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Buccal Films as an Emerging Drug Delivery System: A Comprehensive Review

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REVIEW

Buccal Films as an Emerging Drug Delivery System: A Comprehensive Review

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ABSTRACT

Oral administration through the digestive tract is still the most common means by which drugs are given, as it is simple and cheap. However, it has some biopharmaceutical limitations in general, such as varying gastrointestinal conditions, enzymatic degradation, and extensive hepatic first-pass metabolism, which decrease drug stability and bioavailability To address these challenges, drug delivery through the oral mucosa (OMDD) has emerged as a potential non-invasive option. The buccal mucosa is well supplied with blood, provides a relatively mild environment, and avoids hepatic first-pass metabolism, thereby resulting in a faster onset of action and improved bioavailability. Mucoadhesive buccal films have been the most important choice of many due to their wide-ranging properties like dosing accuracy, flexibility, and patient compliance among different OMDD technologies. These films bind to the mucosal surface, hence prolonging the contact time and facilitating uptake. This review covers in detail the structure and function of the buccal mucosa, the main components of the formulation, and modern fabrication techniques such as solvent casting, hot-melt extrusion, electrospinning, and 3D printing. Besides, the evaluation criteria, like thickness, mucoadhesion, and stability, are also addressed. Limited drug loading, saliva-induced washout, etc. are some of the issues that still exist. However, recent technological breakthroughs keep on improving buccal films as efficient, patient-friendly devices for local and systemic drug delivery.

Keywords: Mucoadhesive buccal films, Patient compliance, Bioavailability enhancement, 3D printing, Oral mucosal drug delivery, First-pass metabolism avoidance, Solvent casting method

1. Introduction

The conventional oral route has been the most preferred and widely accepted method of drug administration for a long time, mainly due to its simplicity, convenience, safety, and cost-effectiveness [1–4]. Nonetheless, traditional oral dosage forms such as tablets and capsules face a number of biopharmaceutical issues that frequently lead to restricted therapeutic efficacy [1–4]. The gastrointestinal (GI) tract is a harsh and variable environment, and its fluctuating pH, enzymatic degradation, and the presence of intestinal microflora can cause drug instability and partial absorption [1, 2, 5]. Besides that, hepatic first-pass metabolism can be so extensive that it causes delayed onset of action and reduced systemic bioavailability [1, 6–8]. These problems are significant to peptides, proteins, and other macromolecules, which are highly vulnerable to degradation in the GI tract [3, 6, 9]. In addition to pharmacokinetic issues, solid oral dosage forms may also be a source of problems for certain patient groups, namely children, the elderly, and people with dysphagia, psychiatric conditions, or poor medication compliance [2, 10, 11].

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Their disadvantages have led researchers to look for different administration routes that would be able to eliminate the oral route's drawbacks.

On the list of possible routes, oral mucosal drug delivery (OMDD), especially through buccal and sublingual mucosa, seems to be the most feasible one. Thus, it has attracted the most interest as an alternative non-invasive route [1, 8, 10, 12–14]. The mouth is a rather easily accessible organ, with a fairly mild physiological environment and a well-vascularized mucosal membrane through which the drug can get directly absorbed into systemic circulation; hence, hepatic first-pass metabolism is avoided [2, 6, 8, 10, 12]. Such an arrangement leads to increased bioavailability, quicker onset of action, and fewer side effects caused by the dose. In addition to that, buccal and sublingual routes are especially suitable for the drugs that need to take effect very quickly, e.g., opioids and emergency drugs [13, 15]. However, the oral mucosa has limitations, making it difficult to achieve the intended dose in this manner. Mucosal tissue is a barrier to drug permeation, and the small surface area limits the maximum dose that can be administered [6, 16, 17]. Besides that, a continued salivary secretion and mechanical action resulting from mastication and tongue movement can bring about rapid drug washout; thus, the residence time is even shorter [6, 16, 17]. Mucoadhesive drug delivery systems are considered one of the solutions to these problems [7, 13, 18]. These systems use bioadhesive polymers that can create strong interactions with the mucosal surface, extending the residence time and facilitating drug absorption. Among the various mucoadhesive platforms, buccal films have garnered a lot of interest due to their thin, flexible, and patient-friendly design [4, 5, 10, 11, 13, 18]. These films make dosing accurate and administration easy and can be developed for either local or systemic delivery, depending on the formulation [10, 11, 19].

This article reviews orally mucosal drug delivery systems in detail, with particular emphasis on the use of mucoadhesive buccal film as a new and alternative form to the traditional oral delivery forms. It describes the anatomical and physiological factors of the buccal mucosa affecting drug absorption and indicates the key aspects of formulation, such as polymers, excipients, and manufacturing methods. The paper also talks about parameters used for evaluation and the latest innovations in technology, like hot-melt extrusion, electrospinning, and 3D printing. Moreover, it discusses difficulties concerning drug loading, permeability, and patient compliance, and at the same time describes coming strategies to solve these problems. In essence, the article serves as a guide to the present state of the art and the forthcoming possible directions in the field of efficient and patient-friendly buccal film systems for local and systemic drug delivery.

