Buccal delivery of small molecules and biologics: of mucoadhesive polymers, films, and nanoparticles – An update

Varsha V. Nair [a], Pablo Cabrera [b,c], Constanza Ramírez-Lecaros [d], Miguel O. Jara [a], David J. Brayden [e], Javier O Morales [b,f,g,*]

[a] Division of Molecular Pharmaceutics and Drug Delivery, College of Pharmacy, The University of Texas at Austin, Austin, Texas, 78712, USA

[b] Advanced Center for Chronic Diseases (ACCDiS), Sergio Livingstone 1007, Independencia, Santiago 8380494, Chile

[c] Departamento de Química Farmacológica y Toxicológica, Facultad de Ciencias Químicas y Farmacéuticas, Universidad de Chile, Santiago 8380494, Chile

[d] Escuela de Farmacia, Universidad de Valparaiso, Gran Bretaña 1093, Playa Ancha, Valparaíso, Chile

e UCD School of Veterinary Medicine and UCD Conway Institute, Belfield, Dublin D04 V1W8, Ireland

[f] Center of New Drugs for Hypertension (CENDHY), Santiago 8380492, Chile

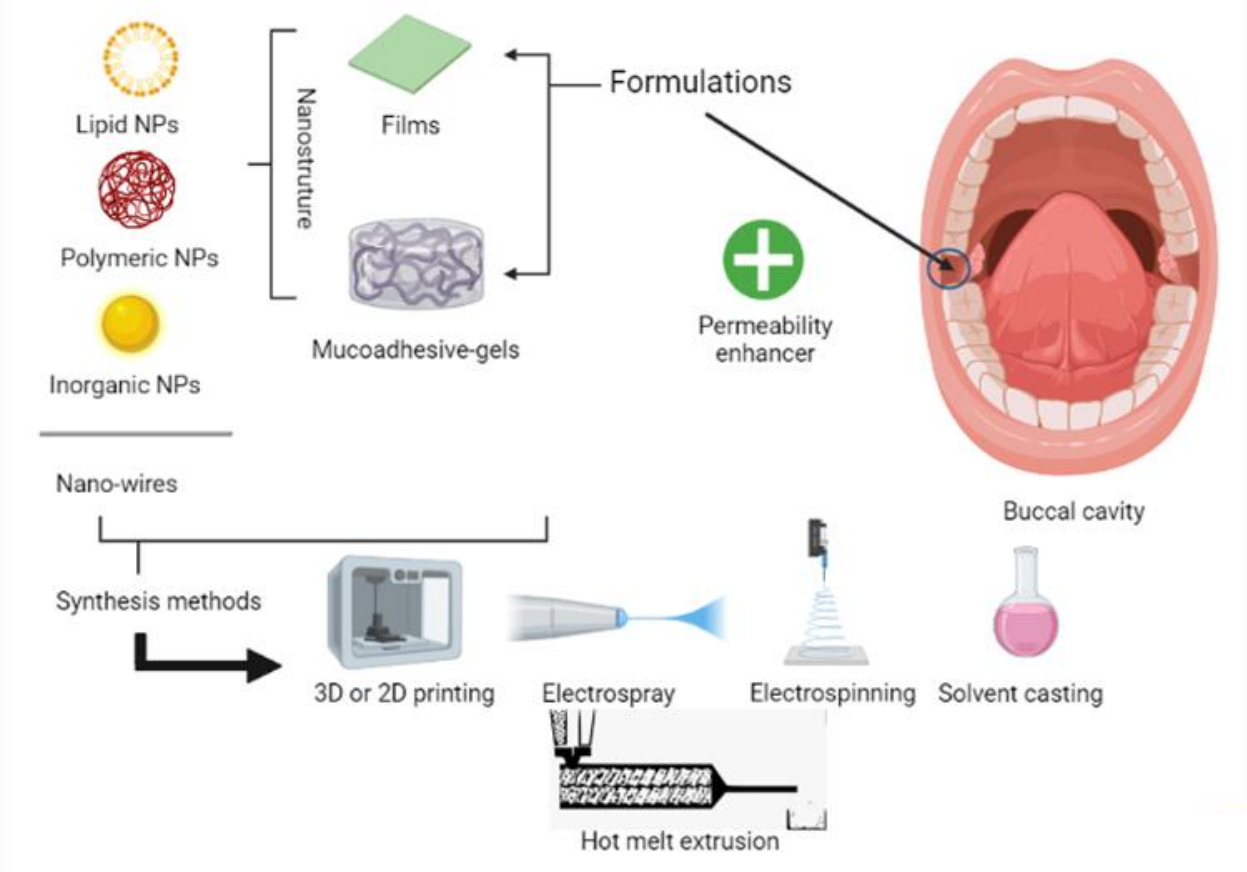
[g] Drug Delivery Laboratory, Departamento de Ciencias y Tecnología Farmacéuticas, Universidad de Chile, Santiago 8380492, Chile

*Corresponding author: Javier O. Morales, Ph.D.

jomorales@ciq.uchile.cl

Tel: +56 22 978 1620

27 Graphical Abstract



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Abstract

Buccal delivery of small and large molecules is an attractive route of administration that has been studied extensively over the past few decades. This route bypasses first-pass metabolism and can be used to deliver therapeutics directly to systemic circulation. Moreover, buccal films are efficient dosage forms for drug delivery due to their simplicity, portability, and patient comfort. Films have traditionally been formulated using conventional techniques, including hot-melt extrusion and solvent casting. However, newer methods are now being exploited to improve the delivery of small molecules and biologics. This review discusses recent advances in buccal film manufacturing, using the latest technologies like 2D and 3D printing, electrospraying, and electrospinning. This review also focuses on the excipients used in the preparation of these films, with emphasis on mucoadhesive polymers and plasticizers. Along with advances in manufacturing technology, newer analytical tools have also been used for the assessment of permeation of the active agent across the buccal mucosa, the most critical biological barrier and limiting factor of this route. Additionally, preclinical and clinical trial challenges are discussed, and some small molecule products already on the market are addressed.

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1. Introduction

The buccal route of administration is an attractive alternative to deliver drugs into systemic circulation, being an option to the oral and intravenous routes of administration. The buccal mucosa is situated on the inner side of the cheeks, and it is a non-keratinized tissue similar to the sublingual mucosa. This non-keratinized mucosa is more elastic and penetrable than keratinized tissues in the oral cavity, being more suitable for active molecules delivery. Nevertheless, when comparing buccal with sublingual mucosa, the latter is relatively more permeable; hence, formulations for sublingual delivery are formulated to release the active agent immediately, whereas buccal formulations seek a controlled release, using mucoadhesive formulations (Boddupalli et al., 2010). The buccal epithelium is stratified, with ~40–50 cell layers, and it has a thickness of 400–700 mm and a surface area of ~50 cm^2 (Morales and Brayden, 2017). In addition, it is a tight junction-free epithelium, which main permeability barrier is in the upper one-third of cell layers, where a lipid-rich domain is found. Table 1 summarizes some properties of the buccal mucosa.

Table 1. Properties of the buccal mucosa.

Properties	**Comments**	**Reference**
Surface area	50 cm^2	(Patel et al., 2011; Sohi et al., 2010a)
pH	6.28 ± 0.36	(Aframian et al., 2006)
Saliva	0.9 mL in the oral cavity. Salivary secretions are between 0.5 and 2.0 L daily.	(Patel et al., 2011)
Thickness	40-50 cell layers 400-700 µm	(Morales and Brayden, 2017)
Turnover time	5-7 days	(Patel et al., 2011; Sohi et al., 2010a)
Enzymes	Aminopeptidase, carboxypeptidase, dehydrogenase, and esterase	(Sohi et al., 2010a)
Mucosal layer	40-300 um thickness Composition: water 95%, mucin and inorganic salts 1- 5%, mineral salts 1%, and free proteins 1%	(Wang et al., 2021)

This epithelium, besides performing standard epithelial processes, such as protection and lining, is highly specialized in processes such as taste and sensory perception, mastication, and secretion (Atukorallaya and Ratnayake, 2021). Likewise, as with other mucosal barriers in the body, buccal epithelium absorption also depends on the physicochemical properties of the molecule, its interaction with cell plasma membranes, and the selected dosage form (Smart, 2005). Generally, small molecules with a log P of 1.6 – 3.3, are absorbed rapidly, whereas drugs with a higher log P have limited absorption due to low water solubility (Smart, 2005). The rate and extent of

absorption from the buccal mucosa are also retarded by saliva, mucus, and membrane-coating granules (Smart, 2005). Furthermore, while buccal delivery offers an easy-to-use administration benefit, it is limited by accidental swallowing of the formulation, a small surface area for absorption, and continuous dilution by saliva, which could lead to low bioavailability (Chinna Reddy et al., 2011). Other limitations include overhydration of the formulation leading to loss of structural integrity, patient acceptance, and difficulty in delivering high concentrations in the dosage form (Madhavi B et al., 2013). Nevertheless, although buccal mucosa acts as a high barrier to drug absorption, especially for biopharmaceutical products (proteins and oligonucleotides), it can be used to bypass first-pass metabolism and gastrointestinal drug degradation (Chinna Reddy et al., 2011).

Over the years, a wide range of formulations have been developed for buccal drug delivery. A list of recently FDA-approved buccal products is provided in Table 2. The global buccal drug delivery market size was about $3.2 billion in 2021. The market size is further estimated to show a 9.8% increase in annual growth rate by 2028 and is estimated to be 7.13 billion by 2030 ("Buccal Drug Delivery Market Dynamics & Industry Scope | 2030," n.d.). Pain management and smoking cessation are the leading targets for therapy using buccal drug delivery systems. The smoking cessation application accounts for more than 30% of the total buccal delivery market share ("Buccal Drug Delivery Systems Market Report, 2021-2028," n.d.). As of 2020, the majority of the nicotine products sold are gums, followed by patches, lozenges, and inhalers ("Nicotine Replacement Therapy (NRT) Market | Global Report, 2028," n.d.). In 2020, gums accounted for 52.7% ($511 million), lozenges accounted for 33.3% ($322 million), and patches accounted for 14.1% ($137 million) of over-the-counter nicotine replacement therapy sales. Three leading brands—private label or store brands (62.8%), Nicorette (30.7%,), and NicoDerm CQ (5.7%)—accounted for 99.2% of the total over-the-counter nicotine replacement therapy market (Trigger et al., 2023). Nicotine lozenges by Dr. Reddy's were approved for use in the U.S market in 2020 and accounted for $200 million in retail sales, which further added to the growth of the buccal delivery market ("Smoking Cessation Aids Market Analysis - Industry Report - Trends, Size & Share," n.d.). The nicotine market is also flooded with a number of generic products, thereby leading to further growth. In terms of sales of pain management medications, Belbuca® was known to have annual sales equaling $315 million as of July 2022 ("IntelGenx receives FDA GDUFA date for partnered buprenorphine buccal film - BioTuesdays," n.d.). However, studies have reported a decline in opioid prescribing rates by 73% over ten years (from 2009 to 2018) due to federal, state, and local initiatives to control the opioid epidemic (Muench et al., 2020). Thus Suboxone, a combination of buprenorphine hydrochloride and naloxone, was developed to counteract the problem of opioid dependence. While Suboxone had market exclusivity, it had peak sales of $1.082 billion in 2013. However, after generics were introduced in the market, the annual sales went down to $232 million in 2021 (McGee et al., 2023; Pierce et al., 2016). Another major player in the pain management application is Fentora®, which is available as a tablet. Fentora showed US sales of $179 million in 2010. However, the implementation of the risk evaluation and

mitigation strategy by the FDA in 2012 led to a decline in prescriptions for the product (Fleischman et al., 2019). The products meant for less common applications like oral thrush, herpes, and schizophrenic agitation maintain market exclusivity for their respective applications. Currently, no generics are available for Sitavig®, Oravig®, or Igalmi®. As of 2014, 20 million prescriptions of Sitavig® were made, comprising $4 billion in annual sales in the US for the treatment of herpes ("Innocutis Holdings LLC Licenses Sitavig from BioAlliance Pharma | Sitavig (acyclovir), 50mg Muco-Adhesive Buccal Tablets," n.d.). Oravig ®, which BioAlliance originally developed in 2010, went through three acquisitions and is currently a product of Galt pharmaceuticals and came off patent in September 2022 (Saxena, 2015). Igalmi® is a first in the category for treating agitation during schizophrenia and was approved for the US market in 2022.

