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Formulation Options for Mucoadhesive Dosage Forms for Use in the Oral Cavity

Special Issue Article

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Abstract Mucoadhesive dosage forms, which are used for topical application in the oral cavity, are currently a very intensively developing field in pharmaceutical technology. Considering the physiological conditions of the oral cavity, the formulation of these mucoadhesive forms is still a challenge. Various types and forms of polymers are used in the experiments, in combination with a large number of drugs, while the achieved effect can be local or systemic and the release rate can be controlled. For many drugs, buccal application is one of the ways to increase their bioavailability.

Keywords *mucoadhesion – polymers – buccal application – buccal films – mucoadhesive dosage forms*

INTRODUCTION

Mucoadhesive medicinal forms are now an integral part of therapeutic options in the treatment of various diseases. As such, mucoadhesion is a very important tool for ensuring prolonged contact of the dosage form to the site of action, while its sufficient retention at the site of action must be ensured, and the composition of the dosage form itself must provide the possibility of drug release in a sufficient range and quantity. The oral cavity is also a very common place for this type of pharmaceutical form. The onset of effect here can be very fast, but also prolonged, and a great advantage is the absence of the need for absorption of active substances in the stomach or lower parts of the gastrointestinal tract. It is also suitable for medicines that are quickly subject to decomposition due to the influence of digestive juices or that are quickly metabolized in the first-pass effect. An interesting alternative to commonly used mucoadhesive polymers is the thermosensitive polymer that can help regulate swelling, for example, with buccal lyophilizates, when rapid disintegration is not desired, but slow drug release. Research at our workplace investigated the possibilities of using a thermosensitive polymer to create a matrix for a local antibiotic, but the mechanical properties of the lyophilizate were not suitable for buccal administration. Currently, the process of producing buccal and topical oral dosage forms is based on several proven methods, one of which is lyophilization, which makes it possible to use a wide range of combinations of polymers and active substances. The resulting lyophilizate can be a suitable application form for some drugs for local administration into the oral cavity.

ADVANTAGES OF BUCCAL APPLICATION

Buccal application, and also application anywhere else on the mucus membrane of the oral cavity, is a highly effective way to improve the bioavailability of many drugs. The reason is the abundant blood supply to the mucus membrane, which facilitates the direct entry of drug molecules into the systemic circulation. Buccal administration of drugs is well received by patients because the buccal cavity is easily accessible for self-medication and does not require any special and difficult application procedures. An advantage is also the possibility of immediately interrupting the delivery of the drug to the body in case of acute allergic or undesirable manifestations. A large number of patients have difficulty swallowing – for example, patients with dysphagia (Shipp et al., 2022) or fear of needles. Therefore, buccal and orodispersible dosage forms

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(ODFs) represent an important strategy to improve patient compliance. In addition to the fact that these dosage forms do not require water intake, swallowing, or needle application, they allow modulation of drug release (Costa et al., 2019), extended residence time, and sustained delivery compared to existing conventional therapies (Sharma et al., 2018). Suitable for application through the oral mucosa are drugs that are rapidly metabolized in the "first-pass effect" upon gastrointestinal administration, such as the antispasmodic tizanidine (Pendekal, Tegginamat, 2012). However, many of the drugs have poor solubility in the aqueous environment, which can be solved by using complexation, for example, hydroxypropyl beta-cyclodextrin was used by Ahmed et al. (2020) in their experiments, where the model drug used was simvastatin in the form of buccal films. Formulations of buccal dosage forms include adhesive tablets, gels, and patches, of which the patches are advantageous in terms of flexibility and comfort. Buccal plasters must be flexible, elastic, and strong to withstand mechanical activity in the mouth. They must also have good mucoadhesion to remain in the mouth for the required time (Pendekal, Tegginamat, 2012; Sharma et al., 2018). Even these special medicinal forms must meet certain requirements, such as suitable pH – the surface pH of lyophilizates or patches applied to the mucus membrane should have values close to the physiological pH in the oral cavity (5.8–7.1) (Pendekal, Tegginamat, 2012). Suitable for application through the oral mucosa are drugs that are quickly metabolized in the first-pass effect upon gastrointestinal administration, such as spasmolytic tizanidine (Pendekal, Tegginamat, 2012). A suitable alternative to these dosage forms can also be lyophilizates with a gradual release of the drug, whose mechanical properties ensure sufficient hardness. Mucoadhesion will create the desired connection between the dosage form and the oral mucosa. According to our experiments, the use of at least two polymers appears to be a good combination, while mainly cellulose derivatives in combination with chitosan and together with the thermosensitive polymer Pluronic F127 were investigated.

