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Expert Opinion

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Advances in orodispersible films for drug delivery

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Introduction: Orodispersible films for oral delivery are gaining popularity. Whereas breath-fresheners and over-the-counter products have already become quite common in the US, the first prescription drug films were introduced into the EU and US markets only very recently. Already considered as a unique Rx (prescription drug) dosage form by the FDA (oral soluble film), such products are not substitutable by conventional oral dosage forms. The official term defined by the European Medicines Agency is orodispersible film (ODF).
Areas covered: This review gives an overview on the benefits of ODFs, typical excipients and products already available on the market. ODFs are defined and differentiated from other films and dosage forms. Possible manufacturing methods are described. As ODFs are not yet listed in one of the pharmacopoeias, possible methods for characterization and quality control are discussed. Required characteristics, advantages and disadvantages are elaborated. Biopharmaceutical considerations are provided because such films can also be used to enhance bioavailability of a drug.
Expert opinion: The magnitude of variants of ODF technology and the advantages over conventional dosage forms promise more applications and more marketed products with ODFs in the near future. Therefore, the authorities have to publish a monograph for ODFs as soon as possible to standardize characterization methods and quality specifications.

Keywords: buccal delivery, disintegration time, film-forming polymer, oral soluble film, orodispersible film, solvent casting, tensile strength, thin strips

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1. Introduction

The oral route is the most acceptable for patients. Orodispersible films are a relatively new dosage form for this route of administration. They are postage stamp-sized strips of thin polymeric films formulated to disintegrate or dissolve almost instantaneously when placed onto the tongue [1]. Different terms can be found in the literature, for example, wafer, oral film, thin strip, orally dissolving film, flash-release wafer, quick dissolve film and melt-away film [1-4]. Melt-away film and melting film are rather inappropriate terms because the films are not melting but dissolving, or at least disintegrating in saliva. Therefore, the term 'soluble film' (in some cases 'buccal or oral soluble film') is preferred by the FDA, whereas the European Medicines Agency (EMA) is using 'orodispersible film' (ODF) [5-7].

The first approaches to the concept of oral films are found in patent literature of the 1960s [8]. Nevertheless, it was some time until ODFs became popular: Pfizer (New York) introduced Listerine® PocketPaks thin strips for breath-freshening in 2001, called as one of the best inventions by *Time Magazine* [9]. InnoZen (Oxnard) launched the first over-the-counter (OTC) ODF to deliver an active pharmaceutical ingredient (API) in 2003 (Chloraseptic® Relief Strips containing benzocaine) [10]. Since then, several other OTC films have become available in the US. The first approval of a prescription drug ODF (Ondansetron Rapidfilm®, BioAlliance, Paris/

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Article highlights.

- Oral films offer a wide range of dissolution characteristics and different sites of application in the oral cavity.
- ODFs do not require either water or swallowing. They can enhance compliance of different patient groups and are an attractive new dosage form.
- Manufacturing of ODFs is very flexible, but some process steps are challenging. The solvent casting technique is the method of choice at present.
- ODFs require moisture protecting packaging.
- Basic excipients of ODFs are film-forming polymers and plasticizers. In most cases taste masking is essential.
- There are no standardized tests for ODFs available yet.
- ODFs often provide a rapid onset of action. Avoiding first-pass metabolism and enhanced bioavailability may be possible.
- The first ODFs have entered the prescription market recently. Others are expected soon.

This box summarizes key points contained in the article.

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APR, Balerna/Labtec GmbH, Langenfeld) happened in the EU in 2010, followed by Strativa, Woodcliff Lake/MonosolRX, Warren/APR, Balerna/Labtec GmbH, Langenfeld in the US Zuplenz oral soluble film, ondansetrone [11,12]. Later, an ODF containing risperidone was the first commercially available prescription drug product (Risperidon HEXAL® SF Schmelzfilm, Hexal AG, Holzkirchen) [4].

1.1 Types of oral film

Depending on disintegration time and design, a distinction between fast-dissolving and sustained-release films, mucoadhesive films or oral patches seem to be useful. However, there is no clear dividing line. Mucoadhesive films and oral patches are commonly present on the market as buccal sustained-release dosage forms. Local or systemic drug therapy can be achieved with all types, whereby particularly for mucoadhesive films systemic therapy may be realized mainly by means of absorption of the API through the oral mucosa.

Different application areas are possible. ODFs are usually placed onto the tongue. Mucoadhesive films are typically placed onto the cheeks, but the palate or sublingual are feasible as well. Further, based on ODF technology, films for vaginal or rectal applications may be possible.

This review focuses on oral soluble films/orodispersible films only, but further information on mucoadhesive and sustained-release films is provided where applicable.

1.2 Advantages and disadvantages

ODFs are intended to be placed onto the tongue where they dissolve rapidly in the saliva. Swallowing whole is not necessary. Therefore, they are very suitable for pediatric and geriatric patients, bedridden patients or patients suffering from dysphagia, Parkinson's disease, mucositis or vomiting [1,2,13]. Owing to the fast wetting, oral films may adhere to the mucosa and/or dissolve rapidly, so they cannot be spat out easily [14]. Some patients even refuse orally disintegrating tablets because of their fear of choking or inhalation. ODF technology completely eliminates these problems [15]. As ODFs are thin and can be administered without water, they are ideal for travellers or patients who do not have continuous access to water. Furthermore, intake is discreet.

Orally disintegrating tablets (ODTs) have gained popularity during the last few years. To accelerate fast disintegration, many ODTs are fragile, which causes problems during manufacturing, storage, handling and administration. On the contrary, ODFs are flexible but still robust to mechanical forces [16]. Whereas lyophilization is a common process for manufacturing ODTs, the manufacturing of ODFs is based on the technology for producing transdermal patches, which is less expensive than lyophilization [17]. Superior to liquid formulations such as drops or syrups, ODFs offer the convenience of accurate dosing [2]. As the drug is released within seconds into the oral cavity, a rapid onset of action could be achieved. If the drug is absorbed through the oral mucosa, first-pass metabolism can be avoided for some drugs, which may improve bioavailability [18,19]. Buccal absorption may be particularly beneficial, for example, for patients suffering from migraine [18,20]. However, some patients may experience drowsiness, owing to the fast onset of action [21].

Drug load is limited. Therefore, ODFs are constricted to highly potent low-dose drugs. Moreover, manufacturing typically requires solvents and heat for drying. These factors potentially affect stability of the drug and/or other excipients such as sweeteners and flavors [18]. A general major drawback of orodispersible dosage forms is taste. Taste masking may reduce maximum drug load further. For extremely bitter APIs, taste masking may even be impossible.

1.3 Required characteristics of ODFs

An ideal ODF should be thin and flexible, but stable to guarantee a robust manufacturing and packaging process and ease of handling and administration [22-24]. The films should be transportable, not tacky and keep a plane form without rolling up [23,24]. They should provide an acceptable taste and a pleasant mouth-feel [24]. Disintegration time should be as short as possible. It is challenging to comply with all these requirements, because of the inverse relationship between mechanical properties and disintegration time [24].

2. Manufacturing

2.1 Process

Manufacturing of ODFs is based mainly on established technologies such as tablet coating, solvent casting or hot-melt extrusion. Usually, a wide web is produced first, which is cut into the final dosage form afterwards. Consequently, the uniformity of the wide web is the key concern during manufacturing.