Table 2. List of approved buccal products by the US FDA ("Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations," n.d.)

Sr. No.	Proprietary Name	Dosage Form	US-FDA Label Indication	Active Ingredient	Action	Company and year of approval
1	BELBUCA®	Film	Management of severe pain	Buprenorphine Hydrochloride	Systemic	Collegium Pharmaceuticals, 2015
2	SUBOXONE®	Film	Maintenance treatment of opioid dependence	Buprenorphine Hydrochloride, Naloxone Hydrochloride	Systemic	Indivior,2002
3	BUPRENORPHINE HYDROCHLORIDE; NALOXONE HYDROCHLORIDE	Film	Management of severe pain	Buprenorphine Hydrochloride, Naloxone Hydrochloride	Systemic	Alvogen Inc, 2019
4	BUPRENORPHINE HYDROCHLORIDE; NALOXONE HYDROCHLORIDE	Film	Management of severe pain	Buprenorphine Hydrochloride, Naloxone Hydrochloride	Systemic	Dr. Reddy's Laboratories, 2018
5	BUPRENORPHINE HYDROCHLORIDE AND NALOXONE HYDROCHLORIDE	Film	Management of severe pain	Buprenorphine Hydrochloride, Naloxone Hydrochloride	Systemic	Mylan Technologies Inc
6	BUPRENORPHINE HYDROCHLORIDE AND NALOXONE HYDROCHLORIDE	Film	Management of severe pain	Buprenorphine Hydrochloride, Naloxone Hydrochloride	Systemic	Aveva Drug Delivery Systems Inc
7	SITAVIG®	Tablet	Herpes labialis (cold sores) in	Acyclovir	Systemic	BioAlliance Pharma, 2013

			immunocompetent adults.			(Currently acquired by EPI Health LLC)
8	FENTORA®	Tablet	Management of breakthrough pain in cancer patients 18 years of age and older	Fentanyl Citrate	Systemic	Cephalon, 2006 (Currently acquired by Teva Pharmaceuticals)
9	ORAVIG®	Tablet	Oropharyngeal candidiasis in adults	Miconazole	Local	BioAlliance Pharma, 2010 (Currently acquired by Galt Pharmaceuticals)
10	NICORETTE	Chewing gum	Reduces withdrawal symptoms associated with quitting smoking	Nicotine Polacrilex	Systemic	Glaxo Smith Kline, 1984 (Currently Haleon)
11	NICOTINE POLACRILEX	Chewing gum	Reduces withdrawal symptoms associated with quitting smoking	Nicotine Polacrilex	Systemic	Circa Pharmaceuticals, 1998 (Currently acquired by PL Developments)
12	NICOTINE POLACRILEX	Chewing Gum	Reduces withdrawal symptoms associated with quitting smoking	Nicotine Polacrilex	Systemic	Perrigo R& D Co, 2006
13	NICOTINE POLACRILEX	Chewing Gum	Reduces withdrawal symptoms associated with quitting smoking	Nicotine Polacrilex	Systemic	Fertin Pharma AS, 2022
14	IGALMI	Film	For Acute treatment of agitation associated with schizophrenia or bipolar I or II disorder in adults	Dexmedetomidine hydrochloride	Systemic	Bioxcel Therapeutics INC, 2022

This review intends to provide a comprehensive update on the progress made in the field since the original article was published (Morales and Brayden, 2017). Established manufacturing technologies used to prepare buccal films are discussed, along with introducing the current state-of-the-art technologies and the commonly used excipients. The review also outlines novel analytical technologies and animal models used in the development of buccal films. Lastly, we summarize the current status of clinical trials involving buccal films.

2. Mucoadhesive polymers

Films, as pharmaceutical dosage forms, can facilitate the permeation of drugs through the buccal epithelium by allowing close interaction between the film's drug-rich surface and the absorption site. Drug permeation across the buccal epithelium depends on their physicochemical properties, permeation kinetics, and dosage form (Lee et al., 2000).

Bioadhesive polymers are preferred for developing films for buccal delivery using films. Among their desirable features, bioadhesive polymers have strong hydrogen bonding groups, strong anionic or cationic charges, high molecular weight, chain flexibility, and surface energy properties, which facilitate their spreading on mucus layers (Lee et al., 2000). These polymers can be

classified by their source (natural or synthetic), water solubility (soluble or insoluble), charge (cationic, anionic, or non-ionic), and bioadhesive forces (covalent, hydrogen bonding, or electrostatic interaction) (Salamat-Miller et al., 2005). As mentioned, mucoadhesive polymers allow extended contact time to enhance buccal bioavailability. Initially, the approach to achieve mucoadhesion was based on using hydrophilic cationic polymers for interacting with the anionic moieties of mucin by electrostatic interactions (Morales and Brayden, 2017; Morales and McConville, 2011). Additionally, mucoadhesive polymers rely on other non-covalent interactions with mucin as polymer chain entanglement to achieve the required mucoadhesive bond. This type of interaction lacks the specificity for targeting, adhering to the mucus non-specifically. Thus, they usually have shorter retention times due to the high turnover rate of overlying mucus (Salamat-Miller et al., 2005). The newer generation of mucoadhesive polymers can adhere with significant specificity to the cell surfaces by interacting with cellular receptors or through covalent bonds. Thiolated polymers (thiomers) are an example, attaching to the cysteine groups of mucin using thiol-derived polymer chains (Laffleur, 2014). The thiol-disulfide exchange reaction leads to the formation of disulfide bridges between the cysteine-rich domains of the mucus and polymer, mimicking the natural behavior of the secreted mucins which also covalently anchor in the mucus by disulfide bonds (Müller and Bernkop-Schnürch, 2014). In tensile studies, thiolated polymers have shown increased mucoadhesiveness regarding non-thiolated ones. Additionally, they have increased mucoadhesiveness at lower pHs (Marschütz and Bernkop-Schnürch, 2002). Thiomers have been employed in several types of pharmaceutical dosage forms, such as buccal tablets, wafers, gels, and films (Boateng and Ayensu, 2014; Mortazavian et al., 2014; Wasnik et al., 2014). I*n vitro* studies in CaCO-2 cells have shown that thiomers maintained cell viability in concentrations ranging from 0 to 1000 ug/mL (Müller and Bernkop-Schnürch, 2014). In another *in vitro* study, 90% cell viability was achieved after using thiomers at a concentration of 0.5 % w/v for 3 hours (Iqbal et al., 2012). A study conducted on healthy human volunteers concluded that thiolated chitosan in a nanofiber mat did not report toxicity or side effects after 2-8 min adhesion to the buccal mucosa (Samprasit et al., 2015). In a different route of administration, thiomers have demonstrated concentration-dependent cytotoxicity. Thiomers at a 0.5% w/v concentration exhibited no change in ciliary beat frequency, thereby rendering them safe in the nasal mucosa (Palmberger et al., 2011). Furthermore, clinical trials are ongoing to study thiolated hyaluronic acid's safety and efficacy in treating persistent corneal epithelial defects (Kiora Pharmaceuticals, Inc., 2022).

Among the considerations for buccal delivery using mucoadhesive polymers, some challenges include saliva turnover in the oral cavity, unpalatable taste, mastication, buccal microbiome, and limited surface area. Additionally, a buccal dosage form faces salivary washouts and mechanical stress due to tongue movements (Kumar et al., 2020).

3. Recent advancements in films as buccal delivery systems

Over the past decades, there have been diverse developments in dosage forms for buccal delivery, such as tablets, lozenges, sprays, mouthwashes, gels, and films (Montenegro-nicolini and Morales, 2016). Among these dosage forms, bioadhesive tablets can be considered the current industry standard due to their ease of manufacturing, high dose capacity, and availability of excipients for

sustained release (Morales and Brayden, 2017). However, in recent years, the development of bioadhesive and biocompatible films for buccal delivery has been dragging attention because of the following reasons: 1) they possess the necessary flexibility and mechanical resistance for adjusting to the buccal mucosa; 2) ease of administration, since they can attach to the buccal mucosa for long period of times: 3) they can be customized for different drug delivery purposes, such as the employment of multiple release profile layers (Montenegro-nicolini and Morales, 2016). In addition, films could be an interesting pediatric dosage form because of the safety of their excipients (Khan et al., 2016; Montero-Padilla et al., 2017; Trastullo et al., 2016).

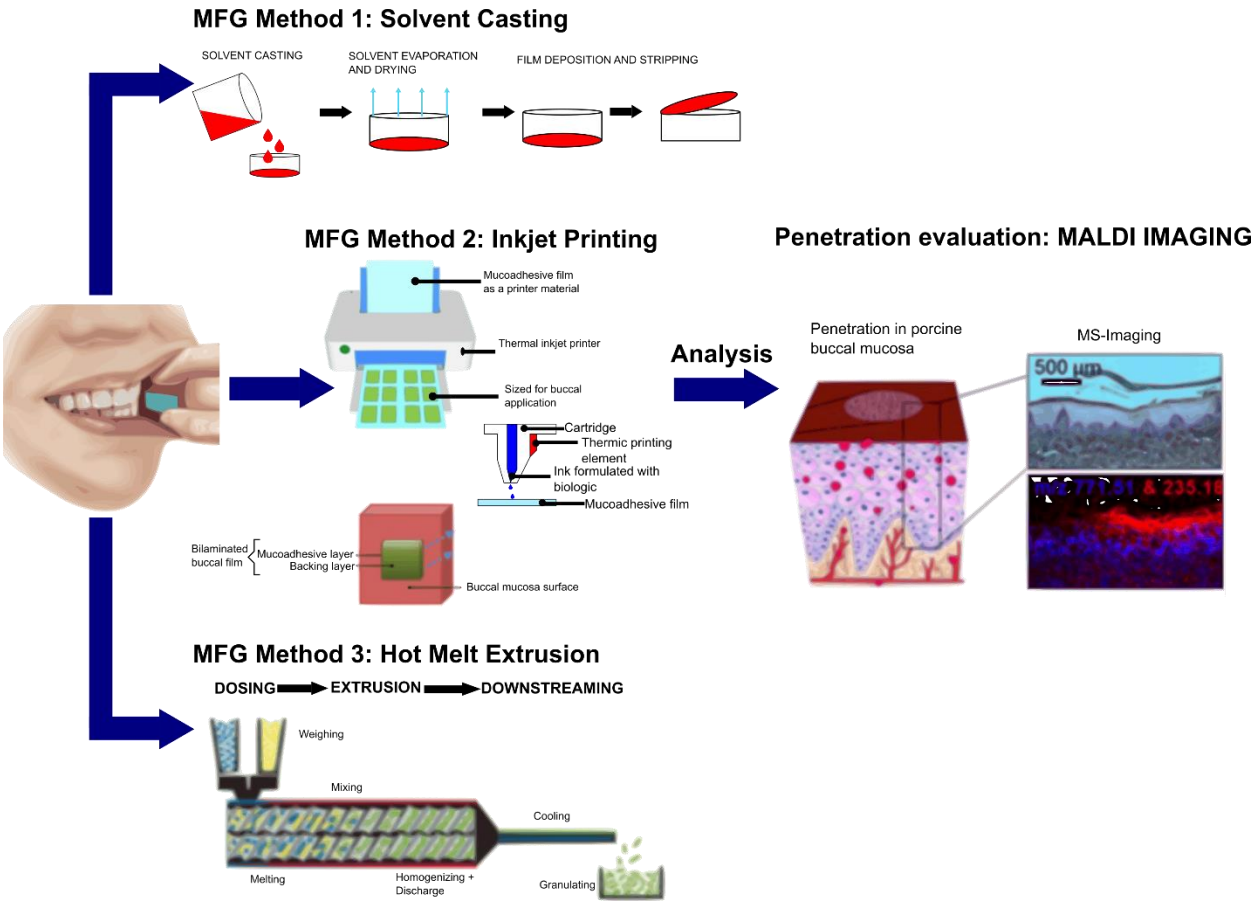

Figure 1. Standard manufacturing methods used in the preparation of buccal films. In addition, the figure shows some novel analytical techniques used to evaluate buccal permeation (Figure modified with permission from Montenegro-nicolini and Morales, 2016). MFG: manufacturing.

