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Oromucosal films: from patient centricity to production by printing techniques

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ABSTRACT

Introduction: Oromucosal films, comprising mucoadhesive buccal films (MBFs) and orodispersible films (ODFs), are considered patient-centric dosage forms. Target groups are patients with special needs. Various active pharmaceutical ingredients have been shown to be suitable for oromucosal film production. A shift is seen in the production techniques, from conventional solvent casting to printing techniques.

Areas covered: In this review, the patient acceptability of oromucosal films is discussed. An overview is given of the small molecule drugs, biopharmaceuticals and herbal extracts that have been incorporated so far. Finally, the current state of 2D and 3D printing techniques for production purposes is discussed.

Expert opinion: The patient-centric features are important for the further development and acceptance of this oral solid dosage form. Oromucosal films perfectly fit in the current attention for personalized medicine. Both MBFs and ODFs are intended for either a local or a systemic effect. For buccal absorption, sufficient mucoadhesion is one of the most important criteria an oromucosal film must comply with. For the preparation, the solvent casting technique is still predominately used. Some limitations of this production method can be tackled by printing techniques. However, these novel techniques introduce new requirements, yet to be set, for oromucosal film preparation.

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1. Introduction

Oromucosal films comprise mucoadhesive buccal films (MBFs) and orodispersible films (ODFs). They are defined as single – or multilayer sheets of suitable material [1]. MBFs are placed in the mouth and attach to the buccal mucosa. MBFs can be used for the treatment of systemic or local diseases. In systemic therapy, the active pharmaceutical ingredient (API) is absorbed via the mucosa, bypassing the gastrointestinal tract, and/or swallowed with saliva [2]. In the treatment of local diseases, MBFs are favorable over oral gels or oral ointments, as they have a longer retention time in the mouth and therefore cannot be washed away easily with saliva [3]. ODFs are placed onto the tongue and disperse rapidly [1]. The API is mainly swallowed with saliva following the gastrointestinal route for absorption [2]. ODFs are commonly used for the treatment of systemic disorders.

Oromucosal films are considered patient-centric dosage forms with high patient acceptability [2]. Patient acceptability has been defined by the European Medicines Agency as the ability and willingness to take a medicinal product as intended [4]. Patient acceptability has now become a key parameter to guide the drug product development in order to ensure adherence to the medicinal treatment and to minimize medication errors. Characteristics such as ease of transportability and handling, thinness and flexibility, dose flexibility, and the

possibility of taking them with no or just little water make oromucosal films suitable drug-delivery systems for patient populations with special needs [2,5]. In particular, patients (older) affected by dysphagia [2], infants and young children [6] and uncooperative [7] or nauseated/vomiting patients [8] may benefit from the patient-centric nature of these dosage forms. The rapid disintegration and/or the mucoadhesive properties of oromucosal films ensure that the formulation cannot be easily spat out [9]. In addition, oromucosal films can be taken without the need of any manipulation steps by following simple instructions, which makes them convenient for administration in any circumstances, and also for patients who may struggle to follow preparation instructions.

Drug compounds of different nature can be incorporated into an oromucosal film: low molecular weight APIs which are either highly water-soluble or poorly water-soluble, biopharmaceuticals, or herbal plant extracts [2,10,11]. Some oromucosal formulations ensure a fast absorption of the API, and therefore a rapid onset of action that can be advantageous in emergency circumstances [5,9]. Conversely, a controlled or delayed drug release from oromucosal formulations [12,13] might represent a more convenient administration method than multiple doses.

A main hurdle in oromucosal film preparation is the limited drug load that can be contained. A relatively simple method to increase the drug load is to increase the surface area and/or

Article highlights

- The patient-centric design of oromucosal films improves acceptability in patient groups with special needs, such as the aging population and children.
- Mucoadhesive buccal films and orodispersible films are suitable dosage forms for the treatment of certain systemic as well as local disorders.
- With oromucosal films, especially mucoadhesive buccal films, absorption of the active pharmaceutical ingredient through the oral mucosa can be achieved.
- Oromucosal films might become a platform for the administration of biopharmaceuticals in the oral cavity.
- The use of oromucosal films with prolonged release may improve patient compliance and adherence due to the lower dosing frequency.
- 2D and 3D printing are promising novel production techniques for oromucosal films next to conventional solvent casting.

This box summarizes the key points contained in the article.

the thickness of the film. This may, however, negatively influence patient acceptance [2]. Another option is the use of multi-layered oromucosal films. These films can be, for example be prepared using the solvent casting method [14,15]. The solvent casting method is up to day the most used preparation technique for oromucosal film preparations. In short, all the excipients are dissolved in a suitable solvent (usually water). The solution is cast, dried, and cut into the desired size. Recently, printing techniques have been proposed for the preparation of oromucosal films. Figure 1 provides an overview of the characteristics of oromucosal films.

This review focuses on the patient-centric features of oromucosal films for systemic and local drug delivery via the oral cavity. Further, an overview is given of APIs recently incorporated into oromucosal films. Finally, it addresses novel printing techniques for the manufacturing of oromucosal films. These techniques can be used for small and large-scale production.