2. Anatomical and physiological characteristics of the buccal mucosa

Buccal mucosa (Fig. 1), which ranks among the most promising areas for drug delivery, is the mucous membrane that lines the inner cheeks and is responsible for approximately 50 cm^2 out of the total oral mucosal surface area of about 200 cm^2 [6, 11, 20]. When viewed under a microscope, this non-keratinized stratified squamous epithelium usually comprises 40–50 cell layers and is between 500 and 800 μm in thickness [5, 11, 17, 21]. The first layers of the epithelium, together with the lamina propria and submucosa of the buccal region, are anatomically and histologically one unit [5]. Because of its dense vascularization, the buccal mucosa gives the drugs the opportunity to take the very first direct route into the systemic circulation through the jugular vein, thus bypassing the first-pass hepatic metabolism as well as destruction in the harsh GIT environment [6, 22]. The buccal mucosa has quite a high permeability level, which has been stated to be 4–4,000 times that of the skin, with the general permeability pattern being sublingual > buccal > palatal [21, 23]. Drugs are primarily taken up in the system via passive diffusion. Small lipophilic molecules can transcellularly (through lipid cell membranes) free the molecules, while small hydrophilic molecules can paracellularly (through intercellular spaces) penetrate the tissue [5, 11]. Drug absorption is affected by many factors, among which physicochemical characteristics of the drug, such as low molecular weight (e.g., < 500 Da), moderate lipophilicity (log P 1.6–3.3), and a unionized state at the mucosal site [5, 22, 24, 25], and formulation factors like the presence of permeation enhancers are the most important ones [11, 26]. The buccal cavity local environment is directly dependent on the saliva's nonstop secretion, which is composed mainly of water (99%), mucins, electrolytes, and different mucosal enzymes [13]. Normal saliva pH is approximately within the range of 5.5–7.5 [17, 27]. Among the most considerable physiological obstacles, there is the continuous flow of saliva (0.5–1.5 L per day), which leads to saliva washout, i.e., the dilution of the drug concentration and shortening of the drug retention time [6, 11, 17]. While the rate of enzymatic activity (including proteases, aminopeptidases, and the cytochrome P450 system) is significantly lower than that in the GI tract, the mucosa still forms an enzymatic barrier that can break down the sensitive

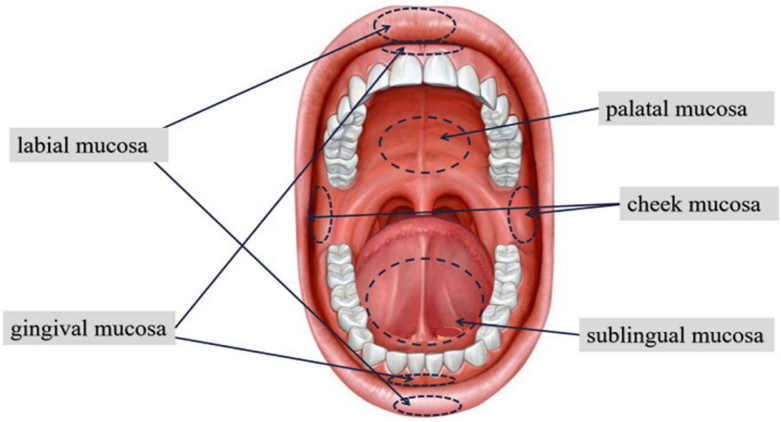

Fig. 1. Anatomical regions of the oral mucosa [10].

Table 1. Comparison of oral mucosal film types and related dosage forms.

Dosage Form	Typical Characteristics	Retention Time (Relative)	Comparison to Buccal Films	Sources
Buccal Films (MBFs)	Thin, flexible sheets; highly conformable to mucosa; provide accurate dosing	Prolonged/Extended	Superior flexibility and comfort vs. tablets; longer residence time than semisolids	[2, 6, 8]
Buccal Tablets	Rigid compressed solids; high dose capacity	Prolonged	Less flexible and comfortable; lower patient compliance	[2]
Gels and Ointments	Easily spreadable semisolids; high mobility	Short	Easily washed away by saliva; poor retention compared to films	[5]
Oromucosal Sprays	Liquid formulations enabling rapid absorption	Very Short /Immediate	Minimal contact time; unsuitable for controlled release	[36]

drugs, and thus it becomes necessary to add protease inhibitors to provide stability [5, 6, 28].

2.1. Types of oral mucosal films

2.1.1. Buccal films (BFs) or mucoadhesive buccal films (MBFs)

Mucoadhesive buccal films (MBFs) are orally adhesive films planned for absorption from the inner lining of the cheek (Table 1). They comprise an API that is best integrated into the film-forming polymer [8, 29, 30]. A significant attribute of MBFs is their mucoadhesive property, which enables them to stay for a long time at an interaction site with the mucosa [8, 31]. These kinds of films are used for delivery both locally and systemically. Drugs administered systemically can be absorbed through the buccal mucosa into the venous system and, thus, combined with the hepatic first-pass metabolism [11, 29]. It is usually present in these films to be very thin, soft, and flexible so patient comfort will be ensured, and mucosal irritation will be minimized [19]. Most of these kinds of films (MBFs) are multilayered, consisting of a mucoadhesive drug layer and a backing layer that might be manufactured from, for instance, ethylcellulose, a hydrophobic polymer, thus protecting the drug from saliva and providing unidirectional release toward the mucosa [14, 32, 33].

