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: polycarbophil; 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: polyethyleneglycol; PAA: poly acrylic 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 micelles; NPs: nanoparticles; MRSA: methicillin resistant staphylococcus aureus; HPβCD: hydroxypropyl beta cyclodextrin; CPM: chlorpheniramine maleat; PEG-b-PLA: polyethylene glycolmethyl ether-block-polylactide; NCT: nicotine; SA-MAS: sodium alginate-magnesium aluminum 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).
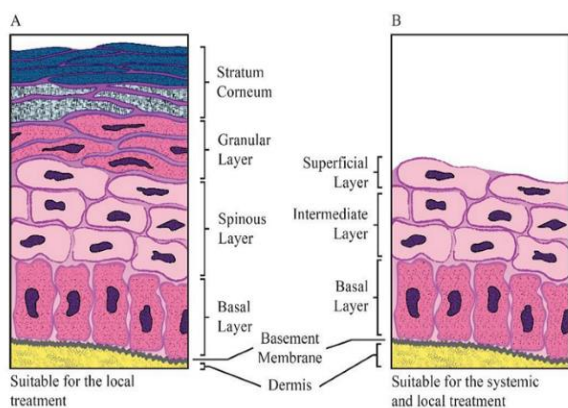

Figure 1. (A) The oral keratinized epithelium (B) non-keratinized epithelium

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 mucoadhestion 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 σ is the fracture strength, E is Young's modulus of

elasticity, ε 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 interprenetration 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).
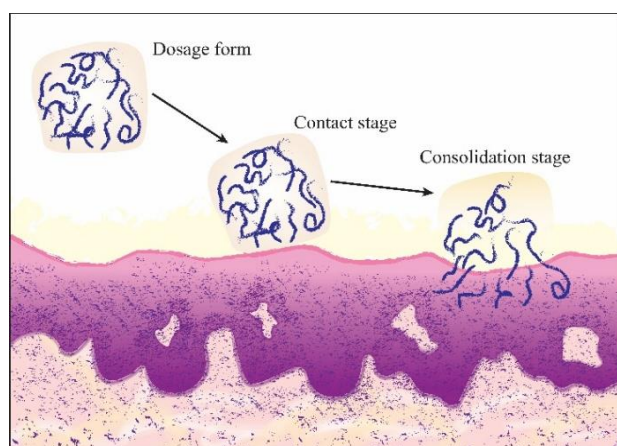

Figure 2. The two stages of the mucoadhesion process. Contact stage: mucoadhesive polymer comes into contact with the mucus membrane. Consolidation stage: penetration of the polymer of mucoadhesive formulation into the mucous.

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).

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
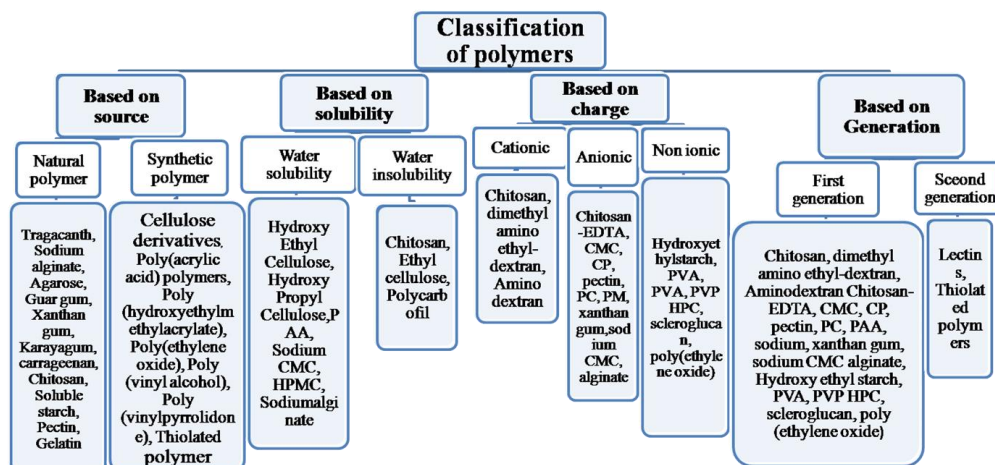

Figure 3. Classification of mucoadhesive polymers based on source, solubility, charge, and generation

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 (KKVVFWVKFK-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 ulexeuropaeus, 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 cross-linking. 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-enkephalin (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 bathe 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-Schn¨urch 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 nanoparticles 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 diproprionate (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 $5HT_3$ 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
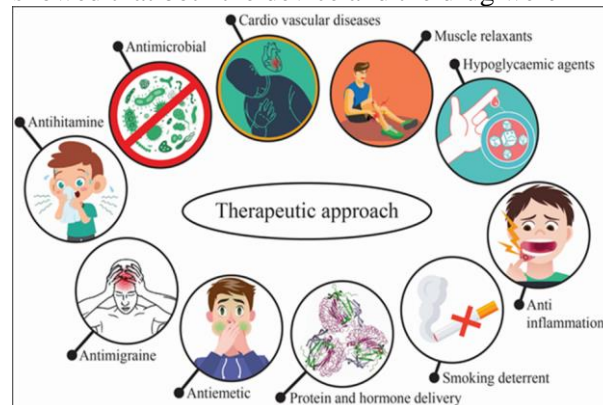

Figure 4. A therapeutic approach of mucoadhesive drug delivery systems in common diseases.

