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Recent advances in oral mucoadhesive drug delivery

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Abstract

The oral cavity is one of the most important local and systemic drug delivery routes, as it has a large surface area, high permeability, and abundant blood supply. Oral administration of drugs has certain advantages, such as improved bioavailability, prevention of first-pass metabolism, reduced dose frequency, and non-invasiveness. In recent years, patents on oral adhesives have been filed in the pharmaceutical field, showing promising potential for therapeutic purposes. Drug delivery across the oral mucosa may play an essential role in the delivery of biological drugs, such as antimicrobial peptides. This article provides an overview of oral adhesive drug delivery systems and offers basic principles for researchers to overcome problems associated with formulation design.

Introduction

Oral mucoadhesive drug delivery has many advantages, including avoidance of first-pass metabolism, ease of administration, enhanced penetration, prevention of enzymatic degradation, and reduced dose-dependent side effects. [1] They are used orally for the cavity, local and systemic drug delivery. This delivery route is used for sustained-release dosage forms to improve the therapeutic performance of drugs. Oral mucoadhesive drug delivery systems are gaining popularity in the pharmaceutical industry. Currently marketed mucosal dosage forms are mainly gels, sprays, tablets, ointments, creams, and chewing gum. [2] Numerous literature reports on clinical trials and registered patents for oral mucoadhesive drugs indicate that oral drug delivery is a promising means to deliver a broad spectrum of therapeutic agents to oral mucosal surfaces. [3]Today, researchers and pharmaceutical companies seek to use mucus adhesion systems in delivering proteins, peptides, and genes. High-molecular antibacterial peptides (AMPs) can be cost-effective in treating various serious infections, Such as sepsis [4]Many polymers have been studied for oral biologic delivery with varying success. [5] Biologics and biosimilars are proliferating.[6] Improving the pharmacokinetic properties of biological drugs may offer new possibilities for drug distribution in a rapidly growing market.[2] Generally, mucosal tissues rapidly absorb the drug through the oral cavity. Improved oral drug delivery pharmacokinetics increase drug bioavailability and controlled release rate.[7] Cmax, AUC and Tmax have also been shown to improve using this system compared to commercial pharmaceutical formulations. In the study of Gary et al., An oral adhesive gel of carvedilol nanoparticles (NPs) was prepared to improve solubility and bioavailability. Results showed a twofold increase in bioavailability due to improved drug solubility and avoidance of first-pass metabolism. 8 Despite developing new mucosal adhesion systems and polymers in the last twenty years, mucosal adhesion still needs to be fully understood. Furthermore, qualitative and quantitative techniques are still treated separately. [9] This study aims to

provide an overview of mucosal adhesion polymer, dosage forms of oral mucosal adhesion, therapeutic effects, recent patents, clinical trial status and commercial products.

Oral mucosa characteristic

The oral mucosa consists of keratinized epithelium and non-keratinized epithelium(figure 1). The keratinized mucosal epithelium is composed primarily of nonpolar lipids (ceramides and acyl ceramides) and is relatively impervious to water. Therefore, it is suitable for topical treatment in the oral cavity. The non-keratinized mucosal epithelium mainly comprises polar lipids (cholesterol sulfate and glucosylceramide). Therefore, it is more porous than keratinized mucosa. Consequently, it is suitable for systemic and local oral cavity treatment. [9] Due to the presence of salivary mucus molecules and their negative charge, the oral cavity is an excellent avenue for drug administration. In mucosal secretions, mucus plays a vital role in lining the oral cavity. They can combine with positively charged drug molecules and affect specific tissues, thus aiding the delivery system. Therefore, they are used to modelling for mucosal adhesion systems. An explanation of the effect of different polymers at the mucin-polymer interface can be used to explain the mechanism of mucosal adhesion. The cohesive force is defined by the molecular bridges between mucin–polymers.[10] The electronic properties of the mucus also contribute to the stickiness of the mucus. Thus, the mucus's adhesion results from the mucus's electrical properties and the bridging between the mucus and the polymer. There is a difference in permeability; blood Flow rate and residence time in different areas of the oral mucosa are a function of many tissue properties. [11]

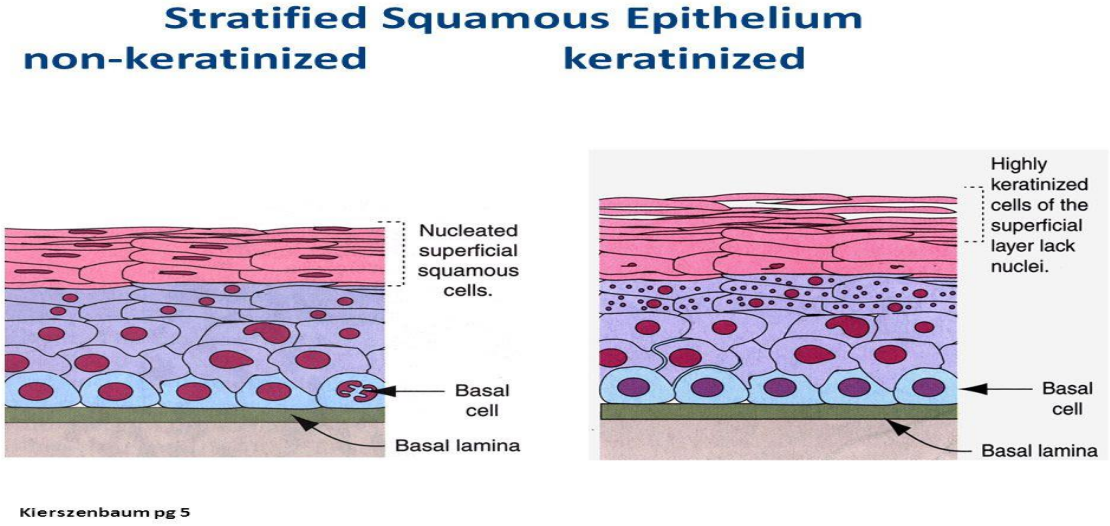


Fig 1 -keratinized and non-keratinized epithelium

Oral mucosal sites [12]

1. Sublingual delivery
2. Buccal delivery
3. Local delivery

1. Sublingual delivery: This is the systemic delivery of drugs through the mucosa lining the floor of the mouth.
2. Buccal delivery: Drug delivery through the mucosa lining the cheek (buccal lining).
3. Local delivery: In treating oral conditions, primarily ulcers, fungal diseases and periodontal disease, these oral mucosal sites depend on their anatomy, permeability to applied drugs, and ability to maintain the desired delivery system. They are very different from each other in some respects to a length of time.[12]

Table 1-Surface area and thickness of oral cavity membranes

Oral cavity membrane	structure	Surface area (cm^2)	Thickness (µm)	Blood flow (ml.min-1 .cm-2)
Buccal mucosa	non-keratinized	50.2	500-800	2.40
Gingival mucosa	Keratinized	-	200	1.47
Palatal	Keratinized	20.1	250	0.89
Sublingual mucosa	non-keratinized	26.5	100-200	0.97

Mucoadhesion theories [13]

Six theories have been presented to explain mucosal adhesions. Mucosal adhesion is defined as the interaction between the mucosal adhesion polymer and the mucosal layer, and these theories describe the different phases of the interaction between the two substrates. Here, these theories are presented.

