



An Overview on Mucoadhesive Polymers for Buccal Drug Delivery

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ABSTRACT

The oral route is the most appropriate, convenient and generally accepted among the different routes of administration. It provides ease of administration and avoids possible drug degradation in the gastrointestinal tract as well as the first passing of hepatic metabolism. By the use of mucoadhesive drug delivery systems drug actions can be enhanced. These systems are generally in close contact with the absorption tissue, the mucous membrane, the release of the drug at the site of action leading to an increase in bioavailability and local and systemic effects. Mucoadhesive polymers are classified as the first-generation and second generation. The current review provides a good overview of theories and mechanisms of mucoadhesion, factors affecting mucoadhesion, properties of mucoadhesive polymers, and recent investigations carried by using mucoadhesion polymers.

Keywords: Mucoadhesive, Buccal Drug Delivery Systems, Mucoadhesive Polymers, Bioadhesive.

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INTRODUCTION

The oral route is the most convincing route for both patient and the clinician among various drug administrations. An oral cavity is an attractive place for the delivery of drugs because it is easy to administer and prevent drug degradation in the gastrointestinal tract and first-pass metabolism¹. The oral cavity has an area of approximately 50cm² but convenient access to the site makes it a preferred place for active agents to be transported².

Buccal drug delivery refers specifically to the provision of medications within or through the oral mucosa, which affect pharmacological local or systemic actions. Pharmaceutical products delivered through the buccal route can be used for the treatment of oral or systemic diseases in the cavity. Due to its ability to optimize the delivery of localized drugs by maintaining the dosage type in its area of action or systemic delivery by maintaining the formulation in close contact with the absorption site, mucoadhesion/bioadhesion has become an important research topic in the last two decades.

Drugs are administered in the oral mucosal cavity via three categories³

1. Sublingual route: delivery of drugs through the mucosal membranes that are bordering the floor of the mouth.

2. Buccal delivery: administration of drugs through the mucosal membrane that are bordering the cheeks.
3. Local delivery: Drugs delivered through the intraoral cavity.

In 1986, longer and Robinson defined bioadhesion/mucoadhesion to attached to the mucus and or epithelial surfaces by either a synthetic or natural macromolecule⁴. The well-defined mucoadhesive is the ability of a substance to bind to a biological tissue for a long time. Mucoadhesion/bioadhesion can be characterized as a phenomenon of interfacial molecular forces between the biological surface and natural or synthetic polymers that allow the polymer to attach for a longer period to the biological surface⁵

To generate mucoadhesion, a sequence of phenomena is required. The stage requires an intimate interaction, either through good mucoadhesive wetting or from mucoadhesive swelling between the mucoadhesive polymer and the membrane. In the second stage, after contact is formed the penetration of the mucoadhesive into the crevice of the tissue surface or interpenetration of the mucoadhesive chains with those of the mucus occurs. After that low chemical bonds will stabilize.

Mucoadhesive polymers are water-insoluble and water-soluble polymers connected by cross-linking agents, which are swellable networks. These polymers have optimal polarity to ensure that they allow adequate mucus wetting and optimal fluidity to allow the polymer and the mucus to be mutually adsorbed and interpenetrated⁶ It is possible to conveniently divide mucoadhesive polymers adhering to the mucin epithelial surface into three classes⁶

1. Polymers that are sticky when put in water and owe their mucoadhesion to stickiness.



2. polymers that conform to non-specific, noncovalent mainly electrostatic interactions (although hydrophobic and hydrogen bonding may be significant).
3. polymers that bind to a particular receptor site on the surface of the tile itself. All three types of polymers can be used for drug delivery.

Advantages of buccal drug delivery

1. The oral mucosa is highly permeable with a high blood volume compared to other mucosal tissues.
2. First pass metabolism can be neglected.
3. It offers an alternative route for the delivery of various substances like hormones, steroids, analgesics, cardiovascular drugs, etc...
4. It enables local modification of tissue permeability, suppression of protease activity, and reduction of immunogenic response. The delivery of therapeutic agents such as proteins, peptides, and ionized species can be carried easily.
5. Quick access to membrane sites so that drug delivery is improved.
6. Due to prolonged contact time with mucosa improve the drug performance.
7. Improves patient compliance ⁷.

Before addressing the widely used mucoadhesive polymers the various theories suggested to explain the phenomenon of mucoadhesion will be discussed. Also, there are various factors influencing mucoadhesion, mucoadhesive properties of polymers, and the ideal properties of polymers.