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2.1.1 Solvent casting

A wet coating mass is prepared first. Typical production steps are summarized in **Figure 1**. Solutions, emulsions and suspensions can be cast [2]. The film-forming polymers are dissolved in a solvent, either in pure water or in mixtures of water and organic solvents. Organic solvents could improve solubility of the API and shorten drying time [20]. Further excipients are added, followed by a homogenization step, resulting in a viscous solution. In the last step the API is added, for example, pre-dissolved or pre-dispersed in a liquid [18]. If suspensions or emulsions are cast, homogeneity has to be assured during the whole casting process. Particle size can be a critical factor. Particles > 250 µm can accumulate in the fluid flow path and cause scratches on the surface of the film [25]. De-aeration of the coating mass is achieved by continuous stirring and application of a vacuum [1,19].

The coating mass is cast as a wide web onto a single belt or a release coated substrate called intermediate liner [2]. The adjusted wet film thickness determines the drug content of the final strip [19]. The wet film is conveyed through an oven for the removal of process solvents and subsequently rolled on itself for intermediate storage and transport (jumbo roll) [2,19]. The jumbo roll is cut into smaller daughter rolls of variable width, which are finally punched or cut into the desired size (**Figure 1**). The intermediate liner is removed and the films are packaged individually.

Some factors are critical. Segregation or sedimentation should not occur in the coating mass [25]. The intermediate liner has to be chosen carefully. The film should show a sufficient adhesion to the liner but has to be removable at the end of the process [1]. During drying, it is important to avoid the so-called ripple effect. Coming into contact with hot dry air, the process solvents can evaporate immediately, leaving a thin dry polymer skin on the surface of the film. This seals the wet casting solution beneath the surface, impeding further evaporation. Raising temperature increases further the vapor pressure until the film surface rips. Surface building and rupturing occurs several times, leading to uneven film surfaces [26]. The end point of drying has to be controlled carefully [19,27]. If organic solvents are used, they have to be removed to acceptable levels [2]. A residual water content is necessary to obtain flexible films [19]. Nevertheless, high water content can lead to tacky films. Particularly if the drug was partly dissolved in the coating mass, crystal growth during the drying process and storage can affect content uniformity [3,28]. Possible variations of the basic process are semi-solvent casting or introducing gas bubbles to shorten disintegration time [29].

Manufacturing of films is very flexible, because various strengths can be cut out of one jumbo roll using different film sizes (**Figure 1**). Usually content uniformity is in the magnitude of 1 – 2% [2]. Therefore, solvent casting is commonly used for the manufacturing of ODFs. Nevertheless, the drying step is energy consuming. Problems may occur with residual solvents and instability of the API or flavors in the final products [18].

2.1.2 Hot-melt extrusion

Hot-melt extrusion has been proposed as a solvent-free manufacturing process for ODFs. The API is blended with excipients in solid-state. The blend is heated and pressed through a slot nozzle to a web, which is cooled down and cut to film size [23,30]. Recently, another method was introduced using hot-melt extrusion and spherical dies. The thin web is prepared by using a cooled roll [31].

Extrusion surely has some advantages over solvent casting, such as lack of solvents and drying. However, the melting process may affect API, flavor or polymer stability [2,18,20]. Yet, the main problem seems to be the lack of suitable polymers [18]. Cilurzo *et al.* compared hot-melt extrusion with solvent casting with maltodextrin as the main polymer. To obtain mechanically stable and non-tacky films by means of hot-melt extrusion microcrystalline cellulose had to be added, which affected disintegration time and mouth-feel substantially [23]. Hot-melt extrusion may be suitable for the manufacturing of sustained release films or patches, but achieving the required small thickness and short disintegration time for ODFs still seems to be impossible with current techniques.

2.1.3 Others

For the rolling method a paste-like or highly viscous material is rolled onto a plane carrier. To obtain a paste-like texture a solvent is necessary, which has to be removed in a following drying step [29]. Yang *et al.* described a method using three rollers. The coating mass is metered on the first roll, which determines the coating thickness. The mass is transferred to a second roller, which conveys the mass on an immediate liner transported by a third roll [32].

Spraying of a drug-loaded solution or suspension onto a plane carrier could be another alternative for film forming. A multilayer film is described in the patent literature. One layer is produced, for example, by a solvent casting method; the second layer is sprayed onto the first as suspension or by electrically charging a powder mixture including the API [33].

Electrostatic spinning is gaining popularity for pharmaceutical applications. Thin polymer fibers are produced by applying a high electric field on a drug-loaded polymer solution. Solid dispersions can be obtained, which may improve the solubility of poorly soluble drugs [34]. A high voltage is applied to a liquid droplet, so that electrostatic repulsion overcomes the surface tension and the droplet is stretched. At a critical point a liquid jet is ejected from the surface. This jet is drawn by electrostatic forces between two electrodes. The solvent evaporates rapidly. The resulting nanoscale fibers form a non-woven web on a collector [35]. Nagy *et al.* [35] and Yu *et al.* [34] produced electrospun API-loaded webs for fast release and compared them with cast films. Owing to the high surface area, dissolution time is improved.

2.2 Packaging

As ODFs are sensitive to moisture, unpacked storage should be avoided [19]. Usually ODFs are sealed individually in