Wetting theory

This theory assumes that the penetration of a mucus-binding polymer into irregularities of the absorption surface hardens, leading to mucus adhesion. The affinity for the surface can be determined by measuring the contact angle.

Absorption theory

According to this theory, adhesion results from the interaction between the adhesive polymer and the mucilage through two chemical bonds, including H-bonds and Van der Waals forces. After the initial contact, the adhesion of the two surfaces is due to the pressure between the atoms of the two surfaces.

Mechanical theory

According to this theory, the adhesion of two surfaces occurs because the rough surface is filled with a mucus-binding fluid. This step affects the adhesion of the mucus, although the anomaly does increase the surface area of the interface.

Electronic theory

This theory explains that the difference in the electronic structures of the two surfaces plays an essential role in their interactions. Bond formation occurs by transferring electrons between the polymer and the mucosa. The development of attractive forces between the polymer and the mucosal surface occurs through a double electron layer.

Diffusion theory

Diffusion theory is based on polymer chains' concentration gradient and penetration time into the mucous glycoprotein network. Diffusion is a two-way process; one is the formation of a permeation layer, and the other is that adequate adhesion is achieved when the thickness of the permeation layer is about 0.2 to 0.5 µm. The formation of this layer depends on factors such as the concentration gradient, molecular weight of the attached macromolecules, hydrodynamic size, mobility, flexibility, and polymer chain length.

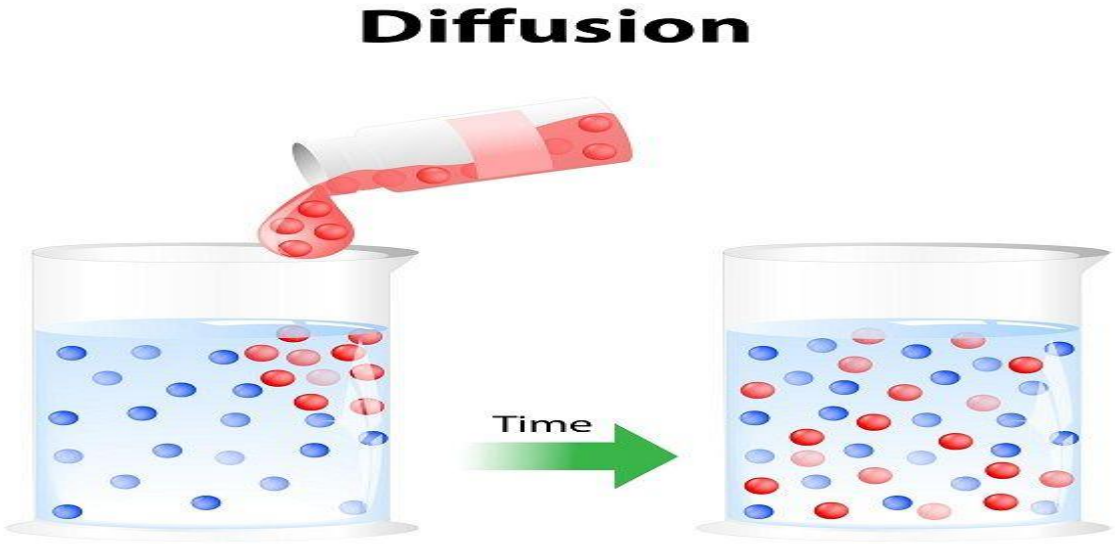


Fig 2 diffusion theory

Fracture theory

According to this theory, the force that causes an adhesive bond between two surfaces and the force required to separate them are related. This assumption determines the amount of force required to separate the polymer from the mucilage via the following equation:

$\sigma = (E*\varepsilon)/L$

where is the breaking strength,

E is Young's modulus of elastic

ε is the fracture energy and

L is the critical crack length.

Mechanism of mucoadhesion[14]

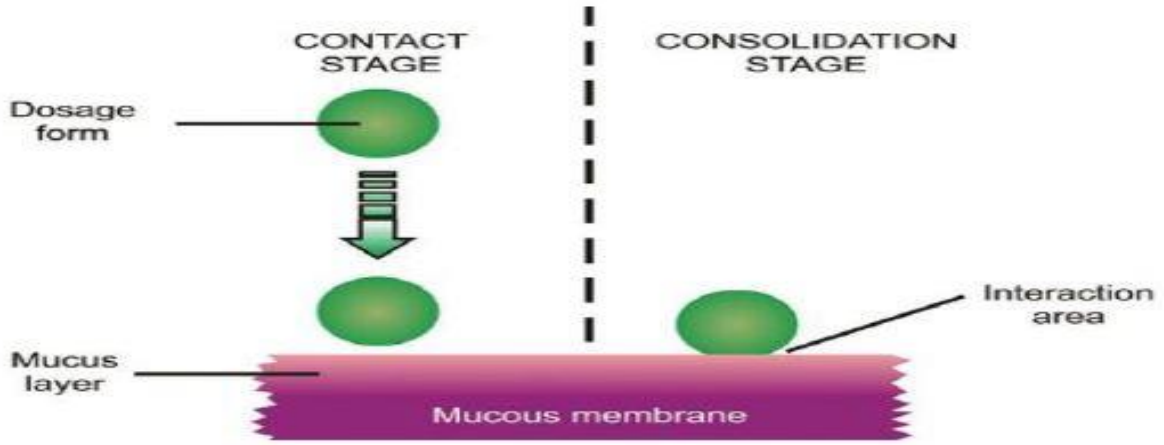


Fig 3-stages of the mucoadhesive process

The adhesion of mucosal adhesion polymers in the mucin layer of mucosal tissue occurs in two steps:

I. During the contact phase, the mucosal adhesive polymer is in contact with the mucosa, and then intimately wet, spread and swelling of the mucosal adhesion formulation occur. These processes are done through the presence of mucus in the mucous membranes.

II. At the consolidation stage, the penetration of the binder polymer formulation into the mucosal surface occurs due to physical entanglement and secondary interactions, such as hydrogen bonding, Vander Waals forces and electrical attraction.