Buccal delivery of molecules in films has thus become a popular approach due to the ease of delivery and non-invasive nature, thus improving patient adherence. Films ensure more accurate dosing than buccal gels as the former cannot be easily washed away and stay on the mucosa, thus improving the residence time to enable drug absorption.

3.1 Buccal films prepared by solvent casting:

Among the different methods used in film preparation (Figure 1), solvent casting is the most employed because of the ease of production and low setup costs (Karki et al., 2016). Usually, a homogeneous mixture is used, and high shear forces are applied to the mix of excipients, polymers, and drugs in either an aqueous or organic solvent. The drugs, excipients, and polymers are selected based on the solubility in the solvent system. This mixture is then spread on a substrate or support, followed by water evaporation and drying (Karki et al., 2016; Siemann, 2005). However, the numerous processing steps involved and the batch-to-batch variation pose limitations to this method of film development (Ghosal et al., 2018; Siemann, 2005). The aesthetic appearance of the films may also be affected by air entrapment during the solvent evaporation stage (Houdhary et al., 2012; Irfan et al., 2016). The following sections discuss solvent casting methods research for film manufacture, providing an update to our previously published review (Morales and Brayden, 2017).

Small molecules:

Rizatriptan was formulated in a mucoadhesive buccal film using solvent casting with a combination of Proloc, hydroxypropyl methylcellulose (HPMC), and Eudragit® RS 100 polymers (Nair et al., 2021). The films had a high degree of mucoadhesive strength and swelling capacity. Another advantage was the conversion of rizatriptan to its amorphous state, improving the solubility and the bioavailability of Rizatriptan (Nair et al., 2021). Compared to the orally administered control, these films increased the drug's bioavailability in rabbits by increasing drug permeation and bypassing first-pass metabolization.

Gelatin is a polymer extensively used in pharmaceutical and medical applications, which is categorized as a GRAS (Generally regarded as Safe) material by the FDA. Type A and Type B gelatin were used to formulate a mucoadhesive buccal film for delivering propranolol hydrochloride. Type B gelatin from bovine skin formed a complex with the drug within the film compared to a physical mixture observed with Type A gelatin from porcine skin. Furthermore, in the film, propranolol hydrochloride exhibited an amorphous structure, leading to improved bioavailability. It was found that Type A gelatin film has higher solubility and faster drug release, while films made with Type B gelatin had lower mechanical strength, stronger mucoadhesion, and slower drug release (Jovanović et al., 2021).

Ciclopirox olamine (CPX), an antifungal agent, was successfully incorporated into the mucoadhesive layer of a combination of poly(ethylene oxide) (PEO) and glycerol, supported by a backing layer of PEO and Eudragit® NM 30D. Eudragit® was used because of its low permeability, making it ideal for prolonged drug release. The use of Eudragit® and PEO in the backing layer gave rise to a zero-order release kinetics of the drug across 700 minutes. (Gajdošová et al., 2020). Tzanova et al. (2021) achieved the delivery of solid lipid nanoparticles (SLNs) using mucoadhesive buccal film made of HPMC and glycerin. The SLNs were prepared by the solvent-injection method, and they were loaded onto buccal films using the solvent casting method. These drug-loaded SLN films had similar mucoadhesiveness to placebo films. Additionally, the drug's

permeability across a mucus-penetrating cell line was improved due to the use of the film when compared to the nanoparticles alone (Tzanova et al., 2020).

In another example, a combination of hydroxypropyl methylcellulose (HPMC) E3 and E15 was used to design a transparent film for delivering frovatriptan succinate monohydrate. PEG was used as a plasticizer to obtain adequate mechanical strength and to enable fast drug dissolution (Bhatt et al., 2021). Winarti et al. (2021) combined HPMC with chitosan with an ethylcellulose backing layer to deliver diltiazem hydrochloride and increase the film's mucoadhesive strength and the residence time in the buccal epithelium. (Winarti et al., 2021). This blend of HPMC and chitosan was also used in a different study and combined with a backing layer of Eudragit® RS 100 to obtain a unidirectional release of alfuzosin hydrochloride for over 8 hours (Mahapatra et al., 2021). It is also noteworthy that buccal films are not only used for better systemic delivery but also have been widely employed for the local treatment of oral infections. Clindamycin and ketorolac have also been entrapped in buccal films for periodontitis treatment (Barpete et al., 2021).

The physicochemical properties of the molecule should be considered when using the solvent-casting method for preparing films. In the case of water-soluble molecules, the best and the most desired outcome is that the drug remains dissolved in the matrix after solvent evaporation and does not recrystallize (Centkowska et al., 2020). On the other hand, for poorly water-soluble drugs, an organic solvent is often employed as a cosolvent; however, this might increase drug recrystallization due to an anti-solvent precipitation effect (Woertz and Kleinebudde, 2015). It is also possible to formulate a biphasic system for solvent casting by micronizing the drug; nevertheless, this is associated with surface roughness and irregularities. Therefore, the drug and the subsequent polymer choice are of utmost importance (Woertz and Kleinebudde, 2015). Other problems associated with the manufacturing process include air entrapment and nonuniform drug distribution caused by poor spreadability during the casting process, leading to batch-to-batch variation (Vidyadhara et al., 2015). Some of these issues can be overcome by using alternative processing techniques.

Large molecules:

Buccal films are promising dosage forms to keep biologics stable during their storage. Buccal drug delivery of insulin avoids subcutaneous self-administration and injection-related anxiety associated with the current treatment (Peyrot et al., 2010). To improve treatment compliance, the oral route of administration is promising due to its ease of administration. However, it would be more challenging than the buccal route of administration in terms of enzymatic degradation, pH, and biological barriers (Elsayed et al., 2023). Diab et al. (2021) exemplified the potential of using films for delivering insulin using the buccal route of administration. The authors not only achieved a 57% of the effects produced by the subcutaneous administration in the rats model but also demonstrated improved physical stability. Indeed, a viable insulin formulation must maintain its secondary structure during storage. Diab et al. (2021) used L-arginine, an amino acid known for

suppressing insulin aggregation, to stabilize the peptide in a mucoadhesive buccal film. The authors used a mixture of low- and high-molecular-weight chitosan, glycerin, and L-arginine to develop flexible transparent films. Additionally, it was observed that chitosan and glycerin increased the content of unordered insulin, leading to the generation of the β-sheet conformation, which is considered detrimental to the molecule's efficacy. L-arginine suppressed the generation of β-sheets by stabilizing the insulin in an α-helix conformation (Diab et al., 2021).

In another approach for stabilizing biologics in films, Hensley et al. (2021) showed the feasibility of incorporating vaccines for buccal delivery. The authors aimed to develop a thermostable vaccine to deal with the differences observed in the efficacy of commercial vaccines among developed and developing countries (90% vs 39-70%), partly due to fluctuations during transportation and storage. The vaccines were produced using the preservation by vaporization (PBV) foam drying process, combining boiling, sublimation, and evaporation (Bronshtein, 2008; Smith et al., 2015). As demonstrated by Hensley et al. (2021), PBV is a gentle drying process; during the drying, the virus titer reduction was lower than 0.3 logs. Then, these vaccines were incorporated into films. These vaccine-loaded films were stored for three months at room temperature, 37 °C, 45 °C, and 50 °C. Interestingly, the reduction in virus titer was lower than 0.5 log in the mentioned temperature ranges. Additionally, the vaccine-loaded films proved to be efficacious after two doses during the *in vivo* testing in a Gnotobiotic pigs model (Hensley et al., 2021).

Bajrovic et al. (2021) employed a different approach for preparing vaccine-loaded films. The authors effectively stabilized adenovirus by incorporating a surfactant in the film composition. Remarkably, the films maintained the original titers even after 84 days of storage at 20 °C. Moreover, during the *in vivo* testing in BALB/c mice, the buccally administered films generated higher levels of neutralizing antibodies than the intramuscularly administered group (Bajrovic et al., 2020).

These are examples of films' capabilities for dealing with biologics' stability. This problem was notably exposed during the COVID-19 pandemic, where the ultracold storage requirement was difficult for immunization in low- and middle-income countries. These disruptions and inequalities might result in the emergence of novel mutations and resistant variants. (Md Khairi et al., 2022)

3.2 Buccal films prepared by hot-melt extrusion

Hot-melt extrusion (HME) is a continuous manufacturing platform with in-process QC tools that has gained attention in the pharmaceutical industry, addressing some of the drawbacks of the solvent casting method. HME is a single-step, solvent-free, and can be considered a green approach for formulation development. It involves feeding a mixture containing the drug, polymer, and excipients into the extruder. This mixture is exposed to high shear and temperature in the extruder to form a homogeneous molten mass. Then, the molten mass is cast onto a clean surface to form smooth films (Irfan et al., 2016; Thakkar et al., 2020).

Small molecules:

Suryawanshi et al. (2021) developed orodispersible films for delivering cyanocobalamin using the HME approach. They achieved a similar plasma concentration profile compared to the marketed Quicobal films (ZIM laboratories) (Suryawanshi et al., 2021). In this case, the use of Soluplus® and glycerin helped develop films with optimal mechanical properties (Suryawanshi et al., 2021). Another study by Bhagurkar et al., (2019) (Bhagurkar et al., 2019) evaluated a range of polymers for buccal film development feasibility, successfully incorporating Salbutamol sulfate into a matrix of HPC, HPMC, and PEG 4500, where the release from the film was dependent on the HPMC concentration (Bhagurkar et al., 2019). On the other hand, Pimparade et. al. (2017) analyzed the use of HME and plasticizers in the development of fast-disintegrating oral films for delivering chlorpheniramine maleate. The group also incorporated sweetening agents for improving palatability and saliva-stimulating agents to improve disintegration. These oral films disintegrated within 6 to 11 seconds and showed a complete dissolution in under 5 min. The use of glycerin helped to extrude the drug in a modified starch matrix at low processing temperatures and shear (Pimparade et al., 2017).

Large molecules:

Given the processing conditions for HME, it might be considered an unfavorable method for biologics, which are very sensitive to such high temperatures and shears. For instance, studies have been carried out where nisin and lysozyme were processed using HME for preparing films, where the final product showed a partial reduction in the inhibitory activity. Therefore, more sensitive and stress-free system optimization needs to be conducted for processing biologics through HME. This, in turn, would help to scale up HME production processes (Dawson et al., 2003; Montenegro-nicolini and Morales, 2016; Padgett and Han, 1998). High shear and high temperatures put restrictions on protein-based molecules that can be processed using this technology, especially in the case of biologics (Censi and Gigliobianco, 2018). In the case of thermolabile drugs, the use of manufacturing additives such as plasticizers should be employed to reduce processing temperatures. However, their use may negatively impact films storage stability (Tambe et al., 2021).

3.3 Buccal films prepared by inkjet printing

Additive manufacturing has been gaining a lot of momentum in formulation sciences post the approval of Spritam® tablets by the FDA for epilepsy (Aprecia, 2015). Among the 3D printing techniques, fused deposition modeling (FDM), semi-solid extrusion-based printing, stereolithography (SLA), and inkjet printing (IJP) have been frequently used to research the feasibility of different drug-loaded films (Mohapatra et al., 2022). Each of these techniques has its pros and cons.

IJP is a non-contact technique based on the deposition of droplets in the volume range of 1 to 100 pL with high resolution and versatility onto a two-dimensional (2D) or a 3D substrate (Chou et al., 2021; Montenegro-nicolini et al., 2018). The substrate can also be prepared using printing technologies and is usually composed of a polymeric blend with the desired physicochemical properties. Then, this substrate is placed onto the printing platform, and the cartridge is loaded with the ink of interest (Sandler et al., 2011). This ink comprises the drug (small molecule or biologic) and the necessary excipients to achieve proper viscosity, fluidity, and surface tension for the defined print quality. This upcoming process has a lot of advantages compared to conventional printing in terms of its low processing costs, variable dosing capabilities, minimized waste generation, and ready automation (Daly et al., 2015). The ink must be formulated and characterized in terms of particle size when suspension-based inks are employed to avoid the print head nozzles clogging. Overcoming challenges such as particle agglomeration or precipitation during the printing process would help improve this method (Alomari et al., 2015; Chou et al., 2021; Montenegro-nicolini et al., 2016; Öblom et al., 2019).

