigated for their use as buccal penetration enhancers in order to increase the flux of drugs through the mucosa as shown in **Table (1)**

MECHANISMS OF ACTION OF PERMEATION ENHANCERS [8]

Mechanisms by which penetration enhancers are thought to improve mucosal absorption are as follows. Also summarised in **Table (2)**

1) Changing mucus rheology: Mucus forms viscoelastic layer of varying thickness that affects drug absorption. Further, saliva covering the mucus layers also hinders the absorption. Some permeation enhancers' act by reducing the viscosity of the mucus and saliva overcomes this barrier.

2) Increasing the fluidity of lipid bilayer membrane:

The most accepted mechanism of drug absorption through buccal mucosa is intracellular route. Some enhancers 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:

Some enhancers act on desmosomes, a major component at the tight junctions there by increases drug absorption.

4) By overcoming the enzymatic barrier:

These act 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.

5) Increasing the thermodynamic activity of drugs:

Some enhancers increase the solubility of drug there by alters the partition coefficient. This leads to

increased thermodynamic activity resulting better absorption.

MUCOADHESION/BIOADHESION:

DEFINITION:

1) In 1986, Longer and Robinson defined the term bioadhesion as the attachment of a synthetic or natural macromolecule to mucus and/or an epithelial surface [24]. The general definition of adherence of a polymeric material to biological surfaces (bioadhesives) or to the mucosal tissue (mucoadhesives) still holds.

2) Bioadhesion may be defined as the state in which two materials, at least one of which is biological in nature, are held together for extended periods of time by interfacial forces. In the pharmaceutical sciences, when the adhesive attachment is to mucus or a mucous membrane, the phenomenon is referred to as mucoadhesion [25]

BUCCAL DRUG DELIVERY SYSTEMS:

IDEAL CHARACTERISTICS OF BUCCAL ADHESIVE POLYMERS [36]:

- 1) Polymer and its degradation products should be non-toxic, non-irritant and free from leachable impurities.
- 2) Should have good spreadability, wetting, swelling and solubility and biodegradability properties.
- 3) Should adhere quickly to buccal mucosa and should possess sufficient mechanical strength.
- 4) Should possess peel, tensile and shear strengths at the bioadhesive range.
- 5) Polymer must be easily available and its cost should not be high.
- 6) Should show bioadhesive properties in both dry and liquid state.
- 7) Should demonstrate local enzyme inhibition and penetration enhancement properties.
- 8) Should demonstrate acceptable shelf life.
- 9) Should have optimum molecular weight.
- 10) Should possess adhesively active groups.
- 11) Should have required spatial conformation.
- 12) Should be sufficiently cross-linked but not to the degree of suppression of bond forming groups.
- 13) Should not aid in development of secondary infections such as dental caries.

MUCOADHESIVE POLYMERS USED IN THE ORAL CAVITY:

Classification of mucoadhesive polymers used in oral cavity is presented in Table (3)

Table (4) summerises list of investigated bioadhesive polymers

Table (5) summerises properties and characteristics of some representative bioadhesive polymers used in buccal delivery

NEW GENERATION OF MUCOADHESIVE POLYMERS:

The new generation of mucoadhesives (with the exception of thiolated polymers) can adhere directly to the cell surface, rather than to mucus. They interact with the cell surface by means of specific receptors or covalent bonding instead of non-specific mechanisms, which are characteristic of the previous polymers. We have chosen to focus on recently discovered bioadhesive polymers in this review. Examples of such are the incorporation of l-cysteine into thiolated polymers and the target-specific, lectin-mediated adhesive polymers. These classes of polymers hold promise for the delivery of a wide variety of new drug molecules, particularly macromolecules, and create new possibilities for more specific drug– receptor interactions and improved targeted drug delivery.

1) THIOLATED MUCOADHESIVE POLYMERS:

Through a covalent attachment between a cysteine (Cys) residue and a polymer of choice, such as polycarbophi [37], poly(acrylic acid) [38], and chitosan [39], a new generation of mucoadhesive polymers have been created. The modified polymers, which contain a carbodiimide-mediated thiol bond, exhibit much-improved bioadhesive properties. Investigations of the GI epithelial mucus have clarified the structure of this gel-like biopolymer [40]. With more than 4500 amino acids, the enormous polypeptide backbone of mucin protein is divided into three major subunits; tandem repeat array, carboxyl and amino-terminal domains. The carboxyl-terminal domain contains more than 10% of cysteine residues. The amino-terminal domain also contains Cys-rich regions. The Cys-rich sub-domains are responsible for forming the large oligomers of mucin through disulfide bonds [40]. Based on the disulfide exchange reaction, disulfide bonds between the mucin glycoprotein and the thiolated mucoadhesive polymer can potentially be formed, which results in a strong covalent interaction [41].