Characteristic of ideal mucoadhesive polymer [15]

1. The mucosal adhesion polymer must be non-toxic and non-irritating to the mucosal surface, be locally specific and be able to adhere rapidly to the applied tissues.
2. It should not prevent drug release, may meet daily drug requirements, and may form strong non-covalent bonds with mucin cells.
3. Mucus adhesive polymers do not degrade during storage and are inexpensive, readily available, and reproducible.

Factors affecting mucoadhesive drug delivery systems

- ❖ Polymer related factor
- ❖ Physiological related factor
- ❖ Environment related factor

Polymer Related Factors

Molecular Weight

The adhesion force of the adhesive polymer is basically dependent on the molecular weight and linearity of the polymer. For linear polymers (e.g., polyethylene glycol), the mucosal adhesion properties are proportional to their molecular weight. However, in the case of non-linear polymers, the adhesion strength of the polymer may or may not be dependent on its molecular weight. In terms of the helical or coiled structure of these polymers, it is possible to shield several groups of binders mainly responsible for adhesive properties.[16]

The flexibility of the polymeric chain

Mucoadhesion begins when the polymer diffuses into the interfacial area. Chain flexibility is Important for expansion and penetration. Increased diffusivity a layer of mucus leads to stronger mucoadhesion. To achieve such diffusion, the polymer chains must be sufficiently flexible. This depends on the diffusion coefficient and viscosity.[17]

Spatial Confirmation

The spatial structure of a molecule is an essential factor in the strength of mucus. The polymer's adhesion strength depends on its spatial arrangement, i.e. whether they are helical or linear. Polymers with linear structures have better adhesion strength than polymers with helical structures because the spiral structure of the polymer consists of many different active groups. So their adhesive strength decreased. [18]

Polymer Concentration

The polymer concentration is significant for forming a solid adhesive bond with the mucus. The low polymer concentration reduces the penetration of polymer chains into the mucus. This leads to unstable

contact between the polymer and the mucus. Highly concentrated polymers generally result in more penetration chain lengths with higher adhesion.[16]

Molecular Charge of the Polymer

Nonionic polymers have a lower degree of adhesion than anionic polymers, according to a study of their molecular charge. The anionic charge of the polymer must be strong enough to have mucilage.[16] the cationic charge on the surface of the polymer increases the interaction between the surface of the polymer and the mucus since the mucus has a negative charge.[19]

Swelling

Hydration is required to swell the mucus-binding polymers to form macromolecules of the desired size. This increases the entanglement process between the polymer and the mucus. Polymer concentration, ionic strength and the presence of water are required for swelling. For the right swelling and adhesion, an optimal method degree of hydration is needed in polymer binders.[20]

Physiological factors

Mucin turnover, mucosal cell regeneration rate, and disease state of the mucus layer are physiological variables that influence mucoadhesion.[21]

Environmental Related

Applied Strength

If pressure is first applied to the site of contact with the adhesive tissue, it may affect penetration· When high pressure is applied, the polymer becomes cohesive, even though it cannot interact.[21]

Initial contact time

Initial contact time between polymer and mucin affects the adhesion strength of the mucosa, the degree of swelling, and the intercalation of polymers. Mucosal adhesion force increased by one increase in the initial contact time.[16]

Moistening

Humidity provides an ideal environment for mucosal adhesion polymers to be distributed on the mucin surface and produce the appropriate particle size for the penetration of the polymer into the mucus. The result of wetting the polymer is to provide close contact of particles with mucosa, and chemical interactions between bio-adhesive polymers and mucus chains, creating a macromolecule chain "grid" is appropriately sized, resulting in modification of the rheological behaviour of two macro molecules species. Therefore, it improves the mobility of the polymer chain to increase penetration between polymers and mucous membranes.[22]

Mucoadhesive polymer

Research on mucosal adhesion polymers and their effects attracted the pharmacy app attention of researchers in this field due to the remarkable properties of mucosal adhesives. These carriers must ensure biodegradability, incompatibility, and swelling ability, among other properties. Wetting of mucosal adhesion polymers leads to an elongated viscous solution that adheres to the mucosal surface. This in turn, induce more cohesive interactions, such as the formation of hydrogen bonding, electrostatic interactions and Covalent bond. Intraoral mucosal adhesion polymer Drug delivery systems can be natural or synthetic[23]

Classification of polymers based on generation

First Generation of Mucoadhesive Polymers

They are natural or synthetic hydrophilic substances with organic functional groups (carboxyl, hydroxyl and amino groups) or hydrogen bonds. Some known binder polymers are carbomer, cellulose derivatives, chitosan and alginate. They come in three types:

(a) Cationic polymers such as chitosan which electrostatic interaction with mucin.

(b)Anionic polymers are mainly derived from polyacrylic acid, which has a negative charge.

(c) Nonionic polymers have more adhesion strength than anionic polymers. Among these polymers are the hydroxyl propyl-methylcellulose, hydroxyethyl cellulose and methylcellulose.[24]

Carbopol

Carbopol, a lightly cross-linked polyacrylic acid (PAA), is an industry-standard for mucosal adhesives polymer. Many companies now use carbopol polymers for certain advantages like being released for a long time, safe and effective oral administration, increasing bioavailability and protecting proteins and peptides derived from degradation .[25] Role of carbopol in protecting peptides and proteins is to change the rate of decomposition reaction. [26] Since carbopol has a pKa value of 6.05, it confers enzymatic activity. In one study, buprenorphine tablets containing carbopol 974, lactose and PEG3350 were made. This formula has a lasting effect. Release record has released all its drug content in 2 hours, which is optimal for one sublingual tablet. 11 Some studies have shown that insulin absorption can significantly improve oral delivery for favourable properties of polyacrylic acid thiomer cysteine, including mucosal adhesion, protection against Enzyme breakdown and permeation reinforcement.[4]

Chitosan

Chitosan is a cationic polymer (polysaccharide) that is becoming increasingly critical in developing mucosal drug delivery systems due to good biocompatibility, biodegradability and Non-toxic characteristics. It binds to the ionic mucosa bond between the amino group and sialic acid residue. Onishi and Machida have shown that chitosan and its derivatives are rapid metabolites excreted by the kidney[27]. In the study of Ayensu et al., lyophilized chitosan platelet preparation containing chitosan, bovine serum albumin (as the template protein), glycerol (as plasticizer) and d-mannitol (as a cryoprotectant), The results show the usefulness of freeze-drying chitosan plates for protein drug administration. 28 In another study, the low molecular weight of chitosan has been optimized for the Gene delivery system.[48] Liposomes loaded with AMP with chitosan improves bioavailability and increase oral MPA management effectiveness. Li et al. formulated KSL (KKVVFWVKFK-CONH2) in mixed PLGA/chitosan microspheres for oral administration bacteria (F. nucleatum). The results show long-lasting antibacterial and inhibitory effects for up to 80 days.[29] In the study of Sharma et al. encapsulates the pep-H peptide in chitosan, leading to the formation of cation-based nanoparticles surface load, resulting in an 80% reduction intracellular load of M. tuberculosis.[30]