2.1.2. Orodispersible films (ODFs) / Oral soluble films (OSFs)

Orodispersible films (ODFs), also known as oral-soluble films (OSFs), are thin sheets intended for quick disintegration or dissolution [14, 32]. Usually, ODFs are made of highly hydrophilic polymers and do not possess mucoadhesive properties [34, 35]. Generally, ODFs are placed on the tongue, where they rapidly dissolve in saliva, typically within 30 seconds [19, 36]. After disintegration, the drug is swallowed and absorbed through the digestive tract. Some advanced forms of ODFs may contain drug-loaded matrix particles that act as vehicles for prolonged or controlled drug release [19].

2.1.3. Sublingual films

Sublingual films refer to films placed under the tongue (Table 2), utilizing this area's thin, non-keratinized epithelium and rich vascular network [12, 37, 38]. Such anatomical design provides very quick systemic drug absorption and avoids hepatic first-pass metabolism, resulting in a rapid onset of action comparable to that of an injection [12, 25]. Due to the high quantity of saliva and mechanical stress resulting from tongue movement, sublingual films are typically of the quick-dissolving type, and prolonged-release formulations are generally unsuitable for this site [37, 39].

Table 2. Overview of structural and functional attributes of oral films.

Feature	Buccal Films (MBF)	Sublingual Films	Orodispersible Films	Palatal Films (PF)	Source
Site of Application	Inner cheek mucosa	Beneath the tongue	On the tongue	Hard palate	[11, 12, 19, 34]
Typical Film Thickness	50–1000 μm	100–200 μm	12–100 μm	200–1000 μm	[12, 42–44]
Onset of Action	Moderate; controlled release	Very rapid	Rapid (via GI absorption)	Slow; sustained release	[12, 19, 34, 36, 42]
Duration	4–6 h (sustained)	Short duration	Very short (seconds)	Long (hours)	[12, 13, 19, 34, 36, 42]
Example	Fentanyl (Onsolis®)	Buprenorphine/Naloxone (Suboxone®)	Ondansetron (Zuplenz®)	–	[10, 12, 21]
Advantages	Avoids first-pass metabolism; controlled release	Rapid onset	No water needed; good for dysphagic patients	Mechanical protection; local effect	[4, 6, 12, 19, 34]
Limitations	Limited drug loading (~40 mg)	Small absorption area	Taste issues; GI absorption	Low permeability	[4, 6, 12, 19, 34]

2.1.4. Palatal films

Palatal films are applied to the hard palate, which is covered by keratinized masticatory mucosa [40, 41]. Because the epithelium is keratinized, the palate is less permeable than the buccal or sublingual regions. Palatal films are designed for prolonged contact, and formulation strategies typically involve limiting the hydration of hydrophilic polymers and creating rigid gel networks that can withstand the mechanical stress of chewing while maintaining controlled drug release at the site [40–42].

3. Formulation consideration

3.1. Active pharmaceutical ingredient (API)

The potency of the active pharmaceutical ingredient (API), its physicochemical characteristics, and the intended dose are the main factors considered when selecting an API for buccal film. Because buccal administration permits direct circulation of the product to the blood, APIs that are typically delivered in a fashion that results in a high first-pass metabolism in the liver are best suited for this method. As a rule, low-dose APIs are the ones to be used, with the single dose being usually advised to be less than or equal to 10 mg [9, 21]. Typically, the API makes up from 1% to 25% w/w of the end product, while the highest drug load of up to 30% w/w can still be allowed without a significant change in the film's inherent properties [45–50]. The size of the molecule, pH, and lipophilicity factors are very important for a successful passage through the mucosa [51]. For better absorption, it is better that the API be in an un-ionized form at the normal pH of the oral cavity [21]. Besides, changing the drug to a micronized or nanoparticle-encapsulated form can not only solve the uniformity of content issue, but it can also change the release profile and increase the loading capacity [2, 52].

3.2. Film-forming polymer

Film-forming polymers represent the principal matrix and the structural framework of the oral film. They are the major component, making up about 40%–50% w/w of the total mass of the film [44]. The single polymer or the polymer mixture selected essentially determines the mechanical strength of the film, its dissolution/disintegration rate, and mucoadhesive capability [44]. The perfect film formers should be hydrophilic, non-toxic, biocompatible, and have good mechanical characteristics [4, 9]. Some of the commonly used cellulose derivatives are hydroxypropyl methylcellulose (HPMC), hydroxypropyl cellulose (HPC), and sodium carboxymethyl cellulose (SCMC). Along with them, synthetic polymers like polyvinyl alcohol (PVA) and polyvinylpyrrolidone (PVP) are also very much in use. Quite often, polymer blending (e.g., mixing pullulan with HPMC) is the method used to get better adhesion and desirable mechanical characteristics [53, 54]. In the case of mucoadhesive formulations, the presence of such polymers as chitosan, carbopol, and mucoadhesive-grade HPMC (e.g., K15M), the most important, is necessary to guarantee the contact time with the mucosa.