Theories of mucoadhesion ^{8,9,10}

Mucoadhesion is a complex phenomenon and various theories have been introduced to explain the mechanism of mucoadhesion these theories include wetting theory, electronic theory, adsorption theory, diffusion theory, fracture theory, mechanical theory.

Wetting theory

The wetting theory applies to liquid systems. The ability of bioadhesive polymers to spread and evolve intimate contact with the mucus membrane. The general rule states that the contact angle is lower than the affinity is greater. To provide sufficient spreadability, the contact angle should be equal to or close to zero.

Electronic theory

According to electronic theory, mucoadhesive and biological materials have opposite electrical charges, and when both materials come in contact, they transfer

electrons to form a double electrical layer at the interface. The adhesion is triggered by attractive forces across the double layer.

Diffusion theory

According to diffusion theory polymer matrix and mucus combine to a sufficient depth to form a semipermanent adhesive bond. The exact depth at which the polymer chain infiltrates the mucus relies on the coefficient of diffusion and the time of contact. In turn, this diffusion coefficient depends on the molecular weight value between links and decreases significantly with the increase in the cross-linking density.

Fracture theory

Fracture theory aims to relate the complexity of spreading two surfaces after adhesion. Through this theory, an explanation of forces needed for separating two surfaces after adhesion. The following equation is required to measure the strength of fracture is equivalent to adhesive strength.

$$\sigma = \left(\frac{E \times \epsilon}{L} \right)^{1/2}$$

Where

σ describes the fracture strength,

ϵ fracture energy,

E young modulus of elasticity and

L the critical crack length.

Mechanical theory

Adhesion occurs from liquid adhesive connecting with gaps on the rough surfaces. Rough surfaces provide an improved contact along with increased viscoelastic and plastic energy dissipation during joint failure, which is more important than a mechanical effect in the adhesion phase.

Adsorption theory

According to the principle of adsorption, the substance adheres to the surface. Forces on the two surfaces after initial contact between two surfaces. There are two types of chemical bonds resulting from these forces.

- a. Primary chemical bonds are covalent and are not ideal for bioadhesion because their high strength can lead to permanent bonds.
- b. Secondary chemical bonds with many different attraction forces, including electrostatic forces, van der Waals forces, hydrogen bonds, and hydrophobic bonds.

Mechanism of mucoadhesion

Bioadhesion is an interfacial process in which two materials, at least one of which is biologically held together employing interfacial forces. The attachment occurs



between the artificial surface and biological surface such as a polymer-copolymer-biological membrane adhesion. The word mucoadhesion is used in the case of polymers bound to the mucosal tissue mucin layer. Bioadhesive is described as a substance that can interact with biological material and can retain for a longer period.

The basic steps involved in the bioadhesion/mucoadhesion include:

1. The contact stage: spreading, wetting, and swelling of tissue surface form, inducing interaction between the polymer and the mucus and interpenetrating between the chains of bioadhesive/mucoadhesive and the network of mucus gel.
2. The consolidation stage: these associations may be ionic, covalent, hydrogen, or hydrophobic, establish secondary chemical bonds between polymer chains and mucin molecules³.

There is no simple mechanism for the forming of mucoadhesion bonds. It is important to describe and understand the force behind adherence bond formation to develop the ideal mucoadhesion drug delivery system. Adhesive bonds between soft tissue and polymer include a surface contribution for the polymer, the first layer of natural tissue, and an interfacial layer between adhesive and tissue. The formation of these mucoadhesive/bioadhesive bonds is explained in three steps (figure 1).

1. Polymer wetting and swelling facilitate intimate contact with biological tissue.

2. Interpretation of mucoadhesive/bioadhesive polymer chains and entanglement of polymer and mucin chains, and
3. Weak chemical bonds are formed between entangled chains¹¹

Polymer adhesion to tissues can be achieved by

- a. Primary ionic or covalent chemical bonds
- b. Secondary chemical bonds
- c. Physical or mechanical bonds

The primary chemical bonds are the products of a chemical reaction of the adhesive substrate functional groups. For most soft tissue applications where semi-permanent adhesive bond strength from few minutes to a couple of hours is hardly desirable.

Secondary chemical bonds correspond to the bioadhesive bonding of van der Waals through dispersive interactions or hydrogen bonding. In bioadhesion/mucoadhesion, hydrogen bonds are significant.