Pectin

Pectin is a natural polysaccharide consisting of mainly D-glucuronic acid and glycosidic units. Pectin can be used for control drug delivery due to its excellent biocompatibility and unique attributes. For example, pectin can easily adhere to the mucosal surface to help improve AMP retention time. Krivorotova et al. indicated antibacterial activity of charged nisin nanoparticles in vitro against two Gram-negative bacteria (E. coli and Klebsiella spp.) and two Gram-positive (Arthrobacter sp. and Bacillus subtilis), using agar diffusion test. Their results show that pectin nanoparticles loaded with nisin have higher antibacterial activity against Gram-positive vs Gram-negative bacteria. In addition, pectin NPs loaded with nisin100 times more effective

than sodium benzoate (a classic preservative) in Kills Gram-negative and Gram-positive bacteria. These results indicate that the charged nisin Pectin nanoparticle is a suitable polymer for antibiotic delivery systems.[31-33]

Second Generation of Mucoadhesive Polymers

Compared to the previous generation, the advantage of this generation is that it can interact with cell surfaces through specific or covalent receptor bonding, resulting in chemical enhancement Interactive. In this group, there are lectins and thiomer.[24]

Lectins

Lectins are glycoproteins or proteins of non-immune origin; they recognize sugar molecules and thus can bind glycosylated membrane components. Sugars in glycolipids and glycoproteins of the mammalian mucosa, are on the surface of the epithelium cells, or in mucosal layers. After binding to the cell, Lectin may remain on the cell's surface or can be obtained from within the cell by endocytosis. Some lectins, including those extracted from ulexeuropaeus, soybean, groundnut and lensculinarius, specifically link to mucosal cells. Shows wheat germ agglutinin has the least immune response of all lectins. Lectins are a suitable choice for delivery, as they provide good protection from acids and enzymes.[34-35]

Thiolated polymer

The thiol polymer is a derivative of hydrophilic polymers such as polyacrylate, chitosan, or deacetylated Galan gum. The presence of these polymers increases residence time through covalently bonded to the cysteine residue in mucus and increases stiffness and cross-linking. The isolated polymer also showed increased osmotic and enzyme-promoting effect inhibitory properties.[36] In Langoth's studies et al., a matrix tablet was made containing the new pentapeptide leu-enkephalin (pain) modulator and isolated polymeric PCP (Polycarbophil). The results show that the matrix and stability of mucilage tablet assets have increased and continue to more than 24 hours.[37]

Table 2- Classification of mucoadhesive polymers

Based on the source-	1)synthetic polymer- Cellulose derivative, poly (acrylic acid)polymer, poly (hydroxyethyl methyl acrylate), poly(ethylene oxide), poly(vinyl alcohol), poly(vinyl pyrrolidone), thiolated polymer. 2)Natural polymer- Tragacanth, sodium alginate, agarose, guar gum, Xanthan gum, Karayagum, carrageenan, chitosan, soluble starch, pectin, and gelatin.
Based on solubility	1)water-soluble polymer-Hydro ethyl cellulose, hydroxyl propyl cellulose, PAA, sodium CMC, HPMC, sodium alginate 2) water-insoluble polymer- Chitosan, ethyl cellulose, polycarbophil
Based on charge	1)Cationic- Chitosan, dimethyl amino ethyl-dextran, Amino dextran. 2)Anionic – Chitosan, EDTA, CMC, CP, pectin, PC, PAA, xanthan gum, sodium CMC, alginate 3) Nonionic-

	Hydroxyethyl starch, PVA, PVA, PVP HPC, scleroglucan, poly(ethylene oxide)
Based on the potential bioadhesive force	1) Covalent – Cyanoacrylate 2)hydrogen bond- CP, PVA, PC, Acrylates 3)Electrostatic bond- Chitosan
Based on generation	1)First generation-Chitosan, dimethyl amino ethyl-dextran, Amino dextran Chitosan-EDTA, CMC, CP, pectin, PC, PAA, sodium, xanthan gum, sodium CMC alginate, Hydroxyl ethyl starch, PVA, PVP HPC, scleroglucan, poly (ethylene oxide 2)second generation-) Lectins, Thiolated polymers

Advantages and disadvantages of mucoadhesive drug delivery system

The main advantage of oral mucosal patch delivery is extended dwell time, increased effective treatment, rapid absorption, and prevention through first-pass metabolism, faster onset of action, prevention of enzymatic degradation, great accessibility and profitability. Oral mucoadhesive drugs have several limitations, such as loss of benefits when swallowing, can only be used in low doses, and food restriction.[11] If these products that cause irritation of the oral mucosa can be managed by this route.[37]

Mucoadhesive dosage forms[37]

Type I

It is a monolayer dosage form with omnidirectional drug release. One of the disadvantages of this dosage form is that it is significantly lost drugs by swallowing.

Type II

This is a type, in which a pre-loaded bioadhesive layer is coated with an impermeable backing layer, creating a dual-layer device and preventing drug loss from the upper surface into the oral cavity.

Type III

It is a unidirectional drug release device, thereby preventing or minimizing drug loss, as the drug is released only from the side that attaches to the oral mucosa. This can be achieved by coating each side of the dosage form except the side in contact with oral mucosa.