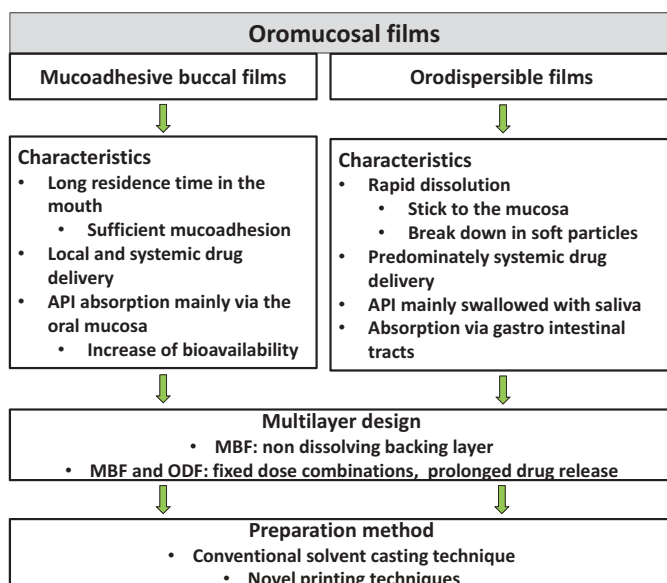


Figure 1. Overview of the characteristics of oromucosal films.

2. Patient-centric features of oromucosal films

2.1. Patient acceptability

The impact that a medicinal product design can have on patient acceptability requires assessment, and novel methodologies are being proposed and tested [4,6]. The number of scientific publications on the assessment of patient acceptability for medicinal products and dosage forms is rapidly increasing [6,16,17].

Depending on whether oromucosal films belong to the MBF or the ODF family, patient-centric features can be described. As the residence time of MBFs is long, they must be thin, soft and flexible in order to avoid irritation to the mucosal tissue. The same features also make them comfortable to keep in the mouth. Several formulation parameters can influence some of the acceptability attributes specific to buccal films. For example, the residence time in the mouth depends, among other factors, on the mucoadhesive strength of the film [18]. Various test methods to determine the mucoadhesive strength in vitro (e.g. using a texture analyzer, rheology, surface tensiometer) and in vivo (in volunteers) were reviewed by Woertz et al. [18]. Also, the film flexibility and resistance to tear represent mechanical properties that can determine the final characteristics of the dosage form, and consequently its sensory attributes. These formulation parameters can be established by determining the folding endurance or by measuring tensile strength and elongation at break [2]. Sufficient mechanical properties will lead to a high quality and robust product ensuring damage-free handling [13]. Such acceptability attributes are heavily influenced by the type of polymer or polymer blend forming the film matrix [12]. For example, molecular weight of a certain type of polymer determines the disintegration time of the polymeric matrix and thus the residence time of the buccal film. Also, the strength of film mucoadhesion may among other factors depend on the abundance of hydrogen-bonding groups of the polymer [13]. Keeping the film pH within the physiological range can also prevent irritation to the oral mucosa [19].

Rapid dissolution and the possibility of intake without the aid of water make ODFs easy to administer. Moreover, ODFs break down into soft particles upon disintegration, thus preventing the patient from experiencing potential discomfort due to the gritty nature of multiparticulates, or orodispersible tablets (ODTs). The addition of sweeteners, flavors, and the application of taste-masking technologies can considerably improve the palatability of ODFs, making medicine administration less imposing, particularly to children [2,6]. Finally, the tendency of ODFs to stick to the mucosa immediately upon placement can facilitate their application to uncooperative patients and patients who due to their illness are unable to take medication.

For MBFs and ODFs, a layered design can represent a promising platform for fixed-dose combinations and for controlled release [14,15]. This will result in lower dosing frequency and thus lead to improved patient adherence and compliance.

There is a limited availability of published literature on the acceptability assessment of MBFs, however, evidence of high

patient acceptability of ODFs is provided in several studies. Different ODF formulations were assessed *in vivo* with regards to swallowability, palatability, presence of residues in the mouth, grittiness, taste-masking, mouth freshening, size, thickness, solubility, disintegration time, and ease of administration [6,20–22]. The ‘gummy’ nature of disintegrating ODFs as a potentially disadvantage contributing to their mouthfeel and possibly to their acceptability was reviewed by Krampe et al. [2].

The patient-centric design of ODFs was found to contribute to the high acceptability observed in infants and preschool children, and their carers [6]. Patient acceptability of ODFs was found to be influenced by individual formulation attributes such as ODF perceived stickiness and disintegration time [16] and by non-formulation-related parameters such as the alteration of the intended use, the subdivision of the dose intake, the use of drink or food to facilitate administration, or the use of restraint [17].

To sum up, patient acceptability of oromucosal film is dependent on several parameters. For MBFs sufficient mucoadhesion and a non-irritable texture of the film are key factors. For ODFs, rapid dissolution and appropriate taste masking are important. Finally, a layered design of oromucosal films may contribute to less dosing frequency.

2.2. Local and systemic drug delivery

According to literature, both MBFs and ODFs are used for the local and systemic delivery route, although the recent focus is mainly on systemic administration.

Oromucosal films can be used for the treatment of various disorders. These include cardiovascular disorders, pain disorders, and mood or mental disorders (see Table 1).

Various (potent) APIs can be incorporated into oromucosal films: water-soluble and poorly water-soluble small molecule drugs, biopharmaceuticals and herbal plant extracts (examples are shown in Table 1). The most common used polymers are cellulose derivatives, such as hypromellose and hydroxypropylcellulose [2,39]. Furthermore, formulations with polyvinylalcohol are often mentioned in literature [9,40–45].

The incorporation of poorly water-soluble drugs is possible but complying with the uniformity of content is challenging. Different strategies for solubility improvement have been suggested, such as the use of organic solvents (e.g. ethanol to improve the solubility of diazepam [46]) or the addition of solubility enhancers [47], the use of organic acids to influence pH-dependent solubility [48], the use of mesoporous silica nanoparticles as a carrier for poorly water-soluble drugs (e.g. prednisolone) [49], and micronization of the API to reduce its particle size [50]. Particle size reduction is an often used method to improve the solubility of poorly water-soluble APIs [51–56]. Krull et al. showed that the dissolution of poorly water-soluble griseofulvin can be enhanced by using wet-milled drug particles. These (nano)particles were incorporated into a pullulan-based film [51] and hypromellose-based films [52,53].