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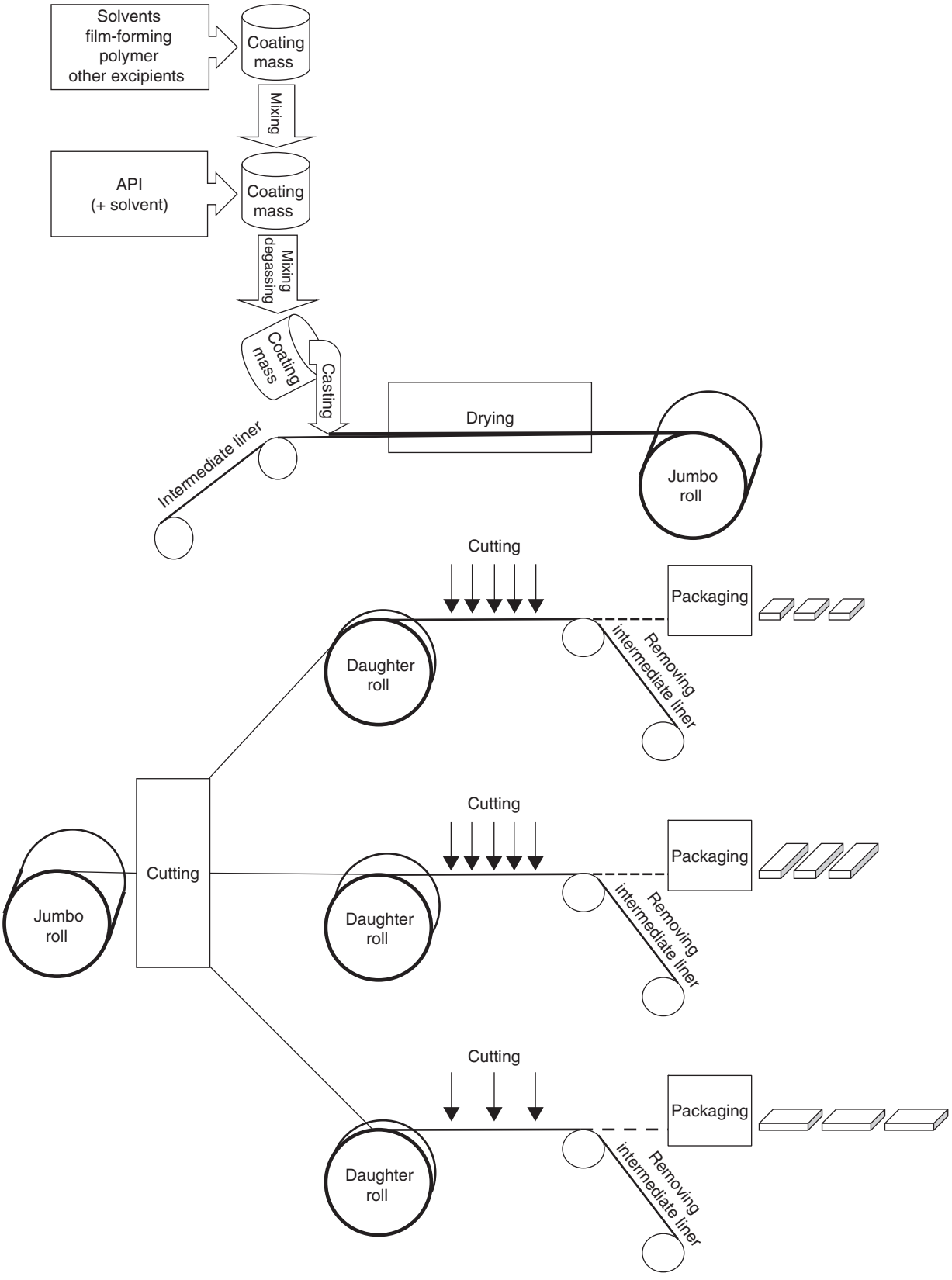

Figure 1. Manufacturing of orodispersible films of varying size.
API: Active pharmaceutical ingredient.

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pouches [1]. Packaging materials providing a moisture barrier are required. Visual inspection by automatic systems would be possible as in-line in-process control; unit weight variation could be measured off-line [1]. Multi-dose and single-dose packaging is possible, but single packages should be preferred to avoid accidental overdosing by films sticking together. A roll dispenser with a continuous film, which can be cut individually into desired sizes (which equals individual dosing), provides new opportunities for personalized medicine [36,37].

Advanced packaging technologies such as the Rapidcard® (Labtec GmbH), having the same size as a credit card with three films on each site, support the idea of an ideal take-away medicine [38]. Some examples for ODFs and different packaging technologies are given in **Figure 2**.

Child-resistant and senior-friendly packaging should be taken into account. To meet industry regulations, necessary information can be printed directly onto the film before packaging [39].

2.3 Ingredients

A typical ODF contains [29]:

- API 1 – 30%
- water-soluble film-forming polymers 40 – 50%
- plasticizers 0 – 20%
- fillers, colors, flavours, and so on, 0 – 40%.

As ODFs are an appropriate dosage form for children and the elderly, excipients should be carefully selected regarding safety to protect them from hazards [40].

2.3.1 *Active pharmaceutical ingredient*

The API can be incorporated into the films as particles or molecularly dispersed/dissolved. Particularly for dispersed APIs, particle size, particle size distribution and polymorphism become critical quality attributes. It is well known that these factors may affect solubility, rate of dissolution and ultimately bioavailability. As drug load is limited, high potency low-dose drugs are preferred [1]. Maximum drug load depends on the solubility of the API and/or its compatibility with the excipients [41]. A critical drug load can result in recrystallization or excessive influence on mechanical or disintegration properties of the films [3,23,28]. Typically, drug load is limited to a maximum of 25 mg. Gas-X® films (Novartis Consumer Health, Basel) contain a surprisingly high loading of 62.5 mg simethicone.

Other challenges may arise from bad API taste (see below), limited API stability resulting from manufacturing conditions or the residual water content of the films as well as potential buccal permeability if only gastrointestinal absorption is targeted.

2.3.2 *Film-forming polymers*

Film-forming polymers are essential excipients for ODFs. Numerous polymers have been proposed in the literature. Yet, the selection remains challenging. Although the films should dissolve as fast as possible in the oral cavity, mechanical properties have to remain sufficient for handling, packaging and storage [24].

Polymer properties depend on their molecular mass. As a general rule, low-molecular-mass polymers dissolve quicker, whereas a higher molecular mass results in better mechanical properties [24,29,41]. Mishra and Amin compared various grades of hypromellose with increasing molecular mass (E3 < E5 < E15). They concluded that E3 quality is superior to E5 and E15 grades for the manufacturing of cetirizine hydrochloride ODFs [21]. Dinge and Nagarsenker preferred E5 over E3 and E15 for the formulation of triclosan ODFs [42]. Cilurzo *et al*. investigated the impact of maltodextrin molecular mass on film properties. Films made of maltodextrin with a high molecular mass were stiffer than films made of maltodextrin with a lower molecular mass. They showed a higher tensile strength, a higher elastic modulus and a lower elongation at break. Further, they were less sticky than the films made of maltodextrin with a lower molecular mass [43].

The viscosity of the coating mass increases with increasing polymer molecular mass [24]. Viscosity must be high enough to prevent sedimentation of the drug in the coating mass but not too high to avoid problems during mixing or during coating by poor spreadability [1]. To achieve the desired film properties, often combinations of different polymers or different molecular masses of the same polymer are used [24].

Cellulose derivates, polyvinyl alcohols and pullulan are commonly used. Low viscosity grades of hypromellose, hyprollose or carmellose are typically used cellulose derivates [27,44,45]. As pullulan, a linear polysaccharide of α-1,6-linked maltotriose, is quite expensive, efforts have been made to replace it in parts by using starches [19]. Further suggested polymers are macrogols, sodium alginate, gelatine and pectin. As pectin dissolves slowly, it is more suitable for sustained-release films [46]. Sharma *et al*. combined hypromellose with a cationic copolymer based on dimethylaminoethyl methacrylate, butyl methacrylate and methyl methacrylate (Eudragit® E PO) to prepare valdecoxibe ODFs [47]. Ali and Quadir prepared ODFs using combinations of various high-molecular-mass povidones and synthetic copolymers of macrogol-polyvinyl alcohol (Kollidon®, Kollicoat®) [48].

Kulkarni *et al*. compared different film-forming polymers and combinations thereof. Pullulan, polyvinyl alcohol, povidone, gelatine, a copolymer of ethyl acrylate, methyl methacrylate and a low content of methacrylic acid ester with quaternary ammonium groups (Eudragit® RL 100), various grades of hypromellose and combinations with guar gum, xanthan gum or carrageenan were investigated regarding their film-forming capacity, appearance and disintegration time [49].

Medicinal carbon films were derived from carmellose, hypromellose or sodium alginate [50]. Films containing caffeine were made from several types of carmellose and

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Figure 2. Examples for different marketed orodispersible films and packaging variants.