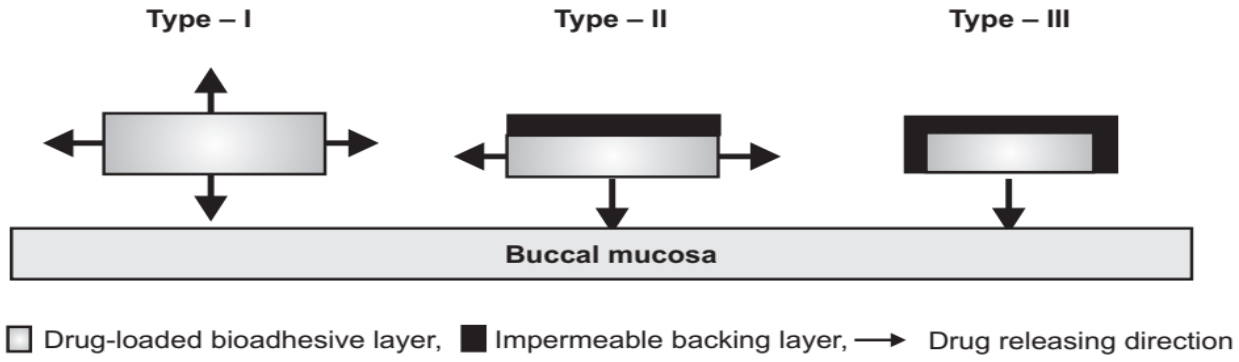


FIG 4 –mucoadhesive dosage form

❖ Solid Dosage Forms

Tablets

The most used polymers for Mucus tablets consisting of carbapols (CP934and CP940 PCP), sodium carboxyl methylcellulose (SCMC), pectin, chitosan, hydroxyl propyl methylcellulose (HPMC) and carboxyl methylcellulose (CMC). These polymers can be used alone or are unsuitable for making compressed bio-adhesive tablets. HPMC and pectin exhibit poor adhesion, while SCMC and chitosan strongly affect biological adhesion. Polyacrylic acid derivatives (CP934, CP940 and PCP) show the highest bio adhesion and longest residence time. In one study, a combination of mucosal adhesion polymers (mixture of 5% CP934, 65% HPMC blend and spray drying lactose) was used, showing bioadhesive and good residence time (2 h) [13]. In another study, a bio-adhesive pill was done with a mixture of CP and CMC, in the ratio of 35% and 15%, respectively, showing optimal bio-adhesion and release time. Another form of mucosal adhesive is double-layer tablets, including backing, adhesives, drug reservoir layer, and inert material ethyl cellulose layer coating. Beneficial dual-layer tablet to overcome the limitations of a class tablet.[38]

Bioadhesive lozenges

Another form of bioadhesives is lozenges, which have good sustainable release potential and patient satisfaction. They are applied as substitutes for patients who cannot swallow. Although tablets have been used for systematic drug administration, they are applied to the bathing oral cavity or throat area. The tablets are used for oral cavities as antibiotics, local anaesthetics, antibiotics, and antifungals.[39]

Polymeric micelles

Polymeric micelles (PM) can deliver poorly water-soluble drugs, especially in oral administration. Polymeric micelle can improve speaking controlled release drug bioavailability and specific stability.[4] Some properties of PM, pH sensitivity and mucosal adhesion, attract a lot of attention and provide a product that improves oral bioavailability.[4] Bernkop-Schn¨urch et al. show that thiolation of classical PM increases mucosal adhesion properties and, thus, oral improvement absorption of therapeutic proteins.[37] While studying, Kumar et al. found that polymers micelles improve the pharmacokinetic parameters of docetaxel versus free docetaxel suspension.[40]

Bioadhesive micro/Nanoparticles

Bio-adhesive micro / Nanoparticles have several advantages, such as being small particles, acceptable to the patient and in close contact with the mucosal area. Small particle size causes less local irritation at the site of contact grip and reduces discomfort in the mouth. These distribution systems are aqueous suspensions, gels, ointment or paste. Carbonyl, polycarbophil, chitosan, magnate and granted (copolymers contain alternating methyl vinyl ether units and maleic anhydride) were used to prepare bio-adhesive microparticles. Several studies have shown that chitosan or gantrez granules persist longer on mucosal tissues. Oral transmucosal nanoparticles can be used for systemic treatment because they penetrate the epithelium. Monti et al. prepare a formulation of atenolol containing microspheres with poloxamer 407, apply this formulation in rabbit, and compare it with a commercially available tablet formula. The results showed that atenolol concentration is still higher than marketable. Its bioavailability is also good. However, it has a lower drug dosage. This study suggests a possible dose reduction using atenolol oral microparticles.[41] A nanoparticle system for AMP release rate can be controlled by modifying the composition of the distribution system, such as the molecular weight of the polymer used. Encapsulating AMP in solid lipid nanoparticles can provide the necessary stability for drinking delivery. Biocompatible and biodegradable polymers, copolymers and lipids have been applied to the construction of nanoparticles/microparticles as a vaccine vector system.[42-43]

Bioadhesive wafer

This bio-adhesive system is in the form of a wafer with an adhesive surface layer and volume class. It consists of an antibacterial agent, matrix polymers and biodegradable polymers. Novel periodontal drug delivery systems have been reported for the treatment of periodontitis.[37]

Powder dosage form

Powdered formulations consist of a physical mixture of an active substance with a bio-binding polymer and can be sprayed into the mouth Mucosa for the treatment of oral disorders. Yamamoto et al. prepared such a powder containing hydroxyl propyl cellulose and beclo methadone di propionate (as an active agent) and sprayed it in the oral cavity of rats. The results show that this powder increased residence time by up to4 hours and was more effective than an oral solution containing the same active substance and polymer with the same concentration[44]

❖ Semi-solid Dosage Forms

Bioadhesive Patches/Films

There are two types of patches for drug delivery in the oral mucosa.

a) Dissolvable matrix patch systems: this patch dissolves slowly and entirely and has a longer duration of action than other solid forms to treat dental diseases.

b) Patch systems with non-dissolvable backing: They are used systematically to administer medication, be protected from saliva, and also there is a controlled release of the drug in the mouth mucosa for 10-15 h.[45]

In a study, an acyclovir patch was prepared for oral administration that contained polyethylene glycol (PEG), a copolymer of acrylic acid, monomethyl ether, monomethacrylate and a waterproof layer. In vivo studies show that when the patch is applied in the mouth area, it stays and releases the drug for about 22 h. This study indicates that the acyclovir patch may be a good choice for medication management. [1] In the study by Rana et al., NPin-microparticle structured buccal patch was designed as a novel platform for the buccal delivery of drugs with high first-pass metabolism. [46]

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.[45] Polymers like sodium CMC, CP 934P, HPMC and PEG 400 were used for buccal films. The outer membrane produced by HPMC has been shown to have higher elasticity, higher bio-adhesion properties, and better-swelling tolerance than buccal film prepared by sodium CMC film.[1] Vaccines can be made into an oral film dosage form, making them more effective and desirable. Various studies The results show the vaccine formula developed for buccal and parallel management development of soluble oral membranes has been very promising to change the future of vaccine transfer.[47]

Gels and hydrogel

Hydrogels and gels are two types of semi-solid adhesive systems. They should be applied to the oral mucosa or periodontal pockets to prolong their residence time and promote their absorption. The gel can direct mucosal contact and rapid drug release at the application site, making it an ideal drug delivery mechanism for the oral cavity. In general, carbomers increase the gel's effectiveness because they increase the time it stays on the mucous membranes and prolong the duration of action. Gels have an advantage over solutions because they provide a longer release time and improved bioavailability.[22] Corsodyl® is an oral mucosal adhesive gel containing chlorhexidine gluconate, the active ingredient that is brushed on the teeth to avoid

plaque formation, thus improving mouth hygiene. It also includes polymers such as Hydroxypropyl cellulose (HPC) helps keep the gel inside the oral cavity.[48]

