Recent Advances in Oral Mucoadhesive Drug Delivery

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ABSTRACT -- The oral cavity is one of the most important routes for local and systemic drug delivery, as it has a large surface, high permeability, and rich blood supply. Oral mucosal drug delivery has some advantages, such as enhancing bioavailability, preventing first-pass metabolism, reducing dose frequency, and non-invasiveness. In recent years, notable oral mucoadhesive patents were introduced to the pharmaceutical field, which indicates promising potentials for therapeutic purposes. Oral mucosal drug delivery can play a key role to deliver the biological drugs, such as antimicrobial peptides. This article gives an overview of oral mucoadhesive drug delivery systems and provides basic principles for the researchers to overcome the problems associated with the formulation design.

INTRODUCTION

Oral mucoadhesive drug delivery has many benefits, such as avoiding first-pass metabolism, easy administration, enhancing permeation, preventing enzymatic degradation, and fewer dose-related side effects (1). They are applied in the oral cavity, for local and systemic drug delivery. This delivery route is used for extended-release dosage forms to improve the therapeutic performance of the drug. Oral mucoadhesive drug delivery systems have gained increasing popularity in the pharmaceutical industry. Current marketed mucosal dosage forms come mainly in gel, spray, tablet, ointment, cream, and chewing gum (2). Many reports in the literature on the clinical trials and registered patents of the oral mucoadhesive drugs indicate that oral drug delivery is a promising way to apply a wide range from the therapeutic agents to the oral mucosal surface (3). Now researchers and pharmaceutical companies are looking further to use the mucoadhesive systems in the delivery of proteins, peptides, and genes. Polymeric antimicrobial peptide (AMP) delivery could be profitable to treat different hard infections such as bloodstream infections (4). Many polymers were investigated for oral delivery of biological drugs with various successes (5). Biological and biosimilar products are undoubtedly growing fast (6). Improving the pharmacokinetic properties of biological drugs can provide new possibilities for drug delivery in a rapidly growing market (7). Generally, drugs are rapidly absorbed into the mucosal tissues through the oral cavity. Oral mucoadhesive drug delivery enhancing pharmacokinetics results in increased drug bioavailability and controlled release rate (8). It was also shown that Cmax, AUC, and Tmax improved using this system in comparison to commercial drug formulations (8). In the study by Garhy et al. buccoadhesive gel of carvedilol nanoparticles (NPs) was prepared for enhancing dissolution and bioavailability. The results showed a two-time increase in bioavailability due to enhancement in drug solubility and avoiding the first-pass metabolism (9). Despite developing novel mucoadhesive systems and polymers in the last twenty years, mucoadhesion is still not fully understood. Furthermore, qualitative and quantitative techniques are still treated separately (10). This study aimed to provide an overview of mucoadhesive polymers, different oral mucoadhesive dosage forms, therapeutic effects, recent patents, the status of clinical trials, and commercial products.

Abbreviations: CP: carbopol; PCP: polycarboxylphil; SCMC: sodium carboxymethyl cellulose; HPMC: hydroxy propyl methyl cellulose; CMC: carboxymethyl cellulose; Cmax : maximum drug concentration; Tmax: time to maximum effect; AUC: area under the curve; AMP: antimicrobial peptide; HEC: hydroxy ethyl cellulose; PEG: polyethylene glycol; PAA: polyacrylic acid; HPC: hydroxypropyl cellulose; ALG: sodium alginate; PVA: polyvinyl alcohol; PVP: polyvinyl pyrrolidone; EC: ethylcellulose; LER: lercanidipine hydrochloride; MPC: methyl-pyrrolidinone chitosan; MHB: myoglobin; LHRH: luteinizing hormone-releasing hormone; PMS: Polymeric microsles; NPs: nanoparticles; MRSA: methicillin resistant staphylococcus aureus; HPβCD: hydroxypropyl beta cyclodextrin; CPM: chlorpheniramine maleate; PEG-b-PLA: polyethylene glycolmethyl ether-block-polyactide; NCT: nicotine; SA-MAS: sodium alginates-magnesium aluminium silicate.
ORAL MUCOSA CHARACTERISTICS

The oral membrane cavity has keratinized and non-keratinized epithelium (Figure 1). The keratinized epithelium of mucosa is mainly non-polar lipids (ceramides and acylceramides), and it is relatively impermeable to water. So, it is suitable for local treatment in the oral cavity. The non-keratinized epithelium of mucosa is mainly polar lipids (cholesterol sulphate and glucosylceramides); therefore, it is more permeable than keratinized mucosa. Thus, it is appropriate for both systemic and local treatment in the oral cavity (11). Due to the presence of salivary mucin molecules and their negative charge, the mouth cavity is an excellent route for drug delivery. In the mucous secretions, mucins play an important role in coating the oral cavity, because they can be conjugated to positively charged molecules of the drug and affect particular tissues and thus help drug delivery system. Therefore, they are used for modelling of mucoadhesive systems. The interpretations of the effect of various polymers at the mucin-polymer interface can be used in explaining the mechanism of mucoadhesion. The adhesive strength is explained by molecular bridges between mucin–polymers. The electronic properties of mucin are also help in mucoadhesion. Thus, mucoadhesion is the result of both electrical properties of mucin and bridges between mucin and polymer (12).

Figure 1. (A) The oral keratinized epithelium (B) non-keratinized epithelium

There are differences in permeability, blood flow, and residence time in various areas of the oral mucosa based on multiple tissue properties (13). The oral mucosal cavity can be divided into three categories for drug delivery: (a) Sublingual delivery: Systemic delivery of drugs by mucosal membranes’ lining in the floor of the mouth; (b) Buccal delivery: Drug delivery through the mucosal membranes’ lining in the cheeks (buccal mucosa); (c) Local delivery: This is drug delivery into the oral cavity for local administration to the tissues of the oral cavity (14).

MUCOADHESION THEORIES

Six theories have been presented to explain mucoadhesion phenomenon. Mucoadhesion is defined as the interaction between a mucoadhesive polymer and mucosal layer, and these theories describe various steps of the interaction between two substrates. In the following, these theories are presented:

Wetting Theory
This theory assumes the penetration of a mucoadhesive polymer into the irregularities of the absorbing surface, which becomes hardened and leads to mucoadhesion. The affinity toward the surface can be determined by measuring the contact angle (15).