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-HT_1 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).

Table 1. Patented oral mucoadhesive formulations.

Active Ingredient	Patent No. or Appl. No.	Dosage form	Rout of administration	Year
Apomorphine Hydrochloride	US10888499	Film	Sublingual	2021
Bupernorphine Hydrochloride, Naloxane Hydrochloride	US10874661	Tablet	Sublingual	2020
Asenapine maleate	A205960	Tablet	Sublingual	2020
Sufentanil citrate	N209128	Tablet	Sublingual	2018
Desmopressin acetate	N022517	Tablet	Sublingual	2018
Extracts of the Marzeh khuzestani	96840	Gel	Buccal	2018
Nicotine	US20060198873A1	Film	Buccal	2017
Zolpidem tartrate	A201509	Tablet	Sublingual	2016
Bupernorphine hydrochloride	N207932	Film	Buccal	2015
Naloxone	US 10617686B2	Liquid spray	Buccal	2014
Bupernorphine	US201140378497A1	Film	Buccal Sublingual	2014
Acyclovir	N203791	Tablet	Buccal	2013
Fentanyl	N202788	Spray	Sublingual	2012
Miconazole	022404	Tablet	Buccal	2010

allergic conditions (88). 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).

Cardio Vascular 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 α_2 receptors, which has myotonolytic effects on skeletal muscles. In the study of Shanker et al., bioadhesive buccal tablets were prepared to

Antihistamine

Chlorpheniramine maleate (CPM) is a histamine H1 receptor antagonist used frequently to treat

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.

Active Ingredient	Dosage form	Status
Asenapine	Wafer	Commercial
Buprenorphine + naloxone	Film	Commercial
Desmopressin	Tablet, wafer	Commercial
Triamcinolone	Paste	Commercial
Miconazole	Gel	Commercial
Desmopressin	Tablet, wafer	Commercial
Nicotine	Tablet, film, gum, lozenge, spray, chewing Gum	Commercial
Buprenorphine	Tablet, film	Commercial
Fentanyl	Tablet, spray, film, lozenge	Commercial
Glyceryltrinitrate	Tablet, spray	Commercial
Sufentanil	Tablet	Commercial
Isosorbidedinitrate	Tablet	Commercial
Allergen extract	Wafer	Commercial
Melatonin	Tablet	Commercial
Zolpidem	Tablet	Commercial
Lorazepam	Tablet	Commercial
Buprenorphine	Tablet, film	Commercial
Insulin	Spray	Commercial
Prochlorperazine	Tablet	Commercial
Methyltestosterone	Tablet	Commercial
Rizatriptan	Wafer	Commercial
Norandrodiol	Tablet	Commercial
BeclomethazoneDipropionate	Spray	Commercial
Midazolam	Oral liquid	Commercial
Nystatin	Oral liquid	Commercial
Vitamin B_{12}	Tablet, spray, oral liquid	Commercial
Ropivacaine	Liposomal gel	Phase I completed
Diazepam	Film	Phase III
Montelukast	Film	Phase II
Apomorphine	Film	Phase II/III
Dexmedetomidine	Film	Phase I
Ketamine	Film, Wafer	Phase I/II completed
Insulin	Film, spray	Phase I/III
Artemether	Spray	Phase III completed
Flumazenil	Spray	Phase I/II completed
Polyoxidonium	Spray	Phase III
Tizanidine	Powder	Phase I/II completed
Ticagrelor	Powder, tablet	Phase IV
Tacrolimus	Oral liquid, powder	Phase IV
Cyclobenzaprine	Oral liquid	Phase IV
Methadone	Oral liquid	Phase I completed
Cholera toxin B subunit	Oral liquid	Phase I completed
Ketorolac	Oral liquid	Phase IV
Naloxone	Oral liquid	Phase I/II completed
Influenza vaccine	Oral liquid	Phase I completed
Cannabidiol	Tablet, oral liquid	Phase I/II/III/IV
Sildenafil	Tablet, wafer	Phase III completed
Agomelatine	Tablet	Phase III completed
Olanzapine	Tablet	Phase IV completed
Cyclobenzaprine	Oral liquid	Phase III
Lobeline	Tablet	Phase I/I
Riluzole	Tablet	Phase I/II/III
Alprazolam	Tablet	Phase I/II/III completed
Misoprostol	Tablet	Phase III/IV
Zolmitriptan	Tablet	Phase IV

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 administrated 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-methyl-pyrrolidinone 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, icompared 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-polylactide (PEG-b-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.