Small molecules:

A proof-of-concept study was carried out by Eleftheriadis et al. (2020) to demonstrate the potential of combining FDM 3D printing with inkjet printing (IJP) for the personalized delivery of thermolabile drugs with mucoadhesive films using HPMC as a substrate. IJP was used to assess dose deposition accuracy and precision. The study showed that the release of the incorporated drug, ibuprofen, depended on the number of IJP passes (layers deposited). The drug release and the mechanical properties of the film were also shown to rely on the passes of the printing process. This method can be used to deliver a multitude of thermolabile drugs with further development and optimization (Eleftheriadis et al., 2020). The dose flexibility and personalization of dosing using thermal drug delivery were also determined by Vuddanda et al. (2018) using warfarin, an anticoagulant with a low therapeutic index. A warfarin-loaded HPMC-and-glycerol matrix film was developed, achieving doses equivalent to 1.25 and 2.5 mg (Vuddanda et al., 2018). IJP has shown that it is possible to obtain linear relationships between theoretical and experimental doses based on the volume deposited by the print head nozzles (Montenegro-nicolini et al., 2018; Montenegro-Nicolini et al., 2017). Piezoelectric IJP was used to prepare films using PVP for indomethacin delivery, a poorly soluble small molecule. This method showed better linear drug deposition compared to the thermal IJP process. These films' resolution was altered by selecting the dots per inch of the image in the data file, which showed a drug release of 60% to 70% in 3 hours. (Arshad et al., 2019).

A study was carried out by Öblom et al., (2019) to test the feasibility of dose adjustment for pediatric patients, using warfarin as a model drug (there are no commercially available products for children). Dosage forms of various strengths were prepared to deliver warfarin by comparing semi-solid extrusion to IJP. The drug-loaded ink was deposited using IJP onto films composed of HPC and PG (films were prepared using the solvent casting method). The ODFs had acceptable

properties and were superior to oral powders for solution in terms of dosing uniformity. Another innovative step was the IJP of QR code patterns on the substrate. The QR codes provided information about the drug, its dose, patient details, etc. Further exploration can be performed in the future, aiming for information preservation in the dosage form and to reduce the chance of counterfeiting (Öblom et al., 2019). Another study by Thabet et al. (2018) established the development of a continuous IJP system for delivering enalapril maleate onto ODF substrates (Thabet et al., 2018), using a piezoelectric IJP system. Results showed uniform and consistent dosing onto the substrate. In addition, fixed-dose combinations were also produced by printing onto hydrochlorothiazide substrate film during the inline manufacturing process (Thabet et al., 2018).

Figure 2. Data Enriched Edible Pharmaceuticals (DEEP) of medical cannabis in 2 x 2 cm size printed by Inkjet printing (Reprinted with permission from Öblom et al., 2020).

Large molecules:

IJP was applied to create customized dosing for thyroid hormones. These were printed successfully despite the stability issues associated with these large molecules. An HP printer was customized to develop a platform for delivering these two drugs for oral use using an ODF. A two-cartridge printer was used, with both black ink and color ink cartridges. The printing was accurate and enabled the delivery of low doses equivalent to 15 to 50 µg of T_3 (liothyronine) and 60 to 180 µg o T_4 (levothyroxine). These films had good mechanical properties and showed rapid disintegration after administration (Alomari et al., 2018). Lysozyme, a large protein widely used as a model, was delivered using thermal IJP onto films casted via solvent casting and electrospinning method using HPMC and chitosan, and PCL, respectively. This study was done to explore the potential of buccal delivery of biologics for better potency. Lysozyme inks were printed onto these film substrates, and differences in mechanical, mucoadhesive, and structural properties were observed based on the substrate used (Montenegro-nicolini et al., 2018). Montenegro-nicolini et al. (2018) also

studied the thermal IJP of lysozyme and ribonuclease A as model proteins on a PET substrate, assessing the effects of thermal IJP on the structural viability of the proteins. Films were recovered from the substrate by thorough washing, after which the preservation of enzyme activity was observed. This method can be exploited widely in the future after further optimizations and developments (Montenegro-nicolini et al., 2016). The main challenges in this process would be to scale up and maintain stability upon storage. Table 3 lists the examples summarized in this section.

Table 3. List of recent investigations using solvent casting, HME, or IJP to make buccal films with small and large molecules.

Active ingredient	Film Forming Excipients	Process	Ref
Insulin	Chitosan, L-arginine, glycerin	Solvent casting	(Diab et al., 2021)
tetravalent human-rhesus rotavirus reassortant vaccine	Calcium carbonate, HPC, triacetin	Solent casting	(Hensley et al., 2021)
Rizatriptan benzoate	Proloc, HPMCs, Eudragit® RS 100	Solvent casting	(Nair et al., 2021)
Propranolol hydrochloride	Type A and type B gelatin	Solvent casting	(Jovanović et al., 2021)
Cetirizine Dihydrochloride	Sodium alginate, HPMC, glycerol	Solvent casting	(Pamlényi et al., 2021)
Ciclopirox olamine	PEG, Eudragit ®NM 30D, glycerol	Solvent casting	(Gajdošová et al., 2021)
Frovatriptan succinate monohydrate	HPMC E3 and E15, PEG	Solvent casting	(Bhatt et al., 2021)
Diltiazem hydrochloride	HPMC, chitosan, glycerol	Solvent casting	(Winarti et al., 2021)
Alfuzosin hydrochloride	HPMC, chitosan, glycerine	Solvent casting	(Mahapatra et al., 2021)
Clindamycin	Sodium alginate, sodium CMC	Solvent Casting	(Pulate et al., n.d.)
Ketorolac	HPMC E15, Eudragit® RLPO and RSPO, PEG	Solvent casting	(Barpete et al., 2021)
Curcumin loaded solid lipid nanoparticles	Lipoid S100, glycerol. HPCM	Solvent casting	(Tzanova et al., 2021)
Cyanocobalamin	Soluplus®, citric acid, menthol	HME	(Suryawanshi et al., 2021)
Salbutamol sulphate	HPC, HPMC, PEG 4500	HME	(Bhagurkar et al., 2019)
Chlorpheniramine maleate	Modifies starch, glycerin, citric acid, Magnasweet	HME	(and Kali S. Thomas, 2017)

Ibuprofen	HPMC, propylene glycol, PEG 400, ethanol	IJP (Thermal)	(Eleftheriadis et al., 2020)
Warfarin	HPMC, glycerol	IJP (Thermal)	(Vuddanda et al., 2018)
Indomethacin	PVP K28	IJP (Piezoelectric)	(Arshad et al., 2020)
Warfarin	HPC, PG	IJP (Piezoelectric)	(Öblom et al., 2019)
Enalpril maleate	HPC, PEG 400	IJP (Piezoelectric)	(Thabet et al., 2018)
T3 and T4 hormones	HPCM	IJP(Thermal)	(Alomari et al., 2018)
Lysozyme	HPMC, chitosan, PCL	IJP (Thermal)	(Montenegro-nicolini et al., 2018)
Lysozyme, ribonuclease A	PET films	IJP (Thermal)	(Montenegro-Nicolini et al., 2017)

3.4 Excipients for buccal films:

Polymers and salts are some of the main excipients in buccal film development (Bala et al., 2013). The selection of excipients dictates the film's mechanical properties and drug release. Therefore, careful considerations for pre-formulation are necessary for a product development plan. Buccal films are intended to disintegrate rapidly, and hence, hydrophilic polymers are usually selected in the pre-formulation stage. A hydrophilic polymer can be used alone or in combination with other polymers to develop a blend for a characteristic release and desired mechanical properties (Irfan et al., 2016). The concentration of the polymer used will determine the plasticity and the tensile strength of the film formed. It will also determine how films disintegrate after getting in contact with the saliva and the buccal epithelium. The amount of polymer used will determine how polymer chains would be arranged in the films, which, in turn, governs the degradation and drug release mechanisms. Generally, the polymer constitutes approximately 45 % w/w of the total weight of the film, but concentrations ranging from 60 to 70% are used. However, excessive polymer concentrations make the film sticky, which impedes its handling. Both natural and synthetic polymers are used to make films. However, the use of the latter has superseded the former. The polymers used need to be non-irritant, and in the FDA's non-active ingredient list or be classified as GRAS. Natural polymers such as chitosan, alginates, pullulan, and high and low-molecular-weight pectins can also be used with cellulose-derived polymers. These cellulose-based polymers include methyl cellulose (MC), carboxymethyl cellulose (CMC), hydroxypropyl cellulose (HPC), and hydroxypropyl methylcellulose (HPMC). The molecular weights of these polymers differ, and thus they are available in different grades under different brand names. The polymer properties determine how the films would be affected (Dinge and Nagarsenker, 2008; Irfan et al., 2016; Pathare et al., 2013; Puratchikody et al., 2011). Polymers are also used to improve the adhesion of the film to the buccal mucosa. A wide range of mucoadhesive polymers can be used based on the requirements and drug-polymer interactions (Asane et al., 2008). These have been summarized (Salamat-Miller et al., 2005).

Polyethylene glycol (PEG) also helps in developing good buccal films, but it is usually used in combination with other polymers, mainly as a plasticizer (Irfan et al., 2016; Pathare et al., 2013). Plasticizers are often used in HME to reduce the processing temperature and improve formulation properties. Many low molecular weight polymers and surfactants are widely used as plasticizers. They are of importance when formulating buccal films due to the flexibility and tensile strength imparted. Low molecular weight PEG, triethyl citrate (TEC), acetyltributyl citrate (ATBC), glycerol, and diethyl phthalate are commonly used plasticizers (Bala et al., 2013; Irfan et al., 2016). They are usually used in concentrations up to 20 %w/w in the formulation process (Irfan et al., 2016). Surfactants are widely employed for improving film disintegration, drug solubilization, and release, achieved by improving wetting and achieving faster release. This is important as slowly disintegrating films lead to increased discomfort in the buccal cavity. Tween® 80 is a very widely used surfactant. Other surfactants include benzalkonium chloride, sodium lauryl sulfate (SLS), and poloxamers.

Other excipients, such as flavoring, sweetening, and saliva-stimulating agents, are employed based on desired characteristics (Siddiqui et al., 2010). Buccal films degrade rapidly in the mouth, where portions of the drug might come in contact with the tongue, potentially causing a bitter taste and impairing patient adherence. Therefore, flavoring agents such as mint or licorice are commonly used to taste masking and reducing the associated feeling of nausea and discomfort. Any US-FDA-approved flavors can be used for the same purpose. Sweetening agents can also be used for taste masking and to help mouth disintegration due to their hygroscopic nature. Widely used sweetening agents include sucrose, fructose, dextrose, sucrose, sorbitol, mannitol, and isomaltose from natural origin, and neotame, alitame, sucralose, aspartame, saccharine from synthetic origin. Each of these differs in the amount of sweetness and caloric value (Irfan et al., 2016; Siddiqui et al., 2010). Salivary secretion aids in film disintegration, which leads to drug release. This can be accomplished by using saliva-stimulating agents, which are acidic, such as citric acid, maleic acid, tartaric acid, ascorbic acid, or lactic acid. FD and C- approved colors can be used to improve the aesthetic appeal of the films (Irfan et al., 2016). The Venn diagram (Figure 3) below shows the composition of a typical buccal film.