Absorption Theory
According to this theory, adhesion is the result of interaction between the adhesive polymer and mucus substrate through two different types of chemical bonding, involving H-bonding and Van der Waals forces. After an initial contact, the adhesion of the two surfaces is due to the force between the atoms of the two surfaces (16).

Electronic Theory
This theory explains that differences in the electronic structures of two surfaces play an important role in their interactions. The formation of bonds takes place through the transfer of electrons between the polymer and the mucous membrane. The development of attractive force between polymer and mucous surface occurs by an electronic double-layer (17).

Mechanical Theory
In this theory the adhesion of two surfaces occurs, because the rough surface is filled by a mucoadhesive fluid. This step is an influential in mucoadhesion processes, although irregularities increase the area of the interface (18).

Fracture Theory
According to this theory, the force that causes the bond of adhesion between two surfaces and the force which is needed to detach them are related. This assumption determines the amount of force required to separate the polymer from the mucus, through following equation: \( \sigma = \sqrt{E*\varepsilon}/L \) where \( \sigma \) is the fracture strength, E is Young’s modulus of
elasticity, $\varepsilon$ is the energy of fracture, and $L$ is the critical length of crack (19).

**Diffusion Theory**
The diffusion theory is based both on the concentration gradient and the time of penetration of the polymer chain in the glycoprotein network of the mucus. The diffusion is a two-way process. One is the formation of a layer of interpenetration, and the other one is the achievement of an effective adhesion, which occurs when the interpenetration layer thickness reaches about 0.2-0.5 µm. The formation of this layer depends on factors like concentration gradient, molecular weight of adhesive macromolecules, hydrodynamic size, mobility, flexibility, and the length of the polymer chains (20).

**MECHANISMS OF MUCOADHESION**
The process of the adhesion of mucoadhesive polymer into the mucin layer of mucosal tissue takes place in the following two stages (21), which are shown in Figure 2. 1- During the contact stage, the mucoadhesive polymer comes into contact with the mucus membrane, and then intimate wetting, spreading, and swelling of mucoadhesive formulation occurs. These processes are accomplished via the presence of mucus in the mucosal membrane (22). 2- At the consolidation stage, penetration of the polymer of mucoadhesive formulation into the mucous surface occurs due to physical entanglement and secondary interaction, such as hydrogen bonding, vander Waals forces, and electrical attractions (23, 24).

**CHARACTERISTICS OF IDEAL MUCOADHESIVE POLYMERS**
A mucoadhesive polymer should be non-toxic and non-irritant to mucous surface, should have site-specificity and should be able to adhere quickly to the applied tissues (25). It should not prevent drug release should be able to take care of the daily requirement of the drug and be able to form strong non-covalent bonds with mucin cells (26). Mucoadhesive polymers should not degrade during storage, be inexpensive, conveniently available, and reproducible (21).

**FACTORS AFFECTING MUCOADHESIVE DRUG DELIVERY SYSTEMS**
The mucoadhesive drug delivery systems are affected by polymer related factors, environmental factors, and physiological factors, which are the followings:

**Polymer Related Factors**

* Molecular Weight
  The mucoadhesion force of a mucoadhesive polymer essentially depends on its molecular weight and polymeric linearity. In general, for the linear polymers (e.g., polyethylene glycol), the mucoadhesive property is proportional to their molecular weight. However, in the case of a nonlinear polymer, the mucoadhesive force of polymer may or may not depend on its molecular weight. This is in terms of the helical or coiled structures of such polymers which may shield some of the adhesive groups which are mainly responsible for the adhesive characteristics (27).

* Flexibility of Polymeric Chains
  Mucoadhesion starts when the polymer diffuses into the interfacial area (22). Chain flexibility is important for enlargement and interpenetration (28). An increase in the degree of diffusion in a mucus layer leads to a stronger mucoadhesion (29). To achieve such diffusion, the polymer chain should have enough flexibility, which depends on the diffusion coefficient and viscosity (25).

* Polymer Concentration
  The concentration of the polymer is critical for forming a strong adhesive connection with the mucus. Low polymer concentrations decrease polymer chain penetration into mucus. As a result, an unstable contact arises between the polymer and the mucus. In general, the highly concentrated polymer would lead to a more infiltrating chain length with higher adhesion (15, 27).

**Figure 2.** The two stages of the mucoadhesion process. Contact stage: mucoadhesive polymer comes into contact with the mucus membrane. Consolidation stage: penetration of the polymer of mucoadhesive formulation into the mucus.
Spatial Confirmation
The spatial conformation of a molecule is an important factor for the mucoadhesion strength. The mucoadhesive strength of a polymer depends on the spatial arrangement of polymers, i.e. whether they are helical or linear. The polymers with linear conformation have greater mucoadhesive strength than polymers with helical conformation, because helical conformation of polymer involves various active groups. Thus, their mucoadhesive strength is reduced (30).

Molecular Charge of the Polymer
Nonionic polymers have a lower degree of adhesion than anionic polymers, according to studies on their molecular charge. The anionic charge of a polymer must be strong enough to have mucoadhesion (27). The cationic charge on the surface of a polymer increases the interaction between polymer’s surface and mucin, as the mucin has a negative charge (31).

Swelling
Hydration is required for the swelling of the mucoadhesive polymers to form the desired size of macromolecules. This increases the entanglement process between polymer and mucin. The polymer concentration, ionic strength, and the presence of water are required for swelling (32). To have a suitable swelling and mucoadhesion, an optimum level of hydration is required in the mucoadhesive polymer (33).

Environmental Related Applied Strength
If the pressure is first applied to the mucoadhesive tissue contact site, it can affect interpenetration (34). When high pressure is applied, the polymer used becomes mucoadhesive, even if it does not have interaction capacity (35).

Initial Contact Time
The initial contact time between polymer and mucin affects the mucoadhesive strength, extent of swelling, and interpenetration of polymers (36). The mucoadhesive strength increases by an increase in the initial contact time (28).