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REFERENCES

1. Puri V, Sharma A, Maman P, Rathore N, Singh I. Overview of mucoadhesive biopolymers for buccal drug delivery systems. Int J App Pharm. 2019; 11:18-29.
2. Datir M. Recent advances in mucoadhesive buccal drug delivery system and its marketed scope and opportunities. IntJAdv PharmSci, 2018; 1: 86-104.
3. Laffleur F. Mucoadhesive therapeutic compositions: a patent review (2011-2014). Expert opinion on therapeutic patents. 2016;26(3):377-88.
    DOI:10.1517/13543776.2016.1145209.
4. Xu W, Ling P, Zhang T. Polymeric micelles, a promising drug delivery system to enhance bioavailability of poorly water-soluble drugs. Journal of drug delivery. 2013;2013 DOI:10.1155/2013/340315.
5. Mantaj J, Vllasaliu D. Recent advances in the oral delivery of biologics. Pharmaceutical Journal. 2020. DOI :10.1211/PJ.2020.20207374
6. Golshani S, Faramarzi MA. Expected Impact of Biosimilars on the Pharmaceutical Companies. Iranian Journal of Medical Sciences. 2021;46(5):399. DOI: 10.30476/ijms.2021.92314.2356
7. West TG, Ash B, Sandler N. Nanopaticle engineering and 3DP delivery for game-changing oral therapeutics. Frederick Furness Publishing Ltd 2021.
8. Feitosa RC, Geraldes DC, Beraldo-de-Araújo VL, Costa JSR, Oliveira-Nascimento L. Pharmacokinetic aspects of nanoparticle-in-matrix drug delivery systems for oral/buccal delivery. Frontiers in Pharmacology. 2019:1057. DOI:10.3389/fphar.2019.01057
9. 9.Garhy DM, Ismail S, Ibrahim HK, Ghorab MM. Buccoadhesive gel of carvedilol nanoparticles for enhanced dissolution and bioavailability. Journal of Drug Delivery Science and Technology. 2018; 47:151-8. DOI: 10.1016/j.jddst.2018.07.009
10. K. Mamatha MDs, P. Venkatesh. A review on: mucoadhesive drug delivery systems. J innov appl pharm Sci. 2022;7. DOI: 10.37022/jiaps. v7i1.278
11. Mamatha K, Venkatesh P. A review on: mucoadhesive drug delivery systems. Journal of Innovations in Applied Pharmaceutical Science (JIAPS). 2022:32-6.
12. Adikwu MU. Mucins and their potentials. Trop J Pharm Res. 2006; 5:581-2.
13. Bhati R, Nagrajan RK. A detailed review on oral mucosal drug delivery system. International Journal of Pharmaceutical Sciences and Research. 2012;3(3):659.
14. Shojaei AH. Buccal mucosa as a route for systemic drug delivery: a review. J Pharm Pharm Sci. 1998;1(1):15-30.
15. Shaikh R, Singh TRR, Garland MJ, Woolfson AD, Donnelly RF. Mucoadhesive drug delivery systems. Journal of pharmacy and Bioallied Sciences. 2011;3(1):89. DOI:10.4103%2F0975-7406.76478
16. Ahuja A, Khar RK, Ali J. Mucoadhesive drug delivery systems. Drug Development and industrial pharmacy. 1997;23(5):489-515. DOI: 10.3109/03639049709148498

17. Dodou D, Breedveld P, Wieringa PA. Mucoadhesives in the gastrointestinal tract: revisiting the literature for novel applications. European journal of pharmaceutics and biopharmaceutics. 2005;60(1):1-16. DOI: 10.1016/j.ejpb.2005.01.007

18. Smart JD. The basics and underlying mechanisms of mucoadhesion. Advanced drug delivery reviews. 2005;57(11):1556-68. DOI: 10.1016/j.addr.2005.07.001

19. Ahagon A, Gent A. Effect of interfacial bonding on the strength of adhesion. Journal of Polymer Science: Polymer Physics Edition. 1975;13(7):1285-300. DOI:10.1002/pol.1975.180130703

20. Zhu Z, Zhai Y, Zhang N, Leng D, Ding P. The development of polycarbophil as a bioadhesive material in pharmacy. asian journal of pharmaceutical sciences. 2013;8(4):218-27. DOI: 10.1016/j.ajps.2013.09.003

21. Bhandari HP, Yadav J. Review on mucoadhesive buccal drug delivery. Pharma Science Monitor. 2018;9(1).

22. Reineke J, Cho D, Dingle Y, Cheifetz P, Laulicht B, Lavin D, et al. Can bioadhesive nanoparticles allow for more effective particle uptake from the small intestine? Journal of Controlled Release. 2013;170(3):477-84. DOI: 10.1016/j.jconrel.2013.05.043

23. Rajaram DM aLS. Buccal Mucoadhesive films: a review. Sys Rev Pharm. 2017;8:31.

24. Tester R, Qi X. Bioadhesive properties of ß-limit dextrin. Journal of Pharmacy and Pharmaceutical Sciences. 2011;14(1):60-6.