The importance of mucoadhesion for the effect of the drug

Mucoadhesion has shown renewed interest in prolonging the residence time of mucoadhesive dosage forms through various mucosal routes in drug delivery applications. Mucoadhesive-based topical and local systems have shown enhanced bioavailability. Mucoadhesive drug delivery gives rapid absorption and good bioavailability due to its considerable surface area and high blood flow. Mucosal drug delivery system could be of value in delivering a growing number of high-molecular-weight sensitive molecules (Shaikh et al., 2011) or we can use them as technologies for oral mucosal vaccination, with emphasis on mucoadhesive biomaterial-based delivery systems (Mokabari et al. 2023).

Mucoadhesion is the interaction between a mucin surface and a synthetic or natural polymer. Mucoadhesion should not be confused with bioadhesion; in bioadhesion, the polymer is attached to the biological membrane, and if the substrate is a mucus membrane, the term mucoadhesion is used (Shaikh et al., 2011).

Bioadhesion can be defined as the state in which two materials, at least one biological in nature, are held together for an extended period of time by interfacial forces. In biological systems, bioadhesion can be classified into three types:

- Type 1 is adhesion between two biological phases, for example, platelet aggregation and wound healing.
- Type 2 means adhesion of a biological phase to an artificial substrate, for example, cell adhesion to culture dishes and biofilm formation on prosthetic devices and inserts.
- Type 3 is adhesion of artificial material to a biological substrate, for example, adhesion of synthetic hydrogels to soft tissues and adhesion of sealants to dental enamel (Shaikh et al., 2011).

Various theories exist to explain at least some of the experimental observations made during the bioadhesion process. Unfortunately, each theoretical model can only explain a limited number of the diverse range of interactions that constitute the bioadhesive bond. However, according to Shaikh et al. (2011), several types of theories can be put forward.

Wetting theory of mucoadhesion

The wetting theory is perhaps the oldest established theory of adhesion. It is best applied to liquid or low-viscosity bioadhesives. It explains adhesion as an embedding process, whereby adhesive agents penetrate into surface irregularities of the substrate and ultimately harden, producing many adhesive anchors. Free movement of the adhesive on the surface of the substrate means that it must overcome any surface tension effects present at the interface. The wetting theory calculates the contact angle and the thermodynamic work of adhesion.

The work done is related to the surface tension of both the adhesive and the substrate. If a bioadhesive material is to successfully adhere to a biological surface, it must first dispel barrier substances and then spontaneously spread across the underlying substrate, either tissue or mucus.

Electrostatic theory of mucoadhesion

According to electrostatic theory, the transfer of electrons occurs across the adhesive interface and the adhering surface. This results in the establishment of an electrical double layer at the interface and a series of attractive forces responsible for maintaining contact between the two layers.

Diffusion theory of mucoadhesion

Diffusion theory describes that polymeric chains from the bioadhesive interpenetrate into glycoprotein mucin chains and reach a sufficient depth within the opposite matrix to allow the formation of a semipermanent bond. The process can be visualized from the point of initial contact. The existence of concentration gradients will drive the polymer chains of the bioadhesive into the mucus network and the glycoprotein mucin chains into the bioadhesive matrix until an equilibrium penetration depth is achieved.

Adsorption theory of mucoadhesion

According to the adsorption theory, after the initial contact between two surfaces, the materials adhere because of surface forces acting between the chemical structures at the two surfaces. When polar molecules or groups are present, they reorientate at the interface. Chemisorption can occur when adhesion is particularly strong. The theory maintains that adherence to tissue is due to the net result of one or more secondary forces (van der Waal's forces, hydrogen bonding, and hydrophobic bonding).

Fracture theory of adhesion

This theory describes the force required for the separation of two surfaces after adhesion. The fracture strength is equivalent to adhesive strength through the following equation. This theory is useful for the study of bioadhesion by tensile apparatus (Shaikh et al., 2011).

$$\sigma = (E \times \varepsilon/L)^{1/2}$$

where σ is the fracture strength, ε - fracture energy, *E* - young modulus of elasticity, and *L* is the critical crack length.

WHAT AFFECTS MUCOADHESION?

There are several factors that influence mucoadhesion, including hydrophilicity, molecular weight, cross-linking, swelling, pH, and the concentration of the active polymer (Shaikh et al., 2011; Mansuri et al., 2016).