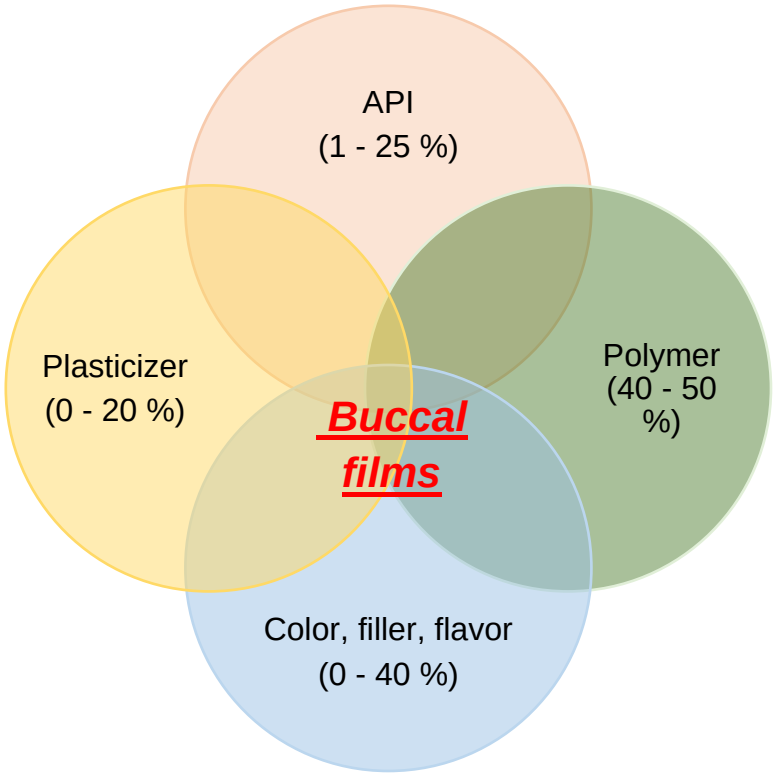

Figure 3: Commonly used components and their respective amounts in formulating buccal films.

With the approval of several dosage forms of products for buccal drug delivery, a wide variety of excipients have been utilized. Table 4 provides a summary of all excipients used in FDA-approved products and their maximum potency per dose. The majority of the excipients fall into fillers, polymers, color, flavor, and antioxidants.

Table 4: List of ALL excipients approved for buccal delivery by the FDA ("Inactive Ingredient Search for Approved Drug Products," n.d.)

	Excipient	**Dosage form**	**Maximum potency per unit dose**
1	Alpha Tocopherol	Film	0.07 mg
2	Alpha.-Tocopherol Acetate	Film	0.09 mg
3	Acacia	Gum, Tablet	9.1 mg
4	Acesulfame Potassium	Chewing Gum	NA
5	Alcohol	Concentrate/Mouthwash	Concentrate – 679 mg/mL Mouthwash – 200 mg/mL
6	Amarnath	Troche	0.05 mg
7	Anhydrous Citric Acid	Film	NA

8	Anhydrous Dibasic Calcium Phosphate	Tablet	60 mg
9	Anhydrous Lactose	Tablet	NA
10	Aspartame	NA	1.1 mg
11	Benzoic Acid	Mouthwash	NA
12	Boric Acid	Mouthwash	7.36 mg/mL
13	Butylated hydroxytoluene	Chewing gum	NA
14	Calcium Carbonate	Chewing Gum	NA
15	Calcium Stearate	Tablet	1.42 mg
16	Carbomer Homopolymer Type B (Allyl Pentaerythritol Crosslinked)	Tablet	NA
17	Carboxymethylcellulose Sodium	Film, Tablet	Tablet -4 mg
18	Carnauba Wax	Chewing Gum	NA
19	Citric Acid Monohydrate	Solution, Tablet	Tablet – 30 mg
20	Corn Syrup	Troche	NA
21	D& C Yellow No.10	Chewing Gum	NA
22	D&C Yellow No. 10 Aluminum Lake	Chewing Gum	NA
23	Dextrose	Lozenge	NA
24	Dipropylene Glycol	NA	29.9
25	Dye Brown Lake Blend	Chewing Gum	NA
26	Fd&C Blue No. 1	Concentrate	NA
27	Fd&C Blue No. 2	Tablet	0.01 mg
28	Fd&C Red No. 40	Chewing Gum, Tablet	Tablet - 0.01 mg
29	Fd&C Yellow No. 5	Lozenge, Tablet	Tablet – 0.11 mg
30	Fd&C Yellow No. 6	Mouthwash, tablet	Mouthwash – 0.01 mg/mL Tablet – 1 mg
31	Fd&C Yellow No. 6 Aluminum Lake	Tablet	1 mg
32	Ferric Oxide Red	Tablet	0.4 mg
33	Ferric Oxide Yellow	Film, tablet	Film – 0.27 mg Tablet -1 mg

34	Flavor Cinnamon	Chewing Gum	NA
35	Flavor Citrus	Chewing Gum	NA
36	Flavor Menthol	Chewing Gum	NA
37	Gelatin	Chewing Gum	NA
38	Glycerin	Chewing Gum, Mouthwash	Chewing Gum - 28.8 mg Mouthwash – 100 mg/1 mL
39	Guar Gum	Tablet	1.1 mg
40	Hydroxyethyl Cellulose (140 MPA.S AT 5%)	Film	NA
41	Hydroxypropyl Cellulose (1600000 WAMW)	Film, Chewing Gum	Chewing Gum – 27.92 mg
42	Hydroxypropyl Cellulose (90000 WAMW)	Film, Chewing Gum	Film – 100.04 mg
43	Hypromellose 2208 (100MPa.s)	Tablet	NA
44	Hypromellose 2208 (15000 MPa.s)	Tablet	17.25 mg
45	Hypromellose 2910 (1500 Mpa.s)	Tablet	NA
46	Hypromellose 2910 (5Mpa.s)	Chewing Gum, Tablet	NA
47	Lactose	Tablet	296.7 mg
48	Lactose Monohydrate	Tablet	NA
49	Levomenthol	Chewing Gum	9.2 mg
50	Magnesium Oxide	Chewing Gum	NA
51	Magnesium Stearate	Tablet	17.5 mg
52	Maltitol	Chewing Gum	NA
53	Mannitol	Chewing Gum, Tablet	Tablet – 180.19 mg
54	Menthol	Chewing Gum, Mouthwash	Mouthwash – 0.15 mg/ 1 mL
55	Methyl Cellulose	Tablet	1 % w/w
56	Methyl Paraben	Film	NA
57	Microcrystalline Cellulose	Tablet	18.04 mg
58	Milk protein concentrate	Tablet	27.43 mg
59	Monosodium Glutamate	Mouthwash	0.2 mg/1 mL
60	Peppermint Oil	Film, Chewing Gum	NA
61	Saccharin Sodium	Film, Tablet	Tablet -0.4 mg
62	Talc	Chewing Gum, Tablet	Tablet – 14 mg
63	Titanium Dioxide	Film, Chewing Gum	NA

64	Tragacanth	Tablet	5 mg
65	Tricalcium phosphate	Tablet	99.2 mg
66	Vegetable Oil	Chewing Gum	14.4 mg
67	Xylitol	Chewing Gum	NA
68	Zinc Stearate	Tablet	2.5 mg
69	Zinc Oxide	Tablet	2.5 mg

4. Novel analytical tools for the characterization of buccal films

The quality of buccal films depends on hydration, elasticity, thickness, swelling properties, and molecule permeation. Several reviews discuss these aspects in detail (Alaei and Omidian, 2021; Irfan et al., 2016; Karki et al., 2016). Traditional methods for permeability assessment involved quantitative measurement of the amount of active agent deposited in buccal tissues. Recently, work has focused on understanding the distribution of the active agent upon administration. Matrix-Assisted Laser Desorption or Ionization (MALDI) Spectrophotometry Imaging (MSI) has been used to evaluate the spatial distribution of the active agent (as well as the excipients) in the tissues based on their molecular masses. Briefly, tissue sections are sliced and sprayed with a MALDI matrix that forms microcrystals; then, they are ionized by exposure of the beam to the areas of interest. One of the added advantages of this technique is that it eliminates the need to label the drug (Murayama et al., 2009). Handler et al. (2019) used MALDI imaging to evaluate the permeation of diazepam and codeine in the presence and absence of laurocapram as an excipient permeation enhancer across excised porcine buccal mucosa. The study helped to understand the exact distribution of the two drugs in the buccal mucosa. One of the advantages of this technique is the capacity to visualize both endogenous and exogenous compounds (Handler et al., 2019). In another study, Marxen et al. (2018) used high-resolution MALDI imaging to assess the permeation behavior of mannitol and nicotine across the buccal mucosa to understand the permeation barriers' exact location and composition and thus enable a further permeation improvement. With this technique, they identified that the barrier to nicotine and mannitol permeability was in the outer layer of the epithelium. Another feature of this technique is the ability to quantify drug metabolites to assess the percentage of metabolic transformation (Marxen et al., 2018). This technique was also used by Clitherow et al. (2019) to understand the distribution of lidocaine hydrochloride in the buccal mucosa compared to lidocaine solutions. The study revealed lower buccal epithelium quantities of lidocaine hydrochloride regarding the reverse phase HPLC system limits of detection, thereby conferring an additional advantage for low amounts of drug detection. Figure 4 has been adapted from the study conducted by Clitherow et al. (2019), where it was possible to visualize and quantify the distribution of lidocaine in the buccal epithelium using MALDI-MSI (Clitherow et al., 2019).

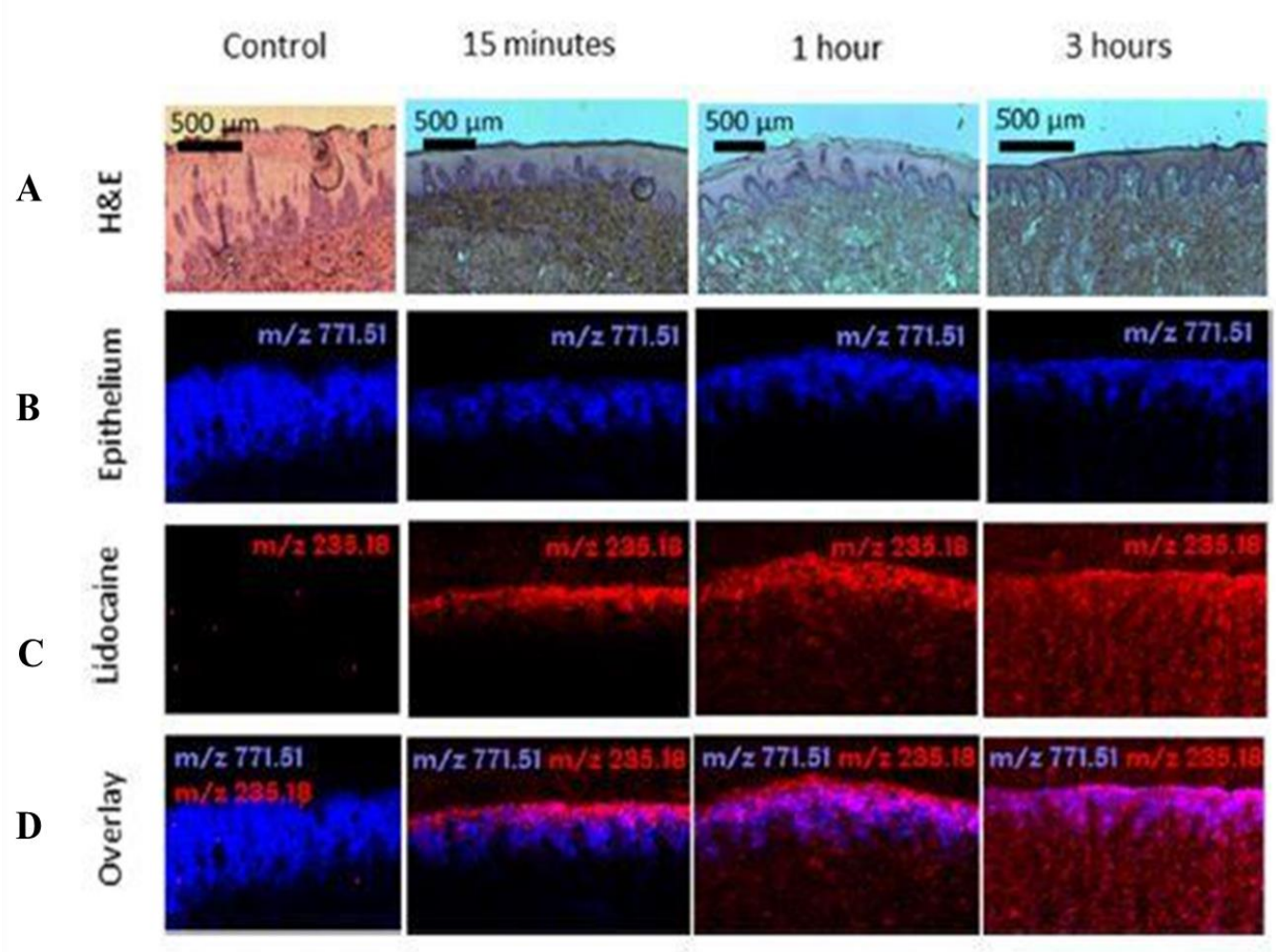

Figure 4: H& E (Hematoxylin and eosin)-stained porcine buccal mucosa for control group as well as for a lidocaine hydrochloride buccal film group after a set amount of time. Panel A is the H& E stained group at different time points. Panel B is the epithelium, Panel C is distribution o f lidocaine while Panel D is an overlay of Panel B and C at various time points (Reprinted with permission from Clitherow et al., 2019)

5. Buccal permeation enhancement strategies

There are two main pathways for drug permeation through the buccal mucosa. (1) In the transcellular or lipoidal pathway, the therapeutic directly diffuses across the membranes (Kokate et al., 2008; Kulkarni et al., 2011; Sohi et al., 2010). On the other hand, (2) in the paracellular or aqueous pathway, the therapeutic diffuses through the tortuous intercellular space. In general, lipophilic molecules diffuse using the transcellular pathway, and hydrophilic molecules follow the paracellular one. However, molecules' lipophilicity or hydrophilicity is affected by pH, as demonstrated by Kokate et al. (2008). In their study, logD at pH 6.8 was found to be a better predictor for buccal permeability than logP; in other words, the state of ionization is relevant during drug permeation (Kokate et al., 2008).