❖ Liquid Dosage Forms

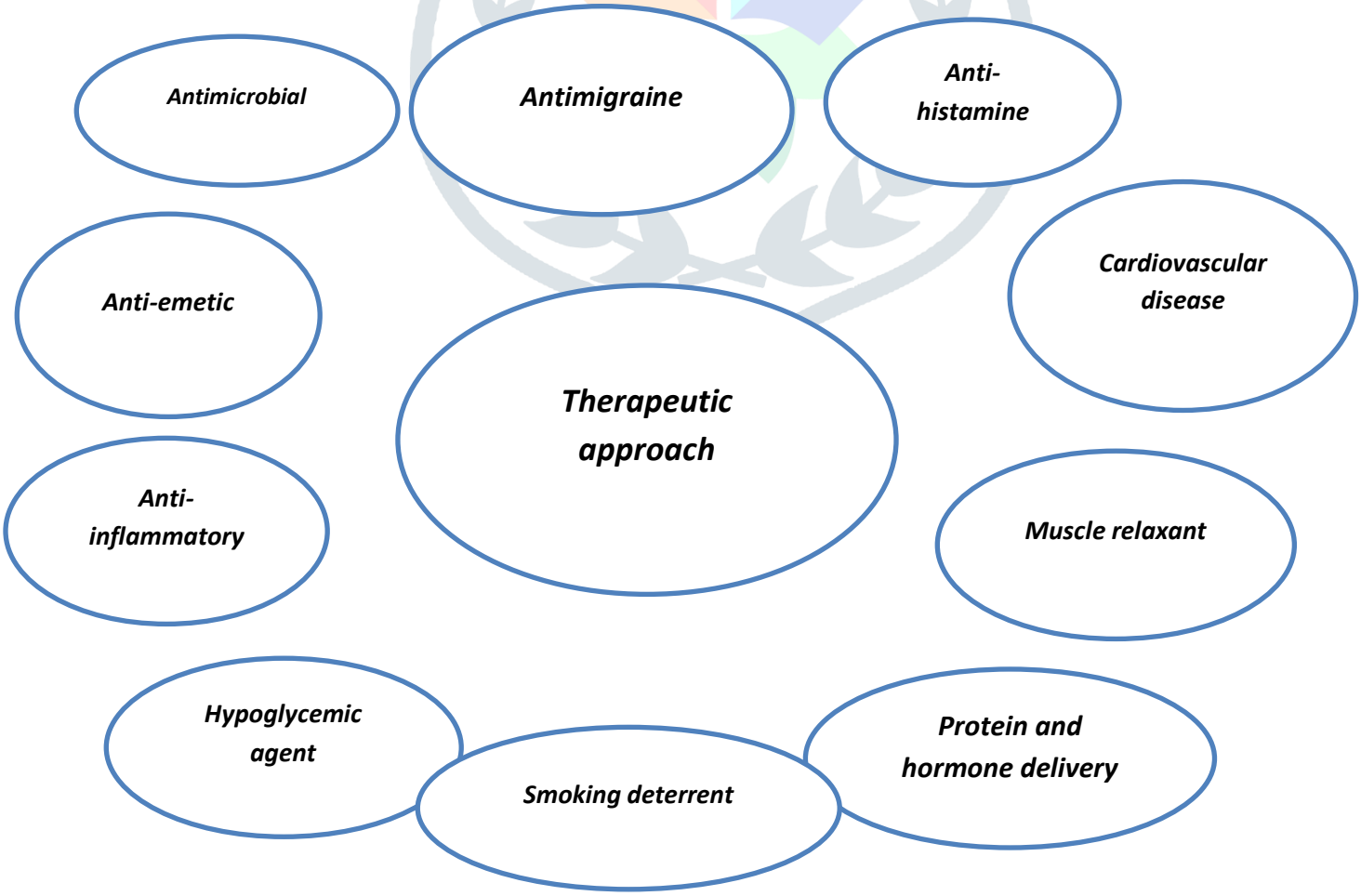
The dosage form or suspension is used as a binder for topical drug delivery in the oral cavity. Chitosan, carbopol, methylcellulose, CMC sodium, gelatin and polycarbophil have the most significant bond among polymer solutions. Viscous liquids may be coated with the aforementioned polymers for use as protection or drug carrier injected into the mucosal surface. A dry mouth can be treated with an artificial saliva solution retained on the mucosal surface to provide Lubrication. These solutions also contain sodium CMC as a mucosal adhesive polymer. [22]

Recent patents, clinical trials and commercial products

Since mucosal adhesion is an excellent way to control drug release, many formulations have been studied both in vitro and in vivo. In recent years, many patents on oral mucus delivery systems have been filed in the pharmaceutical field [3]. Most formulations in clinical trials were in common forms of galena, especially tablets, film and oral translation.[49]

A Therapeutic approach

This delivery system shows controlled drug release, bioavailability enhancement, easy administration, dosage reduction, and usage frequency.[49]



Anti-emetics

Ondansetron hydrochloride is a serotonin 5HT3 antagonist used to prevent nausea and vomiting as a side effect of emetic cancer chemotherapy. To prevent first-pass metabolism by the liver and increase the bioavailability of the drug, the drug should be administered orally.[50-51] Ali and associates. Buccal adhesive Tablets include ondansetron, CP 934, sodium alginate (ALG), low viscosity SCMC, HPMC 15cps and ethyl cellulose. The results showed that the device and the drug were stable in natural human saliva for 6 hours.[52] In another study by Koland et al., a rapidly dissolving membrane was prepared for sublingual administration containing ondansetron, polyvinyl alcohol (PVA)/polyvinylpyrrolidone (PVP), and carpool. The results show that the Carbopol-containing formulations exhibited maximum swelling compared to formulations containing PVP.[53] in the study of Bhalekar et al., oral bio-adhesive hydrophilic matrix pellets were produced, including domperidone, HPMC and carbopol. The results show that the increase in the number of these polymers increases bio adhesion power but reduces the release rate of operation spy.[54]

Antimigraine

Sumatriptan succinate (a 5-HT1 receptor agonist) treats migraine headaches. Shidaye et al. pre-prepared double-layer mucosal patch, consisting of sumatriptan succinate, chitosan and PVP K30. The results show that increased chitosan concentration leads to enhanced mucosal adhesion of the patch. However, the increase in PVP K30 and decreased chitosan concentration leads to better release drugs. On the other hand, improve both chitosan and PVP K30, increasing the degree of plaque swelling.[55]