3.3. Plasticizers

Plasticizers are essential additives incorporated to reduce the rigidity of polymers arising from their inherent nature. Their inclusion improves the flexibility of the film and makes it resistant to tearing during handling, processing, and application [45, 53]. They perform the function of decreasing the glass

transition temperature (Tg) of the polymer, and thus, they intensify the molecular mobility. Approximately ~20% of the dry polymer weight [50], or a range of 10%–30% relative to the total casting solution solids, is what plasticizers are usually composed of. Principally, hydrophilic plasticizers are glycerol, propylene glycol (PG), and polyethylene glycol (PEG), for example, PEG 400 [35, 55]. The right amount is very important; as an example, the glycerol concentration in HPMC K15M formulations has been successfully optimized in the interval of 0.5%–1.5% [56]. Too much (for example, glycerol over 30%) may bring about the negative side of the moisture resistance; thus, the cause of the unwanted phenomenon of the stickiness and the instability of the formulation may be the most probable [57].

3.4. Saliva-stimulating agent

Saliva-stimulating agents are put mainly in the fast-dissolving films to start the process of salivation that, in its turn, helps the quick disintegration and dissolution of the film matrix in the oral cavity [58]. It is especially important because the process of disintegration is dependent on the very limited amount of liquid (approx. 1.1 mL) available in the mouth [59]. These agents are mostly made up of mild, food-grade acids, like citric acid (which is very often the one chosen), malic acid, tartaric acid, and ascorbic acid [2]. They usually make up 2%–6% of the total oral film weight [4, 35].

3.5. Sweetening agents

In terms of taste masking, sweetening agents are essential, mostly when the bitter APIs are being changed and the patient's compliance is affected, especially in the case of the pediatric population [2, 4]. Both natural sweeteners like sucrose, fructose, and xylitol and high-intensity artificial sweeteners like sucralose and acesulfame potassium can be used. Generally, artificial sweeteners are preferred due to the small amounts required to achieve the desired effect and their non-cariogenic properties [45, 60]. In addition, sugar alcohols such as sorbitol and xylitol are known to cause a pleasant cooling effect and good mouthfeel [61]. These compounds are specified within the wider group of additives and usually constitute 10%–30% of the total formulation weight.

3.6. Flavors

The main role of sweeteners is to make the medicine tastier; however, flavoring agents take over this role once sweetening agents are insufficient. In actuality, they accomplish this by preventing the API's unpleasant flavors and odors, which enhances the dosage form's palatability and organoleptic acceptability [2, 4]. The palatability is to a large extent dependent on the first taste, which occurs almost immediately after the administration [2]. The flavor choice mostly depends on the target age group. For example, fruit flavors are most likely to be liked by pediatric patients, while mint or orange are more likely to be preferred by geriatric patients [62]. Flavors are commonly added up to a concentration of 10% w/w in fast-dissolving thin films [4]. Examples are peppermint oil, cinnamon oil, vanilla, and different fruit essences.

3.7. Surfactant

Surfactants, or surface-active agents, are generally considered as one of the main film formulation components that are necessary for the role of wetting agents, dispersants, and solubilizers. Their main role is to ensure the even distribution of the drug (mainly hydrophobic APIs) throughout the polymer matrix and also to facilitate the quick disintegration and thus the release of the API that comes into contact with the saliva [4, 6]. Besides, they can be used as permeation enhancers [63]. The most common surfactants are polysorbates (Tweens, e.g., Tween 80), poloxamers, and sodium lauryl sulfate (SLS) [4]. Surfactants fall within the broad additive range of 10%–30% of the film mass [64], but the concentration of an effective solution can be much lower, such as 0.5% w/v Tween 80 [8].

3.8. Coloring agents

Coloring agents enhance the visual appeal of oromucosal films, which in turn improves patient compliance and acceptability [45]. The options are diverse and comprise natural coloring agents, juice concentrates, and pigments like titanium dioxide [4]. The concentration of coloring agents in oral thin films is usually very low; most of the time it does not go beyond 1% w/w of the formulation [65]. It is necessary for the producers in a children's line of products not only to be careful but also to make sure that the color is not similar to that of candy, thus decreasing the risk of inappropriate consumption or drug abuse [45].