Hydrophilicity

Bioadhesive polymers possess numerous hydrophilic functional groups such as hydroxyl and carboxyl groups. These groups allow hydrogen bonding with the substrate and swelling in aqueous media, thereby allowing maximal exposure of potential anchor sites. In addition, swollen polymers have the maximum distance between their chains, leading to increased chain flexibility and efficient penetration of the substrate.

Molecular weight

The optimum molecular weight for maximum mucoadhesion depends on the type of polymer, with bioadhesive forces increasing with the molecular weight of the polymer up to 100,000. Beyond this level, there is no further gain.

Cross-linking and swelling

Cross-link density is inversely proportional to the degree of swelling. The lower the cross-link density, the higher is the flexibility and hydration rate; the larger the surface area of the polymer, the better is mucoadhesion. To achieve a high degree of swelling, a lightly cross-linked polymer is favored. However, if too much moisture is present and the degree of swelling is too great, a slippery mucilage results and this can be easily removed from the substrate (Shaikh et al., 2011).

Spatial conformation

Besides molecular weight or chain length, the spatial conformation of a polymer is also important. Polymers with a very high molecular weight (e.g., dextrans) have a similar adhesive ability to polymers with a much lower molecular weight (e.g., polyethylene glycols [PEG]). The helical conformation of dextran may shield many active groups primarily responsible for adhesion, unlike PEG polymers which have a linear conformation.

pH value of the environment

This value can influence the adhesion of bioadhesives possessing ionizable groups. Many polymers used as bioadhesives are polyanions with carboxylic acid functionalities.
A systematic investigation of the mechanisms of mucoadhesion clearly showed that the protonated carboxyl groups, rather than the ionized carboxyl groups, react with mucin molecules, presumably by the simultaneous formation of numerous hydrogen bonds (Shaikh et al., 2011).

Concentration of the active polymer

There is an optimum concentration of polymer that provides the best mucoadhesion (Ahuja et al., 1997). In highly concentrated systems, beyond the optimum concentration, the adhesive strength drops significantly because of the coiled molecules which become solvent poor and the chains available for interpenetration are not numerous. But it has been found that in solid dosage forms such as tablets, the higher the polymer concentration, the stronger is the mucoadhesion.

Drug or excipient concentration

Drug/excipient concentration may influence mucoadhesion. Fuente et al. (1996) studied the effect of propranolol hydrochloride on Carbopol® hydrogel adhesion. The authors demonstrated increased adhesion when water was limited in the system, due to an increase in the elasticity caused by the formation of a complex between the drug and the polymer. In the presence of large quantities of water, the complex precipitated out, leading to a slight decrease in the adhesive character.

Physiological and other factors affecting mucoadhesion

Mucoadhesion can also be influenced by the force and method of application. Higher forces lead to high bioadhesion force. Mucoadhesion is also positively influenced by the increasing contact time between the polymer and the substrate. Likewise, the variability of mucus production in different places in the body due to physiological or pathological processes (presence of local or systemic disease) can affect mucoadhesion. With buccal administration, there are many physiological factors that can affect both mucoadhesion and drug release itself, such as buccal surface area, buccal permeability, buccal absorption, salivary flow rate, salivary pH, salivary buffer capacity, salivary composition, stimulation state of saliva, salivary osmolarity, salivary surface tension, and salivary viscosity. All these propositions can change due to age, disease status, gender, bacterial population in the oral cavity, circadian rhythms, the influence of seasons, different psychological settings, and so on (Shaikh et al., 2011)

MUCOADHESIVE DOSAGE FORMS FOR ORAL CAVITY ADMINISTRATION

Mucoadhesive buccal dosage forms may be the answer to the search for dosage forms with improved bioavailability. These dosage forms are also being researched and developed for use in nutraceuticals (Subramanian, 2021) Drug delivery through the oral mucosa has proven particularly useful and offers several advantages over other drug delivery systems, including bypassing hepatic first-pass metabolism, increasing the bioavailability of drugs, improved patient compliance, excellent accessibility, unidirectional drug flux, and improved barrier permeability compared, for example, to intact skin.

Drug delivery through the oral mucosa has gained significant attention due to its convenient accessibility. The buccal and sublingual routes are considered the most commonly used routes. The nonkeratinized epithelium in the oral cavity, such as the soft palate, the mouth floor, the ventral side of the tongue, and the buccal mucosa, offers a relatively permeable barrier for drug transport. Hydrophilic compounds and large or highly polar molecules follow paracellular transport, whereas transcellular transport through the lipid bilayer is followed by lipophilic drugs. The oral cavity has been used as a site for local and systemic drug delivery. Local drug therapy is used to treat disease states like aphthous ulceration gingivitis, periodontal disease, and xerostoma.