Anti-histamine

Chlorpheniramine maleate (CPM) is a histamine H1 receptor antagonist commonly used to treat allergic conditions. In the study by Sekhar et al., external mucosal patches containing CPM and hydroxyethyl cellulose (HEC) were prepared. 1.46 times higher than the oral dosage form, indicating that the dosage form is non-irritating, not cause mucosal damage or irritation by application.[56]

Table 3 –a commercial and clinical trial of oral mucoadhesive formulation

Active ingredients	Dosage form	status
asenapine	wafer	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, film, spray, lozenge	commercial
glyceryl trinitrate	tablet, spray	commercial
sufentanil	tablet	commercial
insulin	spray	commercial
tizanidine	powder	Phase I/II completed
vitamin B12	tablet, spray, oral liquid	commercial
influenza vaccine	oral liquid	phase I completed
cyclobenzaprine	oral liquid	phase III
riluzole	tablet	phase I/II/III
misoprostol	tablet	Phase III/IV
cannabidiol	tablet, oral liquid	phase I/I/III/IV

sildenafil	tablet, wafer	Phase III completed
agomelatine	tablet	phase III completed
ropivacaine	liposomal gel	phase I completed

Antimicrobials

Using conventional pharmaceutical dosage forms such as suspensions, solutions, and Mouthwash is ineffective for oral cavity diseases. This may be due to the ease of removal of these forms of the drug; therefore, several attempts have been made to clinical treatment of oral cavity complications. In the study by Juan et al., a double-layer mucilage tablet consisting of nystatin, a lactose layer and a polymeric layer was prepared. The polymer layer provides a sustained release for about 6 hours. [57] In a study by Fini et al., HPMC, CMC, and Hydroxypropyl Cellulose (HPC) were used to create a novel mucoadhesive gel of chlorhexidine.[60] In another study by Domb et al. We prepared a mucoadhesive tablet consisting of ethyl cellulose (EC) and an iodine complex with HPC, which was used as an antibacterial agent to treat oral infections.[58]Obaidat et al. carvacrol and Tetracycline hydrochloride for treating mouth infections. This formulation showed good activity against Pseudomonas aeruginosa, indicating a synergistic action between carvacrol and tetracycline. However, when used individually, they are not effective against Pseudomonas aeruginosa. This combination is also effective against Bacillu scereus.[59]

Cardio Vascular Medicines

Carvedilol is a non-selective beta-adrenergic antagonist used to treat hypertension and stable angina. To treat hypertension, Yamsani Corporation has manufactured carvedilol mucin tablets, consisting of carbopol 934 and hydroxypropyl methylcellulose (HPMC K4M and K15M), to achieve controlled, out-of-order Release. The results showed that increasing the polymer concentration in the formulations resulted in sustained Release of carvedilol. [61]Lercanidipine hydrochloride (LER) is used to treat high blood pressure. In the study by Charde et al., LER-releasing controlled oral mucosal adhesive tablets were prepared, consisting of polyethylene oxide and different viscosities of HPMC, individually and in combination. In vivo studies in rabbits showed a significant increase in the bioavailability of LER compared with oral administration. Use a placebo. The human formulation revealed that the engineered tablets adhere well to the oral mucosa for more than 4 hours without causing discomfort.[62]

Hypoglycemic Agents

In a study by Semalty et al., Mucoadhesive buccal films containing glipizide, HPMC, CP-934, SCMC and Eudragit RL-100 were formulated. The results indicated that therapeutic levels of glipizide may be adequate via buccal delivery.[63] Mujib and others. Different HPMC grades were used to prepare mucoadhesive buccal films of glibenclamide. The results showed that the matrix integrity depended on the drug's amount and properties. It was found that the greater the presence of hydroxyl groups in HPMC K15, the greater the swelling and the shorter the residence time of various formulations. It was found that the Release of active ingredients from the film depended on the polymer content. We also found that HPMC 3000 can be used at lower concentrations for oral administration. Derived from glibenclamide.[64]

Muscle Relaxants

Tizanidine hydrochloride is a centrally located α2-receptor agonist with a myotropic effect on skeletal muscle. In the study by Shanker et al., intraoral bio-tablets were prepared to avoid first-pass metabolism and prolong the time release. It contains tizanidine and some bio-adhesive polymers, such as HPMC K4M, and SCCM. The results indicate that increasing SCMC concentration leads to enhanced adhesion and a higher degree of swelling in a short time. It turns out that the degree of swelling is directly related to the amount of SCMC and inversely proportional to the amount of HPMC K4M.[65.]

Protein and hormones

Oral administration of proteins and hormones may be easier and safer than other routes of administration. In the study by Cui et al., a bilaminated film of insulin was prepared, and its release behaviour was evaluated. The double-layer film was administered orally to healthy rats. Results demonstrated the hypoglycemic effect of the formulation and increased drug delivery by 17% compared to subcutaneous insulin injections[101]. In the study by Colonna et al., a mucous membrane containing 5-methylpyrrolidinone chitosan (MPC) and myoglobin (MHb) was produced. MPC is a chitosan derivative with good properties for oral administration. It is an excellent polymer for creating bio-adhesive films.[66] In the study by Nakane et al., oral sticky tablets containing luteinizing hormone-releasing hormone (LHRH) were formulated. An in vivo study was performed in the case of beagle dogs, and the pharmacokinetic profile was evaluated to find the mucosal osmotic kinetics of LHRH. The results indicated that the plasma concentration of LHRH reached a steady state within 30 min and was maintained for 2 h after administration of the dosage form, compared with the rapid elimination profile following intravenous administration.[67] In the study by Giovino et al., chitosan-based mucolytic films were created in which insulin was loaded with nanoparticles (NPs) and polyethylene glycol methyl ether-block-polylactide (PEG-bPLA). The results show that these formulations have classical biphasic prolonged protein release of more than 5 weeks.[68]

Smoking deterrents

The nature of the smoking habit is partly due to the presence of the psychostimulant consumed. [69] The route of nicotine use (NCT) is through the skin and mucous membranes such as the nose and mouth. It's neutral, and protonated NCT can easily permeate through mucous membranes. [70-71] In the study of Pongjanyakul et al. A buccal sodium alginate magnesium aluminium silicate (SA-MAS) membrane loaded with NCT was prepared as a potential drug delivery system. SA-MAS movies downloaded by NCT provide higher NCT content and a lower NCT release rate. In addition, NCT-loaded SA-MAS membranes exhibit bioadhesive properties for adhesion to mucous membranes. This study suggests that NCT-loaded SA-MAS membranes have a strong potential for use as an oral delivery system. [72] In the study by Rao et al., NCT was used to create a three-layer mucosal patch consisting of a dry drug-impregnated tablet adhered to an adhesive film. 73 In another study conducted by Bilayer, NCT mucosal patches were prepared. As a nicotine replacement product to aid smoking cessation, the feasibility of this formulation has been determined. The results indicate that mucosal xanthan patches are potential candidates for controlled biphasic nicotine delivery. This rapid initial drug release is followed by a controlled release over 10 hours. This study proposes using such a system, as a potential candidate, for future in vivo studies.[74]