4. Manufacturing methods

4.1. Solvent casting method

In general, the solvent casting method (Fig. 2) is acknowledged as the most prevalent manufacturing

technique for film production due to its convenientness and low cost, especially on a small scale of research [11, 15, 44, 45]. In the solvent casting method for buccal film, a film-forming polymer, typically a hydrophilic polymer like cellulose derivatives, e.g., HPMC, is dissolved in a suitable solvent such as water, ethanol, or their mixture [11, 47, 66]. Next, pharmaceutically active ingredients (APIs), plasticizers like propylene glycol or glycerine, and other excipients such as the taste-masking agents and the permeability enhancers are added to the solution or uniform slurry [15, 66, 67]. To make the films homogeneous and of even thickness, the foam that is trapped during mixing is removed by deaeration, which can be done by ultrasonic defoaming, refrigeration, centrifugation, or vacuum stirring [11, 15, 45]. The homogeneous solution or dispersion is then spread on a suitable mold such as glass, Teflon-coated trays, Petri dishes, or an intermediate liner with the help of a coating knife to maintain a constant thickness [11, 15, 66, 68]. The utilized film is dried by solvent evaporation under regulated conditions, normally in a well-ventilated place or oven at a temperature range of 40°C to 55°C, and requires from 6 to 48 hours to complete the drying process [15, 66, 69, 70]. The process is completed by detaching the dried film, cutting it into the required size, and wrapping it to have the final dosage form containing the appropriate amount of drugs [15]. Several marketed oral films are produced using the solvent casting method, including Suboxone®(buprenorphine/naloxone), Belbuca®(buprenorphine), Onsolis®(fentanyl citrate), Bunavail®(buprenorphine/naloxone), and Listerine®PocketPaks, demonstrating the wide industrial applicability of this technique [10].

Limitations:

- The solvent casting method may result in films of non-uniform thickness and dose inconsistency owing to air being trapped and poor mixing leading to varying quality even within the same batch.
- The quality, stability, and performance of the film may be impacted by residual solvents in the film, drug recrystallization on the surface, and film brittleness as a result of production.
- The method is time-consuming due to the long drying periods, and the removal of the solvent is tedious, which makes it less efficient for large-scale production.
- There are some challenges when it comes to upscaling and several processing steps that further restrict its industrial capability and cost-effectiveness [11, 44, 45].

4.2. Hot melt extrusion

Hot melt extrusion (HME) (Fig. 3) is a continuous, solvent-free process commonly used in the manufacture of pharmaceuticals. Despite significant disadvantages like high processing temperatures and equipment expenses, it is nonetheless advantageous because it provides constant medication dispersion, improved content uniformity, and appropriateness for continuous large-scale manufacturing. In this method, polymers, drug substances (APIs), and excipients are introduced to an extruder, where heat and mechanical shear are used in a controlled manner to melt, mix, and homogenize the materials, followed by forcing them through a die of the required shape to obtain a uniform film [71–73]. The technique gets rid of the use of organic solvents; thus, the problems related to solvent toxicity and environmental hazards are minimized [71, 74]. Moreover, it enables quick and nonstop production, makes excellent content uniformity possible, and permits that the drug is evenly dispersed in the polymer matrix. Besides that, the method also provides the possibility of efficient taste masking and can facilitate large-scale production processes [71, 74].

Limitations:

- The system requires elevated temperatures, which limits the use of thermolabile drugs or bioactive compounds that are heat-sensitive.
- The process demands the presence of a high-value, complex machine, and the operator should have the necessary technical skills to perform the job.
- The local incomplete melting of ingredients may result in low homogeneity, and the quality of the product may be compromised.
- A possible problem is drug recrystallization after the cooling phase; degradation of the stability of the drug and changes in release characteristics may follow [11, 71].

4.3. Printing technology (inkjet and three-dimensional printing)

One of the most advanced manufacturing methods of the future is the set of printing technologies that are capable of finely and non-invasively depositing pharmaceutical substances on or inside films, the methods being inkjet (IJP) and three-dimensional (3D) printing [10, 19, 75]. By this, personal medicine becomes feasible; hence, the main advantage is the capability to produce films with the required dosage, the design, and the release profiles of the drug [10]. The latter obtains products by layer-wise deposition of polymers

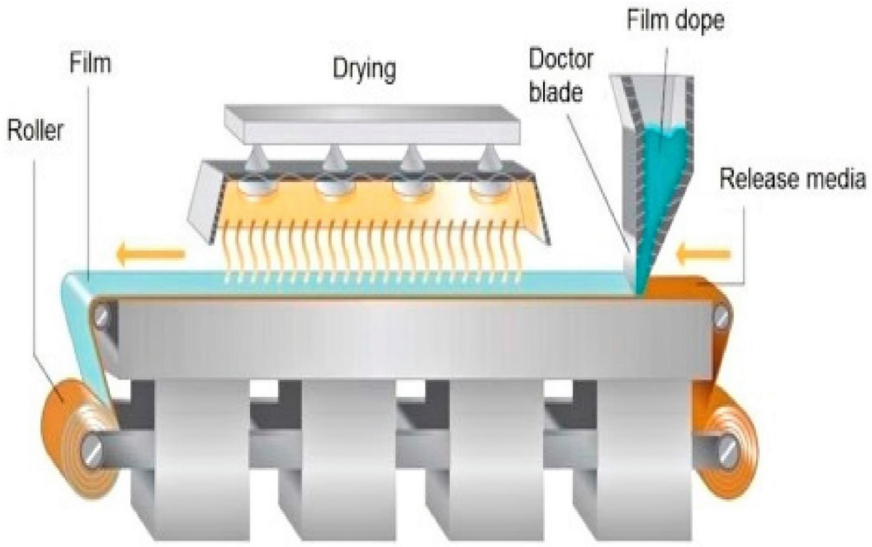

Fig. 2. Commercial film manufacturing via solvent-casting technique [44].