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hypromellose, sodium alginate and a synthetic copolymer of macrogol-polyvinyl alcohol (Kollicoat® IR). Hypromellose films turned out to be the most appropriate because of the fast dissolution and the homogenous API distribution within the films [51].

Cilurzo *et al*. demonstrated that maltodextrins are suitable for manufacturing ODFs by both solvent casting and hot-melt extrusion [23,52]. A combination of maltodextrin and hypromellose was optimized by Patel *et al*. for ondansetron ODFs prepared by solvent casting [53].

As several ODF formulations are patent protected by pharmaceutical drug manufacturers, Roquette offers LYCOAT® NG73, a patent-free granular hydroxypropyl starch polymer specifically designed for ODFs. El-Setouhy and El-Malak compared it with hypromellose, hyetellose and polyvinyl alcohol [54].

For the development of sustained-release films or mucoadhesive films, polymers such as polycarbophil or polyacrylic acid could be added to the formulation [20,55,56].

2.3.3 *Plasticizers*

The addition of a plasticizer is often necessary to obtain flexible, non-brittle ODFs. Glycerol, propylene glycol, sorbitol, low-molecular-mass macrogols, phthalates, citrates or combinations thereof are commonly used [3,18,21,54,57].

As ODFs still have a relatively high water content after drying, water itself acts as plasticizer [27]. Plasticizers interact with the film-forming polymers by lowering their glass transition temperature and thereby improving plasticity and elasticity of the resulting films [18,27]. Most of them have more effects that have to be considered, for example, sorbitol is also used as sweetener. Plasticizers may affect solubility of the API and drug absorption [18]. High concentrations of plasticizers may cause an impaired moisture resistance, resulting in stability problems or tacky films [23,46]. Macrogol 400 as well as the esters of citric acid are inappropriate for plasticizing maltodextrin films because of the lack of miscibility. Increasing the content of glycerol or propylene glycol in maltodextrin ODFs decreased the elastic modulus and increased the elongation at break. Concentrations higher than 18% w/w caused blooming phenomena and stickiness. The taste of glycerol plasticized ODFs was preferred over the taste of propylene glycol plasticized films [23].

Mashru *et al*. used a 3^3 full factorial design to optimize ODF composition with polyvinyl alcohol as polymer, glycerol as plasticizer and mannitol as filler. A higher amount of polyvinyl alcohol resulted in higher tensile strength, lower drug release and higher overall scoring. The addition of glycerol resulted in lower tensile strength, lower drug release and higher overall scoring. A higher amount of mannitol resulted in lower tensile strength, higher drug release and higher overall scoring [57].

2.3.4 *Taste masking*

Many APIs have an unpleasant taste. The use of taste-masking excipients is often essential. Depending on the physical state of the API in the film (dissolved or dispersed) and its solubility in saliva, different taste-masking techniques have to be used. They range from the simple addition of flavors, sweeteners and bitter-blockers to particle coating, encapsulation or complexation with ion exchange resins, where the larger particles may cause scrapes during casting and may

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give an unpleasant gritty mouth-feel [1,2,23,24]. Brown showed that taste and mouth-feel are more important for the acceptability of orally disintegrating dosage forms than short disintegration times [58].

All drugs that are even partly soluble in saliva will be accessible to taste sensation. Suitable sweeteners include natural molecules such as glucose, maltose or stevioside, artificial sweeteners such as acesulfame-K or saccharin-Na, dipeptide-based sweeteners such as aspartame and protein-based sweeteners such as thaumatin [18]. The sweetness has to be perceived on the tongue before onset of the bitter taste and during the bitter aftertaste sensation. Therefore, often combinations of different sweeteners and flavors are incorporated in ODFs. Mishra and Amin found a combination of citric acid and passion fruit flavor to be suitable for complete taste masking of cetirizine hydrochloride ODFs [21]. Dinge and Nagarsenker incorporated eugenol, aspartame and xylitol in triclosan ODFs [42]. Polyhydric alcohols such as xylitol are sweet and can improve mouth-feel further owing to a cooling effect [42,59]. Sprinkling flavors or sweeteners on the film surface has been mentioned as another improvement [24].

Other techniques for taste masking include complexation with cyclodextrins or application of insoluble salts of the API. All commonly applied taste-masking techniques can greatly affect maximum drug load [1]. Further, stability, disintegration time and mechanical properties may be influenced by the type and amount of taste-masking agents. Therefore, a taste-masking system has to be developed carefully for each individual drug. In particular, a 'too pleasant', 'candy-like' formulation should be avoided in the therapy of pediatrics [60]. Overdosing is a potential risk for children, who may see ODFs as sweets or breath-fresheners.

2.3.5 *Others*

Further excipients for ODFs include fillers, colors, opacifiers, cooling agents, lubricants or antitacking agents, preservatives and stabilizers [1,14,18]. Saliva-stimulating agents such as citric acid are reported to enhance salivation and shorten disintegration time [19]. To increase mucoadhesion, appropriate polymers can be added [55]. If absorption through the oral mucosa is desired, penetration enhancer and buffering agents may improve buccal bioavailability [61]. Enzyme inhibitors can prevent drug degradation [62].

For some ODFs solubility enhancers may be necessary [62]. Surfactants can improve spreading of the coating mass on the intermediate liner as well as wetting by saliva in the oral cavity [15,29]. Stabilizers and thickening agents may be necessary to prevent particles from sedimentation. Natural gums such as xanthan or guar gum can improve viscosity and film-forming capacity [19,20,42].

3. Characterization

ODFs are not listed in one of the pharmacopoeias yet. Besides typical parameters such as content, content uniformity and impurity profile, disintegration or dissolution properties and mechanical properties are investigated to ensure a robust manufacturing process and a good patient compliance. Many common tests for solid oral dosage forms such as orodispersible tablets are not transferable to ODFs. Having to comply, for example, with content specifications for conventional oral dosage forms but being manufactured with a technology for transdermal patches, which are allowed for broader content specifications, is one of many issues requiring clarification, soon. **Table 1** gives an overview on possible pharmacopoeial and alternative methods.

3.1 Mechanical properties

Determination of thickness and area weight are routine tests. A typical film thickness ranges from 12 to 100 µm [63]. Further, acceptable mechanical parameters ensure flexibility and robustness of the films during manufacturing and handling. As the USP describes only a tensile strength test for surgical sutures and patches, technical regulations from other industries such as the plastic industry can be used as templates. Tensile tests according to the ASTM International Test Method for Thin Plastic Sheeting (D 882-02) or tests described in the DIN EN ISO 527-1 and 527-3 regulations can be utilized [3,23,64,65].

For a tensile test the ODFs are held between two clamps and pulled. The force and elongation are measured until breakage. The following parameters can be calculated [3,14,21-23,54]:

$$\sigma_{TS} = \frac{F_{max}}{A} \quad (1)$$

$$E = \frac{F}{A} \times \frac{1}{\varepsilon} \quad (2)$$

$$\%\varepsilon = \frac{\Delta L}{L_0} \times 100 \quad (3)$$

where σ_{TS} is tensile strength, F_{max} is maximum load, A is initial cross-sectional area of the sample, E is elastic modulus, which is Young's modulus, F is force at corresponding strain, ε is corresponding strain, $\%\varepsilon$ is elongation at break (%), ΔL is increase in length and L_0 is original length.