25. Gandhi J SI, Shah P, and Naik H. A comprehensive review on buccal drug delivery system. J Pharm Sci. 2019; 8:20-32.

26. Menzel C, Hauser M, Frey A, Jelkmann M, Laffleur F, Götzfried SK, et al. Covalently binding mucoadhesive polymers: N-hydroxysuccinimide grafted polyacrylates. European Journal of Pharmaceutics and Biopharmaceutics. 2019; 139:161-7. DOI: 10.1016/j.ejpb.2019.02.017

27. Mukhopadhyay R, Gain S, Verma S, Singh B, Vyas M, Mehta M, et al. Polymers in designing the mucoadhesive films: A comprehensive review. Int J Green Pharm. 2018;12(2):330-44.

28. Madhav NS OA, Tyagi Y, and Negi M9. Mucoadhesion: a novelistic platform for drug delivery system. International Journal of Pharmaceutics and Drug Analysis. 2014:773-81

29. Zhang Z, Liao M, Lou H, Hu Y, Sun X, Peng H. Conjugated polymers for flexible energy harvesting and storage. Advanced Materials. 2018;30(13):1704261. DOI:10.1002/adma.201704261

30. Singh R, Sharma D, Garg R. Review on mucoadhesive drug delivery system with special emphasis on buccal route: an important tool in designing of novel controlled drug delivery system for the effective delivery of pharmaceuticals. J Dev Drugs. 2017;6(01):1-12. DOI: 10.4172/2329-6631.1000169

31. Witten J, Samad T, Ribbeck K. Molecular characterization of mucus binding. Biomacromolecules. 2019;20(4):1505-13. DOI:10.1021/acs.biomac.8b01467

32. Lalge M, Sharma PK, Bhandari A, Garud A, Garud N. Mucoadhesive Drug Delivery System: A Review. Critical Review in Pharmaceutical Sciences. 2014;3(3):17-29.

33. Schonhorn H. Adhesion and adhesives: Interactions at interfaces. Adhesion in cellulosic and wood-based composites: Springer; 1981. p. 91-111. DOI: 10.1007/978-1-4684-8983-5_5

34. Parmar HK, Pandya KK, Pardasani LJ, Panchal VS, Tandel T. A systematic review on mucoadhesive drug delivery system. World J Pharm Res. 2017;6(9):337-66. DOI: 10.20959/wjpr20179-9281

35. Shridhar GS, Manohar SD, Bhanudas SR, Anjaneri N. Mucoadhesive buccal drug delivery: an overview. Journal of Advanced Pharmacy Education & Research Oct-Dec. 2013;3(4):319-32.

36. Lehr C-M, Boddé HE, Bouwstra JA, Junginger HE. A surface energy analysis of mucoadhesion II. Prediction of mucoadhesive performance by spreading coefficients. European journal of pharmaceutical sciences. 1993;1(1):19-30. DOI: 10.1016/0928-0987(93)90014-2

37. Shinkar DM, Dhake AS, Setty CM. Drug delivery from the oral cavity: a focus on mucoadhesive buccal drug delivery systems. PDA journal of pharmaceutical science and technology. 2012;66(5):466-500. DOI: 10.5731/pdajpst.2012.00877

38. Beri CL, Sood R, Hemraj GA. Stomach specific mucoadhesive microspheres as controlled drug delivery system-A review. International Journal of Pharmacy and Pharmaceutical Sciences. 2013;5(2):21-6.

39. Meirelles LMA, Raffin FN. Clay and polymer-based composites applied to drug release: A scientific and technological prospection. Journal of Pharmacy & Pharmaceutical Sciences. 2017;20:115-34.

40. Salamat-Miller N, Chittchang M, Johnston TP. The use of mucoadhesive polymers in buccal drug delivery. Advanced drug delivery reviews. 2005;57(11):1666-91. DOI: 10.1016/j.addr.2005.07.003

41. Shojaei AH, Li X. Mechanisms of buccal mucoadhesion of novel copolymers of acrylic acid and polyethylene glycol monomethylether monomethacrylate. Journal of controlled release. 1997;47(2):151-61. DOI:10.1016/S0168-3659(96)01626-4

42. Vaidya A, Wigent R, Moore J, Schwartz J. Protective Effect of Carbopol on Enzymatic Degradation of a Peptide-Like Substrate I: Effect of Various Concentrations and Grades of Carbopol and Other Reaction Variables on Trypsin Activity. Pharmaceutical development and technology. 2007;12(1):89-96. DOI: 10.1080/10837450601168656