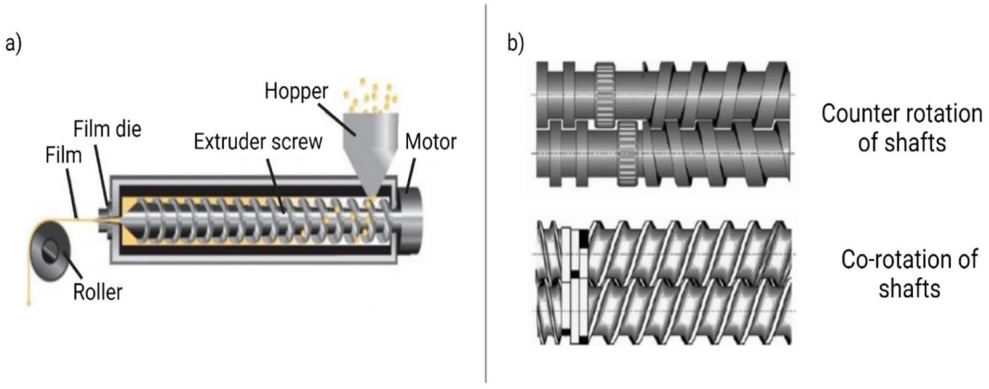

Fig. 3. Film fabrication using hot-melt extrusion technique [44].

through technologies like fused deposition modelling (FDM) or semi-solid extrusion (SSE), while in inkjet printing API-containing inks are locally and precisely delivered to pre-existing substrates through drop-on-demand systems [19, 76]. The printing process offers the highest accuracy in dose, freedom of design, and the possibility to fabricate complicated or layered structures to separate the non-compatible ingredients [6, 77]. Spritam®(levetiracetam), the first commercially available 3D-printed drug product approved by the U.S. Food and Drug Administration (FDA), is a noteworthy example of the pharmaceutical application of 3D printing. It shows the potential of printing technologies for sophisticated and customized drug delivery systems [78].

Limitations:

- The drug load is constrained due to the limited area of the surface available for printing.
- The occurrence of crystallization in the API after the deposition may result in non-uniformity of the drug, lower solubility, and changes in dissolution rate.
- The process requires the use of sophisticated and costly printing machines and needs skilled personnel.
- Certain 3D printing techniques generate high heat, making them inappropriate for thermosensitive drugs [19, 75].

4.4. Electrospinning

Electrospinning is a method used to make nanofibrous buccal films from a polymer solution or melt. A high-voltage electric field is applied to the polymer, and when the electrostatic force overpowers the surface tension of the polymer solution, a fine jet is ejected from the needle tip to a grounded collector. Along the way, the solvent evaporates; thus, solid nanofibers are formed, which are then deposited as a thin, porous film. The fiber morphology and

uniformity are influenced by the polymer concentration, voltage, flow rate, and the distance between the needle and collector parameters. The nanofibrous films obtained have a large surface area, high porosity, and are flexible, which qualities make drug dissolution and permeability and buccal mucosa absorption easier. Moreover, electrospinning also enhances the solubility and bioavailability of poorly water-soluble drugs, and it allows for drug uniformity at the molecular level. Besides, to pave the way for sustained or controlled drug release, the next generation of electrospinning metal-core fibers can be produced by coaxial electrospinning [79, 80]. For example, Colley et al. described a preclinical electrospun bilayer patch (Rivelin-CLO®) that contains the corticosteroid clobetasol-17-propionate for the treatment of oral cavity chronic inflammatory illnesses. A mucoadhesive fiber layer made of polyvinylpyrrolidone (PVP), Eudragit RS100, and poly (ethylene oxide) was used to load up to 20 μg of medication per patch [81].

Limitations:

- Most electrospinning formulations use organic solvents, which bring about safety and environmental issues.
- The process is quite slow and expensive if compared to solvent casting.
- For polymer solutions, the viscosity must be low to be able to get good fibers, which limits the available material that can be used.
- Considering the complex setup and process control requirements, it is difficult to scale up for large-scale production [79, 80].

5. Evaluation parameters

5.1. Thickness

Thickness is one of the leading parameters that guarantees dose uniformity as well as a proper approach to the quality of the film [8, 18, 66]. The thickness is recorded numerous times with a digital micrometer or vernier caliper in order to verify the uniformity [8, 15, 32, 82, 83]. The best buccal film thickness is generally considered to be from 0.12 $\pm$ 0.01 to 0.21 $\pm$ 0.1 mm, or 50–1000 μm [6]. Films with a thickness of about 1.0–1.3 mm are regarded as thin, pliable, and good for the patient's comfort [8].