Further parameters such as tear resistance or tensile energy to break have been mentioned [19,23,59]. An ideal ODF should have moderately high tensile strength, high elongation at break and strain, but a low elastic modulus [14,22,57].

For measuring the folding endurance the films are repeatedly folded at the same position until they break [53]. Cilurzo *et al.* determined film flexibility by adapting the ASTM bend mandrel test D 4338 – 97 [23]. Further tests are the dryness/tack test according to the ASTM paint testing manual, puncture and shear tests, vertical strength and stickiness determination [19,23,50,59,66].

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Table 1. Pharmacopoeial and alternative characterization methods.

Property	Pharmacopoeial method		Alternative method	Ref.
	USP 34 NF 29	Ph.Eur. 7.0		
Appearance and API distribution	<776> Optical microscopy <1181> Scanning electron microscopy	2.9.37. Optical microscopy	Visual inspection Near-infrared chemical imaging	[3,44,45,49]
Content uniformity	<905> Uniformity of dosage units	2.9.5. Uniformity of mass of single-dosage preparations 2.9.6. Uniformity of content of single-dose preparations 2.9.40. Uniformity of dosage units		[13,23,42,52,70]
Crystallinity and Glass transition temperature	<695> Crystallinity <696> Crystallinity determination by solution calorimetry <891> Thermal analysis <941> X-ray diffraction	2.2.34. Thermal analysis 2.9.33. Characterization of crystalline and partially crystalline solids by XRPD		[14,23,28,42,44,56,57]
Disintegration	<701> Disintegration	2.9.1. Disintegration of tablets and capsules	Contact angle measurement Thermomechanical analysis of the swelling behavior Slide frame method Petri dish method Stainless steel wire mesh Swirling Swelling behavior Modified dissolution apparatus Modified disintegration tester Diffusion apparatus	[3,14,21,22,29, 45,50,51,69]
Dissolution	<711> Dissolution <724> Drug release <1088> *In vitro* and *in vivo* evaluation of dosage forms <1090> *In vivo* bioequivalence guidance <1092> The dissolution procedure: development and validation	2.9.3. Dissolution test for solid dosage forms 2.9.4. Dissolution test for transdermal patches 5.17.1. Recommendations on dissolution testing	FIP/AAPS guidelines EMA BE guideline Sinkers Stainless steel wire mesh Modified USP type 1 apparatus Continuous flow-through cell Fiber-optic sensor system Diffusion apparatus	[2,3,6,13,21,42,45, 47,53,57,70-72]
Water content and Hygroscopicity and Moisture uptake	<731> Loss on drying <921> Water determination	2.2.32. Loss on drying 2.5.12. Water-semi-micro determination 2.5.32. Water-micro determination 2.9.45. Wettability of porous solids including powders	Dynamic vapor sorption Determination of water uptake by weight	[22,42,44,45,51]

AAPS: American Association of Pharmaceutical Scientists; API: Active pharmaceutical ingredient; ASTM: American Society for Testing and Materials; BE: Bioequivalence; DIN EN ISO: Deutsches Institut für Normung, Europäische Norm, International Organization for Standardization; EMA: European Medicines Agency; FIP: International Pharmaceutical Federation; ICH: International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use; Ph.Eur.: European Pharmacopoeia; USP: United States Pharmacopoeia; XRPD: X-ray powder diffraction.

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Table 1. Pharmacopoeial and alternative characterization methods (continued).

Property	Pharmacopoeial method		Alternative method	Ref.
	USP 34 NF 29	Ph.Eur. 7.0		
Local tolerance	<1184> Sensitization testing		Animals and humans	[2,19,62]
Mechanical properties	<881> Tensile strength		ASTM D 882-02 ASTM D 4338-97 ASTM paint testing manual: dryness/tack test DIN EN ISO 527-1 and 527-3 Puncture and shear test Vertical strength Folding endurance Stickiness	[3,14,19,21,22,36,50,52, 54,57,59,66]
Microbiology	<61> Microbiological examination of non-sterile products: microbial enumeration tests <1111> Microbiological examination of non-sterile products; Acceptance criteria for pharmaceutical preperations and substances for pharmaceutical use	2.6.12. Microbiological examination of non-sterile products – microbial enumeration tests 5.1.4. Microbiological quality of non-sterile pharmaceutical preparations and substances for pharmaceutical use		
Mucoadhesion			Methods based, e.g., on a texture analyzer Mucosal tissues from animals	[22,55,62,73,74]
Permeation			Diffusion cell Franz cell Mucosal tissues from animals	[62,73,74]
Qualification and quantification of the API	<197> Spectrophotometric identification tests <851> Spectrophotometry and light scattering <1119> Near-infrared spectrophotometry <1120> Raman spectrophotometry	2.2.24. Absorption spectrophotometry, infrared 2.2.40. Near-infrared spectrophotometry 2.2.48. Raman spectrometry		[21,52,78-80]
Residual solvents	<467> Residual solvents	2.4.24. Identification and control of residual solvents 5.4 Residual solvents		[25]
Stability	<1150> Pharmaceutical stability		ICH Guidelines Q1 A – F	[13,16,50,62,70]
Taste			Dissolution test Volunteer taste panel Animal preference test Taste-sensing systems	[23,42,52,75,77]
Viscosity	<911> Viscosity	2.2.8. Viscosity 2.2.10. Viscosity – rotating viscosimeter method		[48]

AAPS: American Association of Pharmaceutical Scientists; API: Active pharmaceutical ingredient; ASTM: American Society for Testing and Materials; BE: Bioequivalence; DIN EN ISO: Deutsches Institut für Normung, Europäische Norm, International Organization for Standardization; EMA: European Medicines Agency; FIP: International Pharmaceutical Federation; ICH: International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use; Ph.Eur.: European Pharmacopoeia; USP: United States Pharmacopoeia; XRPD: X-ray powder diffraction.

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3.2 Disintegration and dissolution

ODFs are developed to dissolve rapidly in the mouth. Therefore, disintegration and dissolution tests have to be performed. For orodispersible tablets or lyophilisates, a disintegration time of < 3 min using the pharmacopoeial disintegration tester is specified in the European Pharmacopoeia and a disintegration time < 1 min is required in the guidance for industry by the FDA [67,68]. ODFs should disintegrate rapidly *in vivo* as well. As a disintegration tester does not mimic the physiological conditions in the oral cavity, it is inappropriate for orally disintegrating dosage forms in general and particularly for ODFs. Nevertheless, it is often used. Typical disintegration times range from 5 to 30 s [2]. Efforts have been made to simulate the *in vivo* disintegration, such as contact angle measurements and thermomechanical analysis of the swelling behavior of the films [3]. Further simple tests such as the slide frame method and the Petri dish method have been described in the literature. These tests deal with a small volume of disintegration medium adapting the small volume of saliva in the mouth. A slide frame holding an ODF is laid on a Petri dish and a drop of distilled water is added. Time until the drop forms a hole in the film is measured. For the Petri dish method the ODFs are placed on the surface of 2 ml distilled water in a Petri dish and time for complete dissolution is recorded [14,51]. Mishra and Amin placed the ODFs on a stainless steel wire mesh containing 10 ml of distilled water. Disintegration time was defined as the time until the film breaks [21]. In another test disintegration is determined in a glass dish with 25 ml distilled water. The dish is swirled every 10 s and the time recorded when the film starts to break [29]. Peh and Wong described the measurement of swelling behavior [22].