Improved mucoadhesive properties of the thiolated polymers:

- 1) Improved tensile strength,
- 2) High cohesive properties,
- 3) Rapid swelling, and water uptake behavior have made them an attractive new generation of bioadhesive polymers.

2) MUCOADHESIVE POLYMERS AS ENZYME INHIBITORS AND PERMEATION ENHANCERS:

It has been shown that some mucoadhesive polymers can act as an enzyme inhibitor. The particular importance of this finding lies in delivering therapeutic compounds that are specifically prone to extensive enzymatic degradation, such as protein and polypeptide drugs. Investigations have demonstrated

that polymers, such as poly(acrylic acid), operate through a competitive mechanism with proteolytic enzymes. This stems from their strong affinity to divalent cations (Ca^{2+} , Zn^{2+}) [42]. These cations are essential

cofactors for the metalloproteinases, such as trypsin. Circular dichroism studies suggest that Ca^{2+} depletion, mediated by the presence of some mucoadhesive polymers, causes the secondary structure of trypsin to change, and initiates a further autodegradation of the enzyme [42]. The increased intestinal permeability of various drugs in the presence of numerous mucoadhesive polymers has also been attributed to their ability to open up the tight junctions by absorbing the water from the epithelial cells. The result of water absorption by a dry and swellable polymer is dehydration of the cells and their subsequent shrinking. This potentially results in an expansion of the spaces between the

cells (increased radius of the paracellular pathway) [43,44]. The use of multifunctional matrices, such as polyacrylates, cellulose derivatives, and chitosan, that display mucoadhesive properties, permeation-enhancing effects, enzyme-inhibiting properties, and/or a high buffer capacity have proven successful strategies in oral drug delivery [45]. The inhibition of the major proteolytic enzymes by these polymers is remarkable and represents yet another possible approach for the delivery of therapeutic compounds, particularly protein and peptide drugs, through the buccal mucosa.

3) TARGET-SPECIFIC, LECTIN-MEDIATED BIOADHESIVE POLYMERS:

Specific proteins or glycoproteins, such as lectins, which are able to bind certain sugars on the cell membrane, can increase bioadhesion and potentially

improve drug delivery via specific binding and increase the residence time of the dosage form. This type of bioadhesion should be more appropriately termed as cytoadhesion [46]. A site-specific interaction with the receptor could potentially trigger intercellular signaling for internalization of the drug or the carrier system (endocytosis through cytoadhesion) into the lysosomes or into other cellular compartments, such as the nucleus, as shown in Fig. 2 [46]. The recent idea of developing blectinomimetics (lectin-like molecules) based on lectins, and even biotechnologically generated derivatives of such molecules, holds an interesting future for this class of bioadhesion molecules [46]. **Fig (2)**

4) BACTERIAL ADHESION:

The adhesive properties of bacterial cells, as a more complicated adhesion system, have recently been investigated. 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 specific receptors. A significant correlation has been found between the presence of fimbriae on the surface of bacteria and their pathogenicity [60]. 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. Bernkop-Schnurch et al. covalently attached a fimbrial protein (antigen K99 from *E. coli*) to poly (acrylic acid) polymer and substantially improved the adhesion of the drug delivery system to the GI epithelium using a system as depicted [48]. in **Fig. 3**