Herbal plant extracts are frequently used as medicines for the treatment of various diseases in Asian countries. The development of oromucosal films containing curcumin [57], cucurbitacin B [58], *Acemella oleracea* extract [59], and ODFs with extracts of *Lagerstroemia speciosa* (L.) Pers., *Phyllanthus niruri* L., *Cinnamomum burmanii* Blume, *Zingiber officinale*

Roscoe, and *Phaleria macrocarpa* Boerl [11] have been reported.

The APIs are usually swallowed together with saliva and follow the gastrointestinal route for absorption. On the other hand, a relatively new delivery route for oromucosal films, especially MBFs, is through the oral mucosa. The absorption via the mucosa is mainly driven by passive diffusion across the lipid membranes. Hydrophilic APIs will be transported predominately via the paracellular pathway and lipophilic APIs via the transcellular pathway [60]. The advantage is that after absorption, the hepatic first pass metabolism is largely bypassed and the API enters the systemic circulation directly. Although the buccal mucosa may act as a barrier, absorption via this route may lead to an increased bioavailability [2] for APIs with low bioavailability after oral administration, for example zolmitriptan and duloxetine [61]. Gastric stasis in migraine may influence bioavailability. Besides, absorption via the buccal mucosa circumvents the degradation due to gastric enzymes or due to the acidic environment of the stomach. A limiting factor is the permeability for larger molecules (>500 kDa according to Lipinski’s rule of five [62]), which can lead to challenges in formulation development.

MBFs are available in a layered design that prevents dissolution of the drug inside the oral cavity but ensures mucosal absorption [14]. Other multi-layered formulations enable the release of multiple APIs in a sequential fashion [13]. The most commonly used polymer in this case is ethyl cellulose [63]. Hypromellose [14] as well as the natural beeswax [64] can alternatively be used as a slowly eroding shield. Another example is the development of a bi-medicated bilayer MBF. This MBF contains lidocaine in the outer side and diclofenac in the inner side and is intended for the treatment of radiation-induced oral mucositis [65].

Sufficient mucoadhesion is one of the most important criteria which a film must comply with application into the oral cavity. Typical polymers used as mucoadhesive components are gelatin, chitosan [66], pullulan [67], guar gum [68], xanthan gum [61], sodium carboxymethylcellulose [69], hydroxypropylcellulose [70] and sodium hyaluronate [71]. Various natural polysaccharides show mucoadhesive properties such as psyllium [72], okra [73] and certain rice varieties with a high amylose content [74].

The mucoadhesive properties of commonly used polymers like chitosan can be increased by thiolation [75]. Naz et al. described that thiolated films of fluconazole for buccal delivery increase the mucoadhesive strength significantly when compared to corresponding, non-thiolated films. The strong mucoadhesive properties of these thiolated polymers are due to the formation of covalent bonds with mucus glycoproteins [76]. Shiledar et al. showed that dimethyl sulfoxide, which is well known for its cell toxicity, enhances the permeability without any kind of buccal mucosal damage [61].

An increased amount of permeated drug can be reached using liposomal formulations [77], nanoparticles [78], or nanofibers [70], which are gaining high impact regarding the buccal transport route [57]. Morales et al. developed MBFs embedded with insulin-coated nanoparticles, which resulted in an enhanced permeation of insulin through mucosa in comparison with an insulin control solution in phosphate-buffered saline [78]. The insulin-coated

Table 1. Examples of oromucosal films, as found in literature, used for the local and systemic delivery route.

Indication	APIs	Excipients used for the preparation of ODFs or MBFs	Film type	Reference
Local delivery route				
Oral inflammatory disorders	Chlorhexidine Loperamide Econazole nitrate Ciclopirox olamine Fluticasone propionate Lidocaine hydrochloride/ diclofenac potassium Ornidazole/dexamethasone sodium phosphate Calculus bovis sativus/ornidazole Prednisolone Benzidine hydrochloride Jambu extract Lidocaine hydrochloride 5-Aminolevulinic acid	Sodium carboxymethylcellulose, glycerol Xyloglucan, hypromellose Gelatin Sodium carboxymethylcellulose, glycerol Different combinations of hypromellose, ethylcellulose, chitosan, sodium carboxymethylcellulose, carbomer, propylene glycol or polyethylene glycol 8000 Different ratios of chitosan, hypromellose, sodium alginate, dibutyl phthalate, propylene glycol, peppermint oil, eucalyptus oil Backing layer: ethylcellulose Mucoadhesive layer: different ratios of hypromellose, chitosan, polyvinyl alcohol, glycerol Different ratios of hypromellose, chitosan, polyvinyl alcohol, sodium carboxymethylcellulose, carbomer, glycerol Sodium alginate, gellan gum, glycerol Maltodextrins, xylitol, sorbitol, crospovidone Chitosan, acetic acid 1% Backing layer hypromellose Mucoadhesive layer: hydroxypropylcellulose, ethanol Chitosan, propylene glycol	MBF ODF MBF MBF MBF Bilayer MBF Bilayer MBF MBF Bilayer MBF ODF MBF Bilayer MBF MBF	[23] [24] [25] [26] [69] [65] [63] [27] [28] [29] [59] [14] [66]
Local anesthesia				
Oral cancer (in premalignant stage and precancerous lesions)				
Systemic delivery route				
Cardiovascular disorders	Propranolol Enalapril maleate/ hydrochlorothiazide Enalapril maleate Enalapril maleate Tizanidine hydrochloride/ meloxicam Tizanidine hydrochloride Diclofenac sodium Rizatriptan benzoate Duloxetine hydrochloride Tetrabenazine Dimenhydrinate Ondansetron Betahistine hydrochloride Insulin Glimepiride Pyrazinamide Isoniazid Ketotifen fumarate Theophylline Sildenafil citrate Sildenafil citrate	Polyvinyl alcohol, polyvinylpyrrolidone, chitosan, gelatin, ethylcellulose Hydroxypropylcellulose or a combination of hydroxypropylcellulose and polyvinyl alcohol, glycerol Hypromellose, carbomer 974P, trometamol, sodium EDTA, glycerol Hypromellose, carbomer 974P, trometamol, sodium EDTA, glycerol Sustained release layer: arabinosylan Immediate release layer: hypromellose Thiolated-arabinosylan, hypromellose, glycerol, sweetener Hypromellose, glycerol Hypromellose, polyvinyl alcohol, polyethylene oxide, glycerol, sweetener Hypromellose, polyvinyl alcohol, propylene glycol Hypromellose, polyvinylpyrrolidone, pullulan, hydroxyethyl cellulose, sorbitol, glycerol Xanthan gum, hydroxyethylcellulose, propylene glycol Hypromellose, chitosan, sodium hyaluronate, gelatin Polyvinyl alcohol, glycerol Chitosan, glycerol, ethyl cellulose, cyanoacrylate adhesive Carbomer, poloxamer, methyl cellulose, Eudragit RL100 Polyvinyl alcohol-polyethylene glycol graft copolymer, glycerol Polyvinyl alcohol-polyethylene glycol graft copolymer, glycerol Granular hydroxypropyl starch (Lycocel NG73 [®]), maltodextrine, glycerol Hypromellose, glycerol Polyvinyl alcohol, sodium alginate Hydroxypropylcellulose, guar gum, propylene glycol, sweetener	Bilayer MBF Multilayer ODF ODF Bilayer ODF MBF MBF ODF ODF MBF MBF ODF ODF MBF MBF MBF MBF ODF ODF ODF ODF ODF ODF ODF	[40] [39] [46] [15] [30] [31] [93] [32] [33] [34] [35] [71] [42] [75] [36] [43] [35] [37] [92] [45] [38]
Pain disorders				
Mood or mental disorders				
Nausea and vomiting				
Diabetes mellitus				
Pulmonary disorders				
Erectile dysfunction				