43. Copeland RA. Enzymes: a practical introduction to structure, mechanism, and data analysis: John Wiley & Sons; 2000.

44. He P DS, and Illum L.Int. J. Pharm. In vitro evaluation of the mucoadhesive properties of chitosan microspheres. 1998; 1:75-88. DOI:10.1016/S0378-5173(98)00027-1

45. Ayensu I, Mitchell JC, Boateng JS. Development and physico-mechanical characterisation of lyophilised chitosan wafers as potential protein drug delivery systems via the buccal mucosa. Colloids and Surfaces B: Biointerfaces. 2012; 91:258-65. DOI: 10.1016/j.colsurfb.2011.11.004

46. Ayensu I, Mitchell JC, Boateng JS. Effect of membrane dialysis on characteristics of lyophilised chitosan wafers for potential buccal delivery of proteins. International journal of biological macromolecules. 2012;50(4):905-9. DOI: 10.1016/j.ijbiomac.2012.02.014

47. Ayensu I, Boateng J. Development and evaluation of lyophilized thiolated-chitosan wafers for buccal delivery of protein. Journal of Science and Technology (Ghana). 2012;32(2):46-55. DOI:10.4314/just. v32i2.7

48. Mohajel N, Najafabadi AR, Azadmanesh K, Vatanara A, Moazeni E, Rahimi A, et al. Optimization of a spray drying process to prepare dry powder microparticles containing plasmid nanocomplex. International journal of pharmaceutics. 2012;423(2):577-85. DOI: 10.1016/j.ijpharm.2011.11.014

49. Li Y, Na R, Wang X, Liu H, Zhao L, Sun X, et al. Fabrication of antimicrobial peptide-loaded PLGA/chitosan composite microspheres for long-acting bacterial

resistance. Molecules. 2017;22(10):1637. DOI:10.3390/molecules22101637

50. Sharma R, Raghav R, Priyanka K, Rishi P, Sharma S, Srivastava S, et al. Exploiting chitosan and gold nanoparticles for antimycobacterial activity of in silico identified antimicrobial motif of human neutrophil peptide-1. Scientific reports. 2019;9(1):1-14. DOI:10.1038/s41598-019-44256-6

51. Sriamornsak P. Application of pectin in oral drug delivery. Expert opinion on drug delivery. 2011;8(8):1009-23. DOI:10.1517/17425247.2011.584867

52. Jonassen H, Treves A, Kjøniksen A-L, Smistad G, Hiorth M. Preparation of ionically cross-linked pectin nanoparticles in the presence of chlorides of divalent and monovalent cations. Biomacromolecules. 2013;14(10):3523-31. DOI:10.1021/bm4008474

53. Krivorotova T, Cirkovas A, Maciulyte S, Staneviciene R, Budriene S, Serviene E, et al. Nisin-loaded pectin nanoparticles for food preservation. Food Hydrocolloids. 2016; 54:49-56. DOI: 10.1016/j.foodhyd.2015.09.015

54. González-Alvarez M, González-Alvarez I, Bermejo M. Hydrogels: an interesting strategy for smart drug delivery. Therapeutic delivery. 2013;4(2):157-60. DOI:10.4155/tde.12.142

55. Madhav NS OA, Tyagi Y, and Negi M9. Mucoadhesion: a novelistic platform for drug delivery system. International Journal of Pharmaceutics and Drug Analysis. 2014:773-81.

56. Gajbhiye V, Gong S. Lectin functionalized nanocarriers for gene delivery. Biotechnology advances. 2013;31(5):552-62. DOI: 10.1016/j.biotechadv.2013.01.005

57. Lehr C-M. Lectin-mediated drug delivery: The second generation of bioadhesives. Journal of Controlled Release. 2000;65(1-2):19-29. DOI:10.1016/S0168-3659(99)00228-X

58. Insua I, Majok S, Peacock AF, Krachler AM, Fernandez-Trillo F. Preparation and antimicrobial evaluation of polyion complex (PIC) nanoparticles loaded with polymyxin B. European polymer journal. 2017; 87:478-86. DOI: 10.1016/j.eurpolymj.2016.08.023

59. Bhati R aNR. A detaililed review on oral mucosal drug delivery system. Int J PharmSci Res. 2012; 3:659-81.

60. 60.Uddin MN, Allon A, Roni MA, Kouzi S. Overview and future potential of fast dissolving buccal films as drug delivery

system for vaccines. Journal of Pharmacy & Pharmaceutical Sciences. 2019; 22:388-406. DOI:10.18433/jpps30528

61. Tangri P, Madhav NS. Recent advances in oral mucoadhesive drug delivery systems: a review. International Journal of Pharmaceutical Research and Development. 2011;3(2):151-61.

62. Phanindra B, Moorthy BK, Muthukumaran M. Recent advances in mucoadhesive/bioadhesive drug delivery system: A review. 2013.