Fig (1): Anatomy of oral mucosa

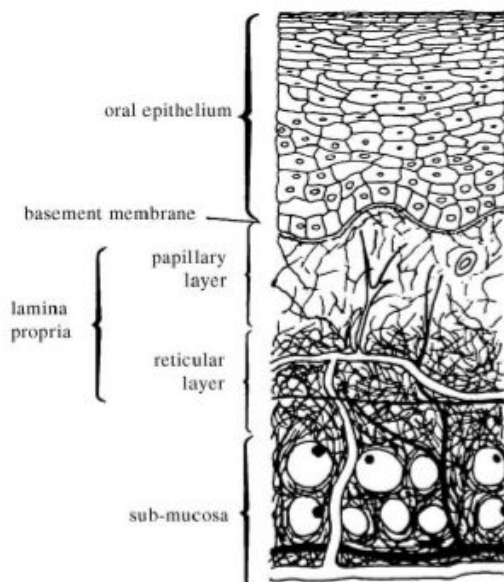
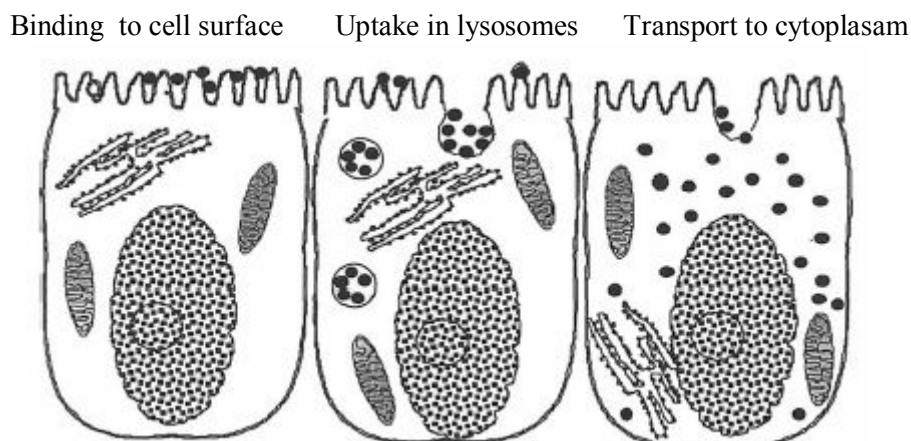
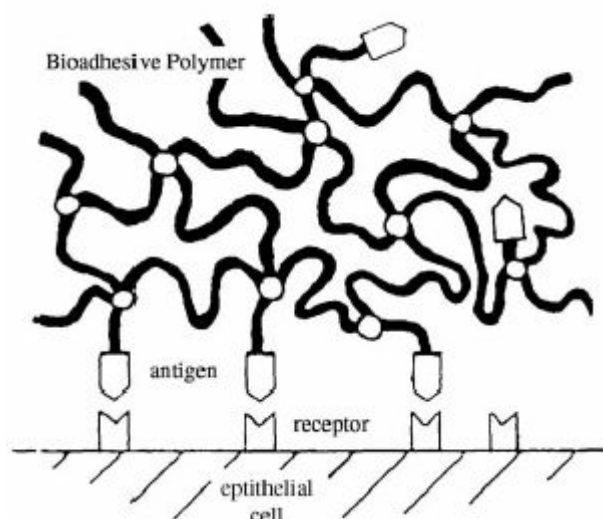


Fig (2): Lectin mediated bioadhesive system



. Different fates of lectin-mediated cytoadhesive ligands or drug carrier systems upon specific binding to surface receptors on the epithelial cell

Fig (3): Bacterial adhesion



A diagram of covalently attached fimbrial protein (K99 from *E. coli*) to poly(acrylic acid) as a carrier system

CONCLUSION:

The buccal mucosa offers several advantages for 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. 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 non-invasive 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.

Table (1): List of compounds used as oral mucosal permeation enhancers

Sr. No.	Permeation Enhancer	Reference(s)
1	23-lauryl ether	[9]
2	Aprotinin	[10]
3	Azone	[11, 12, 13]
4	Benzalkonium chloride	[14]
5	Cetylpyridinium chloride	[15], [16]
6	Cetyltrimethylammonium bromide	[14]
7	Cyclodextrin	[16]
8	Dextran sulfate	[9]
9	Lauric acid	[17]
10	Lauric acid/Propylene glycol	[18]
11	Lysophosphatidylcholine	[19]
12	Menthol	[17]
13	Methoxysalicylate	[17], [9]
14	Methyloleate	[20]
15	Oleic acid	[20]
16	Phosphatidylcholine	[17]
17	Polyoxyethylene	[9]
18	Polysorbate 80	[15], [16]
19	Sodium EDTA	[9], [10]
20	Sodium glycocholate	[11]
21	Sodium glycodeoxycholate	[18]
22	Sodium lauryl sulfate	[18]
23	Sodium salicylate	[10]
24	Sodium taurocholate (43-48, 54)	[9]
25	Sodium taurodeoxycholate	[21]
26	Sulfoxides	[18]
27	Various alkyl glycosides	[22]

Table (2): Mucosal penetration enhancers and mechanisms of action²⁸

Sr. No.	Classification	Examples	Mechanism
1	Surfactants	Anionic: sodium lauryl, sodium lauryl Cationic: cetylpyridinium Chloride Nonionic: poloxamer, Brij, Span, Myrj, Tween Bile salts: sodium glycodeoxycholate, sodium glycocholate, sodium taurodeoxycholate, sodium taurocholate Azone	Perturbation of intercellular lipids, protein domain integrity
2	Fatty acids	Oleic acid, caprylic acid	Increase fluidity of phospholipid domains
3	Cyclodextrins	α , β , γ , cyclodextrin, methylated β -cyclodextrins	Inclusion of membrane compounds
4	Chelators	EDTA, sodium citrate	Interfere with Ca Polyacrylates
5	Positively charged polymers	Chitosan, trimethyl chitosan	Ionic interaction with negative charge on the mucosal surface
6	Cationic compounds	Poly-L-arginine, L-lysine	Ionic interaction with negative charge on the mucosal surface