Anti-inflammatory drugs

Inflammation is one of the leading causes of diseases of the oral cavity.[75] To manage this problem, topical anti-inflammatory drugs such as flurbiprofen, flufenamic acid, ibuprofen, etc., are used. In these treatments, drug dosage is reduced, and systemic side effects are minimized.[76-77] In the study of Anahita Ghorbani et al., Mucus tablets have been prepared to contain carbopol 940, sodium alginate, zinc sulfate and starch. Clinical and statistical results demonstrate the efficacy of zinc mucoadhesive tablets as a local drug delivery system in terms of analgesia, wound diameter and recovery time after aphthous stomatitis. Recurrence compared with the control group.[108]

In another study by Perioli et al., Dual-layer mucolytic extended-release tablets were designed by mixing mucus-binding polymers and an inorganic substrate (hydrotalcite) to apply flurbiprofen to the oral cavity. The results indicate that a sustained release of appropriate anti-inflammatory in the oral cavity occurs over 12 hours, reducing the drug's daily dose (40 mg versus 70 mg). Mura et al. prepared mucous membrane consisting of flufenamic acid and hydroxypropyl beta-cyclodextrin) HPβCD (, which improves drug release and dissolution rates. The results showed that administration of a complex drug with HPβCD resulted in

complete drug release after 4-5 hours. This is the maximum duration of drug application on the cheek side. Milani et al. have shown that HPβCD has different roles in stabilizing protein formulations ranging from concentration.[79]

Table 4-Patented oral mucoadhesive dosage form

Active ingredient	Patent Number	Route of administration	Dosages form	year
Apo morphine Hydrochloride	US10888499	Sublingual	Film	2021
Asenapine maleate	A205960	Sublingual	tablet	2020
Buprenorphine Hydrochloride, Naloxone Hydrochloride	US10874661	Sublingual	tablet	2020
Desmopressin acetate	N022517	Sublingual	tablet	2018
Sufentanil citrate	N209128	sublingual	tablet	2018
Extracts of the Marzeh khuzestani	96840	buccal	gel	2018
nicotine	US20060198873A1	buccal	film	2017
Zolpidem tartrate	A201509	sublingual	tablet	2016
Buprenorphine hydrochloride	N207932	Buccal	film	2015
Naloxone	US 10617686B2	buccal	Liquid spray	2014

Conclusion

Efforts have been reported to develop oral adhesive drug delivery systems for (I) longer residence time, (ii) controlled drug release, and (iii) prevention of degradation due to enzymes. The oral mucosal drug delivery system is a good alternative to conventional drug delivery due to its ability to prevent first-pass metabolism, improve bioavailability and reduce dose frequency. Undoubtedly, mucosal adhesions have moved into a new field with the introduction of specific compounds, and the development of oral adhesives accelerated due to their different therapeutic uses. The use of oral binders will play an important role in transporting these molecules through the introduction of a large number of drug molecules. Many potential oral mucosal adhesion systems under investigation may appear on the market soon. Numerous reports of clinical trials and patents of oral mucoadhesive drugs suggest that oral drug delivery is a promising means of applying many drugs for Treatment agent on the surface of the oral mucosa. In addition, the use of biologics, such as antibodies, peptides, and proteins, is on the rise.

This evaluation may be useful for designing new dosage forms with oral mucosal adhesion effects. The development of oral binders allows the production of biological formulations with varying degrees of adhesion, drug protection, controlled Release and improved absorption. For this, a better understanding of mucosal adhesion could help researchers develop new solutions. Pharmaceutical binders can be more effective, safer and less expensive.

Reference

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 the 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 Biosimilar on the Pharmaceutical Companies, Iranian Journal of Medical Sciences, 2021;46(5):399. DOI: 10.30476/ijms.2021.92314.2356

7. N.k.Jain. Advances in controlled and Novel drug delivery published by CBS publisher and distributors pvt .Ltd, first edition-2001, 249-282

8. Garly 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

9. Mamatha K, Venkatesh P. A review on mucoadhesive drug delivery systems,Journal of Innovations in Applied Pharmaceutical Science (JIAPS). 2022:32-6.

10. Adikwu MU. A review on Mucins and their potentials, Trop J Pharm Res. 2006; 5:581-2.

11. Bhati R, Nagrajan RK. A detailed review on oral mucosal drug delivery system,International Journal of Pharmaceutical Sciences and Research. 2012;3(3):659.

12. Shojaei AH. Buccal mucosa as a route for systemic drug delivery: a review. J Pharm Pharm Sci. 1998;1(1):15-30.

13. Tangri P . et al. Oral mucoadhesive drug delivery system:a review.International Journal of biopharma.2011;2(1):36-46

14. 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

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

16. 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.

17. 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

18. Singh R, Sharma D, Garg R. Review on mucoadhesive drug delivery system with special emphasis on a 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

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

20. 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.

21. 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

22. 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

23. 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.

24. 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

25. 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

26. 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.

27. 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

28. 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

29. 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

Journal of Pharmaceutical Sciences. 2020; 153:105466. DOI: 10.1016/j.ejps.2020.105466

41. 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. 30. Sharma R, Raghav R, Priyanka K, Rishi P, Sharma S, Srivastava S, et al. Exploiting chitosan and gold nanoparticles for the 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

31. 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

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

33. 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

34. 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

35. 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

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

37. 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

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

39. 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

40. 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 DOI:10.1016/0168-3659(92)90066-Z

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

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

44. 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.

45. H. B. Formulation strategies in mucoadhesive drug delivery.J Control Release. 2005; 22:4-5

46. 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

47.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.

48. 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.

49. 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: 104. Giovino C, Ayensu I, Tetteh J, Boateng JS. Development and 10.7555/JBR.27.20120136

50. 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

51. 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.

52. 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.

53. 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

54. 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).

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

56. 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

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

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

59. 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

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

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

62. 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.

63. 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

64. 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

65. 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

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

67. 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

68. characterization of chitosan films impregnated with insulin loaded PEG-bPLA 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

69. 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.

70. 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

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

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

73. 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

74. 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

75. 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

76. 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

78. 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.

79. 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