5.2. Visual aspects & appearance

Appearance is a key parameter that decides the patient's willingness to accept the product and the simplicity of the product's handling [3, 45]. The buccal films must be smooth, flexible, clear, and consistent without being inflated and without defects [82–84]. The presence of opacities or white spots might suggest that the drug has precipitated because of the limited solubility of the polymer [83]. For instance, films fabricated with Eudragit RL100 show clear and consistent films [84]. The macroscopic evaluation also involves the observation of the surface, color, and flexibility [82–84].

5.3. Disintegration time

One of the primary qualities that distinguishes fast-dissolving films from mucoadhesive buccal films is disintegration time (DT). Currently, there is no officially designated protocol for the determination of DT [3], and the methods usually entail placing the film in purified water or phosphate buffer that simulates saliva (pH 6.75) and recording the time for complete disintegration or erosion to take place [32, 85, 86]. For fast-dissolving films, the disintegration time normally is between 5 and 60 seconds [3]. Some laboratories determine the disintegration time as the time during which a drop of phosphate buffer on the film surface disappears due to disintegration, resulting in the formation of an orifice [85].

5.4. Folding endurance

Folding endurance evaluates the flexibility and mechanical strength of buccal films and, thus, their resistance to damage during the stages of processing and usage [15, 18, 82]. The method consists of folding the film at the same point repeatedly until it breaks, thereby determining the number of folds, with around 300 folds being considered acceptable [6, 8, 66]. The best effect of plasticizers such as PEG 400 or glycerin on the folding endurance can be achieved [45, 53, 87].

5.5. Tensile strength

Tensile strength (TS) is the capability of a film to oppose tearing when the film is stretched or put under tension [11, 15]. It is accomplished by means of a texture analyzer or a universal testing machine, most usually following ASTM D882 standards [6, 11, 85, 88]. TS is computed through the breaking force being divided by the cross-sectional area of the film [6]. Increased TS is an indication of the film being mechanically stronger as well as more flexible [82], and, as a rule, polymer concentration is responsible for both these properties to increase [82, 89]. Although plasticizers may lower TS, they can be of great help in enhancing the film's elasticity, for instance, in the case of Eudragit RL100-based films [84].

5.6. Mucoadhesiveness

Mucoadhesion is one of the most important features of buccal films, as it ensures that the contact time between the dosage form and mucosal tissues is long enough, which is basically needed for the release of the drug in a sustained manner and thus successful systemic absorption [3, 11]. Mucoadhesion is quantified in terms of the force necessary to separate the film from the mucosal surface, which is also known as mucoadhesive force or mucoadhesive strength [8, 15].

5.7. In vitro drug release

In vitro drug release studies are a must to grasp the release kinetics of the active pharmaceutical ingredient (API) from the film matrix to the mucosal surface [8]. Although the regulation frequently lacks precise standards, an evaluation of medication release/dissolution should include a guarantee of "appropriate drug release." The USP Type II equipment (paddle-over-disc method) is typically utilized [8, 32]. A glass slide with a stuck film is placed at the bottom of the dissolution vessel. The dissolution medium is usually a saliva simulant, for instance, a phosphate buffer solution (pH 6.8 or 6.8 ± 0.5) [8, 82]. In the case of sustained-release buccal films, the release profile is mostly biphasic and thus can be characterized and also desired as such; the first few hours show a higher drug release rate to ensure absorption, followed by a sustained release phase [8, 16]. Drug release kinetics are often aligned with such models as Higuchi diffusion [84] or Weibull model kinetics [8].

5.8. Surface pH

Surface pH is a significant factor, as very acidic or very basic values may lead to mucosal irritation [2, 6, 32]. To prevent the pH from being the source of discomfort, the film's pH must be very close to the physiological buccal pH (~6.4) [8, 90]. The measurement involves the film swelling on an agar plate or in phosphate buffer (pH 6.8), and a pH electrode or pH strip is used to determine the pH [2, 8]. Usually, buccal films have pH ranges of 5.3 ± 0.1 to 6.5 ± 0.1 [2, 6, 32, 82].

5.9. Contact angle

The contact angle is the parameter that describes the hydrophilicity or wettability of the oral disintegrating films. This characteristic is critical, as it can be used to foresee features like the disintegration time of the film. One drop of ultrapure water is put on the film surface, and the angle is ascertained by means of an optical tensiometer [85].

5.10. Stability test

Stability studies are the main instrument to check the film's physical integrity and to make sure that the API content is acceptable throughout its shelf life. These studies focus mainly on the resistance of the film to moisture, light, and oxygen [3, 45]. According to ICH guidelines, films are subjected to accelerated testing conditions (40 ± 2°C, 75 ± 5% RH) for 30, 60, and 90 days to determine changes in appearance, weight, and drug content [15, 56]. Ideal products should be able to retain a proper moisture level and be free from microbial contamination [3, 15].

5.11. In vivo and ex vivo permeation

To evaluate the potential for systemic drug delivery, getting through the oral mucosa is a must. This is usually done with the help of excised rabbit or porcine buccal tissues in Franz diffusion cells [8, 15, 32, 91].