Abbreviations: EDTA (ethylenediaminetetraacetic acid)

nanoparticles were prepared with d,l valine and acid phthalate buffer (pH 2.2) [78].

Mortazavian et al. revealed that the combination of applying thiolation of chitosan as a mucoadhesive component in buccal films and the incorporation of insulin nanoparticles further increased permeation [75]. Through the use of nanoparticles with biodegradable polymers such as poly(lactic-co-glycolic acid), it was feasible to allow a slow release of antihypertensive peptides through the buccal epithelium [68].

Products for mucosal drug delivery, which are already on the pharmaceutical market, include Breakyl® (fentanyl buccal film) and Belbuca® (buprenorphine buccal film). Breakyl® is available in different dosages of 200–1200 µg, whereby the dosage increase is achieved by increasing the film area [79]. Belbuca® is available in dosages from 75 to 900 µg. No information about the film area of the different dosages is available [80].

MBFs and ODFs are, although mainly used in the treatment of systemic disorders, also used in the treatment of local disorders such as oral inflammatory diseases, cancer in the oral cavity, or for local anesthesia.

Table 1 gives examples of the oromucosal films for local and systemic treatment, respectively, that have been found in literature over the past 5 years, and the beginning of 2019. Various APIs were incorporated into oromucosal films. MBFs were predominately developed for the treatment of local disorders, whereas ODFs were predominately developed for the treatment of systemic disorders.

2.2.1. Biopharmaceuticals

As biopharmaceuticals, e.g. vaccines, after oral intake are prone to degradation by gastro-intestinal fluids, the buccal or sublingual route may be a suitable alternative [81]. Literature reveals multiple preparation methods to improve the stability and penetration of biopharmaceuticals with the aim to increase their bioavailability. Tian et al. developed an ODF based on a blend of trehalose and pullulan for protein delivery [10]. Morales et al. developed insulin-coated nanoparticles for insulin permeation through the mucosa [78], an ODF containing a microparticulate measles vaccine formulation for buccal delivery has been developed by Gala et al. [82], and an ODF with probiotics has been developed by Heinemann et al. [83]. Due to the very low log P value of biopharmaceuticals, passive diffusion is limited. Hence, the main route for absorption of biopharmaceuticals upon buccal administration is via the transcellular pathway, via receptor-mediated transport, and via the paracellular pathway. However, the tight junctions hamper the absorption of biopharmaceuticals with higher molecular weights (>200 Da) [84].

In conclusion, oromucosal films may become a platform for the administration of biopharmaceuticals with lower molecular weights in the oral cavity.

2.2.2. Permeation testing

The buccal mucosa acts as a natural barrier. Therefore, one of the essential tools for the evaluation of MBFs intended for systemic drug administration is permeation testing. In literature, various animal tissues have been used, which are supposed to mimic the human buccal mucosa. Mostly used are

esophageal [40,85] and buccal porcine membranes [86] as well as buccal membranes from chicken [87], sheep [61], rabbit [88] and goat [76]. Investigations with cell cultures are gaining popularity, as shown by experiments by Castro et al. with cell TR146 lines [68] and Morales et al. with tridimensional human buccal tissue (EpiOral) [78]. When performing permeation tests, Franz diffusion cells are conventionally used, which are modified sometimes according to the specific use [87]. The permeation rate is analyzed based on the flux determination by calculating the slope of the resulting plot. A further evaluation method is the determination of the apparent permeability which requires the flux (J) over the concentration (c_0) [68].

The main disadvantage of permeation tests via animal tissues is the high variability of the data. The storage conditions of the tissue, the integrity and the viability of the tissue are important parameters that should be monitored and determined prior to use [89].