Bi *et al*. developed a disintegration test for orodispersible tablets using a modified dissolution apparatus, which might work for ODFs as well, although an unphysiologically high volume of dissolution medium is applied [69]. Sakuda *et al*. used the disintegration tester in a modified set up. The film is clipped onto the arm of the tester without using its basket. Then the film is dipped in and out of the medium [50].

Boateng *et al*. measured the hydration of films in a diffusion apparatus. The films are placed on a stainless steel mesh and wetted on the bottom by contact with distilled water. Hydration is observed by a digital camera until the formulation completely disappears [45].

Most of the test methods used are sufficient to discriminate between different film formulations and may be useful for quality control. However, none of them imitates the physiological conditions sufficiently. In particular, the mechanical force of the tongue acting on the films is not simulated.

In most cases distilled water is used as the disintegration medium. There is no simulated saliva described in the European Pharmacopoeia. Phosphate buffer pH 6.0 is recommended for the dissolution test for medicated chewing gum and was therefore used for the dissolution test for ODFs as well by Garsuch and Breitkreutz [3]. Other groups used phosphate buffers between pH 1.2 and pH 6.8, as recommended, for example, in the EMA guideline on investigation of bioequivalence [6,13,53,57,70]. If the drug is molecularly dispersed in the film, the limiting factor for drug dissolution is the disintegration of the film. Therefore, for fast-dissolving films a disintegration test may be used instead of the dissolution test. This was recommended for orodispersible tablets in the FIP/AAPS guidelines for dissolution and may be transferred to ODFs [71]. If drug particles are dispersed in the film to be swallowed after film disintegration, solubility and dissolution rate of the drug particles are the limiting factors. In this case a paddle or basket apparatus can be used. For quality control a single point measurement may be sufficient to assure complete drug release for immediate-release systems [71]. As the films tend to float, sinkers may be necessary [2]. Stainless steel wire meshes or the paddle-over-disk apparatus were recommended to prevent the films from floating as well [21,47,57].

Dinge and Nagarsenker used 20 ml of phosphate buffer pH 6.4 as medium in a 50 ml glass beaker. They utilized only the shaft of the USP type 1 apparatus without the basket attached to it for agitation [42]. Hughes and Gehris introduced a new method of characterizing the buccal dissolution of drugs developed by Rohm and Haas. It consists of a single, stirred, continuous flow-through cell with a volume of 10 ml. Finely disintegrated particles were removed from the test vessel during testing by a dip probe to simulate swallowing [72].

Garsuch and Breitkreutz compared manual sample withdrawing with automatic sample withdrawing by a peristaltic pump and a fiber-optic sensor system. The fibre-optic sensor system makes possible online measurements at high sample rates per minute and may be very helpful for dissolution measurements of fast-releasing dosage forms. They observed a square root kinetic release profile for caffeine films [3]. Patel *et al*. assumed a zero-order kinetic of a film formulation of ondansetron [53]. Boateng *et al*. used their diffusion apparatus as described above for determination of dissolution. They fitted their dissolution profiles of paracetamol films to the Korsmeyer-Peppas, Highuchi equation, zero- and first-order equations. They generally yielded sustained release profiles dependent on polymer content [45].

For the evaluation of sustained-release films or buccal patches, permeation studies may be useful. Different *in vivo* and *in vitro* models have been investigated to quantify permeation, including diffusion cells such as the so-called Franz cells. Usually mucosal tissue from animals is used as surrogates for human mucosa, for example, porcine mucosa [62,73,74].

The biopharmaceutics of the API after disintegration of the dosage form are discussed in detail in Section 4.

3.3 Taste

Taste is one of the critical features of ODFs influencing patient acceptability. Different approaches for taste assessment

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have been made. Dissolution testing with pharmacopoeial dissolution testers is possible, if saliva-resistant coated particles are incorporated in the ODFs. Methods and suitable dissolution media have to be validated carefully [75]. Dissolution testing is not suitable if taste masking is based on flavors and sweeteners or complex formers. In this case volunteer taste panels have to be employed [23,42]. Animal preference tests have been mentioned but may be potentially invalid [76].

There are some disadvantages of using human taste panels. The main problem is the ethical concern, especially for toxic drugs or for drugs intended for pediatric use. Further, there is often a lack of objectivity. Taste preferences depend on ethnicity and age. Younger people favor sweeter and exciting flavors, whereas the elderly may prefer traditional flavors, such as mint [58]. A formulation preferred by adults may be rejected by children, a European taste by the US.

Taste-sensing systems, so-called electronic tongues, have been developed as an *in vitro* alternative. A recent overview on these systems in the pharmaceutical area is given by Woertz *et al.* [77]. Cilurzo *et al.* evaluated the suppression of bitterness in a sodium diclofenac ODF by a taste-sensing system and concluded that these systems could assist or even replace sensory evaluation [52]. However, as grittiness and mouth-feel also play a major role in patient's acceptability, human taste panels cannot be replaced completely.

3.4 Others

Other methods for characterization and quality control of ODFs include viscosity measurement of the coating mass, content uniformity and determination of residual solvents [13,23,25,70]. Further, the appearance of the films is evaluated by visual inspection, optical microscopy and scanning electron microscopy [44,45]. Garsuch and Breitkreutz found caffeine recrystallization in ODFs varying between the upper and lower surface by scanning electron microscopy, X-ray diffraction and near-infrared chemical imaging [3].

Near-infrared spectroscopy and Raman spectroscopy are suitable technologies to qualify and quantify APIs within the films [78,79]. Further, Fourier transformation infrared spectroscopy has been used [21,23]. Tumuluri *et al.* investigated online measurements with Raman spectroscopy and suggested its suitability as a process analytical tool [80].

Differential scanning calorimetry, thermomechanical analysis and X-ray diffraction are used to investigate crystallinity and glass transition temperature [23,42,44,56,57]. Gaisford *et al.* monitored crystallization of drugs from ODFs with isothermal calorimetry [28].

Hygroscopicy and residual water content are investigated by dynamic vapor sorption or by weight [44,51,54]. Further, microbiological studies and stability tests should be investigated regarding common guidelines [13,18,42,51,70].

For the development of sustained-release films or oral patches, some tests on bioadhesion can be helpful [22,55,62,73,74]. Local oral mucosal irritation studies in animals and humans should be investigated as well [2,16,19,62].

4. Biopharmaceutical aspects

Oral mucosa is described in detail elsewhere [62,73,74,81]. The mucosa of the gingival (gums) and hard palate is known as the masticatory mucosa and is keratinized. The mucosa of the floor of the mouth and the buccal mucosa are known as lining mucosa and are non-keratinized [73]. In general, the permeability of oral mucosa is somewhere between that of the epidermis and the intestinal mucosa. The permeability of the oral mucosa decreases in the order sublingual to buccal to palatal [74]. The application of oral films is possible on the tongue, the cheeks, the hard palate or sublingual. Usually the side of application for ODFs is the tongue, and for sustained release and mucoadhesive patches the mucosa of the cheeks. Sublingual application is possible as well [57]. Local delivery of triclosan has been described as well [42].