63. Khan AB, Mahamana R, Pal E. Review on mucoadhesive drug delivery system: novel approaches in modern era. RGUHS J Pharm Sci. 2014;4(4):128-41. DOI: 10.5530/rjps.2014.4.2

64. Rameshwar V, Kishor D, Tushar G. Bi-layer tablets for various drugs: A review. Scholars Academic Journal of Pharmacy. 2014;3(3):271-9.

65. Pramanik J, Ray S, Kundu S, Basak T, Mondal S, Panigrahi S, et al. Modern approaches of mucoadhesive drug delivery system. World Journal of Pharmaceutical Research. 2018;7(14):381-403. DOI: 10.20959/wjpr201814-12889

66. Kumar R, Sirvi A, Kaur S, Samal SK, Roy S, Sangamwar AT. Polymeric micelles based on amphiphilic oleic acid modified carboxymethyl chitosan for oral drug delivery of bcs class iv compound: Intestinal permeability and pharmacokinetic evaluation. European Journal of Pharmaceutical Sciences. 2020; 153:105466. DOI: 10.1016/j.ejps.2020.105466

67. Hoogstraate A, Cullander C, Senel S, Verhoef J, Boddé H, Junqinger H. Diffusion rates and transport pathways of FITC-labelled model compounds through buccal epithelium. Journal of Controlled Release. 1994;28(1-3):274.

68. Dowly ME, Knuth KE, Robinson JR. Enzyme characterization studies on the rate-limiting barrier in rabbit buccal mucosa. International journal of pharmaceutics. 1992;88(1-3):293-302. DOI:10.1016/0378-5173(92)90327-X

69. Mehta M, Kemppainen B, Stafford R. In vitro penetration of tritium-labelled water (THO) and [3H] PbTx-3 (a red tide toxin) through monkey buccal mucosa and skin. Toxicology letters. 1991;55(2):185-94. DOI:10.1016/0378-4274(91)90133-Q

70. Quadros E, Cassidy J, Gniecko K, LeRoy S. Buccal and colonic absorption of CGS 16617, a novel ACE inhibitor. Journal of controlled release. 1992;19(1-3):77-85. DOI:10.1016/0168-3659(92)90066-Z

71. Gamvrellis A, Gloster S, Jefferies M, Mottram PL, Smooker P, Plebanski M, et al. Characterisation of local immune responses induced by a novel nano-particle based carrier-adjuvant in sheep. Veterinary immunology and immunopathology. 2013;155(1-2):21-9. DOI: 10.1016/j.vetimm.2013.05.015

72. Hamdy S, Haddadi A, Hung RW, Lavasanifar A. Targeting dendritic cells with nano-particulate PLGA cancer vaccine formulations. Advanced drug delivery reviews. 2011;63(10-11):943-55. DOI: 10.1016/j.addr.2011.05.021

73. Elamanchili P, Lutsiak CM, Hamdy S, Diwan M, Samuel J. "Pathogen-mimicking" nanoparticles for vaccine delivery to dendritic cells. Journal of immunotherapy. 2007;30(4):378-95. DOI: 10.1097/CJI.0b013e31802cf3e3

74. Richards W, Platzker A, Church J, Yamamoto F, Foster S. Steroid-dependent asthma treated with inhaled beclomethasone dipropionate in children. Annals of Allergy. 1978;41(5):274-7.

75. Nagai T, Konishi R. Buccal/gingival drug delivery systems. journal of Controlled Release. 1987;6(1):353-60. DOI:10.1016/0168-3659(87)90088-5

76. H. B. Formulation strategies in mucosal-adhesive drug delivery.J Control Release. 2005; 22:4-5.

77. Yoo J-W, Dharmala K, Lee CH. The physicodynamic properties of mucoadhesive polymeric films developed as female controlled drug delivery system. International journal of pharmaceutics. 2006;309(1-2):139-45. DOI: 10.1016/j.ijpharm.2005.11.020

78. Rana P, Murthy R. Formulation and evaluation of mucoadhesive buccal films impregnated with carvedilol nanosuspension: a potential approach for delivery of drugs having high first-pass metabolism. Drug delivery. 2013;20(5):224-35. DOI:10.3109/10717544.2013.779331

79. Avachat AM, Gujar KN, Wagh KV. Development and evaluation of tamarind seed xyloglucan-based mucoadhesive buccal films of rizatriptan benzoate. Carbohydrate polymers. 2013;91(2):537-42. DOI: 10.1016/j.carbpol.2012.08.062

80. Meher JG, Tarai M, Yadav NP, Patnaik A, Mishra P, Yadav KS. Development and characterization of cellulose–polymethacrylate mucoadhesive film for

buccal delivery of carvedilol. Carbohydrate polymers. 2013;96(1):172-80. DOI: 10.1016/j.carbpol.2013.03.076

81. Dehghan M, Dandge BH, Gaikwad VM, Jagdale S. Bioadhesive Drug Delivery Systems-Background, Applications and Trends. Research Journal of Pharmacy and Technology. 2010;3(1):25-31.