Moistening
Moistening provides an ideal environment for the mucoadhesive polymer to distribute over the surface of mucin and creates a particle size suitable for polymer penetration into mucin. The result of moistening of polymer is to provide a close contact of particles with the mucosa, and chemical interactions between the bioadhesive polymer and mucin chains, which create a “macromolecular mesh” of adequate size, leading to changes in the rheological behavior of two macromolecular species. So, it enhances the mobility of polymer chains to increase penetration process between polymer and mucous (37).

Physiological Factors
Mucin turnover, renewal rate of mucosal cells, and disease state of mucus layer are physiological variables that may affect mucoadhesion (38).

MUCOADHESIVE POLYMERS
The study of mucoadhesive polymers and their applications in pharmaceuticals have attracted the attention of researchers in this field, because of mucoadhesives’ notable properties. These carriers must provide biodegradability, biocompatibility, swelling capacity, among other properties (39). Wetting mucoadhesive polymers results in the formation of a viscous solution that prolongs adherence to the mucosal surface. This, in turn, causes more adhesive interactions, such as forming of hydrogen bonds, electrostatic interactions, and covalent bonding. Mucoadhesive polymers in oral drug delivery systems may be natural or synthetic (40). They are classified according to Figure 3.

CLASSIFICATION OF POLYMERS BASED ON GENERATION
First Generation Of Mucoadhesive Polymers
These are either natural or synthetic hydrophilic substances which have organic functional groups (carboxyl, hydroxyl, and amino groups) or hydrogen bonds. Some known mucoadhesive polymers are carbomers, cellulose derivatives, chitosan and, alginates. They come into three types: (a) Cationic polymers such as chitosan that have electrostatic interactions with mucin. (b) Anionic polymers are mainly derived from poly acrylic acids, which have a negative charge. (c) Non-ionic polymers that have weaker mucoadhesion force than anionic polymers. Among these polymers are hydroxyl propyl-methyl cellulose, hydroxyethyl cellulose and methyl cellulose (18).

Carbopol
Carbopol, a lightly cross-linked polyacrylic acid (PAA), is an industry standard for mucoadhesive polymers (4). These days, many companies use carbopol polymers, because of some advantages such as releasing in a long period of time, being safe and effective for oral administration, increasing bioavailability, and protecting protein
and peptides from degradation (41). The role of carbopol in protecting peptides and protein is to change the velocity of degradation reaction (42). As carbopol has a pKa value of 6.05, it makes polymer to swell in an aqueous medium, and so increasing medium’s viscosity. This inhibits the enzyme to access the substrate, thus reducing the enzymatic activity (43). In a study, Buprenorphine tablet, containing carbopol 974, lactose, and PEG 3350 were made. This formulation had a sustained release profile that released their entire drug content within 2h, which is an optimum result for a sublingual tablet (13). Several studies have shown that insulin absorption may be greatly enhanced upon oral delivery because of the positive properties of the thiomer polyacrylic acid cysteine, which include mucoadhesion, protection against enzymatic degradation and permeation enhancement (4).

**Chitosan**

Chitosan is a cationic polymer (polysaccharide) that is gaining importance in developing mucoadhesive drug delivery systems, because of its good biocompatibility, biodegradability, and nontoxic nature. It binds to the mucosa via ionic bonds between the amino group and sialic acid residues. Onishi and Machida showed that chitosan and its metabolized derivatives are quickly eliminated by the kidney (44). In the study of Ayensu et al., lyophilized chitosan wafers were prepared that contained chitosan, bovine serum albumin (as a model protein), glycerol (as plasticizer), and d-mannitol (as cryoprotectant). The results indicated the usefulness of lyophilized chitosan wafers for buccal delivery of protein-based drugs (45-47). In another study, low molecular weight chitosan was optimized for a gene delivery system (48). AMP-loaded liposomes with chitosan improve the bioavailability and increase the effectiveness of AMP upon oral administration. Li et al. formulated KSL (KKVVFVKFK-CONH2) peptide into PLGA/chitosan composite microspheres for oral bacteria (F. nucleatum). The results showed a prolonged antimicrobial and inhibitory effect for up to 80 days (49). In the study of Sharma et al. encapsulation of the peptide pep-H in chitosan, led to the formation of nanoparticles with a cationic surface charge, resulting in 80% reduction of intracellular M. tuberculosis load (50).

**Pectin**

Pectin is a natural polysaccharide consisting of mainly D-galacturonic acid and glycosidic units (51). Pectin can be used for controlled drug delivery because of its excellent biocompatibility and unique properties. For instance, pectin can easily adhere to mucosal surfaces which improve the retention time of AMPs (52). Krivorotova et al. indicated the antimicrobial activity of nisin-loaded nanoparticles in vitro against two Gram-negative bacteria (E. coli and Klebsiella spp.) and two Gram-positive (Arthrobacter sp. and Bacillus subtilis), using the agar-diffusion assay (53). Their results showed that the nisin-loaded pectin NPs possessed a higher antimicrobial activity against Gram-positive compared to Gram-negative bacteria. Furthermore, nisin-loaded pectin NPs were 100-fold more effective compared to sodium benzoate (a conventional preservative) in the killing of Gram negative bacteria and Gram-positive. These findings indicate that nisin-loaded pectin nanoparticles are an appropriate polymeric for antimicrobial delivery systems (54).

**Second Generation Of Mucoadhesive Polymers**

Compared to the previous one, the advantage of this generation is that they can interact with cell
surfaces through specific receptors or covalent bonding, which leads to improved chemical interactions. Among this group are lectins and thiomers (55).

Lectins
Lectins are glycoproteins or proteins of nonimmunological origin which specifically recognize sugar molecules, and therefore can bind to glycosylated membrane components (56, 57). Sugars are present in glycolipids and glycoproteins of mammalian mucosa, at the surface of epithelial cells, or in mucous layers (4). Lectins after binding to the cell may either remain on the cell surface or may be taken inside the cell via endocytosis. Some lectins, including those extracted from ulex europaeus, soybean, peanut, and lensculinarius, have been found to bind specifically to mucosal cells. Wheat germ agglutinin exhibits the fewest immunogenic responses of all lectins (55, 56). Lectins are a suitable option for oral delivery, because they provide good protection from acids and enzymes (27).