To date, no pharmacopoeia contains a standardized test to measure permeation.

2.2.3. Prolonged drug release

Thus far, a number of oromucosal films with prolonged release properties have been developed. The compliance and adherence of the patient is substantially improved by a lower dosing frequency. Some drugs have already succeeded in achieving prolonged release (2–8 h) via MBFs and also in increasing bioavailability, for example prednisolone [86], ondansetron [71], griseofulvin [90] and doxepin [91].

Even though rapid disintegrating is the main feature of ODFs, in particular cases prolonged drug release from ODFs would also be beneficial, especially for patients with swallowing deficiencies. Prolonged drug release from ODFs has been achieved by incorporating drug-loaded matrix particles based on Eudragit® RS and silicon dioxide [92]. In that study, the matrix particles, with theophylline as a model drug, were produced by hot melt extrusion (HME), and the ODFs were subsequently produced by the solvent casting method. The downside of this method was the inhomogeneous distribution of the particles due to a large particle size distribution and different particles shapes. To overcome this problem, micropellets with microcrystalline cellulose and sodium carboxymethylcellulose were prepared. The researchers investigated the incorporation of prolonged release small-size micropellets into ODFs with diclofenac as a model drug [93]. After disintegration of ODFs in the oral cavity, the incorporated matrix particles or micropellets can be swallowed together with the saliva after which the drug is slowly released in the gastrointestinal tract. Prolonged release can also be achieved by using a drug – ion exchange resin complex. For this, Shang et al. used betahistine as a model drug. Betahistine has unfavorable characteristics for ODF production: it is very hygroscopic, has a short half time and a bitter taste. All these issues were tackled by the drug – ion exchange resin complex. Although the ODF was dissolved in the oral cavity, betahistine was released in the gastrointestinal tract from the complex [42].

For improving drug load and achieving sustained release of poorly water-soluble fenofibrate, Kevadiya et al. developed

a sandwiched film. This film contained a drug-loaded hydrophilic layer between two hydrophobic layers. Sustained release up to 480 min was achieved, depending on the thickness of the inner layer. The control films without hydrophobic layer released the API within 45 min [94].

3. Novel production techniques

Printing technologies have gained interest in pharmaceutical manufacturing purposes. Many printing technologies exist and are based on various different principles. The application of printing requires investments in reliable printers and competence in handling sophisticated tools (software) to enable the design of drug-delivery systems. However, automated systems with integrated quality control can be developed even to be used at point-of-care. General challenges in applying printing techniques are related to the maximum applicable dose, choice, and development of a functional substrate, development of suitable inks, interactions of substrate and ink to name a few important ones. Examples of printers used for pharmaceutical manufacturing are shown in Figure 2.

3.1. Pharmaceutical inkjet printing

Besides 3D printing, inkjet printing also referred to as 2D printing, moved into the focus. Inkjet printing is a contactless process of droplet deposition onto an appropriate carrier substrate, classically a paper sheet or foil. In case of drug printing, oromucosal films are the most reported substrates in literature [41,95–98]. They resemble the usual types of substrates and offer a higher surface for drug imprints compared to tablets.

The printing fluid consists of the drug dissolved in a suitable solvent or dispersed in a dispersant. As viscosity and surface tension are the most important properties to be considered to create a printable fluid, addition of one or more excipients is usually required. Obviously, these excipients should be non-toxic and of pharmaceutical grade, which limits the application of inkjet printing. In inkjet printing, the ink may also be formulated as a nanosuspension. The composition of the nanosuspensions and the physicochemical properties of the particles

(size, polydispersity, and net surface charge), particle concentration, excipient addition (surfactants), and solvent system will have an impact on the performance and stability of the ink formulation.

The main advantage of the inkjet technology is that the required dosage can be precisely printed on demand and tailored to the patients' specific requirements by a community or hospital pharmacist according to the prescription of the physician. There is no need to meet an exact wet film thickness as in the solvent casting technique because the dosage is controlled by the printing parameters, concentration of the printing fluid and the number of layers. This avoids trial and error adjustments of the wet film thickness or concentration of the polymer solutions [99] to reach the desired content as it is the case when solvent casting is used.

The predominantly used inkjet technique is the drop-on-demand (DoD) technology where a drop is only ejected on request. There are two implemented DoD printer driving methods: thermal and piezoelectric method (see Table 2). Liquid piezo-driven micro-dispensing systems may be also applied as they have usually larger nozzle diameters and can handle more viscous and higher particle-loaded fluids. (see Table 2). In thermal DoD process, the drops are ejected by pressure caused by an ink bubble due to rapid vaporization after brief heat treatment. Only water-based printing fluids can be used in this case. In piezoelectric systems, applied voltage leads to deformation of the ink chamber walls and generates a pressure wave ejecting drops. Solvent- and water-based fluids can be printed.

Different types of microdispensers systems have been also used to study the manufacturing of drug-delivery systems. Bonhoeffer et al. used a piezo-actuated micro-valve to investigate the dispensing of drug nanosuspensions onto substrates to make solid oral dosage forms. The micro-valve system in question was characterized regarding dispensing behavior, mass flow, accuracy, and robustness. And the study showed that adjusted from a few micrograms to several milligrams with high accuracy is possible and that the fluid properties, dispensing parameters of the micro-valve, and steady state mass flow was correlated for low-viscous drug nanosuspensions.) [102].