Table (3): Mucoadhesive polymers used in the oral cavity⁴⁷:

Criteria	Categories	Examples
Source	Semi-natural/natural	Agarose, chitosan, gelatin Hyaluronic acid Various gums (guar, hakea, xanthan, gellan, carragenan, pectin, and sodium alginate)
	Synthetic	Cellulose derivatives [CMC, thiolated CMC, sodium CMC, HEC, HPC, HPMC, MC, methylhydroxyethylcellulose] Poly(acrylic acid)-based polymers [CP, PC, PAA, polyacrylates, poly (methylvinylether-co-methacrylic acid), poly (2-hydroxyethyl methacrylate), poly(acrylic acid-co-ethylhexylacrylate), poly (methacrylate), poly (alkylcyanoacrylate), poly (isohexylcyanoacrylate), poly (isobutylcyanoacrylate), copolymer of acrylic acid and PEG] Others: Poly PHPMAM, polyoxyethylene, PVA, PVP, thiolated polymers
Aqueous solubility	Water-soluble	CP, HEC, HPC (waterb38 8C), HPMC (cold water), PAA, sodium CMC, 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, sodium CMC, xanthan gum
	Non-ionic	Hydroxyethyl starch, HPC, poly(ethylene oxide), PVA, PVP, scleroglucan
Potential Bioadhesive forces	Covalent	Cyanoacrylate
	Hydrogen bond	Acrylates [hydroxylated methacrylate, poly(methacrylic acid)], CP, PC, PVA
	Electrostatic interaction	Chitosan

Table (4): List of investigated bioadhesive polymers¹

Sr No.	Bioadhesive Polymer(s) Studied	Investigation Objectives
1	HPC and CP	Preferred mucoadhesive strength on CP, HPC, and HPCCP combination
2	HPC and CP	Measured Bioadhesive property using mouse peritoneal Membrane
3	CP, HPC, PVP, CMC	Studied inter polymer complexation and its effects on bioadhesive strength
4	CP and HPMC	Formulation and evaluation of buccoadhesive controlled release delivery systems
5	HPC, HEC, PVP,PVA	Tested mucosal adhesion on patches with two-ply laminates with an impermeable backing layer and hydrocolloid polymer layer
6	HPC and CP	Used HPC-CP powder mixture as peripheral base for strong adhesion and HPC-CP freeze dried mixture as core base
7	CP, PIP, and PIB	Used a two roll milling method to prepare a new bioadhesive patch formulation

8	Xanthum gum and Locust bean gum	Hydrogel formation by combination of natural gums
9	Chitosan, HPC, CMC, Pectin, Xantham gum, Polycarbophil	Evaluate mucoadhesive properties by routinely measuring the detachment force form pig intestinal Mucosa
10	Hyaluronic acid benzyl esters Polycarbophil,HPMC	Evaluate mucoadhesive properties
11	Hydroxyethylcellulose	Design and synthesis of a bilayer patch (polytef-disk) for thyroid gland diagnosis
12	Polycarbophil	Design of a unidirectional buccal patch for oral mucosal delivery of peptide drugs
13	Poly(acrylic acid), Poly(methacrylic acid)	Synthesized and evaluated crosslinked polymers differing in charge densities and hydrophobicity
14	Number of Polymers including HPC, HPMC, CP, CMC.	.Measurement of bioadhesive potential and to derive meaningful information on the structural requirement for bioadhesion
15	Poly(acrylic acid-co-acrylamide)	Adhesion strength to the gastric mucus layer as a function of crosslinking agent, degree of swelling, and carboxyl group density
16	Poly(acrylic acid)	Effects of PAA molecular weight and crosslinking concentration on swelling and drug release characteristics
17	Poly(acrylic acid-co-methyl methacrylate)	Relationships between structure and adhesion for mucoadhesive polymers
18	HEMA copolymerized with Polymeg® (polytetramethylene glycol)	Bioadhesive buccal hydrogel for controlled release delivery of buprenorphine
19	Cydot by 3M (bioadhesive polymeric blend of CP and PIB)	Patch system for buccal mucoadhesive drug delivery
20	Formulation consisting of PVP, CP, and cetylpyridinium chloride (as stabilizer)	Device for oramucosal delivery of LHRH – device containing a fast release and a slow release layer
21	CMC, Carbopol 974P, Carbopol EX- 55, Pectin (low viscosity), Chitosan chloride,	Mucoadhesive gels for intraoral delivery (100)
22	CMC, CP, Polyethylene oxide, Polymethylvinylether /Maleic anhydride (PME/MA), and Tragacanth	Buccal mucoadhesive device for controlled release anticandidal device - CMC tablets yielded the highest adhesive force
23	HPMC and Polycarbophil (PC)	Buccal mucoadhesive tablets with optimum blend ratio of 80:20 PC to HPMC yielding the highest force of adhesion
24	PVP, Poly(acrylic acid)	Transmucosal controlled delivery of isosorbide dinitrate
25	Poly(acrylic acid-co-poly ethyleneglycol) copolymer of acrylic acid and polyethyleneglycol monomethyl-ether monomethacryalte	To enhance the mucoadhesive properties of PAA for buccal mucoadhesive drug delivery
26	Poly acrylic acid and poly ethylene glycol	To enhance mucoadhesive properties of PAA by interpolymer complexation through template polymerization