Different dosage designs and dosage forms include adhesive gels, tablets, films, patches, ointments, mouthwashes, and pastes (Shaikh et al., 2011). Oral and buccal lyophilizates obtained by lyophilization of various types of gels containing excipients, as well as effective ones, also have good potential. Lyophilization is a gentle method even for drugs that are thermosensitive. Thanks to its mucoadhesive properties, the lyophilizate can adhere to the wall of the oral mucosa and release the active substance for some time.

Until now, adhesive tablets have been the most commonly used dosage forms for buccal drug delivery. Tablets can be applied to different regions of the oral cavity, such as cheeks, lips, gums, and palate. Unlike conventional tablets, buccal tablets allow drinking, eating, and speaking without any major discomfort (Shaikh et al., 2011).

Oral mucosal ulceration is a common condition, with up to 50% of healthy adults suffering from recurrent minor mouth ulcers (aphthous stomatitis). Shemer et al. (2008) evaluated the efficacy and tolerability of a mucoadhesive patch compared to a pain-relieving oral solution for the treatment of aphthous stomatitis. The mucoadhesive patch was found to be more effective than the oral solution in terms of healing time and pain intensity after 12 and 24 h. Local adverse effects were significantly less frequent at 1 h after the treatment among the mucoadhesive patch patients compared to the oral solution patients.

Periodontitis is an inflammatory disease of the oral cavity. There is destruction of the gums and supporting structures of the teeth. Inflammatory periodontitis disease can be treated by a combination of mechanical and intraperiondontal pocket chemotherapeutic agents, containing tetracycline, metronidazole, or other model protein drugs, mucoadhesive properties, and sustained release of therapeutic agents within this environment.

Mucosal delivery of drugs via the buccal route is still very challenging in spite of extensive clinical studies carried out on this. Interesting results brought 3M research that resulted in the buprenorphine patch system, which consists of a matrix patch containing the drug, mucoadhesive polymers, and polymeric elastomers surrounded by a backing material. The patch is capable of delivering the drug for a period of up to 12 h, with good patient comfort reported (Shaikh et al., 2011).

MUCOADHESIVE POLYMERS AND ACTIVE SUBSTANCES

Mucoadhesive polymers have numerous hydrophilic groups such as hydroxyl, carboxyl, amide, and sulfate, which give them good properties for bioadhesive dosage forms. These groups attach to mucus or the cell membrane by various

interactions such as hydrogen bonding and hydrophobic or electrostatic interactions. These hydrophilic groups also cause the polymers to swell in water, and thus expose the maximum number of adhesive sites.

An ideal polymer for a bioadhesive drug delivery system should have the following characteristics: the polymer and its degradation products should be nontoxic, nonirritant, and nonabsorbable; it should preferably form a strong noncovalent bond with the mucus or epithelial cell surface. The polymer should adhere quickly to moist tissue, possess some site specificity, and allow easy incorporation of the drug and offer no hindrance to its release. The polymer must not decompose on storage or during the shelf life of the dosage form. The cost of the polymer should not be high, so that the prepared dosage form remains competitive (Shaikh et al., 2011).

Polymers that adhere to biological surfaces can be divided into three broad categories:

1. Polymers that adhere through nonspecific, noncovalent interactions which are primarily electrostatic in nature
2. Polymers possessing hydrophilic functional groups that hydrogen bond with similar groups on biological substrates
3. Polymers that bind to specific receptor sites on the cell or mucus surface, for example, lectins and thiolated polymers. Lectins are generally defined as proteins or glycoprotein complexes of nonimmune origin that are able to bind sugars selectively in a noncovalent manner. Lectins are capable of attaching themselves to carbohydrates on the mucus or epithelial cell surface and have been extensively studied, notably for drug-targeting applications. Their possibilities of use as glycoprobes and useful tools for cancer diagnosis and therapy are currently being investigated (Van Damme, 2022). These second-generation bioadhesives not only help in cellular binding, but also subsequent endocytosis and transcytosis. Thiolated polymers, also designated trimers, are hydrophilic macromolecules with free thiol groups on the polymeric backbone. Due to these functional groups, various features of polyacrylates and cellulose derivatives were strongly improved. The presence of thiol groups in the polymer allows the formation of stable covalent bonds with cysteine-rich subdomains of mucus glycoproteins, leading to increased residence time and improved bioavailability. Other advantageous mucoadhesive properties of thiolated polymers include improved tensile strength, rapid swelling, and water uptake behavior (Shaikh et al., 2011). A semi-synthetic derivative of chitin obtained by its partial deacetylation is also a widely used polymer. Chitosan has many advantageous properties, such as acting as a permeation enhancer and enzyme inhibitor (Pendekal, Tegginamat, 2012). An interesting possibility in this field of application appears to be still little-explored lectins (Van Damme, 2022), which, in combination with various polymers, can create promising mucoadhesive formulations. For mucoadhesive applications in the oral cavity, the following were also investigated: Eudragit® RS 100, Eudragit® RL100 (Pendekal, Tegginamat, 2012), cellulose derivatives (carboxymethyl cellulose and hydroxypropylmethylcellulose), polyacrylic acid derivatives (carbomers), Carbopol940 (Dinte et al., 2023), poly(methacrylate) polymers (Eudragit), thiolated polymers (thiolated chitosan and thiolated polyacrylic acid derivatives), chitosan, gelatin, hyaluronic acid, carrageenan, pectin, and sodium alginate (Ahmed et al., 2020). Table 1 provides an overview of the polymers used in the formulation of mucoadhesive buccal films.

THERAPEUTIC APPLICATIONS OF MUCOADHESIVE BUCCAL FILMS

Therapeutic areas and diseases where the use of mucoadhesive buccal films has been demonstrated are as follows:

- Cardiovascular disease
- Antioxidant, anti-inflammatory, antimicrobial
- Antiemetic
- Diabetes, Parkinson's disease
- Antifungal, antiviral
- Periodontitis
- Smoking cessation
- Gastrointestinal disease
- Chagas disease, xerostomia
- Anaphylaxis, depressant
- Anesthetic, analgesic, and pain management
- Contraception, erectile dysfunction
- Diuretic, osteoporosis
- Corticosteroids, immune response modifier, wound healing (Shaikh et al., 2011)

Table 2 lists the techniques that are used for the production of mucoadhesive buccal films. Lyophilization can be one of the alternative techniques if the required mechanical resistance of the lyophilizates is achieved with a good release of the active substance, which starts shortly after application to the mucus membrane in the oral cavity.

CONCLUSION

Mucoadhesive dosage forms are modern alternatives to classic dosage forms. They provide a painless possibility of applying many drugs and a sufficiently long stay in the required place, while the patient's compliance is also very good. The requirement to respect the physiological parameters of the oral cavity and at the same time ensure the desired release of active substances represents a formulation challenge for drugs for use in the oral cavity.

Table 1. Mucoadhesive polymers used in mucoadhesive buccal film formulations identified in the literature[a]