Oromucosal films can be prepared by inkjet printing non-continuously for small batches (e.g. community or hospital

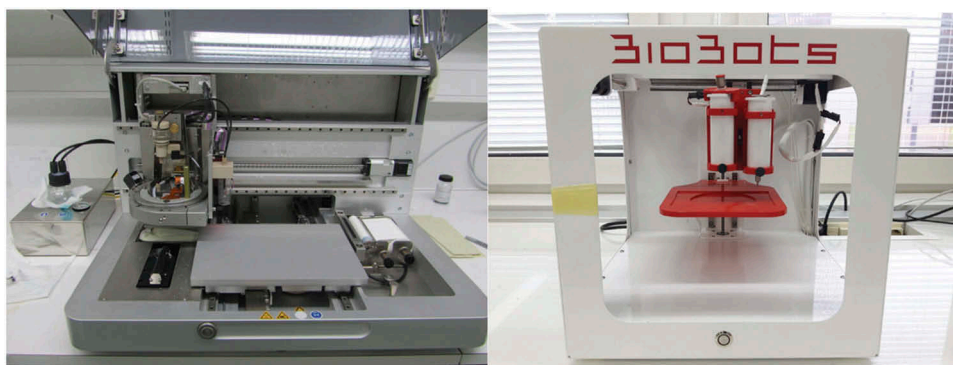


Figure 2. Examples of printers used for pharmaceutical manufacturing (left: piezoelectric inkjet printer PixDro LP 50, right: a dual syringe BioBots (Allevi) semi-solid extrusion (SSE) printer).

Table 2. Examples of oromucosal films, as found in literature, prepared by printing.

APIs	Printing device	Substrate	Printing fluid composition	Filament	Printing technique	Reference
Clonidine	HP Deskjet 460 (TIJ)	Polyvinyl alcohol- sodium carboxymethylcellulose films	Methanol:water:glycerol (20:70:10)	n.a.	Thermal inkjet printing	[41]
Enalapril maleate	JS 20 (PIJ), Spectra SE-128 AA	Hydroxypropylcellulose films (+ hydrochlorothiazide)	Polyethylene glycol: water + methylene blue Polyethylene glycol: water: methanol + methylene blue Ethanol: dimethyl sulfoxide: propylene glycol(45:45:10) Lactic acid: ethanol (16:84) + erythrosine Solution: water Nano-suspension: PEGylated poly (lactic-co-glycolic) acid Polymeric coating: Water: polyethylene glycol 3000 (75:15) Water: polyethylene glycol 6000 (92.5:7.5) Ethanol: glycerol: water (20:10:70) Propylene glycol: water (40:60)	n.a.	Piezoelectric inkjet printing	[95]
Levothyroxine and liothyronine	HP 5940 (TIJ)	Hypromellose films (+ glycerol)		n.a.	Thermal inkjet printing	[96]
Haloperidol	PixDro LP50 (PIJ), Spectra SL-128 AA	Hypromellose films (+ mesoporous fumed silica and glycerol)		n.a.	Piezoelectric inkjet printing	[97]
Sodium picosulfate	SciFLEXARRAYER S3 SciDROP Nano SciDROP Pico	RapidFilm® (Tesa Labtec) Hydrophilic/hydrophobic films (Cure Pharmaceutical)		n.a.	Microdispensing system	[98]
Lidocaine hydrochloride	PixDro LP50 (PIJ), Spectra SL-128 AA	Electrospun gelatine substrates (+ piroxicam and glucose)		n.a.	Piezoelectric inkjet printing	[103]
Propranolol hydrochloride	Pixma iP7250 (TIJ)	Edible rice paper Edible hydroxypropylcellulose -coated rice paper Edible icing sheets Hypromellose films	Water: glycerol (90:10) + red edible ink	n.a.	Thermal inkjet printing	[104]
Naproxen	DAMPP	Hypromellose films	Polyvinylpyrrolidone K90:ethanol (0.3:10)	n.a.	Microdispensing system	[105]
Diclofenac sodium	HPD4260 (TIJ)	Edible sugar sheets	Ethanol:propylene glycol (diff. ratios)	n.a.	Thermal inkjet printing	[106]
Rasagiline mesylate or tadalafil	A F.P.100/300 (FP)	Hypromellose films (+ polyvinylpyrrolidone)	Rasagiline mesylate: hydroxypropylcellulose (5%) Tadalafil: hydroxypropylcellulose (8.33%)	n.a.	Roll-to-roll printing	[108]
Piroxicam	IGT Global Standard Tester 2	Edible icing sheets	Polyethylene glycol-400 (100%)	n.a.	Roll-to-roll printing	[109]
Ibuprofen or paracetamol	Wanhao Duplicator 4 (FDM)	-	-	Polyvinyl alcohol, polyethylene oxide, sodium starch glycolate, croscarmellose	FDM 3D printing	[112]
Paracetamol	Cartesian (FDM)	-	-	Maltodextrins, glycerin	FDM 3D printing	[113]
Aripiprazole	ZMorph 2.05 (FDM)	-	-	Polyvinyl alcohol	FDM 3D printing	[114]
Sodium picosulfate	SciFLEXARRAYER S3	Hypromellose films (+ titanium dioxide) Gelatine films (+ titanium dioxide) Hydrophilic/hydrophobic microcrystalline cellulose films (Cure Pharmaceutical) RapidFilm® (Tesa Labtec) Listerine®	Water	n.a.	Microdispensing system	[100]
Lysozyme	Modified HP Deskjet 1000 (TIJ)	Solvent casting method: hypromellose films (+ glycerol), chitosan films (+ polysorbate 80) Electrospinning method: polycaprolactone films	Lysozyme: glycerol (7:3 v/v)	n.a.	Thermal inkjet printing	[101]

Abbreviations: Thermal inkjet (TIJ), piezoelectric inkjet (PIJ), flexographic printing (FP), fuzed deposition modeling (FDM).

pharmacy) or continuously for larger scale (in hospital pharmacy or pharmaceutical industry) [95].