Thiolated Polymers
The thiolated polymers are derivatives of hydrophilic polymers like polyacrylates, chitosan, or deacetylatedgallan gum. The presence of these polymers increases the residence time via the covalent bonds with the residuals of cysteine in mucus and also increases rigidity and crosslinking. Thiolated polymers also show an increased permeation-enhancing effect and enzyme inhibitory properties (58). In the studies of Langoth et al., matrix-based tablets were made that contained novel pentapeptideleu-enkaphalin (pain modulating) and thiolated polymer PCP (Polycarbophil). The results showed that the stability of the matrix tablet and mucoadhesive properties were increased and continued for more than 24 hours (59).

ADVANTAGES AND DISADVANTAGES OF ORAL MUCOADHESIVE DRUG DELIVERY

The main advantages of oral mucoadhesive drug delivery are prolonged residence time, increased therapeutic efficacy, rapid absorption, preventing first pass metabolism, faster onset of action, preventing enzymatic degradation, excellent accessibility, and cost-effective (60-62). Using the oral mucoadhesive drug delivery has some limitations, such as losing advantages in swallowing, being usable only in small dosage, and limitation in eating and drinking (13). If this form of drug irritates the oral mucosa, it cannot be administered by this route (63).

MUCOADHESIVE DOSAGE FORMS

Solid Dosage Forms
Tablets
The polymers which are mostly used for mucoadhesive tablets include carbopols (CP934 and CP940 PCP), sodium carboxymethyl cellulose (SCMC), pectin, chitosan, hydroxypropylmethyl cellulose (HPMC), and carboxymethyl cellulose (CMC). These polymers can be used alone or in combination to make compressed bioadhesive tablets. HPMC and pectin show weak bioadhesion, while SCMC and chitosan have strong bioadhesion. The derivatives of polyacrylic acid (CP934, CP940, and PCP) show the highest bioadhesion and longest residence time. In a study, a combination of mucoadhesive polymers (a mixture of 5% CP934, 65% HPMC and spray-dried lactose) was used, which indicated optimal bioadhesion and good residence time (2 h)(13). In another study, a bioadhesive tablet was made by mixing CP and CMC, in the ratios of 35% and 15%, respectively, which showed optimum bioadhesion and release time (13). Another form of mucoadhesive tablets is bilayer tablets which consist of a backing layer, an adhesive, a drug reservoir layer, and a covering with an inert ethylcellulose layer. Bilayer tablets are beneficial to overcome the limitations of single layered tablets (64).

Bioadhesive Lozenges
A different form of bioadhesive drugs is a lozenge, which has good potential for prolonged release and patient compliance. They are applied as an alternative for those patients who are unable to swallow. Although lozenges were used for systemic drug delivery, they are applied to bath oral cavity or throat areas. Lozenges are used for the oral cavity as antibiotics, local anesthetics, antimicrobials, and antifungals (65).

Polymeric Micelle
Polymeric Micelles (PMs) can be used to deliver poorly water-soluble drugs, particularly in the areas of oral delivery. PMs could enhance the oral drug bioavailability due to their controlled release and special stability (4). Some properties of PMs, such as pH-sensitive and mucoadhesive, have gained much attention and provide a promising way to improve the bioavailability of oral delivery (4). Bernkop-Schnürch et al. showed that the thiolation of classical PMs increases their mucoadhesive properties and so improves the oral absorption of therapeutic proteins (58). In the study by Kumar et al., it turned out that polymeric
micelles improved pharmacokinetic parameters for
docetaxel, compared to free docetaxel suspension
(66).

Bioadhesive Micro/Nano Particles
Bioadhesive micro/nano particles have some
advantages, such as being small particles,
acceptable by the patients, and making intimate
contact with the mucosal area. The small size of
particles causes less local irritation at the site of
adhesion and reduces uncomfortable sensations in
the oral cavity (67). These delivery systems are
presented in the forms of aqueous suspension, gel,
ointment, or paste. Carbopol, polycarbophil,
chitosan, alginate, and gantrez (copolymers
containing alternating units of methylvinylether
and maleic anhydride) are used for the preparation
of bioadhesive microparticles. Some studies
showed that particles of chitosan or gantrez remain
on mucosal tissue for a longer time (68, 69). Oral
transmucosal nanoparticles can be used for
systemic treatment, because they can penetrate via
the epithelium. Monti et al. prepared an atenolol
formulation, containing a microsphere with
poloxamer 407 and applied this formulation in
rabbits, and compared it with a marketed tablet
formulation. The results showed that atenolol
concentration remained higher than the marketed
tablets. Its bioavailability was also good, however,
it had a lower drug dose. This study suggested a
possible dose reduction using atenolol
microparticles via oral transmucosal
administration (70). Using a nanoparticle system
for AMP release rate, can be controlled by
modifying the composition of the delivery system,
such as the molecular weight of the polymer used.
The encapsulation of AMPs in solid lipid
microparticles can provide stability needed for oral
delivery (5). Biocompatible and biodegradable
polymers, copolymers, and lipids were applied to
formulate nano/micro-particle as vaccine-delivery
systems (71-73).

Bioadhesive Wafers
This kind of bioadhesive system is in the form of a
wafer with an adhesive surface layer and a bulk
layer. It consists of an antibacterial agent, matrix
polymers, and biodegradable polymers. A novel
periodontal drug delivery system was reported for
the treatment of periodontitis (67).

Powder Dosage Forms
The powder forms of drugs are made of a physical
mixture of an active agent with a bioadhesive
polymer and they can be sprayed into the buccal
mucosa to treat the buccal disorders. Yamamoto et
al. prepared such powder form which contained
hydroxypropyl cellulose and beclomethasone
dipropionate (as an active agent) and sprayed it
into the buccal cavity of rats. The results showed
that this powder increased the residence time up to
4 hours and was more effective than oral solutions
containing the same active agent and polymer with
the same concentration (74).