Mucoadhesive polymer	Application in mucoadhesive buccal films – API	Used plasticizer(s)
Methyl cellulose (MC)	Cetylpyridinium chloride, carvedilol, omeprazole, nebivolol	Propylene glycol, PEG-400
Ethyl cellulose (EC)	Allantoin, fluticasone propionate, propranolol hydrochloride, ketorolac tromethamine, resveratrol, propranolol hydrochloride & nifedipine	PEG-400, triethyl citrate, propylene glycol, PEG-800, PEG-600, castor oil, glycerol, dibutylphthalate
Hydroxypropyl methyl cellulose (HPMC)	Cetylpyridinium chloride, carvedilol, omeprazole, allantoin, fluticasone propionate, propranolol hydrochloride, ketorolac tromethamine, enalapril maleate, glibenclamide, cetirizine dihydrochloride, glimepiride, nitrendipine, clotrimazole, lidocaine hydrochloride, ibuprofen, ondansetron hydrochloride, meloxicam, prednisolone, rizatriptan benzoate, lycopene, risedronate sodium, clinidipine, furosemide, domperidone, catechin, lidocaine hydrochloride & benzydamine hydrochloride & *N*-acetyl-l-cysteine, nebivolol, nicotine, piroxicam	Propylene glycol, PEG-400, triethyl citrate, PEG-800, PEG-600, castor oil glycerol, PEG-3350, triethanolamine, sorbitol, PEG-200
Hydroxypropyl cellulose (HPC)	Ketorolac tromethamine, resveratrol, nitrendipine, clotrimazole, lidocaine hydrochloride, diltiazem hydrochloride, indomethacin, lycopene	Propylene glycol, PEG-400, glycerol, PEG-3350
Hydroxyethyl cellulose (HEC)	Cetylpyridinium chloride, allantoin, propranolol hydrochloride, meloxicam, moxifloxacin hydrochloride & clove oil, acyclovir, hyaluronic acid, nebivolol	PEG-400, triethyl citrate, PEG-600, castor oil, glycerol propylene glycol
Carboxymethyl cellulose (CMC, SCMC)	Allantoin, fluticasone propionate, ketorolac tromethamine, enalapril maleate, nitrendipine, ibuprofen, meloxicam, diltiazem hydrochloride, lysozyme, rizatriptan benzoate, ciprofloxacin, glipizide, carvedilol, lycopene, lidocaine hydrochloride & benzydamine hydrochloride & *N*-acetyl-L-cysteine, simvastatin, lysozyme & epidermal growth factor, imiquimod	PEG-400, triethyl citrate, propylene glycol, PEG-800, glycerol, triethanolamine, sorbitol
Xyloglucan (XYL)	Rizatriptan benzoate	Glycerol
Polycarbophil (PCP)	Lidocaine hydrochloride, ibuprofen	Glycerol, PEG-3350, triethanolamine, propylene glycol
Polyethylene oxide (PEO)	Lidocaine hydrochloride, streptomycin & diclofenac, rizatriptan benzoate, domperidone	PEG-3350, glycerol
Poloxamer (POL)	Glimepiride, ibuprofen, methylene blue	Propylene glycol, PEG- 600, glycerol
Polyacrylic acid (PAA)	Carvedilol, fluticasone propionate, ketorolac, tromethamine, glimepiride, nitrendipine, clotrimazole, ibuprofen, rizatriptan benzoate, atenolol, prednisolone, lycopene, piroxicam, glipizide	Propylene glycol, PEG-800, glycerol, triethanolamine, PEG-400
Polymethacrylic acid (PMA)	Carvedilol, glibenclamide, glimepiride, clotrimazole, ibuprofen, acyclovir, penciclovir, almotriptan, prednisolone, glipizide, rizatriptan benzoate	Propylene glycol, triethanolamine, PEG-400, PEG-200
Chitosan (CHT)	Cetylpyridinium chloride, fluticasone propionate, propranolol hydrochloride & nifedipine, propranolol hydrochloride, ondansetron hydrochloride, tenoxicam, tramadol, progesterone, insulin, lidocaine hydrochloride, clotrimazole, paracetamol, metronidazole, miconazole nitrate, risedronate sodium, lidocaine hydrochloride & benzydamine hydrochloride & *N*-acetyl-l-cysteine, ropinirole hydrochloride, piroxicam	Propylene glycol, PEG-800, glycerol, dibutylphthalate, PEG-400, sorbitol
Polyvinyl alcohol (PVA)	Cetylpyridinium chloride, nitrendipine, meloxicam, methylene blue, benznidazole, dexamethasone, paracetamol, rizatriptan benzoate, carvedilol, propranolol hydrochloride, allantoin, propranolol	Glycerol, PEG-400, propylene glycol, sorbitol, triethyl citrate, PEG-600, castor oil
Polyvinylpyrrolidone (PVP)	Hydrochloride, ketorolac tromethamine, enalapril maleate, nitrendipine, ibuprofen, methylene blue, penciclovir, ondansetron hydrochloride, tenoxicam, tramadol, progesterone, lysine clonixinate, carvedilol, lycopene, simvastatin, ropinirole hydrochloride, epidermal growth factor & lysozyme	Glycerol, triethanolamine, propylene glycol

Continued *Table 1. Mucoadhesive polymers used in mucoadhesive buccal film formulations identified in the literature*[a]