As 2D printing is a new approach for dosage form production there are some challenges to overcome. The main challenge is clogging of nozzles. If the required volume is not ejected because of blockage, the target dose cannot be reached. However, similar is the case when the calculated drug content is not achieved because of a mismatch of theoretical and practical wet film thickness during solvent casting of oromucosal films [103]. Furthermore, the drug has to be stable in the printing fluid during production and storage as well as in the polymer solution using the casting method. Finally, inkjet printing is so far limited to low-dose applications just like conventional manufactured film formulations.

The application of inkjet technology leads to different requirements for the oromucosal films as functional substrates. They have to be stable enough for imprinting while avoiding disintegration during the process, but should maintain their orodispersible and/or mucoadhesive properties. The substrates can be developed based on specific needs such as the absorptive capability and mechanical strength and, e.g. print quality if for instance if high-resolution QR codes needs to be printed on the substrates. The interaction between printing fluid and substrate determines besides whether the drug get lost due to rebounding effects [102], stays on the surface or penetrates inside the film matrix. There is the possibility to use additional excipients like mesoporous fumed silica to increase the absorptive properties of the films [97]. Furthermore, the oromucosal preparations should be sufficiently wetted by the applied printing fluid avoiding irregularities. A new approach is to produce the films by electrospinning gaining a fibrous structure with high surface area [103]. Pre-coatings containing high molecular polyethylene glycol aim at a better spreading of hydrophilic fluid on the films [98]. Edible rice paper and icing sheets can be used instead of cast films [104].

Crystallization behavior of the drugs after deposition on the substrate should be monitored during formulation development as it may significantly influence the solubility, dissolution, and handling. Amorphous-printed dosage forms were produced by adding polymers to the printing fluid [105]. In this study, it was also shown that the bigger the drop volume the higher is the crystalline proportion because small drops dry faster and the drug substance has less time for crystallization. The more printing passes the higher was the amorphous ratio due to the increasing amount of propylene glycol and higher solvation of

the drug [103,106]. With increased drug content, the recrystallization rate can increase and drug crystals can be formed on the top of the oromucosal films [95].

Besides single-dosed medicines, there are further progresses described in literature. Drug combinations were produced by printing levothyroxine and liothyronine onto a drug-free ODF [96]. Enalapril maleate was printed onto hydrochlorothiazide containing ODFs [95] and lidocaine hydrochloride onto fibrous gelatine substrates containing piroxicam [103].

With regard to security measure, a traceability system in the form of QR codes was printed onto ODFs [97]. On the one hand, drug loading and drug therapy safety are ensured and, on the other hand, anti-counterfeiting and patients assignment may be enabled by printed film products. Hereby, one more future-oriented step would be done toward digitalization and safety improvement of individualized medicine. In Figure 3 examples are shown of printed oromucosal films, with and without QR codes.

3.2. Roll-to-roll printing

Inkjet printing is, to date, the most utilized printing technology to produce drug-loaded oromucosal films, however, other printing techniques have also been explored. Flexographic printing is a fast roll-to-roll printing method [107]. The pharmaceutical ink is transferred from an anilox roller to the printing cylinder. By applying a pressure between the printing cylinder and the impression cylinder, the ink is printed onto the polymer. Hypromellose-based drug-free ODFs were flexographically imprinted with either rasagiline or tadalafil [108]. Another study revealed an improved dissolution rate of the poorly water-soluble drug piroxicam when flexographically printing ODFs. This was probably due to the fact that piroxicam was in solution state [109]. The dose in ODFs prepared by flexographic printing is adjustable and can be increased by the number of applied printing cycles.

Flexographic printing can also be a production method of choice for the conversion of nanosuspensions into solid dosage forms [110].

3.3. Fused deposition modeling and semi-solid extrusion printing

3D printing, also called additive manufacturing, is associated with great flexibility regarding the size, geometry, and inner



Figure 3. Examples of oromucosal films prepared with printing techniques (left: SSE printed warfarin films (transparent films) and inkjet printed substrates (yellow colorant in warfarin ink), right: QR code printed on substrates (blue placebo ink)).

structure of the printed object [111]. 3D printing in the pharmaceutical field has typically involved printing of, for example personalized tablets, orodispersible tablets, and implants. But the suitability to utilize 3D printing for the production of ODFs has been explored. One type of 3D printing is extrusion-based 3D printing, which further can be divided into fused deposition modeling (FDM) and semi-solid extrusion (SSE) based 3D printing. FDM 3D printing requires a drug-loaded feedstock material, which typically is produced by means of HME. The produced filament, with a specific diameter, is fed into the FDM 3D printer. By the use of high temperatures, the thermoplastic material is melted and extruded through the nozzle, and sequential layers of material are deposited to create the pre-determined 3D structure designed using a computer-aided design program. Ehtezazi et al. produced fast dissolving single or multi-layered oromucosal films by means of FDM 3D printing where polyethylene oxide-based solid films containing ibuprofen and polyvinyl alcohol-based mesh structured films loaded with paracetamol were printed [112]. Taste-masking was introduced by printing a single or double taste-masking layer consisting of a mixture of polyethylene oxide and strawberry mixture on top of the ODFs containing paracetamol. The additional taste-masking layers resulted in a significantly slower drug release than the single layer ODF without an additional layer printed on top. Another approach to achieve taste-masking of ODFs or FDM 3D-printed dosage forms, in general, is to select polymers with taste-masking properties (for example maltodextrin [113]) as starting material when performing the HME. In this way, no additional coating of the ODF is needed. FDM 3D-printed aripiprazole-loaded PVA-based ODFs has also been produced [114]. Amorphization of the poorly water-soluble drug aripiprazole during the HME or printing step combined with the porous-printed structure of the ODF resulted in improved dissolution rates of the drug as compared to solvent cast films.