Semisolid Dosage Forms
Bioadhesive Patches/Films
There are two types of patches for drug delivery in
oral mucosa: a) Dissolvable matrix patch systems:
These patches dissolve slowly and completely and
have a longer acting time than other solid forms for
treating oral diseases. b) Patch systems with non-
dissolvable backing: They are used for systemic
drug delivery, being protected from saliva, and also
have controlled release of the drug into oral
mucosa for 10-15 h (75-77). In a study, an
Acyclovir patch was prepared for buccal drug
delivery, which contained polyethyleneglycol
(PEG), acrylic acid copolymer, monomethyl ether,
monomethacrylate and an impermeable layer. In
vivo study showed that when the patch was applied
in the buccal area, it remained there and released
the drug for about 22 h. This study indicated that
Acyclovir patch could be a good option for buccal
drug delivery (1). In the study by Rana et al., NP-
in-microparticle structured buccal patch was
designed as a novel platform for buccal delivery of
drugs that have high first-pass metabolism (78).

Buccal films have more flexibility and
mechanical resistance than other dosage forms.
Furthermore, it can be easily removed in
emergency cases and can have a controlled release
system (79, 80). Polymers like sodium CMC, CP
934P, HPMC and PEG 400 were used for buccal
films. It was shown that buccal films made by
HPMC have more elasticity, more bioadhesive
properties, and better tolerable swelling than
buccal films prepared by sodium CMC films (1).
Vaccines could be formulated in an oral film
dosage form which would make them more
effective and very desirable. Various research
results showed that vaccine formulation
development for buccal administration and parallel
development of easily soluble oral films have been
very promising for changing the future of vaccine
delivery (60).

Gels and Hydrogels
Hydrogels and gels are two types of semi-solid
adhesive systems. They should be applied to the
buccal mucosa or intra-periodontal pocket to
extend their residence duration and boost their
absorption. Gels have the benefit of being able to
make direct contact with the mucosa and releasing
the drug rapidly in the region of application, making them an ideal drug delivery mechanism for the oral cavity. In general, carbomers increase gels’ efficacy as they increase residence time on mucous and prolong the duration of action. Gels have advantages over solutions as they provide longer release time and improved bioavailability (37). Corsodyl® is an oral mucoadhesive gel which contains chlorhexidine gluconate, as an active ingredient, that is brushed on the teeth to prevent the formation of plaque, thus improving oral hygiene. It also contains the polymer Hydroxypropyl cellulose (HPC) which aids to keep the gel inside the oral cavity (81).

**Liquid Dosage Forms**

The solutions or suspensions of dosage forms are applied as mucoadhesive for local drug delivery in the oral cavity. Chitosan, carbopol, methylcellulose, sodium CMC, gelatin, and polycarbophil have the greatest bindings among polymer solutions. Viscous liquids may be coated with the aforementioned polymers for utilizing as protectants or as vehicles for medication administration to the mucosal surface. Dry mouth can be treated with artificial saliva solutions that are retained on mucosal surfaces to provide lubrication. These solutions also contain sodium CMC as mucoadhesive polymer (37).

**RECENT PATENTS, CLINICAL TRIALS AND COMMERCIAL PRODUCTS**

As mucoadhesion is a good way for controlled drug release, many formulations are investigated both in vitro and in vivo. In recent years, many patents on oral mucoadhesive delivery systems have been introduced in the pharmaceutical field (3). The majority of the formulations in clinical trials are in conventional dosage forms, particularly tablets, films, and oral liquids. Some of the recent patents, clinical trials, and commercial products of oral mucoadhesive drugs are summarized in Tables 1 and 2 (82).

**A Therapeutic Approach**

Oral mucoadhesive drug delivery is used for the treatment of numerous diseases (Figure 4). This delivery system shows controlled drug release, enhancement of bioavailability, easy administration, reduction of dosage, and frequency of usage (83).

**Antiemetics**

Ondansetron hydrochloride is a 5HT₃ serotonin antagonist and is used to prevent nausea and vomiting as a side effect of emetogenic cancer chemotherapy. To prevent hepatic first-pass metabolism and to increase the bioavailability of the drug, it should be used through the buccal route (84, 85). Ali et al. formulated a buccal adhesive tablet which consisted of ondansetron, CP 934, sodium alginate (ALG), SCMC of low viscosity, HPMC 15cps, and ethyl cellulose. The results showed that both the device and the drug were stable in natural human saliva for 6 hours (86). In another study done by Koland et al., a fast-dissolving film was prepared for sublingual administration which contained ondansetron, polyvinyl alcohol (PVA)/polyvinyl pyrrolidone (PVP), and carpool. The results indicated that the formulation containing carbopol had maximum swelling, compared to the formulation containing PVP (87). In the study of Bhalekar et al., buccal bioadhesive hydrophilic matrix tablets were made, which consisted of domperidone, HPMC, and carbopol. The results showed that increasing the amount of these polymers increases bioadhesive strength, but reduces the releasing rate of the active agent (88).

**Antimigraine**

Sumatriptan succinate (a 5-HT₁ receptor agonist) is used to treat the migraine. Shidhaye et al. prepared mucoadhesive bilayered buccal patches, which consisted of Sumatriptan succinate, chitosan, and PVP K30. The results showed that increasing the concentration of chitosan, leads to an increase in the mucoadhesive strength of patches. But, the increase in PVP K30 and a decrease in the concentration of chitosan leads to a better release of the drug. On the other hand, enhancing both chitosan and PVP K30, lead to an increase in the extent of swelling of the patches. Sumatriptan succinate has low permeability via the buccal mucosa. Therefore, to improve its buccal penetration, different penetration enhancers such as polysorbate 80, transcutol and Dimethyl
sulfoxide (DMSO) were used. The results indicate that using this kind of enhancers and the buccal route can be a satisfying way for drug delivery and can also prevent the first-pass metabolism (89).

In the study of Sekhar et al., mucoadhesive buccal patches were formulated that contained CPM and hydroxyethylcellulose (HEC). The results revealed that bioavailability from the buccal patch was 1.46 times higher than the case of the oral dosage form. It indicated that the dosage form was non-irritating and did not cause mucosal damage or irritation by buccal application (90).