Physical or mechanical attachments are obtained by including adhesive material in the cervices of the tissue. The surface roughness of the substrate is an essential mucoadhesion/bioadhesion factor. Successful adhesive systems can only be seen as highly fluid materials or suspensions that can be incorporated within these tissue anomalies¹².

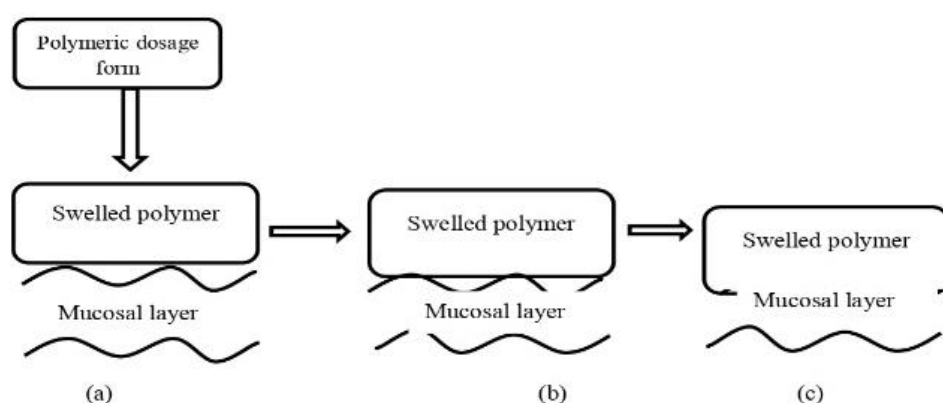


Figure 1: Mechanism of mucoadhesion

- (a) Polymer layer and mucosal layer before contact
- (b) Both layers upon contact (starting to create bonds).
- (c) Interpenetration of entanglement

Factors affecting mucoadhesion^{8,13,14,5}

Factors affecting mucoadhesion/bioadhesion are polymer related, environmental-related, and physiological related factors.

Polymer related factors

Factor	Characterization
Molecular weight	The mucus layer penetrated easier by low molecular weight polymers. Physical entanglement is induced by high molecular weight polymers. Optimum polymer molecular weight is required for optimum mucoadhesion. It depends upon the polymer used.
The concentration of active polymer	Hydrogen bonding is a crucial aspect of polymer mucoadhesion. Desired polymers must have functional groups (COOH, OH, etc.) that can form hydrogen bonds for the occurrence of mucoadhesion.
The flexibility of polymer chains	The flexibility of the chain is important for mucoadhesive polymer interpretation and entanglement.
Cross-linking density	There is an inverse relationship between the degree of polymer crosslinking and the degree of swelling at equilibrium. Therefore, the diffusion of water in the polymer network occurs at a lower rate as the density increases, which in turn induces inadequate polymer swelling and reduces the interpenetration rate between polymer and mucin.
Charge	Peppas and buri it seems that the high anionic load on the polymer is one of the desired specifications for mucoadhesion. Non-ionic polymer shows a lower degree of adhesion compared to the anionic polymer. In neutral or slightly alkaline, some cationic polymers have superior cationic properties.
Swelling	Swelling in polymers allow the intimate contact of hydrogen and electrostatic interactions between the polymer and mucosal networks by exposure to mucoadhesive sites. To enhance the interpenetration process between polymer and mucin, hydration is needed for the mucoadhesive polymer to expand and produce a proper macromolecular mesh of different sizes and also to induce mobility in the polymer chains.
Spatial conformation	Apart from chain length or molecular weight, the spatial conformation of a molecule is also important. Numerous studies have been shown that there is a certain molecular weight at which bioadhesion is at its limit, despite a high molecular weight of 19,500,000 for dextran.
Hydrophilicity	Mucoadhesive polymers include several functional hydrophilic groups, such as carboxyl and hydroxyl. These groups facilitate hydrogen bonding with the substrate, swelling in aqueous media allowing optimal exposure of ideal binding sites.