Some FDM printability issues of HME filaments have been reported. To ensure successful printing and excellent content uniformity of the printed dosage form, the diameter and dimensional consistency of the filaments is of great importance and needs to be in the specific range stated by the manufacturer of the printer. Other examples of identified important filament parameters are filament stiffness, brittleness, softness, moisture content, as well as melt rheology of the filament [111,115,116]. To overcome the difficulties faced with producing API-containing filaments by HME, Musazzi et al. modified a commercial FDM 3D printer to a hot-melt ram-extrusion 3D printer. Exploiting the hot-melt ram-extrusion 3D printer the drug/polymer/plasticizer blend can directly be fed into the FDM printer overcoming the need of a pre-made filament. Maltodextrin-based ODFs loaded with paracetamol were produced taking advantage of this setup [113].

In SSE 3D printing, the 3D object is formed by extruding a semi-solid material (e.g. pastes and gels) either by pressurized air, syringe plunger or by a rotating screw gear through the nozzle onto the build plate. SSE 3D printing can be used to prepare dosage forms with a high drug load [111]. An additional advantage of SSE compared to FDM is that the operation procedure can be performed at low temperatures. Therefore, also

thermolabile drugs can be incorporated in oromucosal films by this technique. As high temperature, which is required for both in HME and FDM may degrade thermolabile APIs and polymers. On the other hand, a disadvantage for the SSE-based 3D printing technology is the required drying or solidification period after printing. SSE 3D printing has successfully been utilized to produce ODFs containing warfarin sodium in combination with the film-forming polymer hydroxypropylcellulose [117]. A recent example in the literature compares direct SSE printing of drug-loaded warfarin films to inkjet dispensed ink onto substrates and manual compounding of sachets [118].

In Table 2 examples of oromucosal films prepared with printing techniques are shown.

4. Conclusion

Oromucosal films are considered a class of patient-centric dosage forms suitable for patients with special needs, such as children or older patients suffering from dysphagia. Patient acceptability can be optimized by the design of the dosage form. Stickiness, disintegration time and user friendliness are important parameters for patient acceptance.

ODFs are predominately used in the treatment of systemic disorders, whereas MBFs are used in the treatment of local as well as systemic disorders. The incorporation of poorly water-soluble drugs into oromucosal films may be challenging. However, the reduction of particle size may improve solubility. Recently, oromucosal films (multilayer) with prolonged release have been developed. These tailor-made films may, due to less frequent dosing, increase patient adherence and compliance.

A relatively new application path with potential is drug delivery over the oral mucosa for small molecule drugs as well as biopharmaceuticals. Via this route, the hepatic first-pass metabolism is largely bypassed, which may lead to an increased bioavailability.

Newly applied preparations methods are printing techniques (inkjet printing, flexographic printing, and 3D printing). Up to date inkjet printing is the most used technique.

5. Expert opinion

Oromucosal films are a relatively new addition to the arsenal of pharmaceutical dosage forms for personalized medicine. Nowadays there is broad focus on increasing the patient acceptance of oromucosal films by developing better formulations.

Medication for the treatment of certain local and systemic disorders, such as oral inflammatory disorders, cardiovascular disorders, and disorders of the central nervous system, can be administered via both MBFs and ODFs, with immediate as well as prolonged release characteristics. The latter will improve patient compliance and adherence due to a lower dosing frequency. The APIs are swallowed or will penetrate the buccal mucosa. In case of the latter, an increased bioavailability may be obtained by the addition of penetration enhancers. Sufficient mucoadhesion is, however, a precondition for buccal absorption.

Oromucosal films are potential dosage forms for vaccine and protein delivery. Both mucosal and systemic immunity can be obtained due to the richness of antigen-presenting cells and mucosal-associated lymphoid tissue like tonsils, salivary glands, Waldeyer's ring, and pharyngeal lymphoid tissue is present in the oral cavity. This would benefit patients who suffer from needle phobia and would avoid the use of contaminated needles, as may be the case in developing countries. Attention should be paid to the stability of the biopharmaceutical during preparation and storage of the oromucosal films. The addition of vaccine in dry state circumvents stability issues. Also, the addition of biopharmaceutical stabilizers (sugars such as trehalose and inulin) could solve this problem. In terms of production methods, conventional solvent casting as well as novel printing techniques can be used, but the temperature should be carefully monitored during production.

Although water is not required for the intake of oromucosal films, a suitable application device would simplify the placement on the tongue or attachment to the mucosa. Especially if caregivers administer the oromucosal films to patients who are unable to take medication, for example at late-stage Parkinson's disease, or for the removal of a non-dissolving backing layer from the buccal mucosa. This application device may be a pair of tweezers comparable to those used to remove a soft contact lens from a storage case. An application device would also be favorable in terms of hygiene.

The conventional preparation technique for oromucosal films is the solvent casting technique. This technique has some limitations, such as trial and error adjustments of the wet film thickness or concentration of the polymer solutions. With printing techniques, these limitations are tackled. In addition, a precise amount of API can be printed per dosage unit and it is feasible to print fixed API combinations. However, challenges such as increased dosing remain. This makes the oromucosal films especially interesting for the administration of potent (and thus low dosed) APIs, for example for the treatment of cardiovascular disorders, disorders of the central nervous system, schizophrenia and migraine.

New preparation techniques introduce new requirements for oromucosal film preparation. Solubility, dissolution, uniformity of content and handling properties may significantly be influenced by crystallization behavior of the APIs after deposition on substrate. In inkjet printing, the droplet volume is influenced by the viscosity of the printable fluid. Most of the 3D printing techniques are not suitable for thermolabile APIs as elevated temperatures are often used.

Nonetheless, a huge advantage of printing technique is the possibility to integrate safety features in the form of QR codes with the dosage form.

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