### Antimicrobials

Using the conventional pharmaceutical dosage forms like suspensions, solutions, and mouthwashes is not very effective for oral cavity diseases. This could be attributed to the easy removal of such forms of drugs; therefore, some efforts have been done for the clinical treatment of oral cavity complications. In the study of Juan et al., a bilayered mucoadhesive tablet, which consisted of nystatin, a lactose layer, and a polymeric layer was prepared. The polymer layer causes sustained release for approximately 6 hours (91). In the study of Fini et al., HPMC, CMC and hydroxypropyl cellulose (HPC) were used for a novel mucoadhesive gel of chlorhexidine (92). In another study by Domb et al., mucoadhesive tablets consisting of iodine complexes with ethylcellulose (EC) and HPC were made, which were used as antimicrobial agents for treating oral infections (93). Obaidat et al., prepared mucoadhesive patches, which consisted of carvacrol and tetracycline hydrochloride for the treatment of mouth infections. This formulation showed very good activity against Pseudomonas aeruginosa, which indicated a synergistic action between carvacrol and tetracycline. On the other hand, when they were separately used, they were ineffective against Pseudomonas aeruginosa. This combination was also effective against Bacillus cereus (94).

### Cardiovascular Medicines

Carvedilol is a non-selective beta-adrenergic antagonist and is used for treating hypertension and stable angina pectoris. For treating the hypertension, Yamsani group made carvedilol mucoadhesive tablets, which consisted of carbopol 934 and hydroxypropylmethyl cellulose (HPMC K4M and K15M) to achieve controlled and zero-order release. The results showed that increasing polymer concentration in the formulations leads to sustained release of carvedilol (95). Lercanidipine hydrochloride (LER) is used to treat the hypertension. In the study of Charde et al., buccal mucoadhesive controlled-release tablets of LER were prepared, which consisted of polyethylene oxide and different viscosity grades of HPMC, individually and in combination. In vivo studies on rabbits indicated significant increase in the bioavailability of LER, in comparison to oral administration of the drug. The use of placebo formulations in the case of humans revealed that the designed tablets adhered well to buccal mucosa for more than 4 h, without resulting in any discomfort (96).

### Muscle Relaxants

Tizanidine hydrochloride is an agonist on centrally located α2 receptors, which has myotonolytic effects on skeletal muscles. In the study of Shanker et al., bioadhesive buccal tablets were prepared to

### Table 1. Patented oral mucoadhesive formulations.

<table>
<thead>
<tr>
<th>Active Ingredient</th>
<th>Patent No. or Appl. No.</th>
<th>Dosage form</th>
<th>Route of administration</th>
<th>Year</th>
</tr>
</thead>
<tbody>
<tr>
<td>Apomorphine Hydrochloride</td>
<td>US10888499</td>
<td>Film</td>
<td>Sublingual</td>
<td>2021</td>
</tr>
<tr>
<td>Bupernorphine Hydrochloride, Naloxone Hydrochloride</td>
<td>US10874661</td>
<td>Tablet</td>
<td>Sublingual</td>
<td>2020</td>
</tr>
<tr>
<td>Asenapine maleate</td>
<td>A205960</td>
<td>Tablet</td>
<td>Sublingual</td>
<td>2020</td>
</tr>
<tr>
<td>Sufentanil citrate</td>
<td>N209128</td>
<td>Tablet</td>
<td>Sublingual</td>
<td>2018</td>
</tr>
<tr>
<td>Desmopressin acetate</td>
<td>N022517</td>
<td>Tablet</td>
<td>Sublingual</td>
<td>2018</td>
</tr>
<tr>
<td>Extracts of the Marzeh khuzestani</td>
<td>96840</td>
<td>Gel</td>
<td>Buccal</td>
<td>2018</td>
</tr>
<tr>
<td>Nicotine</td>
<td>US20060198873A1</td>
<td>Film</td>
<td>Buccal</td>
<td>2017</td>
</tr>
<tr>
<td>Zolpidem tartrate</td>
<td>A201509</td>
<td>Tablet</td>
<td>Sublingual</td>
<td>2016</td>
</tr>
<tr>
<td>Bupernorphine hydrochloride</td>
<td>N207932</td>
<td>Film</td>
<td>Buccal</td>
<td>2015</td>
</tr>
<tr>
<td>Naloxone</td>
<td>US 10617686B2</td>
<td>Liquid spray</td>
<td>Buccal</td>
<td>2014</td>
</tr>
<tr>
<td>Bupernorphine</td>
<td>US20114037497A1</td>
<td>Film</td>
<td>Sublingual</td>
<td>2014</td>
</tr>
<tr>
<td>Ayclovir</td>
<td>N203791</td>
<td>Tablet</td>
<td>Buccal</td>
<td>2013</td>
</tr>
<tr>
<td>Fentanyl</td>
<td>N202788</td>
<td>Spray</td>
<td>Sublingual</td>
<td>2012</td>
</tr>
<tr>
<td>Miconazole</td>
<td>022404</td>
<td>Tablet</td>
<td>Buccal</td>
<td>2010</td>
</tr>
</tbody>
</table>
avoid first-pass metabolism and prolong drug release. It contained tizanidine and some bioadhesive polymers, such as HPMC K4M, SCMC. The results indicated that increasing the concentration of SCMC leads to an increase in bioadhesion strength and a higher degree of swelling in a short time. It turned out that the degree of swelling was directly related to the amount of SCMC and inversely related to the amount of HPMC K4M (97).

Table 2. Commercial and clinical trial of oral mucoadhesive formulations.