82. Hua. S. Advances in nanoparticulate drug delivery approaches for sublingual and buccal administration: a review. Frontiers in Pharmacology, 2019; 10:1328. DOI:10.3389/fphar.2019.01328

83. Gilhotra RM, Ikram M, Srivastava S, Gilhotra N. A clinical perspective on mucoadhesive buccal drug delivery systems. Journal of biomedical research. 2014;28(2):81. DOI: 10.7555/JBR.27.20120136

84. Chandra Mohan K, Ravikumar K. Ondansetron hydrochloride: a competitive serotonin 5-HT3 receptor blocker. Acta Crystallographica Section C: Crystal Structure Communications. 1995;51(12):2627-9. DOI:10.1107/S0108270195008043

85. Nahata MC, Hui LN, Koepke J. Efficacy and safety of ondansetron in pediatric patients undergoing bone marrow transplantation. Clinical therapeutics. 1996;18(3):466-76. DOI: 10.1016/S0149-2918(96)80027-0.

86. Hassan N, Khar R, Ali M, Ali J. Development and evaluation of buccal bioadhesive tablet of an anti-emetic agent ondansetron. Aaps Pharmscitech. 2009;10(4):1085-92. DOI: 10.1208/s12249-009-9304-4.

87. Koland M, Sandeep V, Charyulu N. Fast dissolving sublingual films of ondansetron hydrochloride: effect of additives on in vitro drug release and mucosal permeation. Journal of Young Pharmacists. 2010;2(3):216-22. DOI:10.4103/0975-1483.66790

88. Madgulkar AR, Bhalekar MR, Ner AS, Wable ND. Formulation development of domperidone buccal bioadhesive hydrophilic matrix tablets. Asian Journal of Pharmaceutics (AJP): Free full text articles from Asian J Pharm. 2014;5(1).

89. Shidhaye SS, Saindane NS, Sutar S, Kadam V. Mucoadhesive bilayered patches for administration of sumatriptan succinate. Aaps Pharmscitech. 2008;9(3):909-16. DOI:10.1208/s12249-008-9125-x

90. Sekhar KC NK, Vishnu YV, Gannu R, Kishan V, and Rao YM. Transbuccal delivery of chlorpheniramine maleate from mucoadhesive buccal patches. J Drug Deliv.

2008; 15:185-91. DOI:10.1080/10717540801952639

91. Llabot JM MR, and Allemandi DA. Double-layered mucoadhesive tablets containing nystatin. AAPS J. 2002; 3:47-52. DOI:10.1208/pt030322

92. Fini A, Bergamante V, Ceschel GC. Mucoadhesive gels designed for the controlled release of chlorhexidine in the oral cavity. Pharmaceutics. 2011;3(4):665-79. DOI:10.3390/pharmaceutics3040665

93. Mizrahi B, Domb AJ. Mucoadhesive tablet releasing iodine for treating oral infections. Journal of pharmaceutical sciences. 2007;96(11):3144-50. DOI:10.1002/jps.20876

94. Obaidat RM, Bader A, Al-Rajab W, ABU SHEIKHA G, Obaidat AA. Preparation of mucoadhesive oral patches containing tetracycline hydrochloride and carvacrol for treatment of local mouth bacterial infections and candidiasis. Scientia Pharmaceutica. 2011;79(1):197-212. DOI:10.3797/scipharm.1004-18

95. Yamsani V, Gannu R, Kolli C, Rao M, Yamsani M. Development and evaluation of buccoadhesive carvedilol tablets. Acta Pharmaceutica. 2007;57(2):185-97.

96. Charde S, Mudgal M, Kumar L, Saha R. Development and evaluation of buccoadhesive controlled release tablets of lercanidipine. AAPS PharmSciTech. 2008;9(1):182-90. DOI:10.1208/s12249-007-9031-7.

97. Shanker G, Kumar CK, Gonugunta CSR, Kumar BV, Veerareddy PR. Formulation and evaluation of bioadhesive buccal drug delivery of tizanidine hydrochloride tablets. AAPS pharmscitech. 2009;10(2):530-9. DOI:10.1208/s12249-009-9241-2

98. 98. Semalty M, Semalty A, Kumar G. Formulation and characterization of mucoadhesive buccal films of glipizide. Indian journal of pharmaceutical sciences. 2008;70(1):43. DOI:10.4103/0250-474X.40330

99. Muzib YI, Kumari KS. Mucoadhesive buccal films of glibenclamide: Development and evaluation. International journal of pharmaceutical investigation. 2011;1(1):42. DOI: 10.4103/2230-973X.76728

100. Eid EE, Abdul AB, Suliman FEO, Sukari MA, Rasedee A, Fatah SS. Characterization of the inclusion complex of zerumbone with hydroxypropyl-β-cyclodextrin. Carbohydrate Polymers. 2011;83(4):1707-14. DOI: 10.1016/j.carbpol.2010.10.033