Environmental factors

Factor	Characterization
p ^H	The polymer-substrate interface and the pH of the saliva as a dissolution medium affect the behavior of the polymer. The pH of the mucoadhesive polymer microenvironment will change the state of ionization and, thus the properties of the polymer adhesion.
Applied strength	A specified strength must be added to the solid bioadhesive framework. By applied force or application length the adhesion increases. The initial pressure on the tissue contact site of mucoadhesive will influence the deep penetration of the tissue.
Initial contact time	The extent of swelling and interpenetration of the bioadhesive polymer chains is determined by the contact time between the bioadhesive and the mucus layer. In addition to bioadhesion strength increases as the initial contact time increases.
Swelling	The swelling aspect is related to the polymer itself, as well as to the environment. Swelling depends on both the concentration of polymer and the presence of water there is a decrease in bioadhesion when swelling is too large. To lead sufficient action by the bioadhesive system, such a phenomenon must not occur too easily.

Physiological factors

Factor	Characterization
Mucin turnover	For two reasons, the natural turnover of the mucus layer is important. The time of residence of the mucus coating on the mucus layer is expected to be limited. Substantial amounts of soluble mucin molecules result from mucin turnover.
Disease state	Physicochemical properties of mucus are known to alter conditions such as ulcerative colitis, cystic fibrosis, fungal infections, etc... The specific structural modifications in mucus are not well known in these conditions. For such diseases, the mucoadhesive properties should be tested in the same conditions.

Mucoadhesive polymers

Mucoadhesive polymers are identified for locating the active agents at a certain location. Polymers have played a significant role in designing such systems to increase the adhesion of the active agent at the specified area. Mucoadhesive polymer properties and their structure are discussed in table 1. The ideal properties of the mucoadhesive polymers are as follows

Ideal properties of mucoadhesive polymers

1. They should have good wetting, swelling, spreading, solubility, and biodegradable properties.
2. They should have good viscoelastic property and p^H should be biocompatible
3. They should adhere quickly to the mucosa and possess some site-specificity.
4. Polymers should be non-toxic, non-irritant, and free from impurities
5. The cost of the polymer is less.
6. The polymer should be stable on storage and during the self-life of the dosage form ^{11,15}.

Molecular characteristics

Studies made by many authors on polymers with different molecular properties have lead to a range of conclusions based on molecular properties required for mucoadhesion.

The properties exhibited by good mucoadhesive are as follow ¹⁵

1. Strong hydrogen bonding groups (-OH, -COOH).

2. Strong anionic charges.
3. Sufficient flexibility to penetrate the mucus network or tissue crevices.
4. Surface tension characteristics suitable for wetting mucus/ mucosal tissue surface.
5. High molecular weight.

Classification of mucoadhesive polymers

Mucoadhesive polymers are generally categorized based on source, aqueous solubility, and charge. They are ⁴

Based on source

- a. Natural:- Agarose, Gelatin, Hyaluronic Acid, Gums (Guar, Xanthan, Gellan, Carrageenan).
- b. Synthetic:- Cellulose Derivatives (HPMC, CMC, SODIUM CMC, HPC, HEC, MC), Poly(Acrylic Acid)-Based Polymers (CP, PC, PAA, Polyacrylates).

Based on solubility

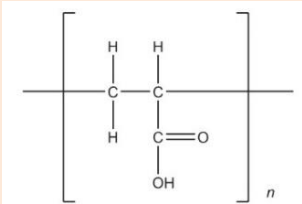
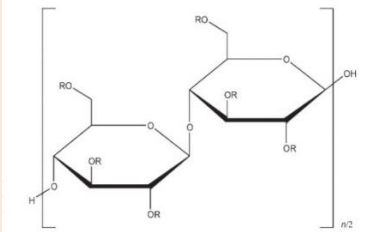
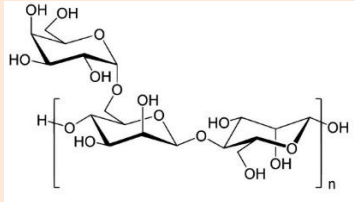
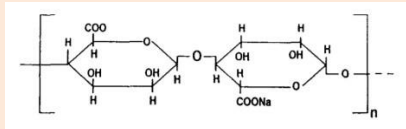
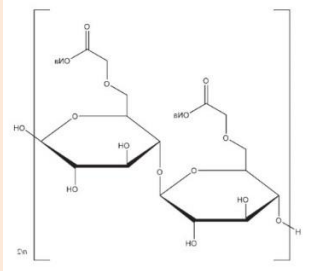
- a. Water-soluble:- CP, HEC, HPC, HPMC, PAA, sodium CMC.
- b. Water-insoluble:- chitosan, EC, PC.