<table>
<thead>
<tr>
<th>Active Ingredient</th>
<th>Dosage Form</th>
<th>Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>Asenapine</td>
<td>Wafer</td>
<td>Commercial</td>
</tr>
<tr>
<td>Buprenorphine + naloxone</td>
<td>Film</td>
<td>Commercial</td>
</tr>
<tr>
<td>Desmopressin</td>
<td>Tablet, wafer</td>
<td>Commercial</td>
</tr>
<tr>
<td>Triamcinolone</td>
<td>Paste</td>
<td>Commercial</td>
</tr>
<tr>
<td>Miconazole</td>
<td>Gel</td>
<td>Commercial</td>
</tr>
<tr>
<td>Desmopressin</td>
<td>Tablet, wafer</td>
<td>Commercial</td>
</tr>
<tr>
<td>Nicotine</td>
<td>Tablet, film, gum, lozenge, spray, chewing Gum</td>
<td>Commercial</td>
</tr>
<tr>
<td>Buprenorphine</td>
<td>Tablet, film</td>
<td>Commercial</td>
</tr>
<tr>
<td>Fentanyl</td>
<td>Tablet, spray, film, lozenge</td>
<td>Commercial</td>
</tr>
<tr>
<td>Glyceryltrinitrate</td>
<td>Tablet, spray</td>
<td>Commercial</td>
</tr>
<tr>
<td>Sufentanil</td>
<td>Tablet</td>
<td>Commercial</td>
</tr>
<tr>
<td>Isosorbidedinitrate</td>
<td>Tablet</td>
<td>Commercial</td>
</tr>
<tr>
<td>Allergen extract</td>
<td>Wafer</td>
<td>Commercial</td>
</tr>
<tr>
<td>Melatonin</td>
<td>Tablet</td>
<td>Commercial</td>
</tr>
<tr>
<td>Zolpidem</td>
<td>Tablet</td>
<td>Commercial</td>
</tr>
<tr>
<td>Lorazepam</td>
<td>Tablet</td>
<td>Commercial</td>
</tr>
<tr>
<td>Buprenorphine</td>
<td>Tablet, film</td>
<td>Commercial</td>
</tr>
<tr>
<td>Insulin</td>
<td>Spray</td>
<td>Commercial</td>
</tr>
<tr>
<td>Prochlorperazone</td>
<td>Tablet</td>
<td>Commercial</td>
</tr>
<tr>
<td>Methyltestosterone</td>
<td>Tablet</td>
<td>Commercial</td>
</tr>
<tr>
<td>Rizatriptan</td>
<td>Wafer</td>
<td>Commercial</td>
</tr>
<tr>
<td>Norandrodiol</td>
<td>Tablet</td>
<td>Commercial</td>
</tr>
<tr>
<td>BeclometazineDipropionate</td>
<td>Spray</td>
<td>Commercial</td>
</tr>
<tr>
<td>Midazolam</td>
<td>Oral liquid</td>
<td>Commercial</td>
</tr>
<tr>
<td>Nystatin</td>
<td>Oral liquid</td>
<td>Commercial</td>
</tr>
<tr>
<td>Vitamin B₁₂</td>
<td>Tablet, spray, oral liquid</td>
<td>Commercial</td>
</tr>
<tr>
<td>Ropivacaine</td>
<td>Liposomal gel</td>
<td>Phase I completed</td>
</tr>
<tr>
<td>Diazepam</td>
<td>Film</td>
<td>Phase III</td>
</tr>
<tr>
<td>Montelukast</td>
<td>Film</td>
<td>Phase II</td>
</tr>
<tr>
<td>Apomorphine</td>
<td>Film</td>
<td>Phase II/III</td>
</tr>
<tr>
<td>Dexamethasone</td>
<td>Film</td>
<td>Phase I</td>
</tr>
<tr>
<td>Ketamine</td>
<td>Film, Wafer</td>
<td>Phase II/III completed</td>
</tr>
<tr>
<td>Insulin</td>
<td>Film, spray</td>
<td>Phase III</td>
</tr>
<tr>
<td>Arteether</td>
<td>Spray</td>
<td>Phase III completed</td>
</tr>
<tr>
<td>Flumazenil</td>
<td>Spray</td>
<td>Phase II/III completed</td>
</tr>
<tr>
<td>Polyoxidonium</td>
<td>Spray</td>
<td>Phase III</td>
</tr>
<tr>
<td>Tizanidine</td>
<td>Powder</td>
<td>Phase VII completed</td>
</tr>
<tr>
<td>Ticagrelor</td>
<td>Powder, tablet</td>
<td>Phase IV</td>
</tr>
<tr>
<td>Tacrolimus</td>
<td>Oral liquid, powder</td>
<td>Phase IV</td>
</tr>
<tr>
<td>Cyclobenzaprine</td>
<td>Oral liquid</td>
<td>Phase IV</td>
</tr>
<tr>
<td>Methadone</td>
<td>Oral liquid</td>
<td>Phase I completed</td>
</tr>
<tr>
<td>Cholera toxin B subunit</td>
<td>Oral liquid</td>
<td>Phase I completed</td>
</tr>
<tr>
<td>Ketonolac</td>
<td>Oral liquid</td>
<td>Phase IV</td>
</tr>
<tr>
<td>Naloxone</td>
<td>Oral liquid</td>
<td>Phase II/III completed</td>
</tr>
<tr>
<td>Influenza vaccine</td>
<td>Oral liquid</td>
<td>Phase I completed</td>
</tr>
<tr>
<td>Cannabidiol</td>
<td>Tablet, oral liquid</td>
<td>Phase II/III/IV</td>
</tr>
<tr>
<td>Sildenafil</td>
<td>Tablet, wafer</td>
<td>Phase III completed</td>
</tr>
<tr>
<td>Agomelatine</td>
<td>Tablet</td>
<td>Phase III completed</td>
</tr>
<tr>
<td>Ofanzapine</td>
<td>Tablet</td>
<td>Phase IV completed</td>
</tr>
<tr>
<td>Cyclobenzaprine</td>
<td>Oral liquid</td>
<td>Phase III</td>
</tr>
<tr>
<td>Lobeline</td>
<td>Tablet</td>
<td>Phase I</td>
</tr>
<tr>
<td>Riluzole</td>
<td>Tablet</td>
<td>Phase III/III</td>
</tr>
<tr>
<td>Alprazolam</td>
<td>Tablet</td>
<td>Phase II/III/III completed</td>
</tr>
<tr>
<td>Misoprostol</td>
<td>Tablet</td>
<td>Phase III/IV</td>
</tr>
<tr>
<td>Zolmitriptan</td>
<td>Tablet</td>
<td>Phase IV</td>
</tr>
</tbody>
</table>

**Hypoglycaemic Agents**

In the study of Semalty et al., mucoadhesive buccal films were formulated which contained glipizide, HPMC, CP-934, SCMC and Eudragit RL-100. The result was that the therapeutic levels of glipizide could be efficient by the buccal delivery (98). Muzib et al. used different HPMC grades to prepare mucoadhesive buccal films of glibenclamide. The results indicated that matrix integrity depends on the amount and properties of the drug. It was found that more presence of hydroxyl groups in HPMC K15 leads to higher swelling, and reduces the residence time of different formulations. It turned out that drug...
release from the films depends on the proportion of polymers. It was also found that HPMC 3000 of low concentrations can be used for buccal delivery of glibenclamide (99).