27	Drum dried waxy maize starch (DDWM), Carbopol 974P, and sodium stearyl fumarate	Bioadhesive erodible buccal tablet for progesterone delivery
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Table (5): Properties and characteristics of some representative bioadhesive polymers used in buccal delivery⁴⁸

Sr. No.	Bioadhesives	Properties	Characteristics
1	Polycarbophil (polyacrylic acid crosslinked with divinyl glycol)	<ul style="list-style-type: none"> • Mw 2.2×10^5 • η 2000–22,500 cps (1% aq. soln.) • κ 15–35 mL/g in acidic media (pH 1–3) 100 mL/g in neutral and basic media • ϕ viscous colloid in cold water • Insoluble in water, but swell to varying degrees in common organic solvents, strong mineral acids, and bases. 	<ul style="list-style-type: none"> • Synthesized by lightly crosslinking of 0.5–1% w/w divinyl glycol • Swellable depending on pH and ionic strength • Swelling increases as pH increases • At pH 1–3, absorbs 15–35 ml of water per gram but absorbs 100 ml per gram at neutral and alkaline pH • Entangle the polymer with mucus on the surface of the tissue • Hydrogen bonding between the nonionized carboxylic acid and mucin
2	Carbopol/carbomer (carboxy polymethylene)	<ul style="list-style-type: none"> • Pharmaceutical grades: 934 P, 940 P, 971 P and 974 P. • Mw 1×10^6–4×10^6 • κ 5 g/cm³ in bulk, 1.4 g/cm³ tapped. • pH 2.5–3.0 • ϕ water, alcohol, glycerin • White, fluffy, acidic, hygroscopic powder with a slight characteristic odour. 	<ul style="list-style-type: none"> • Excellent thickening, emulsifying, suspending, gelling agent. • Synthesized by cross-linker of allyl sucrose or allyl pentaerythritol • Common component in bioadhesive dosage forms • Gel loses viscosity on exposure to sunlight. • Unaffected by temperature variations, hydrolysis, oxidation and resistant to bacterial growth. • It contributes no off-taste and may mask the undesirable taste of the formulation. • Incompatible with Phenols, cationic polymers, high concentrations of electrolytes and resorcinol
3	Sodium carboxymethyl cellulose SCMC	<ul style="list-style-type: none"> • It is an anionic polymer made by swelling cellulose with NaOH and then reacting it with monochloroacetic acid. • Grades H, M, and L • Mw 9×10^4–7×10^5 	<ul style="list-style-type: none"> • Emulsifying, gelling, binding agent • Sterilization in dry and solution form, irradiation of solution loses the viscosity • Stable on storage. • Incompatible with strongly