Mucoadhesive polymer	Application in mucoadhesive buccal films – API	Used plasticizer(s)
Gelatin (GEL)	Ondansetron hydrochloride, lysozyme, progesterone, propranolol hydrochloride, lidocaine hydrochloride	Glycerol
Sodium alginate (SA)	Cetylpyridinium chloride, omeprazole, cetirizine dihydrochloride, nitrendipine, ciprofloxacin, atenolol, nicotine, carvedilol, lycopene	PEG- 400, glycerol, propylene glycol
Gellan gum (GLG)	Moxifloxacin hydrochloride & clove oil, triamcinolone, acetonide, fluconazole	Glycerol, propylene glycol
Guar gum (GUG)	Lysine clonixinate, zolmitriptan succinate, α-casozepine	Propylene glycol, glycerol
Xanthan gum (XG)	Domperidone	Not stated
Carrageenan (CRG)	Omeprazole, streptomycin & diclofenac, ibuprofen, miconazole nitrate	PEG-400, glycerol, PEG-600, propylene glycol
Pectin (PCT)	Meloxicam, clotrimazole, paracetamol, metronidazole, triamcinolone acetonide	PEG-400, glycerol propylene glycol
Hyaluronic acid (HA)	Ondansetron hydrochloride, hyaluronic acid, benzydamine hydrochloride	PEG-400, glycerol
Rice starch (RS)	Lidocaine hydrochloride, diclofenac sodium, paracetamol	Glycerol, PEG-400, propylene glycol, sorbitol
Tapioca starch (TS)	Lidocaine hydrochloride	Glycerol
Arrowroot starch (AS)	Glipizide	Glycerol
Agarose (AGR)	Zolmitriptan succinate	Glycerol
Pullulan (PLL)	Enalapril maleate, yonkenafil, methylene blue	Glycerol, propylene glycol
Maltodextrin (MAL)	Methylene blue	Propylene glycol

[a]*The table also includes used plasticizers, as they are an important element in the formulation of buccal films from the point of view of ensuring the necessary properties of the film (Shaikh et al., 2011; Ahmed et al., 2020; Ammar et al., 2017; Sharma et al., 2018; Dinte et al., 2023; Salehi, Bodohi, 2017; Bahri-Najafi et al., 2014).*

Table 2. Various techniques used to produce mucoadhesive buccal films (Shipp et al., 2022).

Method	Advantages	Disadvantages
Solvent casting	Simple, reproducible, and established process; industrial solvent casting offers better control over film thickness and polymer concentrations	Drug recrystallization after production; changes in film mechanical properties due to plasticizing small molecules; difficult to achieve dose uniformity; potential for entrapped air bubbles; lack of control over film thickness and polymer concentration
Hot melt extrusion	Solventless, continuous process, with fewer operations and better content uniformity than solvent casting; ability to incorporate poorly soluble drugs	Drug recrystallization after production; swelling of film after leaving the die; limited and specialist excipients required; agglomeration of ingredients; weight variations due to improper flow, problems with chemical stability; not suitable for thermosensitive drugs
Inkjet printing	Recrystallization prevented by depositing API onto the film, rather than building API in; mechanical properties of drug-free film retained; able to precisely deposit small volumes of liquids; ability to personalize treatment	Requires another process to make the film deposit drug substances onto; primarily applicable where a low dose of active substance is required; nozzle blockage may lead to inaccurate printed dosages
3D printing	Continuous process capability, with personalized treatment; compartmentalization can prevent incompatible excipient interactions; increases precision of manufacture; thermosensitive drugs can be used with high loading capacity	FDM (fused deposition modelling) filament production by HME (hot melt extrusion) has the same challenges; drying in SSE (semi-solid extrusion) may alter the dimensions of printed objects; only small-scale, nonreproducible manufacture possible; barriers to clinical adoption for this emerging technology

References

[1] Ahmed TA, Bawazir AO, Alharbi WS, Safo MK. Enhancement of Simvastatin ex vivo Permeation from Mucoadhesive Buccal Films Loaded with Dual Drug Release Carriers. Int J Nanomedicine. 2020 Jun 9;15:4001-4020. doi: 10.2147/IJN.S256925. PMID: 32606661; PMCID: PMC7294046.

[2] Ammar HO, Ghorab MM, Mahmoud AA, Shahin HI. Design and In Vitro/In Vivo Evaluation of Ultra-Thin Mucoadhesive Buccal Film Containing Fluticasone Propionate. AAPS PharmSciTech. 2017 Jan 1;18(1):93-103. doi: 10.1208/s12249-016-0496-0. Epub 2016 Feb 16. PMID: 26883262.

[3] Ahuja A, Khar RK, Ali J. Mucoadhesive drug delivery systems. Drug Dev Ind Pharm 1997;23:489-515. https://doi.org/10.3109/03639049709148498

[4] Bahri-Najafi R, Tavakoli N, Senemar M, Peikanpour M. Preparation and pharmaceutical evaluation of glibenclamide slow release mucoadhesive buccal film. Res Pharm Sci. 2014 May-Jun;9(3):213-23. PMID: 25657792; PMCID: PMC4311287.