101. Martin L, Wilson CG, Koosha F, Uchegbu IF. Sustained buccal delivery of the hydrophobic drug denbufylline using physically cross-linked palmitoyl glycol chitosan hydrogels. European journal of pharmaceutics and biopharmaceutics. 2003;55(1):35-45. DOI: 10.1016/S0939-6411(02)00118-2

102. Colonna C, Genta I, Perugini P, Pavanetto F, Modena T, Valli M, et al. 5-methyl-pyrrolidinone chitosan films as carriers for buccal administration of proteins. AAPS PharmSciTech. 2006;7(3):E107-E13. DOI:10.1208/pt070370

103. Nakane S, Kakumoto M, Yukimatsu K, Chien YW. Oramucosal delivery of LHRH: pharmacokinetic studies of controlled and enhanced transmucosal permeation. Pharmaceutical Development and Technology. 1996;1(3):251-9. DOI:10.3109/10837459609022593

104. Giovino C, Ayensu I, Tetteh J, Boateng JS. Development and characterisation of chitosan films impregnated with insulin loaded PEG-b-PLA nanoparticles (NPs): a potential approach for buccal delivery of macromolecules. International journal of pharmaceutics. 2012;428(1-2):143-51. DOI: 10.1016/j.ijpharm.2012.02.035

105. Perioli L, Ambrogi V, Giovagnoli S, Ricci M, Blasi P, Rossi C. Mucoadhesive bilayered tablets for buccal sustained release of flurbiprofen. AAPS PharmSciTech. 2007;8(3):E20-E7. DOI: 10.1208/pt0803054.

106. Roszkowski MT, Swift JQ, Hargreaves KM. Effect of NSAID administration on tissue levels of immunoreactive prostaglandin E2, leukotriene B4, and (S)-flurbiprofen following extraction of impacted third molars. Pain. 1997;73(3):339-45. DOI:10.1016/S0304-3959(97)00120-6

107. Heasman P, Offenbacher S, Collins J, Edwards G, Seymour R. Flurbiprofen in the prevention and treatment of experimental gingivitis. Journal of Clinical Periodontology. 1993;20(10):732-8. DOI: 10.1111/j.1600-051X.1993.tb00699.x

108. Ghorbani A, Akbari J, Boorboor M, Nekoukar Z, Eslami G. Evaluation of zinc sulfate mucoadhesive formulation on recurrent aphthous stomatitis: a randomized double-blind, placebo-controlled clinical trial. BMC Oral Health. 2020;20(1):1-6.

109. Mura P, Corti G, Cirri M, Maestrelli F, Mennini N, Bragagni M. Development of mucoadhesive films for buccal administration of flufenamic acid: effect of cyclodextrin complexation. Journal of pharmaceutical sciences. 2010;99(7):3019-29. DOI:10.1002/jps.22068

110. Milani S, Faghihi H, Roulholamini Najafabadi A, Amini M, Montazeri H, Vatanara A. Hydroxypropyl beta cyclodextrin: a water-replacement agent or a surfactant upon spray freeze-drying of IgG with enhanced stability and aerosolization. Drug development and industrial pharmacy. 2020;46(3):403-11. DOI:10.1080/03639045.2020.1724131

111. Palmer K. Buckley. MM, & Faulds, D.(1992). Transdermal nicotine: A review of its pharmacodynamic and pharmacokinetic properties, and therapeutic efficacy as an aid to smoking cessation. Drugs.44:498-529.

112. Nair MK, Chetty DJ, Chien YW, Ho H. Biomembrane permeation of nicotine: mechanistic studies with porcine mucosae and skin. Journal of pharmaceutical sciences. 1997;86(2):257-62. DOI: 10.1021/js960095w

113. Chen L-LH, Chetty DJ, Chien YW. A mechanistic analysis to characterize oramucosal permeation properties. International journal of pharmaceutics. 1999;184(1):63-72. DOI:10.1016/S0378-5173(99)00091-5.

114. Pongjanyakul T, Suksri H. Alginate-magnesium aluminum silicate films for buccal delivery of nicotine. Colloids and Surfaces B: Biointerfaces. 2009;74(1):103-13. DOI: 10.1016/j.colsurfb.2009.06.033

115. Rao S, Song Y, Peddie F, Evans AM. A novel tri-layered buccal mucoadhesive patch for drug delivery: assessment of nicotine delivery. Journal of Pharmacy and Pharmacology. 2011;63(6):794-9. DOI:10.1111/j.2042-7158.2011. 01283.x

116. Huwaij RA OR, Sweidan K, and Hiari YA. Formulation and in vitro evaluation of xanthan gum or carbopol 934-based mucoadhesive patches, loaded with nicotine. AAPS J. 2011; 12:21-7. DOI: 10.1208/s12249-010-9534-5