	(cellulose carboxymethyl ether sodium salt)	<ul style="list-style-type: none"> • η 1200 cps with 1.0% soln. • ρ 0.75 g/cm³ in bulk • pH 6.5–8.5 • ϕ water • White to faint yellow, odorless, hygroscopic powder or granular material having faint paper-like taste. 	<p>acidic solutions</p> <ul style="list-style-type: none"> • In general, stability with monovalent salts is very good; with divalent salts good to marginal; with trivalent and heavy metal salts poor, resulting in gelation or precipitation • CMC solutions offer good tolerance of water miscible solvents, good viscosity stability over the pH 4 to pH 10 range, compatibility with most water soluble nonionic gums, and synergism with HEC and HPC • Most CMC solutions are thixotropic; some are strictly pseudoplastic. • All solutions show a reversible decrease in viscosity at elevated temperatures. CMC solutions lack yield value. • Solutions are susceptible to shear, heat, bacterial, enzyme, and UV degradation. • Good bioadhesive strength. • Cell immobilization via a combination of ionotropic gelation and polyelectrolyte complex formation (e.g., with chitosan) in drug delivery systems and dialysis membranes.
4	. Hydroxypropyl cellulose partially substituted polyhydroxy propylether of cellulose HPC (cellulose 2-hydroxypropyl ether)	<ul style="list-style-type: none"> • Grades: Klucel EF, LF, JF, GF, MF and HF • Best pH is between 6.0 and 8.0 • Mw 6×10⁴–1×10⁶ • η 4–6500 cps with 2.0% aq. soln. • pH 5.0–8.0 • Soluble in water below 38 °C, ethanol, propylene glycol, dioxane, methanol, isopropyl alcohol, dimethyl sulfoxide, dimethyl formamide etc • Insoluble in hot water • White to slightly yellowish, odorless powder. 	<ul style="list-style-type: none"> • Solutions of HPC are susceptible to shear, heat, bacterial, enzymatic and bacterial degradation • It is inert and showed no evidence of skin irritation or sensitization. • ρ 0.5 g/cm³ in bulk • Compatible with most water-soluble gums and resins. • Synergistic with CMC and sodium alginate • Not metabolized in the body. • It may not tolerate high concentrations of dissolved materials and tend to be salting out • It is also incompatible with the substituted phenolic derivatives such as

			methyl and propyl parahydroxy benzoate <ul style="list-style-type: none"> • Granulating and film coating agent for tablet • Thickening agent, emulsion • Stabilizer, suspending agent in oral and topical solution or suspension
5	Hydroxypropylmethyl Cellulose HPMC (cellulose 2-hydroxypropylmethyl ether)	<ul style="list-style-type: none"> • Methocel E5, E15, E50, E4M, F50, F4M, K100, K4M, K15M, K100M. • Mw 8.6×10^4 • η E15–15 cps, E4M–400 cps and K4M–4000 cps (2% aqueous solution.) • ϕ Cold water, mixtures of methylene chloride and isopropylalcohol • Insoluble in alcohol, chloroform and ether. • Odorless, tasteless, white or creamy white fibrous or granular powder 	<ul style="list-style-type: none"> • Mixed alkyl hydroxyalkyl cellulosic ether • Suspending, viscosity-increasing and filmforming Agent • Tablet binder and adhesive ointment ingredient • E grades are generally suitable as film formers while the K grades are used as thickeners. • Stable when dry. • Solutions are stable at pH 3.0 to 11.0 • Incompatible to extreme pH conditions and oxidizing materials.
6	. Hydroxyethyl Cellulose non-ionic polymer made by swelling cellulose with NaOH and treating with ethylene oxide.	<ul style="list-style-type: none"> • Available in grades ranging from 2 to 8,00,000 cps at 2%. • Light tan or cream to white powder, odorless and tasteless. It may contain suitable anticaking agents • ρ 0.6 g/mL • pH 6–8.5 • ϕ in hot or cold water and gives a clear, colorless solution. 	<ul style="list-style-type: none"> • Solutions are pseudoplastic and show a reversible decrease in viscosity at elevated temperatures • HEC solutions lack yield value. • Solutions show only a fair tolerance with water miscible solvents (10 to 30% of solution weight). • Compatible with most water-soluble gums and resins • Synergistic with CMC and sodium alginate. • Susceptible for bacterial and enzymatic degradation. • Polyvalent inorganic salts will salt out HEC at lower concentrations than monovalent salts. • Shows good viscosity stability over the pH 2 to pH 12 ranges. • Used as suspending or viscosity builder