**Proteins and Hormones**

The delivery of proteins and hormones via the buccal mucosa could be easier and safer than other routes of administration (100, 101). In the study of Cui et al., bilaminated films of insulin were prepared, and its release behavior was evaluated. Bilaminated films were administered through buccal in healthy rats. The findings demonstrated the formulation's hypoglycemic impact and a 17 percent increase in pharmaceutical availability as compared to subcutaneous insulin injection (101). In the study of Colonna et al., mucoadhesive films were formulated which contained 5-methylpyrrolidinone chitosan (MPC) and myoglobin (MHb). MPC is a derivative of chitosan that has good properties for buccal drug delivery. It turned out that it is an excellent polymer for the manufacturing of bioadhesive films (102). In the study of Nakane et al., buccoadhesive tablets were prepared which contained luteinizing hormone-releasing hormone (LHRH). In vivo study was done for the case of beagle dogs and pharmacokinetic profiles were evaluated to find the transmucosal permeation kinetics of LHRH. The results indicated that plasma LHRH concentrations reached the plateau level within 30 min, and it was maintained for 2 hr after using the dosage form, which compared to rapid elimination profile after IV administration (103). In the study of Giovino et al., mucoadhesive chitosan-based films were formulated, in which insulin was loaded on nanoparticles (NPs) and polyethylene glycolmethyl ether-block-polyactide (PEG-PLA). The results showed that these formulations had the classic biphasic sustained release of protein over 5 weeks (104).

**Anti-Inflammatory Drugs**

One of the major reasons for oral cavity diseases is inflammation (105). To take care of this problem, topical administration of various anti-inflammatory drugs such as flurbiprofen, flufenamic acid, ibuprofen etc., are used. In these treatments, the dosage of the drug is reduced, and the systemic side effects are minimized (106, 107). In the study of Anahita Ghorbani et al, mucoadhesive tablets were prepared which contained carbopol 940, sodium alginate, zinc sulfate and starch. Results showed clinically and statistically the effectiveness of zinc mucoadhesive tablets as a topical drug delivery system, on decreasing pain, the diameter of the wound, and length of the recovery period of recurrent aphthous stomatitis compared to the control group (108). Another study by Perioli et al. sustained-release mucoadhesive bilayered tablets were designed by mixing mucoadhesive polymers and an inorganic matrix (hydrotalcite) to apply flurbiprofen in oral cavity. The results indicated that a suitable anti-inflammatory sustained release in the buccal cavity occurs during 12 hours, which results in the reduction in daily drug dosage (40 mg vs 70 mg) (105). Mura et al. prepared mucoadhesive films that consisted of flufenamic acid and Hydroxypropyl beta cyclodextrin (HPβCD), which improves release rate and drug dissolution. The results revealed that using a complex drug with HPβCD leads to the complete release of drug within 4-5 h. This is the maximum duration for buccal drug delivery (109). Milani et al., showed that HPβCD has different roles in the stabilization of protein formulations in a wide range from the concentrations (110).

**Smoking Deterrents**

The nature of the smoking habit is partly due to the presence of a psychoactive substance used (111). The nicotine (NCT) delivery routes are skin and mucosal membranes such as nasal mucosa and buccal. This is because neutral and protonated NCT could easily permeate across the mucosal membranes (112, 113). In the study of Pongjanyakul et al., sodium alginate-magnesium aluminum silicate (SA-MAS) buccal films, loaded with NCT, were prepared as a potential drug delivery system. NCT-loaded SA-MAS films provided higher NCT content and a lower NCT released rate. Besides, the NCT-loaded SA-MAS films displayed a bioadhesive property for adhesion to mucosal membrane. This study suggested that NCT-loaded SA-MAS films have a strong potential to be used as a buccal delivery system (114). In the study of Rao et al., NCT was used to formulate a tri-layered buccal mucoadhesive patch which consisted of a medicated dry tablet that adheres to a mucoadhesive film (115). In another study, done by Bilayer, NCT mucoadhesive patches were prepared. As a nicotine replacement product to help smoking cessation, the feasibility of this formulation was determined. The results indicated that xanthan mucoadhesive buccal patches are potential candidates for controlled biphasic nicotine delivery. This fast initial drug release is followed by controlled release over 10 h. This study suggested using such a system, as a potential candidate, for future in vivo studies (116).
CONCLUSION

Many efforts have been reported to develop oral mucoadhesive drug delivery systems for (i) longer residence time, (ii) controlled drug release, and (iii) prevention of enzymatic degradation. The oral mucoadhesive drug delivery system is a good alternative to conventional drug delivery because of its ability to prevent first pass metabolism, enhance bioavailability, and reduce dose frequency. Undoubtedly, mucoadhesion has moved into a new area with the introduction of specific compounds and the development of oral mucoadhesives was increased because of their various therapeutic usages. By the introduction of a large number of drug molecules, oral mucoadhesive drug delivery will play a significant role in the delivery of these molecules. Many potential oral mucoadhesive systems under investigation, may find their way into the market in the near future. There are plenty of reports about clinical trials and patents of oral mucoadhesive drugs, which show that oral drug delivery is a promising way to apply large numbers of therapeutic agents to the oral mucosal surface. Furthermore, using the biological products, such as antibodies, peptide and protein are being increased.

This review could be probably helpful for a proficient design of new oral mucoadhesive dosage forms. The developments in oral mucoadhesive drugs provide the way for making biological formulations with varying degrees of adhesion, drug protection, controlled release, and enhancement of absorption. To that end, a better understanding of the mucoadhesion phenomenon can help the researchers develop new oral mucoadhesive pharmaceutical products that could be more effective, safer and lower in cost.

CONFLICTS OF INTEREST. The authors declare no conflict of interest.

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