5.12. Swelling index

It is a measurement of a film's capacity to absorb water, which subsequently establishes mucoadhesion and drug release by erosion and diffusion. The swelling ability is very dependent on the structure of the film and the polymer content [8, 32, 82].

5.13. Organoleptic evaluation/taste assessment

Since the film is placed in the oral cavity, the taste and the palatability of it are the major factors of patient acceptance, in particular, the pediatric and geriatric populations. The taste panels or the electronic tongue can be used for this kind of evaluation [2, 3, 32].

6. Challenges and future perspectives

The physiological environment of the mouth cavity and the constraints of formulation technologies present several challenges to the development of mucosal drug delivery systems such as mucoadhesive buccal films (MBFs). One of the most difficult physiological obstacles is the continuous secretion of saliva, which causes dilution, drug washout, and hence rapid washing of the drug from the site of absorption [6, 12]. The challenge of fast saliva renewal

combined with mechanical factors of chewing and speaking requires that the dosage forms have very good mucoadhesive properties in order to maintain contact for a longer time [6, 49]. In addition, the limited surface area of the buccal mucosa (about 50 cm^2) is a factor restricting the total quantity of drug that can be locally delivered [2, 6]. Additionally, the epithelium acts as a barrier, particularly for big hydrophilic molecules, which causes the primary issue of low medication transbuccal permeability [5, 12]. At the same time, this problem is intensified by enzymatic degradation by proteases and peptidases in the oral cavity, thus making it a severe hurdle to peptide and protein delivery. Looking at the formulations side, the drug loading capacity in buccal films is a consistent limitation arising due to the small size of the dosage form [6, 33, 49]. In addition, even highly purified cellulose ether–based buccal films face such drawbacks as poor adhesion and strong hygroscopicity of hydrophilic polymers [10]. When coupling advanced materials, problems also arise because the incorporation of nanoscale carriers is very limited due to the risk of particle aggregation during the film-forming process [90]. Last but not least, giving adequate taste masking to unpalatable active ingredients and lessening mucosal irritation are the two patient-centric issues that need to be solved so that adherence and therapeutic success can be guaranteed [1, 91].

Technological advancements aimed at resolving formulation issues and expanding therapeutic applications are quickly realizing the enormous promise of oral mucosal drug delivery methods, such as buccal and sublingual films. A main developmental trend in this respect is the employment of cutting-edge manufacturing methods to facilitate personalized medicine and ensure product quality. Utilization of different 3D printing techniques, like fused deposition modeling and inkjet printing, is enormously changing the way dosage forms are designed by enabling accurate, patient-specific tailoring, which is a great benefit, especially for pediatric and geriatric patients. Alongside them, hot-melt extrusion can accomplish continuous production while maintaining the stability and uniformity of the film, thereby resolving the issues with the conventional solvent casting approach.

The breakthrough in material science is also expected to a great extent to pave the way for the better performance of these systems. One of the main advantages brought by the sophisticated mucoadhesive polymers is longer retention, increased stability, and controlled drug release with the application of new generations of thiomers, among others. The problem of insufficient drug load remains a main issue, with the proposal of inserting nanocarriers or solid dispersions into the film matrices being the main solution. The method of electrospinning is rapidly gaining popularity as a way of making nanofiber films that have higher drug-loading capacity, are more permeable, and allow faster drug release.

The oral mucosal route is being considered as a new and promising area for the delivery of vaccines and antigens as well as large peptide-based drugs, with this injection-free way being the non-invasive alternative. Physical enhancement methods like iontophoresis, sonophoresis, and electroporation are gaining support through research as ways of increasing drug permeation and thus the range of molecules that can be used. Furthermore, the development of oral mucosal systems that can be integrated with intelligent, responsive closed-loop delivery systems that are specifically made for rescue medicines may be the next step in this sector.

7. Conclusion

Oral mucosal drug delivery, especially via mucoadhesive buccal films, is one of the most promising approaches that have been used to solve the problem of conventional oral dosage forms such as hepatic first-pass metabolism and enzymatic degradation in the gastrointestinal tract. These systems have proven rapid drug onset, increased bioavailability, and patient compliance improvement, especially in patients with swallowing difficulties. However, the formulation issues of salivary washout, mucosal permeability, and limited drug loading continue to limit their potential. The recent progress in manufacturing methods such as 3D printing, hot-melt extrusion, and electrospinning, combined with the use of novel materials like thiolated polymers and nanocarriers, has resulted in the evolution of more efficient and versatile delivery systems. These breakthroughs have led to very accurate dose control, enhanced stability, and programmable drug release profiles, thereby opening up the possibility of using buccal films for the delivery of complex molecules such as peptides and vaccines. Further studies on smart and stimuli-responsive delivery systems as well as physical enhancement methods like iontophoresis will, most likely, continue to propel this area forward. At its core, muco-dynamic buccal film has the potential to transform patient-oriented therapeutics, which may become a reality if technological and material innovation continues to be sustained.

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Conflict of interest

The authors declare that there are no potential conflicts of interest regarding this work.

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