Based on charge

- a. Anionic :- Chitosan-EDTA, CP, CMC, PAA, PC, Sodium Alginate, Sodium CMC.
- b. Cationic :-Chitosan, Trimethylated Chitosan, Amino Dextran, Dimethylaminoethyl (DEAE)-dextran.

Non-ionic :- Hydroxyethyl starch, PVA, PVP, HPC.

Table 1: List of mucoadhesive polymers and their properties ¹⁶

S.no	Polymer	Properties	Structures
1	Carbopol ¹⁶	Chemical name : Carboxy polymethylene M.W : 7×10^5 to 4×10^9 E.F : $C_3H_4O_2$ Grades : 907, 910, 934, 934P, 940, 971, 971P, 941, 980, 981. Viscosity : 29,400 to 39,400 cps. Density : 5 g/cm ³ pH: 2.5-3.0 Solubility: Water, Alcohol, Glycerine. Description: white, fluffy, acidic, hygroscopic powder with a slight characteristic odor	
2	Hydroxypropyl methyl Cellulose (HPMC) (16)	Chemical name: 2-hydroxypropyl methyl ether M.W : 86,000. E.F: $C_8H_{15}O_6-(C_{10}H_{18}O_6) -C_8H_{15}O_5$. Grades: Methocel- E5, E15, E50, E4M, K100, K15M, K4M Viscosity : HPMC E15-15 cps, HPMC E4M-4000 cps, HPMC K4M-4000 cps Density : 0.25-0.70 g/cm ³ pH: 6.0-8.0 Solubility: Soluble in cold water, insoluble in alcohol, ether, and chloroform, but soluble in mixtures of methyl alcohol and methylene chloride. Description: odorless, tasteless, white or creamy white fibrous or granular powder	 <p>where R is H, CH₃, or CH₂CH(OH)CH₂</p>
3	Guar Gum(16)	Chemical name: Galactomannan polysaccharide M.W : 220,000 E.F : $(C_6H_{12}O_6)_n$ Viscosity : 2000 to 22,500 cps Density : 1.492 g/cm ³ pH: 5.0–7.0 Solubility: Freely soluble in water, practically insoluble in organic solvents. Description: white to yellowish-white, odorless powder with a bland taste	
4	Sodium Alginate(16)	M.W: 216.121 E.F : $(C_6H_7O_6Na)_n$ Viscosity: 20 to 400 cps at 20°C pH: 7.2 Solubility: It is slowly soluble in water, insoluble in alcohol, In hydroalcoholic solutions. insoluble in other organic solvents and acids where the pH <3.0. Description: white or buff powder, odorless and tasteless.	
5	Sodium Carboxymethyl Cellulose (CMC) (16)	Chemical name : cellulose carboxymethyl ether sodium salt M.W : 90,000-700,000. E.F : $[C_6H_7O_2(OH)_3(OCH_2COONa)]_n$ Viscosity: 1200 cps Density : 0.75 g/cm ³ pH: 6.5-8.5 Solubility: It is soluble in water and practically insoluble in most organic solvents. Description: white to faintly yellow, odorless, hygroscopic powder or granular material having a faint paper-like taste.	