In the case of macromolecules, their permeation is limited to the paracellular pathway because of their size and hydrophilicity (Caon et al., 2015; Rawas-Qalaji et al., 2022). In porcine mucosa, the paracellular pathway has a pore radius that ranges from 1.5 to 3 nm, imposing restrictions on the molecular weight or particle size that can cross the buccal mucosa. (Goswami et al., 2009; Wanasathop et al., 2021). However, there are strategies for carrier-mediated diffusion and endocytosis (discussed in section 6) (Rawas-Qalaji et al., 2022). Additionally, Fantini et al. (2023) aimed to determine the effect of molecular weight on permeation using dextrans. The authors demonstrated that permeability enhancers (PEs) allowed the permeation of 70 and 150 kDa dextrans that cannot cross without these excipients (Fantini et al., 2023).

Achieving adequate drug permeability often is challenging in drug administration by non-injected routes, limiting their absorption and bioavailability (Fonseca-Santos and Chorilli, 2018; Nicolazzo et al., 2005). For the buccal route of administration, some permeability enhancers can be used to increase the absorption of poorly permeable drugs (Chen et al., 2014; Maher et al., 2019). The increase in permeability can be chemical and/or physical. Chemical permeability enhancers are commonly used in buccal delivery dosage form designs. Research on functional excipients such as PEs has mainly focused on oral administration, where enhancers are classified according to the permeation mechanism into two main categories, transcellular and paracellular enhancers (Maher et al., 2019). Table 3 shows some examples of permeation enhancers used in buccal delivery research. Most of the PEs used in buccal delivery increase paracellular permeation mainly by interacting with the buccal epithelium lipids. Additionally, the use of mucoadhesive polymers increases permeation due to an intimate interaction between the dosage form (usually films) and the buccal epithelium (Guo and Pratap Singh, 2019).

Table 5. Classification according to type of permeation enhancer (PE).

Type of PE	Example	Mode of transport	Proposed mechanism	References
Surfactants	Sodium lauryl sulphate	Mostly paracellular (they can affect transcellular permeation at higher concentrations)	Modification of lipid packing in the buccal epithelium, enzymatic activity, membrane fluidity, and reduction in mucus viscosity.	(Morales and McConville, 2014; Shidhaye et al., 2010)
Bile salts	Sodium glycodeoxycholate; sodium glycocholate	paracellular	Membrane fluidisation	(Brayden and Stuettgen, 2021)
Long chain fatty acids	Oleic acid	paracellular	Modification of lipid packing in buccal epithelium	(Caon et al., 2015; Padula et al., 2018)

Ionic liquids	Choline and geranic acid based ionic liquid (CAGE)	paracellular	Intercellular lipid extraction and fluidization of the upper buccal epithelium	(Vaidya and Mitragotri, 2020)
Polymers	chitosan HPMC Alginate	paracellular	bio-adhesion and intimate interaction with the epithelium	(Guo and Pratap Singh, 2019)
Peptides	Penetratin	paracellular	Formation of hydrophobic interactions with the active principle, and penetration due to hydrophobization	(Keum et al., 2020)

6. Nanoparticles

As previously mentioned, the buccal mucosa is a stratified epithelium and might represent a challenge for delivering macromolecules or nanoparticles because of its limited permeability. Some authors have focused on developing nanoparticles to improve drug dissolution and increase the buccal bioavailability of poorly-water soluble drugs. (Baumgartner et al., 2016; Morales et al., 2014, 2013; Morales and Brayden, 2017; Rao et al., 2011). Additionally, other authors have employed drug-releasing nanoparticles to permeate across the buccal epithelium (Abd El Azim et al., 2015; Al-Dhubiab et al., 2015; Giovino et al., 2013; Lv et al., 2015; Mazzarino et al., 2014; Mouftah et al., 2016). The permeation mechanisms across the buccal epithelium have been studied using some model nanoparticles (similar to the concept of "model molecule" used in the pharmaceutical field). Studies using silver nanoparticles (19 nm in diameter) and titanium dioxide nanoparticles (30–150 nm in diameter), have shown that nanoparticle permeation depends on their physicochemical properties (Mauro et al., 2015; Teubl et al., 2015). Furthermore, polymeric nanoparticles have shown that both mean particle size and aggregation influence their permeability across the buccal epithelium (Roblegg et al., 2012; Teubl et al., 2013). Specifically, a study using anionic carboxylated-modified polystyrene nanoparticles (20 and 200 nm) and cationic amine-modified polystyrene nanoparticles (200 nm) indicated that cationic nanoparticles, at the same particle size, showed better permeation through isolated porcine buccal mucosa than the anionic nanoparticles (Roblegg et al., 2012). While these 200 nm anionic nanoparticles agglomerated and failed to permeate, the smaller ones (20 nm) permeated across the top third region of the buccal epithelium using the transcellular route. On the other hand, the cationic nanoparticles (200 nm) tended to agglomerate, but they were able to permeate into lower regions of the buccal epithelium by endocytotic mechanisms (Roblegg et al., 2012). Interestingly, these mechanisms have been

observed using neutral polystyrene nanoparticles as well. Using the isolated porcine buccal mucosa model, 200 nm neutral nanoparticles penetrated faster to deeper sections of the buccal mucosa when compared to smaller nanoparticles (25 and 50 nm) (Teubl et al., 2013).

Xu et al. (2018) prepared an insulin-phospholipid complex combined with deformable nanovesicles (IPC-DNV) to facilitate penetration without generating mucosal irritation to the buccal mucosa (Xu et al., 2018). These nanovesicles were able to use transcellular and paracellular transport to move across the buccal mucosa. Then, Yang et al. (2020) studied *in vivo* variables such as the drug dose, type of buccal administration, deformability, and particle size (Yang et al., 2020). In another approach, Bashyal et al. (2021) studied the enhancement of buccal delivery of insulin using *ex vivo* assessments of elastic liposomes (Bashyal et al., 2021). The authors prepared sodium-cholate-incorporated elastic liposomes (SC-EL) and sodium-glycodeoxycholate-incorporated elastic liposomes (SGDC-EL) using the thin-film hydration method. SGDC-EL nanocarriers showed better ex-vivo permeability since they had higher deformability when compared to the other nanocarriers (Bashyal et al., 2021).

There is a wide range of nanoparticle-delivered dosage form types for buccal delivery. Tran et al., (2019) classified them into three groups: 1) Nanoparticle-delivered mucoadhesive films; 2) Nanoparticle-delivered mucoadhesive gels, and 3) Nanoparticle-delivered mucoadhesive solid matrix forms (Tran et al., 2019). The synthesis of mucoadhesive films for nanoparticle delivery requires the development of drug-loaded nanoparticles before the mucoadhesive films formation. This can be done in several ways (Figure 5).

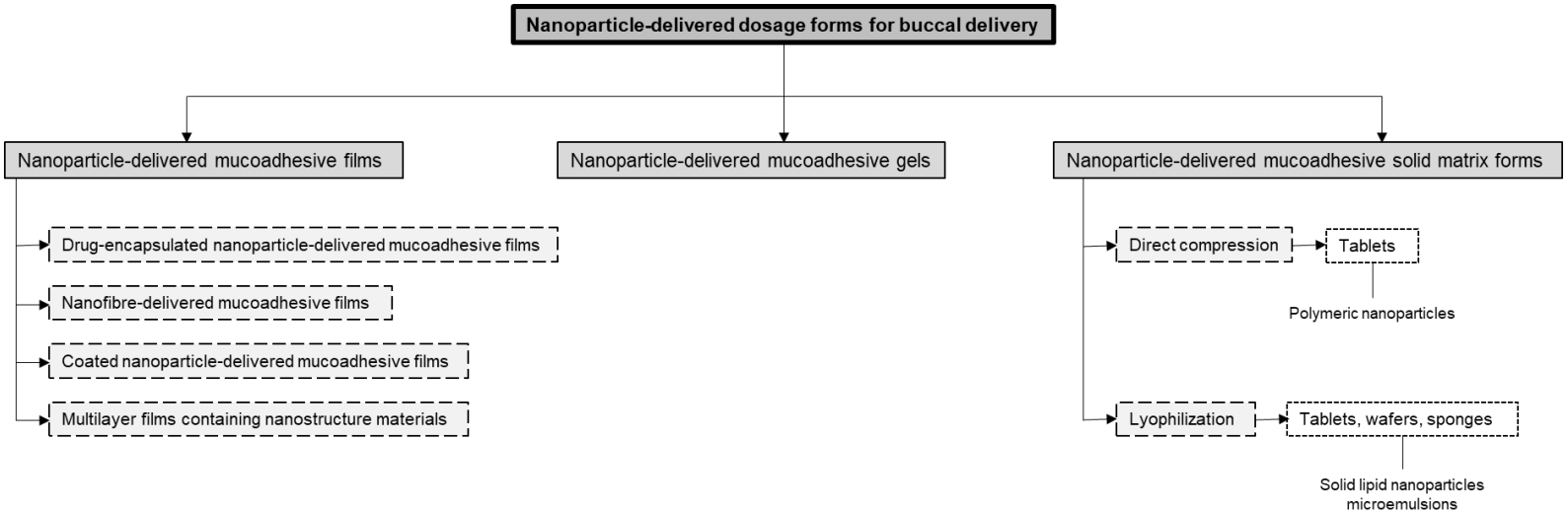

Figure 5: Nanoparticle-delivered dosage forms for buccal delivery. Figure modified with permission from Tran et al., 2019).

These techniques have been used for drug delivery and other components, such as vitamins. Lv et al. (2015) utilized phospholipid-bile salt-mixed micelles in mucoadhesive buccal films made from

carboxymethyl chitosan for cucurbitacin B delivery and compared them to a film without nanoparticles. The nanoparticle-containing system showed a bioavailability enhancement and a 10-fold release improvement. (Lv et al., 2015).

On the other hand, some nanoparticle-delivered mucoadhesive gels aim for buccal cavity topical treatments (Tran et al., 2019). For instance, Karavana et al. (2012) treated recurrent aphthous stomatitis with cyclosporine A incorporated into a bioadhesive gel. It was found that after 24 hours of treatment, approximately 70% of cyclosporine-A was found in the buccal mucosa. In addition, the *in vivo* studies showed an increase in the mucosal repair rate (Karavana et al., 2012). Finally, nanoparticle-delivered mucoadhesive solid matrix forms are used for drug stability improvement, patient compliance, and control of drug release. Examples of these dosage forms are sponges, wafers, or tablets for buccal delivery (Tran et al., 2019).
Le et al. (2019) used solid lipid nanoparticles to evaluate drug release from tablets for buccal delivery. They concluded that a high concentration of solid lipid nanoparticles could be used to retard drug release by affecting particle size and permeability. On the other hand, a low concentration of solid lipid nanoparticles led to smaller particle sizes, significantly improving mucosa plasma membrane permeation (Le et al., 2019).