			<ul style="list-style-type: none"> • Binder, film former.
7	<p>Hydroxyethyl Cellulose non-ionic polymer made by swelling cellulose with NaOH and treating with ethylene oxide.</p>	<ul style="list-style-type: none"> • Available in grades ranging from 2 to 8,00,000 cps at 2%. • Light tan or cream to white powder, odorless and tasteless. It may contain suitable anticaking agents • ρ 0.6 g/mL • pH 6–8.5 • ϕ in hot or cold water and gives a clear, colorless solution 	<ul style="list-style-type: none"> • Solutions are pseudoplastic and show a reversible decrease in viscosity at elevated temperatures • HEC solutions lack yield value. • Solutions show only a fair tolerance with water miscible solvents (10 to 30% of solution weight) • Compatible with most water-soluble gums and resins • Synergistic with CMC and sodium alginate. • Susceptible for bacterial and enzymatic degradation • Polyvalent inorganic salts will salt out HEC at lower concentrations than monovalent salts • Shows good viscosity stability over the pH 2 to pH 12 ranges. • Used as suspending or viscosity builder • Binder, film former.
8	<p>Xanthan gum xanthan gum is an anionic polysaccharide derived from the fermentation of the plant bacteria <i>Xanthomonas campestris</i></p>	<ul style="list-style-type: none"> • It is soluble in hot or cold water and gives visually hazy, neutral pH solutions • It will dissolve in hot glycerin • Solutions are typically in the 1500 to 2500 cps range at 1%; they are pseudoplastic and especially shear-thinning. In the presence of small amounts of salt, solutions show good viscosity stability at elevated temperatures • Solutions possess excellent yield value • It is more resistant to shear, heat, bacterial, enzyme, and UV degradation than most gums 	<ul style="list-style-type: none"> • Xanthan gum is more tolerant of electrolytes, acids and bases than most other organic gums. • It can, nevertheless, be gelled or precipitated with certain polyvalent metal cations under specific circumstances • Solutions show very good viscosity stability over the pH 2 to 12 range and good tolerance of watermiscible solvents • It is more compatible with most nonionic and anionic gums, featuring useful synergism with galactomannans
9	<p>Guar gum (galactomannan polysaccharide)</p>	<ul style="list-style-type: none"> • Obtained from the ground endosperms of the seeds of <i>Cyamopsis tetragonolobus</i> (family leguminosae). • MW approx. 220,000 	<ul style="list-style-type: none"> • Stable in solution over a pH range of 1.0–10.5 • Prolonged heating degrades viscosity. Bacteriological stability can be improved by the addition of mixture of 0.15%

		<ul style="list-style-type: none"> • η 2000–22500 Cps (1% aqueous solution.) • Forms viscous colloidal solution when hydrated in cold water. The optimum rate of hydration is between pH 7.5 and 9.0. 	<p>methyl paraben or 0.1% benzoic acid</p> <ul style="list-style-type: none"> • The FDA recognizes guar gum as a substance added directly to human food and has been affirmed as generally recognized as safe • Incompatible with acetone, tannins, strong acids, and the alkalis. Borate ions, if present in the dispersing water, will prevent hydration of guar. • Used as thickener for lotions and creams, as tablet binder, and as emulsion stabilizer.
10	Hydroxypropyl Guar non-ionic derivative of guar. Prepared by reacting guar gum with propylene oxide.	<ul style="list-style-type: none"> • Φ in hot and cold water • Gives high viscosity, pseudoplastic solutions that show reversible decrease in viscosity at elevated temperatures • Lacks yield value. 	<ul style="list-style-type: none"> • Compatible with high concentration of most salts. • Shows good tolerance of water miscible solvents • Better compatibility with minerals than guar gum. • Good viscosity stability in the pH range of 2 to 13. • More resistance to bacterial and enzymatic degradation.
11	Chitosan a linear polysaccharide composed of randomly distributed β -(1-4)-linked Dglucosamine (deacetylated unit) and N-acetyl-Dglucosamine (acetylated unit).	<ul style="list-style-type: none"> • Prepared from chitin of crabs and lobsters by Ndeacetylation with alkali • Φ dilute acids to produce a linear polyelectrolyte with a high positive charge density and forms salts with inorganic and organic acids such as glutamic acid, hydrochloric acid, lactic acid, and acetic acid. • The amino group in chitosan has a pKa value of ≈ 6.5, thus, chitosan is positively charged and soluble in acidic to neutral solution with a charge density dependent on pH and the %DA-value 	<ul style="list-style-type: none"> • Mucoadhesive agent due to either secondary chemical bonds such as hydrogen bonds or ionic interactions between the positively charged amino groups of chitosan and the negatively charged sialic acid residues of mucus glycoproteins or mucins. • Possesses cell-binding activity due to polymer cationic polyelectrolyte structure and to the negative charge of the cell surface • Biocompatible and biodegradable. • Excellent gel forming and film forming ability • Widely used in controlled delivery systems such as gels, membranes, microspheres • Chitosan enhance the transport of polar drugs across epithelial surfaces. Purified qualities of chitosans are available for biomedical applications. Chitosan and its derivatives such as trimethylchitosan