[5] Blanco Fuente H, AnguianoIgea S, OteroEspinar FJ, BlancoMendez J. *In vitro* bioadhesion of carbopol hydrogels. Int J Pharm 1996;142:169-74. https://doi.org/10.1016/0378-5173(96)04665-0

[6] Costa, J. S. R; Cruvinel, K.de O., Oliveira-Nascimento, L.: A mini-review on drug delivery through wafer technology: Formulation and manufacturing of buccal and oral lyophilizates, Journal of Advanced Research, Volume 20, 2019, Pages 33-41, ISSN 2090-1232, doi: https://doi.org/10.1016/j.jare.2019.04.010.

[7] Dinte E, Muntean DM, Andrei V, Boșca BA, Dudescu CM, Barbu-Tudoran L, Borodi G, Andrei S, Gal AF, Rus V, Gherman LM, Cadar O, Barabas R, Niculae M, Ilea A. In Vitro and In Vivo Characterisation of a Mucoadhesive Buccal Film Loaded with Doxycycline Hyclate for Topical Application in Periodontitis. Pharmaceutics. 2023 Feb 8;15(2):580. doi: 10.3390/pharmaceutics15020580. PMID: 36839899; PMCID: PMC9963859.

[8] Mokabari K, Iriti M, Varoni EM. Mucoadhesive Vaccine Delivery Systems for the Oral Mucosa. J Dent Res. 2023 May 6:220345231164111. doi: 10.1177/00220345231164111. Epub ahead of print. PMID: 37148290.

[9] Pendekal, M.S.; Tegginamat, P. K.: Formulation and evaluation of a bioadhesive patch for buccal delivery of tizanidine, Acta Pharmaceutica Sinica B, Volume 2, Issue 3, 2012, p. 318-324, ISSN 2211-3835, doi: https://doi.org/10.1016/j.apsb.2011.12.012.

[10] Salehi S, Boddohi S. New formulation and approach for mucoadhesive buccal film of rizatriptan benzoate. Prog Biomater. 2017 Dec;6(4):175-187. doi: 10.1007/s40204-017-0077-7. Epub 2017 Nov 6. PMID: 29110144; PMCID: PMC5700911. https://pubmed.ncbi.nlm.nih.gov/29110144/

[11] Shaikh R, Singh TRR, Garland MJ, Woolfson AD, Donnelly RF. Mucoadhesive drug delivery systems. J Pharm Bioall Sci 2011;1:89-100. PMCID: PMC3053525, PMID: 21430958. doi: 10.4103/0975-7406.76478

[12] Shakir Mansuri, Prashant Kesharwani, Keerti Jain, Rakesh K. Tekade, N.K. Jain, Mucoadhesion: A promising approach in drug delivery system, Reactive and Functional Polymers, Volume 100, 2016, p.151-172, ISSN 1381-5148, https://doi.org/10.1016/j.reactfunctpolym.2016.01.011.

[13] Sharma D, Sharma A, Garg R. Design, Development and In vitro/Ex vivo Evaluation of Mucoadhesive Buccal Film of Benzydamine Hydrochloride for the Effective Treatment of Aphthous Stomatitis. Recent Pat Drug Deliv Formul. 2018;12(4):277-294. doi: 10.2174/1872211313666190128151038. PMID: 30706830.

[14] Shemer A, Amichai B, Trau H, Nathansohn N, Mizrahi B, Domb AJ. Efficacy of a mucoadhesive patch compared with an oral solution for treatment of aphthous stomatitis. Drugs R D 2008;9:29-35. doi: 10.2165/00126839-200809010-00003

[15] Shipp L, Liu F, Kerai-Varsani L, Okwuosa TC. Buccal films: A review of therapeutic opportunities, formulations & relevant evaluation approaches. J Control Release. 2022 Dec;352:1071-1092. doi: 10.1016/j.jconrel.2022.10.058. Epub 2022 Nov 18. PMID: 36351519.

[16] Subramanian P. Mucoadhesive Delivery System: A Smart Way to Improve Bioavailability of Nutraceuticals. Foods. 2021 Jun 11;10(6):1362. doi: 10.3390/foods10061362. PMID: 34208328; PMCID: PMC8231213.

[17] Van Damme EJM. 35 years in plant lectin research: a journey from basic science to applications in agriculture and medicine. Glycoconj J. 2022 Feb;39(1):83-97. doi: 10.1007/s10719-021-10015-x. Epub 2021 Aug 24. PMID: 34427812; PMCID: PMC8383723.