The buccal mucosa has great potential for vaccination because of its accessibility and the presence of antigen-presenting cells for innate and adaptative immune responses (Kweon, 2011; Upadhyay et al., 2013). Similarly, rapid clearance by saliva and tongue movement is still a challenge when vaccinating using the buccal route of administration. Among the strategies used to overcome these challenges, there are formulations employing nanoparticles, nanofibers, iontophoresis, and electroporation (Baudner and O'Hagan, 2010; Wang et al., 2014b, 2014a). As an example, Mašek et al. (2017) used nanofibers that have an increased surface area, which allows higher drug loadings of nanoencapsulated vaccines. In their study, PEGylated liposomes and PLGA nanoparticles were able to penetrate the porcine sublingual epithelium and were recognized by dendritic cells both ex-vivo and in-vivo (Mašek et al., 2017). Nanofibers have a high surface-to-volume ratio, and since electrospinning is a charge-driven process, it facilitates electrostatically driven mucoadhesion with anionic mucin threads; they also enhance solubility, favor a controlled drug release and have a high drug loading (Sofi et al., 2020).

Besides electrospinning, nanofibers can be fabricated by self-assembly, as shown by Suvannasara et al. (2014), by a one-step procedure using modified chitosan (Suvannasara et al., 2014). In addition, phase separation, as presented by Garg et al. (2014), is amongst other techniques used in nanofiber fabrication (Garg et al., 2014).

Another strategy to increase vaccine exposure is microneedles use, as shown by Zhen et al. (2015). The authors developed liposome-loaded microneedles for convenient and stable mucosal vaccination. The formulation was administrated to mice, achieving systemic and mucosal immune

responses against the model antigen (Zhen et al., 2015). This liposome-loaded microneedles strategy was also used to develop a vaccine against the hepatitis B virus. The vaccine was stable for up to 3 days at 40 °C and was capable of generating strong systemic and mucosal immune responses (Wang et al., 2015). However, it is relevant to the different animal models and humans. For example, there are notable differences in terms of surface area and the degree of keratinization (Morales and Brayden, 2017). This will be further discussed in section 8.

7. Novel delivery technologies

There are several strategies used to improve buccal drug delivery of drugs (Scarpa et al., 2017). In addition, the buccal route has been proposed as a vaccination strategy, thanks to the large population of dendritic cells in the local tissue (Uddin et al., 2019). In this way, methodologies have been developed for the delivery of antigens that allow the generation of immunity, such as the case of films with multilayers, which can be 2 or 3 layers, fulfilling a specific function. The inner layer function is adhesion by containing mucoadhesive elements such as chitosan polymers or cellulose derivatives (Baus et al., 2019; Calixto et al., 2018). In addition, it could contain permeability-enhancing elements such as cyclodextrins or EDTA (Patel et al., 2013). The inner layer contains the active principle, while the outer layer is formulated in such a way that the passage of saliva is unidirectional, thus avoiding the loss of the drug. Currently, there are not many formulations available with this technology; however, there are several different applications in development (Uddin et al., 2019) (Figure 6).

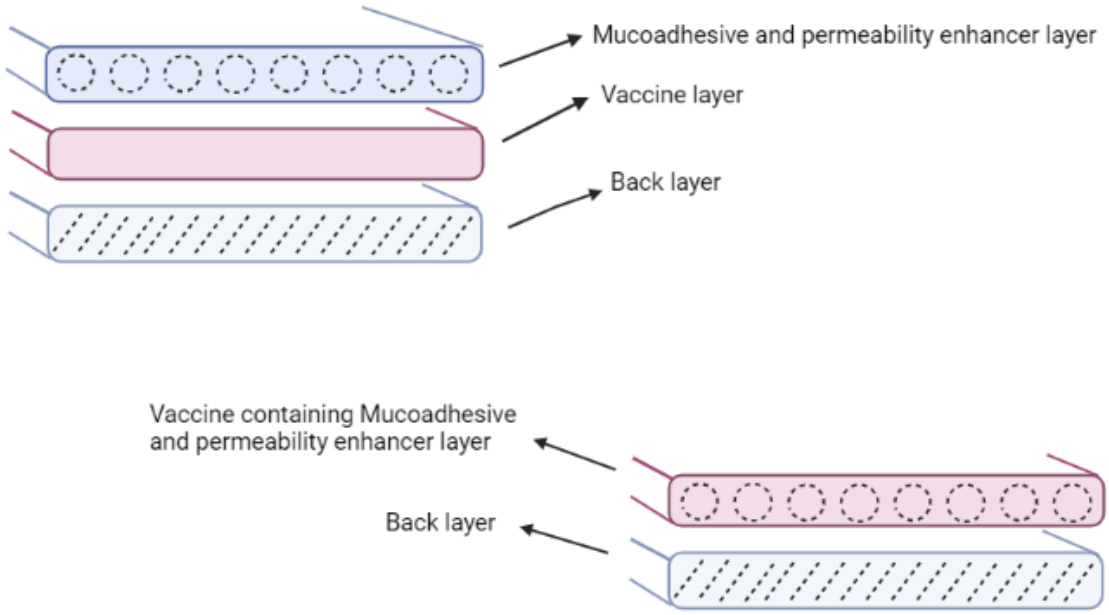

Figure 6: Graphical representation of multilayered film dosage forms. The upper figure represents a triple-layered film with a vaccine layer in the middle. On the other hand, the lower figure represents a double layered film with vaccines in the mucoadhesive layer. Figure modified with permission from Uddin et al., 2019).

Other relevant technologies in research in recent years are the manufacture of "smart" self-adhesive patches or films, which may have several designs already discussed in previous sections (De Barros et al., 2014; Rohani Shirvan et al., 2019) The general strategy is based on sensitive excipients (e.g., polymers) that can release the active principle after being triggered by physical and chemical changes such as pH, temperature, humidity, enzymes, electromagnetic fields, etc (Rohani Shirvan et al., 2019).

Some manufacturing technologies allow the loading of a variety of therapeutics. One example is electrospinning technology, where fibers might contain several drugs by a simple, cost-effective, and versatile manufacturing method. Electrospinning generates continuous, porous fibers with a high surface area/volume ratio, which tend to have a high encapsulation efficiency (EE). This significantly increases the drug concentration at the local level, enabling greater buccal absorption. In this context, Chen et al. (2020) developed a system for oral delivery of carvedilol, obtaining an encapsulation efficiency between 26.3 to 36.9%, modulable release profiles according to the composition of the system, increased *in vitro* permeability, and appropriate cytotoxicity (Chen et al., 2020). Likewise, Alkahtani et al. (2021) developed a system for the delivery of escitalopram

and quetiapine, showing a higher in vitro permeability of drugs with high EE% (Alkahtani et al., 2021).

Another interesting manufacturing process for developing buccal drug delivery formulations is the electrospray technology, which helps obtain solvents and surfactant-free polymeric nanoparticles, which can cause unwanted effects. The synthesis by electrospray, likewise by electrospinning, increases the surface/volume ratio, the amount of loaded drug, and the permeation of the drug by enhancing the local drug concentration (Jaworek and Sobczyk, 2008; Juntapram et al., 2012; Moreno et al., 2018; Rohani Shirvan et al., 2019; Wang et al., 2010).

The electrospray generates various nanoparticles of different sizes depending on the characteristics of the polymer and the solvents used. For example, Moreno et al. (2018) generated stable chitosan particles in an aqueous medium using ethanol/water mixtures as a solvent. Stable particles were obtained by dissolving 3% w/v low molecular weight chitosan (28-49KDa), with a DD of 82-07% and DP of 177-292, using a 50/50 ethanol/water mixture as solvent. On the other hand, sizes of 1.34 ± 0.12um and zeta potential of +41.15 ±2.69 mV were obtained. These parameters make it possible for these nanoparticles to be interesting for drug delivery. In this way, the electrospray methodology is a good alternative for preparing films for drug release applications (Moreno et al., 2018).

8. Preclinical drug delivery strategies and challenges with animal models

The choice of an *in vivo* model is often challenging when evaluating disruptive formulations. Several considerations must be taken when choosing an animal model for buccal delivery due to the species differences between the tissue in the mouth, which has consequences on the permeability, adhesiveness, stability, and permanence of the device in the oral cavity, which has direct influence on the effectiveness of the potential treatment (Franz-Montan et al., 2017; Nair et al., 2013; Nicolazzo and Finnin, 2007; Paderni et al., 2012). The differences should be considered when extrapolating results from *in vivo* models to humans. In the translation of formulations for buccal delivery, one of the closest in vivo models is the pig model; unfortunately, this model might be expensive for initial developments (Patel et al., 2012). Several models can be used in the initial stages of development, which are cheaper than the pig in terms of the resources necessary for maintenance. However, it is required to consider structural and physiological differences of the oral cavity to achieve a successful translation to other models or humans (Figure 7).

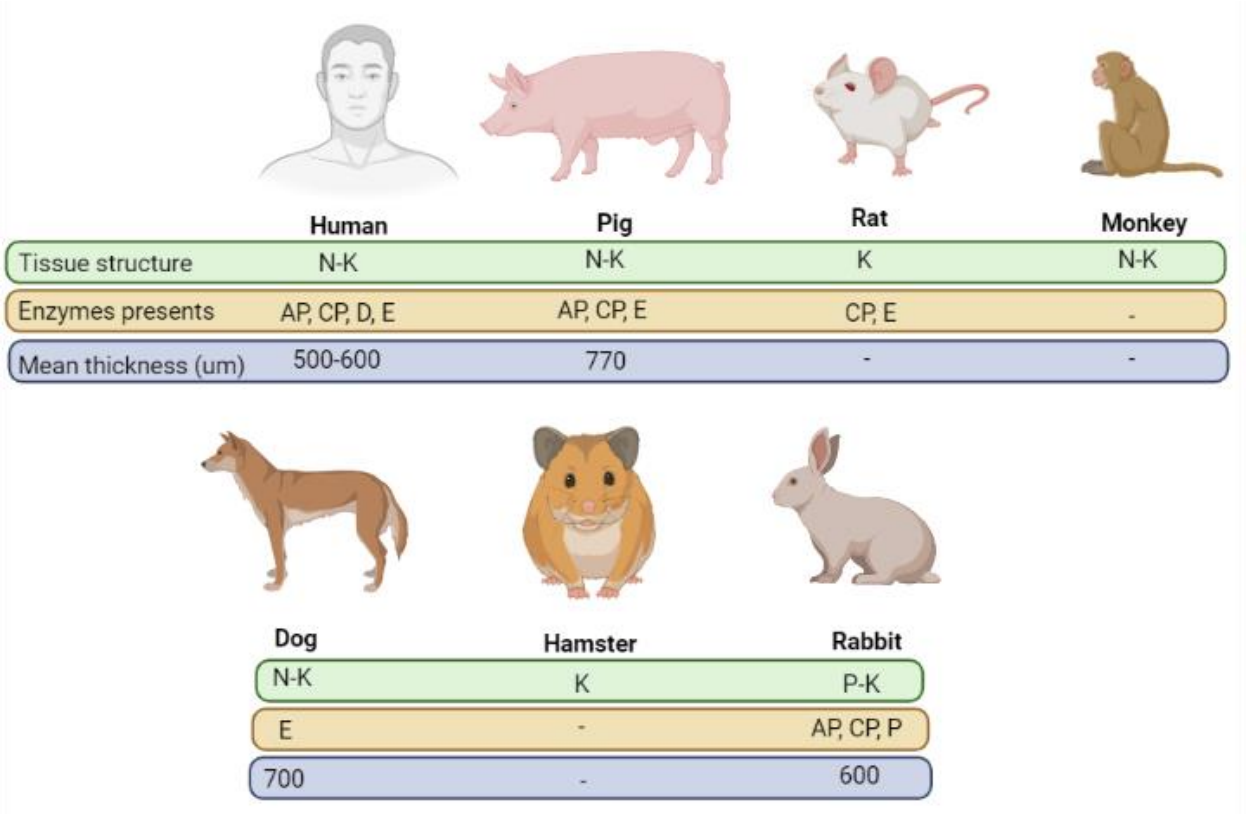

Figure 7: Comparison of oral mucosa composition between different in vivo models. NK: nonkeratinized K: keratinized PK: para-keratinized E: esterase AP: aminopeptidase CP: carboxypeptidase D: dehydrogenase.NK: nonkeratinized K: keratinized PK: para-keratinized E: esterase AP: aminopeptidase CP: carboxypeptidase D: dehydrogenase.NK: nonkeratinized K: keratinized PK: para-keratinized E: esterase AP: aminopeptidase CP: carboxypeptidase D:

754 dehydrogenase.NK: nonkeratinized K: keratinized PK: para-keratinized E: esterase AP:
755 aminopeptidase CP: carboxypeptidase D: dehydrogenase.
756
757 Lately, using *in vitro* or *ex vivo* elements has been proposed to avoid animal models due to their
758 high cost, difficult handling, and demanding bioethical considerations (Pinto et al., 2020). Murine
759 models, such as rats and hamsters, have been widely used in permeability studies. However, their
760 buccal mucosa is keratinized in contrast to the human buccal mucosa. In addition, rodents have
761 the limitation of having a small surface area available for buccal permeation. Alternatively, rabbit,
762 monkey, and dog models have non-keratinized buccal mucosae (Cuine et al., 2017; Dowty et al.,
763 1992; Gandhi and Robinson, 1992; Sa et al., 2015). The use of monkeys and dog models is usually
764 not culturally accepted, and their buccal mucosa tends to be more permeable than humans'. Porcine
765 models have been described as ideal for buccal delivery since their buccal mucosa is similar to the
766 human buccal mucosa in morphology, composition, and enzymatic presence (Patel et al., 2012;
767 Sohi et al., 2010b). The use of bovine oral tissue has also been considered as an alternative tool,
768 having non-keratinized tissue in the oral cavity, like the pig (Pather et al., 2008).
769
770 As an alternative animal testing, the *in vitro* TR146 human buccal epithelial cell line model might
771 be used. This model is formed by non-keratinized stratified epithelium structures, which, in terms
772 of morphology and permeability are similar to the porcine oral mucosa, making them an excellent
773 cell line to be used for initial screenings (Kalu et al., 2017; Li et al., 2017; Nilsen et al., 2016;
774 Pistone et al., 2017). An example of this was reported by Holm et al., (2013) when testing the
775 buccal permeability of metoprolol. In this work, the correlation of in vitro permeability in TR146
776 human buccal epithelial cell line and the *ex vivo* permeability in porcine buccal mucosa were
777 evaluated using a modified Ussing chamber. On the other hand, in vivo in vitro correlation
778 (IVIVC) level C was established in Göttingen mini-pigs, obtaining results of r2 = 0.98 for IVIVC
779 (Holm et al., 2013)

780 ## 9. Clinical translation of buccally-administered molecules:

781
782 The initial products for the buccal route were developed for local effects, and small molecule
783 products have only been exploited recently for systemic drug action. Some examples are marketed
784 small drug molecules in buccal and sub-lingual dosage forms: fentanyl, nicotine, ondansetron,
785 donepezil, risperidone, diphenhydramine, dextromethorphan, phenylephrine, buprenorphine, and
786 naloxone (Table 2). Unfortunately, to date, the buccal delivery of biologics has achieved limited
787 success in clinical trial progress. Among biologics, the buccal delivery of insulin has been
788 extensively researched (Caon et al., 2015; Montenegro-nicolini and Morales, 2016; Morales and
789 McConville, 2014). Oral-lyn™ by Generex (Canada) is a micellar insulin solution in a buccal
790 spray (Pozzilli et al., 2005); the formulation contains PEs, including bile salts and sodium caprate
791 as excipients, and it has been approved for commercialization in Ecuador and Lebanon. Oral-lyn™
792 was discontinued in India because of pending evidence of low clinical efficacy. Ora-lyn™ has

been under review by the US-FDA since 2011 without being granted its approval, despite an initial emergency authorization, now long expired. The main problem is that a patient would require up to 12 puffs after a meal, which could be considered an inefficient drug delivery and potentially hinder treatment compliance. To our knowledge, it is not available in any major market and has effectively been discontinued.

Another example of a buccal insulin product is PharmaFilm1, a MonoSol Rx (USA) and Midatech (USA) collaboration, which is a film containing recombinant human insulin non-covalently bound to gold glycan-coated nanoparticles. The Phase I clinical trial for this product was encouraging. However, the program was terminated due to a Phase II clinical trial that revealed reduced buccal insulin bioavailability (Morales and Brayden, 2017).

MonoSol Rx, now known as Aquestive Therapeutics, expanded the PharmaFilm® technology to deliver diazepam using the buccal route of administration to treat epilepsy seizures over a minimum 6-month period using a range of doses (Warren, 2017). here is a recently completed Phase III clinical trial in adults and a pediatric Phase II clinical trial (NCT03222349).

Another example of translation is a Phase II clinical trial sponsored by Xiamen LP Pharmaceutical Co., Ltd, where palonosetron is delivered using buccal films for chemotherapy-induced nausea and vomiting (Xiamen LP Pharmaceutical Co., 2021). This is an ongoing study and its results are pending submission to ensure safety, efficacy and assess pharmacokinetics. In addition, IntelGenx Corp. completed a Phase IIa study to test the efficacy of Montelukast buccal films in patients with mild to moderate Alzheimer's disease (IntelGenx Corp., 2020).

The challenge of delivering biologics across the buccal epithelium remains. Nonetheless, there is interest in testing the buccal route for formulated stable low molecular weight macromolecules with long half-lives. Overall, there has also been a shift in the use of small molecule buccal films from local to systemic use (Table 6).

Table 6. List of relevant clinical trials that have been completed or are ongoing.

Sr. No	Trial Number	Title	Sponsor	Status	Conditions
1	NCT05199818	Buccal Film vs IV Palonosetron for Prevention of CINV in Cancer Patients Receiving MEC	Xiamen LP Pharmaceutical Co., Ltd.	Recruiting	Chemotherapy induced nausea and vomiting
2	NCT03953820	Diazepam Buccal Film (DBF) - Diastat Rectal Gel (DRG) Crossover Study	Aquestive Therapeutics	Completed	Epilepsy

3	NCT04592198	Buccal Film Versus IV Injection Palonosetron for Moderately Emetogenic Chemotherapy Induced Nausea and Vomiting	Xiamen LP Pharmaceutical Co., Ltd.	Completed	Nausea with vomiting associated with chemotherapy
4	NCT03402503	Safety, and Efficacy of a New Buccal Film of Montelukast in Patients With Mild to Moderate Alzheimer's Disease	IntelGenx Corp.	Recruiting	Alzheimer Disease
5	NCT01675167	Efficacy Study to Evaluate Buprenorphine HCl Buccal Film in Opioid-Experienced Subjects	BioDelivery Sciences International	Completed	Low Back Pain
6	NCT01633944	Efficacy Study to Evaluate Buprenorphine HCl Buccal Film in Opioid-Naive Subjects	BioDelivery Sciences International	Completed	Low Back Pain
7	NCT01871285	Evaluation of the Tolerability of Switching Subjects on Chronic ATC Opioid Therapy to Buprenorphine HCl Buccal Film	BioDelivery Sciences International	Completed	Pain
8	NCT00941304	Study of Buprenorphine HCl Buccal Film in the Treatment of Dental Pain	BioDelivery Sciences International	Completed	Pain
9	NCT03222349	Pharmacokinetics and Safety Study of Diazepam Buccal Film (DBF) in Pediatric Subjects With Epilepsy	Aquestive Therapeutics	Completed	Epilepsy
10	NCT01256450	Efficacy and Safety Study of Buprenorphine HCl Buccal Film	BioDelivery Sciences International	Completed	Pain Lower Back pain

		in Subjects With Low Back Pain			
11	NCT03428360	Safety and Tolerability Study of Diazepam Buccal Film (DBF) in Subjects With Epilepsy	Acquestive Therapeutics	Completed	Epilepsy
12	NCT05392842	Corchorus Olitorius Buccal Films for the Treatment of Recurrent Minor Aphthous Ulcerations	Deraya University	Enrolling by invitation	Aphthous Ulcer Recurrent
13	NCT03179891	Study of Diazepam Buccal Film Administered in the Interictal and in the Ictal-Periictal States to Adults With Epilepsy	Aquestive Therapeutics	Completed	Epilepsy
14	NCT02516436	The Safety of Using Buprenorphine With Naloxone in a Buccal Film to Initiate Treatment of Opioid Dependent Subjects	BioDelivery Sciences International	Completed	Pain Lower Back pain
15	NCT01755546	Long-term Open-Label Safety Study to Evaluate EN3409	BioDelivery Sciences International	Completed	Low Back Pain Osteoarthritis Neuropathic Pain
16	NCT05419297	True Functional Restoration and Analgesia in Non-Radicular Low Back Pain	Carolinas Pain Institute BioDelivery Sciences International	Recruiting	Back Pain Lower Back Chronic Chronic Pain
17	NCT05427981	Anti-suicidal Effects of Buprenorphine In Depressed Individuals	New York State Psychiatric Institute	Recruiting	Suicidal Ideation Major Depressive Disorder
18	NCT03996694	Single Dose Crossover Study to Compare the Respiratory Drive After Administration of Belbuca, Oxycodone and Placebo	BioDelivery Sciences International PRA Health Sciences	Completed	Respiratory Depression
19	NCT03669263	A Dose Titration Study of	Chang Gung Memorial	Completed	Breakthrough Cancer Pain

		Fentanyl Buccal Soluble Film for Breakthrough Cancer Pain in Taiwan	Hospital TTY Biopharm		
20	NCT00640835	Safety and Tolerability of Buprenorphine/Naloxone Film Strips	Indivior Inc.	Completed	Opioid related disorders
21	NCT01702532	Nicotine Mouth Film for Craving Relief.	GlaxoSmithKline	Completed	Smoking Cessation
22	NCT00761137	Safety and Efficacy Study of NH004 Films for Relief of Sialorrhea Symptoms in Parkinson's Disease Patients	NeuroHealing Pharmaceuticals Inc. Michael J. Fox Foundation for Parkinson's Research	Completed	Sialorrhea Secondary to Parkinson's Disease
23	NCT05209906	An Observation Study to Assess the Efficacy and Safety of Proportional Doses of Painkyl® in Patients With Breakthrough Cancer Pain	Mackay Memorial Hospital	Recruiting	Cancer Pain
24	NCT01446120	Insulin Loaded Orally Dissolved Films (Insulin-ODF)	Hadassah Medical Organization	Unknown status	Healthy Volunteers
25	NCT03070561	Evaluating Peanut Immunotherapy Dissolving Film in Healthy Subjects	Johns Hopkins University National Institutes of Health (NIH)	Completed	Peanut Allergy Immunotherapy Pharmacokinetics
26	NCT00696137	Long-term Extension Study of BEMA™ Fentanyl	BioDelivery Sciences International	Completed	Respiratory Depression
27	NCT01298765	Longterm Safety Study of BEMA Buprenorphine in Subjects With Chronic Pain	BioDelivery Sciences International	Completed	Pain Low Back pain Osteoarthritis Neuropathic Pain
28	NCT01431742	Longterm Safety Study of BEMA Buprenorphine in Subjects With Chronic Low Back Pain	BioDelivery Sciences International	Withdrawn	Pain Low Back pain

29	NCT00293033	Study of BEMA™ Fentanyl in the Treatment of Breakthrough Pain in Cancer Subjects	BioDelivery Sciences International	Completed	Pain Cancer

Conclusions and future directions

Buccal delivery of drugs and biologics has been extensively studied using various manufacturing techniques. The buccal route of administration bypasses first-pass metabolization and facilitates drug administration. Nevertheless, currently, there is a gap between preclinical research and market translation of buccal formulations, especially in the case of biologics. The successful biologics delivery, using the buccal route of administration is a major milestone in drug delivery science, given the fragile nature and molecular weight of these therapeutics. Interestingly, the 3D printing of biologic-loaded films has shown promising results for clinical translation. In addition, techniques such as iontophoresis, electrospinning, and electrospraying are also becoming more prominent in the preparation of buccal dosage forms. It is crucial to ensure the stability of these molecules in the dosage form and when delivered through the buccal route, which is highly dependent on the excipients used. Emphasis also needs to be laid on analytical methods and animal models used in the assessment of these films. There has also been a shift in evaluation methods, with a renewed emphasis on permeation barriers and enhancement strategies.

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