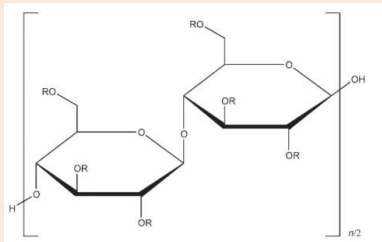
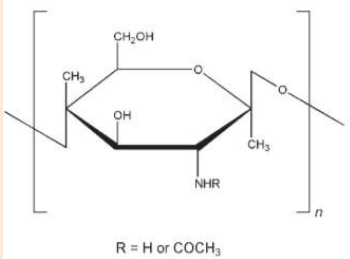
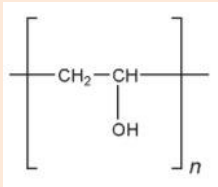
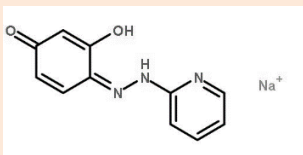
6	Hydroxypropyl Cellulose (HPC) (16)	<p>Chemical name: 2-hydroxypropyl ether</p> <p>M.W : 60,000 to 1,000,000</p> <p>E.F : $(C_{15}H_{28}O_8)_n$</p> <p>Grades: Klucel- EF, LF, HF, MF</p> <p>Viscosity: 1500-3000</p> <p>Density : 0.5 g/cm³</p> <p>pH: 5.0-8.0</p> <p>Solubility: Soluble in the water below 38°C. Also soluble in many polar organic solvents such as ethanol, propylene glycol, dioxane, methanol, isopropyl alcohol (95 %), dimethyl sulfoxide, and dimethylformamide. Insoluble in hot water.</p> <p>Description: white to slightly yellowish, odorless powder</p>	
7	Chitosan(16)	<p>Chemical name : Poly-b-(1,4)-2-Amino-2-deoxy-D-glucose</p> <p>M.W : 10 000–1 000 000,</p> <p>E.F : $(C_6H_{11}NO_4)_n$</p> <p>Density : 1.35–1.40 g/cm³</p> <p>pH: 4.0–6.0</p> <p>Solubility: Sparingly soluble in water; practically insoluble in ethanol (95%), other organic solvents.</p> <p>Description: odorless, white or creamy-white powder or flakes.</p>	 <p>R = H or COCH₃</p>
8	Polyvinyl Alcohol(16)	<p>M.W : 20000-200000</p> <p>E.F : $(C_2H_4O)_n$</p> <p>Viscosity : 4.0-65.0 mPas</p> <p>Density: 1.19-1.31</p> <p>Solubility: Soluble in water; slightly soluble in ethanol (95%); insoluble in organic solvents.</p> <p>Description: odorless, white to a cream-colored granular powder</p>	
9	Polycarbophil(16)	<p>M.W: 700 000 to 3–4 billion.</p> <p>Density : 0.19–0.24 g/cm³</p> <p>PH: 2.7–3.5</p> <p>Solubility: Polycarbophil polymers do not dissolve in water but can swell in water to around 1000 times their original volume</p> <p>Description: Polycarbophil occurs as fluffy, white to off-white, mildly acidic polymer powder with a slightly acetic odor.</p>	

Table 2: List of investigated formulations using mucoadhesive polymers

S.no	Active ingredient	polymers	Reference
1	Nifedipine	Polyethylene glycol 400, carbomer, sodium carboxymethyl cellulose	17
2.	baclofen	Carbopol 974p, sodium carboxymethyl cellulose, sodium alginate, PVP-K30	18
3.	Timolol maleate	Carbopol 974p, sodium alginate	19
4.	Selegiline	Polycarbophil	20
5.	Flurbiprofen and lidocaine	Hydroxypropyl methylcellulose, sodium alginate	21
6.	Domperidone	Hydroxypropyl methylcellulose E5	22
7.	Buspiron hydrochloride	Carbopol, hydroxypropyl methylcellulose. Sodium alginate, sodium CMC, guar gum	23
8.	Prochlorperazine maleate	Hydroxypropyl methylcellulose, sodium alginate, Carbopol 934P	24

9.	Nebivolol hydrochloride and nateglinide	Hydroxypropyl methylcellulose E15, ethylcellulose, guar gum, xanthan gum	25
10.	Hydrocortisone	Carbopol (974 and 971)	26
11.	Salbutamol sulphate	Carbopol 934, HPMC 4000, HEC, PEG6000	27
12.	Diltiazem hydrochloride	HPMC, Sodium CMC, sodium alginate, Guar gum, Carbopol 934	28
13.	Indomethacin	Chitosan, Carbopol, HPMC	29
14.	Loratadine	Carbopol 940	30
15.	Miconazole	Polyvinyl alcohol, propylene glycol, CMC,	31
16.	flurbiprofen	HPMC K15M, HEC, Carbopol 971 and carbomer 940	32
17.	Clonazepam	Carbopol 971P, HPC, poloxamer, chitosan	33)
18.	Risperidone	Carbopol, sodium alginate	34
19.	Itraconazole	Carbopol 934P, HPMC K4M	35

CONCLUSION

The dramatic rise in the targeted drug delivery is advantageous. Many studies have been conducted with mucoadhesive polymers such as first-generation and second-generation polymers for oral drug delivery. Second generation mucoadhesive polymers have many Advantages compared to first-generation polymers such as increased polymer contact time, site-specific adhesion having a wide range in buccal drug delivery systems The development of these drug delivery systems focused on the selection of appropriate polymers with excellent adhesive properties. The use of bioadhesive polymers to enhance contact time for a wide range of drugs and routes of administration has shown significant improvements in both specific therapies and more general patient compliance.

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