If the drug penetrates through the oral mucosa, it is absorbed into the reticulated and jugular veins and then drained into the systemic circulation. Hepatic first-pass metabolism is prevented [81]. Therefore, this application site may improve bioavailability and reduce unwanted side effects. Absorption through the mucosa can be either transcellular or paracellular, whereby lipophilic drugs mainly penetrate through the transcellular route, whereas more hydrophilic drugs penetrate through the paracellular route, but usually both routes coexist [62,81].

An ideal API for absorption through oral mucosa should be soluble in the saliva but non-ionized in the pH of the saliva, which ranges from 5.5 to 7 depending on flow rate [74,82]. Further, a moderate molecular mass facilitates absorption [82]. As ODFs have a very short residence time in the oral cavity, absorption through the oral mucosa will not play an important role in most cases. Some APIs may be absorbed in part, whereas most of the drug is absorbed after swallowing and transition of the gastrointestinal tract, which leads to complex pharmacokinetic profiles [20]. Selegiline is an example for an improvement of bioavailability by administering an orally disintegrating dosage form. It is absorbed pre-gastrically from a Zydis® freeze-dried formulation. First-pass metabolism can be avoided. To yield similar plasma concentrations as conventional selegiline hydrochloride tablets, the dose can be reduced to one-eighth in the oral lyophilisates [83,84]. A similar effect can be expected delivering selegiline as ODF.

Most ODFs on the market contain the API as particles, which are swallowed after disintegration of the film. Therefore, bioavailability often is approximately the same as immediate release or orodispersible tablets. Bioequivalence between Rapidfilm® and an oral lyophilisate, both containing ondansetron, was demonstrated in a randomized two-way single-dose crossover study with 24 healthy volunteers [17]. Risperidon as before, it is HEXAL® SF Schmelzfilm was shown to be bioequivalent to film-coated tablets [85]. Comparable plasma level-time profiles for ODFs and tablets (dissolved in distilled water) with tineptine sodium were obtained in a bioavailability study

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with rabbits [54]. Shimoda *et al.* used a bioavailability study with rats to compare dexamethasone ODFs with a suspension [70]. Nishimura *et al.* could not observe significant differences in pharmacokinetic parameters after administration of prochlorperazine ODFs or solution to rats but did not fulfil the FDA approval for bioequivalence, because the 90% confidence interval of the ratio of the means of C_{max} and AUC between the test drug and the reference drug was not within the required range [13].

5. Marketed products and future potential

Since Listerine® PocketPaks were introduced as breath-fresheners, ODFs have gained popularity, especially in North America. Several OTC products with APIs have been available on the US market for years. Novartis, Basel, celebrated great success with the introduction of ODFs of old brands such as Gas-X® and Triaminic®. Vitamins, nutraceuticals and a lot of other lifestyle products have been commercialized, also homeopathic films are available. Some examples are given in **Tables 2** and **3**. The first prescription products are already available or will be available soon, and since 2010 also in Europe. As the breath-fresheners are less popular in Europe, pharmacists have to educate patients in the handling of ODFs. Reckitt Benckiser Pharmaceuticals, Slough received approval from the FDA for Suboxone® sublingual films containing buprenorphine and naloxone for maintenance treatment of opioid dependence. Prescription use is limited to physicians certified under the Drug Addiction Treatment Act 2000 [86].

The market for fast-disintegrating dosage forms including ODFs, fast-disintegrating tablets and lyophilisates is growing fast. Between 2003 and 2007, > 50 different ODF brands were launched in the US and Canada; a further increase is assumed [87]. For companies, the ODF technology is suitable for life cycle management and extending patent protection of branded APIs [2]. Several companies such as Labtec GmbH, MonoSol Rx, Hughes Medical Corp. or ODF Technologies offer platform technologies and development of ODFs ready for licensing. ODFs will not be the solution for all problems, because drug load is limited and pharmacokinetics is complicated. Nevertheless, they will compete with orodispersible tablets, immediate-release dosage forms and oral lyophilisates in future. Gavaskar *et al.* concluded that many pharmaceutical companies are switching their product franchise from orally disintegrating tablets to ODFs [59]. Various APIs are in the pipeline for ODFs, for example, for CNS applications such as Parkinson's disease, depression, schizophrenia or Alzheimer's disease. Further potential APIs include loperamide, oxycodon, fentanyl, triptans or sildenafil [4]. Nevertheless, future decisions of the authorities on equivalence of ODFs and orally disintegrating tablets as well as other dosage forms will influence the market [63].

Johns Hopkins University in Baltimore developed a film for administering a vaccine [88]. Incorporation of pollen and antigens may improve therapy of allergies. Animal treatments may be another market in future as well [2]. Meathrel and Moritz mentioned the benefit of ODFs for *in vitro* diagnostics. Reagents incorporated in films improve manufacturing, handling and stability of *in vitro* diagnostics [89].

6. Conclusion

OTCs in ODF formulations have been available in the US for years; the first drug-loaded films have entered the prescription sector. ODFs are a very suitable dosage form for children and the elderly, because they are easy to swallow and involve no risk of choking. They usually consist of film-forming polymers, plasticizers and further excipients, for example, for improvement of taste. The main disadvantage of ODFs is the limited drug load. ODFs are commonly manufactured by solvent casting. Basic characterization methods are determination of mechanical properties and disintegration behavior. Validated methods and pharmacopoeial specifications are still lacking.

7. Expert opinion

ODFs have gained popularity during the past few years. The market will probably grow further. If the novelty effect diminishes over time, success may slow down, especially for OTC products. Nevertheless, for special patient groups ODFs are beneficial and can enhance compliance. In particular, ODFs will be marketed in future for geriatric and pediatric patients as well as for patients with neurological diseases, mainly as prescription drugs.

Solvent casting is the manufacturing method of choice at the moment, but hot-melt extrusion could be an interesting alternative. Finding suitable polymers for hot-melt extrusion will be a focus of research. Focusing on the specific requirements of ODFs, further research has to be done regarding polymers, composition, manufacturing and quality control. As drug load is limited and taste masking is challenging, ODFs will not be the answer to all problems.

Manufacturing of ODFs is very flexible. Different dose strengths can be obtained easily. Therefore, suitable doses, for example for children, can be manufactured and small batch sizes realized in a cost-effective manner. Using a roll-dispenser, ODFs may also be a suitable dosage form for personalized medicine.

It is up to the authorities to publish a pharmacopoeial monograph as soon as possible to define ODFs and their quality requirements. Characterization and quality control should be standardized. Specifications at least for mechanical properties and disintegration time should be given. The development of suitable disintegration and dissolution tests for ODFs as well as for orodispersible tablets and lyophilisates mimicking their *in vivo* behavior is necessary.

For pharmaceutical companies, ODFs are an attractive option for life cycle management. They will compete with

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Table 2. Examples of marketed orodispersible films for systemic drug delivery.