			<p>(where the amino group has been trimethylated) have been used in non-viral gene delivery. Trimethylchitosan, or quaternised chitosan, has been shown to transfect breast cancer cells. As the degree of trimethylation increases the cytotoxicity of the derivative increases. At approximately 50% trimethylation the derivative is the most efficient at gene delivery. Oligomeric derivatives (3–6 kDa) are relatively non-toxic and have good gene delivery properties.</p>
12	<p>Carrageenan an anionic polysaccharide, extracted from the red seaweed <i>Chondrus crispus</i></p>	<ul style="list-style-type: none"> • Available in sodium, potassium, magnesium, calcium and mixed cation forms • Three structural types exist: Iota, Kappa, and Lambda, differing in solubility and rheology. • The sodium form of all three types is soluble in both cold and hot water • Other cation forms of kappa and Iota are soluble only in hot water. • All forms of lambda are soluble in cold water. 	<ul style="list-style-type: none"> • All solutions are pseudoplastic with some degree of yield value. Certain ca-Iota solutions are thixotropic. Lambda is non-gelling, Kappa can produce brittle gels; Iota can produce elastic gels. All solutions show a reversible decrease in viscosity at elevated temperatures. Iota and Lambda carrageenan have excellent electrolyte tolerance; kappa's being somewhat less. Electrolytes will however decrease solution viscosity. The best solution stability occurs in the pH 6 to 10. It is compatible with most nonionic and anionic watersoluble thickeners. It is strongly synergistic with locust bean gum and strongly interactive with proteins. Solutions are susceptible to shear and heat degradation. • Excellent thermoreversible properties. • Used also for microencapsulation
13	<p>Sodium Alginate consists chiefly of the alginic acid, a polyuronic acid composed of β-D-</p>	<ul style="list-style-type: none"> • Purified carbohydrate product extracted from brown seaweed by the use of dilute alkali. 	<ul style="list-style-type: none"> • Safe and nonallergenic • Incompatible with acridine derivatives, crystal violet, phenyl mercuric nitrate and

	<p>mannuronic acid residues. empirical formula: $(C_6H_7O_6Na)_n$</p> <p>anionic polysaccharide extracted principally from the giant kelp <i>Macrocystis Pyrifera</i> as alginic acid and neutralized to sodium salt.</p>	<ul style="list-style-type: none"> • Occurs as a white or buff powder, which is odorless and tasteless • pH 7.2 • η 20–400 Cps (1% aqueous solution.) • ϕ Water, forming a viscous, colloidal solution. • Insoluble in other organic solvents and acids where the pH of the resulting solution and acids where the pH of the resulting solution falls below 3.0. 	<p>acetate, calcium salts, alcohol in concentrations greater than 5%, and heavy metals</p> <ul style="list-style-type: none"> • Stabilizer in emulsion, suspending agent, tablet disintegrant, tablet binder. • It is also used as haemostatic agent in surgical dressings • Excellent gel formation properties • Biocompatible • Microstructure and viscosity are dependent on the chemical composition. • Used as immobilization matrices for cells and enzymes, controlled release of bioactive substances, injectable microcapsules for treating neurodegenerative and hormone deficiency diseases • Lacks yield value. • Solutions show fair to good tolerance of water miscible solvents (10–30% of volatile solvents; 40–70% of glycols) • Compatible with most water-soluble thickeners and resins. • Its solutions are more resistant to bacterial and enzymatic degradation than many other organic thickeners.
14	<p>. Poly (hydroxy butyrate), Poly (e-caprolactone) and copolymers</p>	<ul style="list-style-type: none"> • Biodegradable • Properties can be changed by chemical modification, copolymerization and blending. 	<ul style="list-style-type: none"> • Used as a matrix for drug delivery systems, cell microencapsulation
15	<p>Poly (ortho esters.)</p>	<ul style="list-style-type: none"> • Surface eroding polymers 	<ul style="list-style-type: none"> • Application in sustained drug delivery and ophthalmology.
16	<p>Poly (cyano acrylates)</p>	<ul style="list-style-type: none"> • Biodegradable depending on the length of the alkylchain. 	<ul style="list-style-type: none"> • Used as surgical adhesives and glues. • Potentially used in drug delivery.
17	<p>Polyphosphazenes</p>	<ul style="list-style-type: none"> • Can be tailored with versatile side chain functionality 	<ul style="list-style-type: none"> • Can be made into films and hydrogels. • Applications in drug delivery.
18	<p>. Poly (vinyl alcohol)</p>	<ul style="list-style-type: none"> • Biocompatible 	<ul style="list-style-type: none"> • Gels and blended membranes are used in drug delivery and cell immobilization.

19	.Poly (ethylene oxide)	• Highly biocompatible	• Its derivatives and copolymers are used in various biomedical applications.
20	.Poly (hydroxyethyl methacrylate)	• Biocompatible	• Hydrogels have been used as soft contact lenses, for drug delivery, as skin coatings, and for Immunoisolation membranes.
21	.Poly (ethylene oxide-b-propylene oxide)	• Surfactants with amphiphilic properties	• Used in protein delivery and skin treatments.

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