Brand	Distributor	Active ingredients	Excipients
Benadryl® Allergy quick dissolve strips	McNeil-PPC	Diphenhydramine HCl	Acesulfame-K, carrageenan, FD&C blue No. 2, aluminum lake, flavors, glycerin, glycerol oleate, locust bean gum, medium chain triglycerides, polysorbate 80, povidone, propylene glycol, pullulan, sodium polystyrene sulfonate, sucralose, xanthan gum, edible ink
Gas-X® Thin Strips	Novartis Consumer Health	Simethicone	Modified corn starch, alcohol, FD&C blue No. 1, flavor, hypromellose, maltodextrin, menthol, macrogol, sorbitol, sucralose, titanium dioxide, water
Hyland's Cold Relief with Zinc 4 Kids™	Hyland's	Aconitum napellus 6X HPUS, allium cepa 6X HPUS, gelsemium sempervirens 6X HPUS, zincum gluconicum 2X HPUS	Cellulose gum, lactose, purified water, propylene glycol, honey, glycerine, microcrystalline cellulose
Pedia Lax® Quick Dissolve Strips	C.B. Fleet Company	Sennosides, standardized	Butylated hydroxytoluene, FD&C red No. 40, flavor, hypromellose, malic acid, methylparaben, polydextrose, macrogol, simethicone, sodium bicarbonate, sucralose, white ink
Risperidon HEXAL® SF Schmelzfilm	Hexal AG	Risperidone	Citric acid, glycerol, hypromellose, menthol, maltodextrin, microcrystalline cellulose, sucralose, titanium dioxide
Suboxone® Sublingual Film	Reckitt Benckiser Pharmaceuticals	Buprenorphine, naloxone	Macrogol, hypromellose, maltitol, acesulfame-K, lime flavor, citric acid, sodium citrate, FD&C yellow No. 6, white ink
Sudafed® PE Quick dissolve strips	McNeil-PPC	Phenylephrine HCl	Acesulfame-K, aspartame, carmine, carrageenan, edetate disodium, flavors, glycerin, glyceryl oleate, locust bean gum, maltodextrin, medium chain triglycerides, pectin, polysorbate 80, macrogol, pullulan, sodium hydroxide, sodium polystyrene sulfonate, xanthan gum, edible ink
Theraflu® Thin Strips multi symptom	Novartis Consumer Health	Diphenhydramine HCl	Acetone, alcohol, FD&C red No. 40, flavors, hyprolose, hypromellose, maltodextrin, microcrystalline cellulose, macrogol, pregelatinized starch, propylene glycol, purified water, sodium polystyrene sulfonate, sorbitol, sucralose, titanium dioxide

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Table 2. Examples of marketed orodispersible films for systemic drug delivery (continued).

Brand	Distributor	Active ingredients	Excipients
Theraflu® Thin Strips long acting cough	Novartis Consumer Health	Dextromethorphan HBr	Acetone, alcohol, dibasic sodium phosphate, divinylbenzene methacrylic acid copolymer, FD&C red No. 40, flavours, hyprolose, hypromellose, maltodextrin, microcrystalline cellulose, macrogol, pregelatinized starch, propylene glycol, purified water, sorbitol, sucralose, titanium dioxide
Triaminic® Thin Strips allergy	Novartis Consumer Health	Diphenhydramine HCl	Acetone, alcohol, FD&C blue No. 1, FD&C red No. 40, flavors, hyprolose, hypromellose, isopropyl alcohol, maltodextrin, microcrystalline cellulose, macrogol, pregelatinized starch, propylene glycol, purified water, sodium polystyrene sulfonate, sorbitol, sucralose, titanium dioxide
Triaminic® Thin Strips cold with stuffy nose	Novartis Consumer Health	Phenylephrine HCl	Acetone, alcohol, FD&C blue No. 1, FD&C red No. 40, flavors, hypromellose, isopropyl alcohol, maltodextrin, microcrystalline cellulose, macrogol, propylene glycol, purified water, sodium polystyrene sulfonate, sucralose, titanium dioxide
Triaminic® Thin Strips day time cold & cough	Novartis Consumer Health	Dextromethorphan HBr, phenylephrine HCl	Acetone, alcohol, FD&C blue No. 1, FD&C red No. 40, flavors, hypromellose, isopropyl alcohol, microcrystalline cellulose, polacrilin, macrogol, propylene glycol, purified water, sodium polystyrene sulfonate, sucralose, titanium dioxide
Triaminic® Thin Strips night time cold & cough	Novartis Consumer Health	Diphenhydramine HCl, phenylephrine HCl	Acetone, FD&C blue No. 1, FD&C red No. 40, flavors, hypromellose, maltodextrin, mannitol, macrogol, polypropylene glycol, purified water, sodium polystyrene sulfonate, sucralose, titanium dioxide
Zuplenz™	Strativa Pharmaceuticals	Ondansetron	Butylated hydroxytoluene, calcium carbonate, colloidal silicon dioxide, erythritol, hypromellose, monoammonium glycyrrhiuinate, peppermint flavor, macrogol, sodium bicarbonate, sucralose, titanium oxide, xanthan gum

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Table 3. Examples of marketed orodispersible films for local drug delivery.

Brand	Distributor	Active ingredients	Excipients
Chloraseptic® Sore Throat Relief Strips	Prestige Brands	Benzocaine	Butylated hydroxtoluene, corn starch, erythritol, FD&C blue No. 1, FD&C red No. 40, hyprolose, malic acid, menthol, monoammonium glycyrrhizinate, natural and artificial flavors, macrogol, sucralose
Listerine® Pocket Paks	Pfizer		Pullulan, menthol, flavors, aspartame, acesulfame K, copper gluconate, polysorbate 80, carrageenan, glyceryl oleate, thymol, eucalyptol, methyl salicylate, locust bean gum, macrogol, xanthan gum, FD&C green No. 3, FD&C yellow No. 6
Orajel® Kids Sore Throat Relief Strips	Church & Dwight Co.	Pectin	Glycerin, purified water, flavor, sucralose, menthol, cellulose gum, polysorbate 80, lecithin, acesulfame-K, FD&C red No. 40
Snoreeze Oral Strips	Passion for Life Healthcare	Peppermint oil, vitamin E, sodium hyaluronate, guar gum	Pectin, water, glycerin peppermint oil, cellulose, sorbitan stearate, polysorbate 60, tocopheryl acetate, menthol, aspartame, potassium sorbate, saccharin-Na, acesulfame-K, hyaluronic acid, guar gum, citric acid, FD&C blue No. 1

orodispersible tablets and lyophilisates in future, especially if their manufacturing is cost-effective. Up to now, approvals of ODFs from the governments were realized by bioequivalence studies in comparison with lyophilisates or immediate release tablets. Many pharmaceutical companies seem to avoid the development of ODFs with APIs, which may have an improved bioavailability because it would require specific clinical trials. Improvement of bioavailability may be interesting for mucoadhesive, sustained-release films rather than for ODFs. Mucoadhesive patches may be a suitable dosage form for administering macromolecular therapeutics such as proteins.

Although approved ODFs are bioequivalent to lyophilisates or immediate-release tablets, substitution is not allowed. Regulatory agencies seem to accept them as a different dosage form, taking the compliance aspect into account. Substitution of an ODF with an immediate-release tablet would lead to enormous problems for patients with swallowing difficulties. Substitution of an immediate-release tablet with an ODF is less critical.

The magnitude of variants of ODF technology and the advantages over conventional dosage forms promise more applications and more marketed products with ODFs in the near future.

Declaration of interest

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