

How to assess orodispersible film quality? A review of applied methods and their modifications

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In recent years, there has been a tendency toward creating innovative, easy to use and patient-friendly drug delivery systems suitable for every consumer profile, which would ensure safety, stability and acceptability of a drug. One of the relatively novel and promising approaches is the manufacture of orodispersible films (ODFs), which is an upcoming area of interest in drug delivery. They are defined as polymer thin films that disintegrate in the oral cavity within seconds, without drinking water or chewing, and eliminate the risk of choking. Gaining special usefulness in therapies of children and the elderly, ODFs seem to fill the gap in the range of preparations available for these groups of patients. As no detailed monography of ODFs including testing methods and uniform requirements has been presented in any of the pharmacopoeias to date, the aim of this article is to give an overview of the applied testing methods, their modifications and innovative approaches related to ODF quality assessment.

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INTRODUCTION

Oral application is the most acceptable, noninvasive and widely used route of drug administration (1). Various dosage forms for oral drug delivery: syrups, suspensions, drops, tablets, capsules or chewing gums are available (2). However, each of them raises some problems related to their administration and dosing (3). Moreover, several groups of patients have considerable swallowing difficulties, dysphagia or fear of choking, which hamper their therapy as well as complicate patient compliance and adherence (4–9). In order to eliminate difficulties exhibited by traditional solid oral dosage forms and meet the expectations of today's patients, more and more formulations appear as orodispersible drug delivery systems, which include orodispersible tablets (ODTs) and orodispersible films (ODFs) (10, 11). Use of orodispersible formulations avoids the risk of choking, which may occur in the case of conventional tablets or capsules (5). It is also suitable for patients

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Table I. Examples of ODFs available as OTC or Rx products in chronological order

Registration year	Product	Reference
2001	Listerine PocketPaks [®] Oral Care Strips (OTC)	17, 24, 25, 27
2004	Chloraseptic [®] Sore Throat Relief Strips (OTC), Triaminic Thin Strips [®] (OTC), Theraflu [®] Thin Strips (OTC)	24, 25
2005	Sudafed [®] Pe Quick Dissolve Strips (OTC)	25
2006	Gas-X Thin Strips [®] , Benadryl [®] Allergy Quick Dissolve Strips (OTC)	25, 28
2008	Pedia-Lax [™] Quick Dissolve Strips (OTC)	25, 28
2010	Ondansetron RapidFilm [®] (Rx), Risperidon HEXAL [®] SF (Rx)	25, 29
2012	Niquitin [®] Strips (OTC), Zuplenz (Rx)	25
2013	Zolmitriptan RapidFilm [®] (Rx)	25
2014	Sildenafil Sandoz Orodispersible Film [®] (Rx)	30
2016	IvyFilm [®] , IvyFilm Kiddies [®] (OTC)	31
2018	Clobazam OSF [®] (Rx)	32

who are not willing to cooperate or face the difficulties associated with complete dosage intake, such as patients with depression, schizophrenia, dementia and other neurodegenerative diseases (11–13). In particular, ODFs are at the cutting edge of drug technology as they offer a good alternative for rapid drug delivery (14). Their origins date back to the 1970s but only after being marketed by Pfizer in 2001 as refreshing breath strips Listerine PocketPaks[®], they started gaining popularity and their potential as a drug delivery system was discerned (Table I) (15–17). According to the European Pharmacopoeia (Ph. Eur.), ODFs are defined as “single or multilayered sheets of suitable materials, to be placed in the mouth where they disperse rapidly” (18). European Medicines Agency (EMA) recommended the nomenclature “orodispersible films” (19) and Food and Drug Administration (FDA) named them “oral soluble films” (20).

A number of other terms can be found in literature: oral strips, thin strips, fast dissolving films, mouth dissolving films, oral wafers or fast dissolving films (21–23). ODFs appear as over the counter (OTC) and prescription (Rx) preparations from different therapeutic classes (Table II) (24). The first Rx films approved in the European Union in 2010 (Table I) were Ondansetron RapidFilm[®] and Risperidon HEXAL[®] SF Schmelzfilm (24, 25). Interestingly, ODFs are a suitable dosage form not only for humans but they are also an alternative for animal oral drug administration, which is usually troublesome (Table II) (26).

ODFs are described as postage stamp-sized polymer films, with a thickness ranging from 12 to 100 μm and surface from 2 to 8 cm^2 (commonly given dimensions in literature are $3 \times 2 \text{ cm}^2$, $2 \times 2 \text{ cm}^2$) (39–41). ODFs contain one or more therapeutic substances that constitute up to 30 % of film mass. Essential excipients are polymers, which seem to be the backbone of film formulations (40–50 % of film mass), and plasticizers usually adding up to 20 % of dry polymer weight. Other components include: taste masking agents, sweeteners, surfactants or saliva stimulating agents (14, 24, 39–43). ODFs are manufactured by the following methods: solvent casting, hot melt extrusion, semisolid casting method, rolling

Table II. Composition of selected ODF preparations as OTC or Rx products

Trade name	API	Polymer	Plasticizer	Reference
OTC products				
Listerine PocketPaks® Oral Care Strips (Johnson&Johnson)	Menthol	Pullulan	Glyceryl Oleate Macrogol	17, 24, 33
Sudafed® PE (Johnson&Johnson)	Phenylephrine	Maltodextrin Pullulan Carragen	Glycerin	24, 34, 35
Theraflu® Day Time Thin Strips (Novartis Consumer Healthcare)	Dextromethorphan Diphenhydramine Phenylephrine	Hypromellose (HPMC) Maltodextrin	Propylene Glycol Macrogol	24, 27
Gas-X Thin Strips® (Novartis Consumer Healthcare)	Simethicone	Maltodextrin HPMC	Polyethylene glycol Sorbitol	34, 35
Chloraseptic® Sore Throat Relief Strips (InnoZen)	Benzocaine	Corn starch	Erythritol Macrogol	23, 27, 35
Supress Cough Strips® (InnoZen)	Menthol	Carragen Pectin Sodium alginate	Glycerin	23, 27
Pedia-Lax™ Quick Dissolve Strip (C. B. Fleet)	Sennosides	HPMC	Glycerin	28, 35
SpotScent Oral Care Strips® (breathfreshener for dogs) (Spotscent)	Parsleyseed oil	Modified cellulose	Glycerin	26
Orajel™ Kids Sore Throat Relief Strips (Church & Dwight Co.)	Benzocaine	Pectin	Glycerin	24
Day Time Triaminic Thin Strips® Cough & Cold (NovartisConsumer Healthcare)	Phenylephrine Dextromethorphan	HPMC	Polyethylene Glycol	24, 27
IvyFilm®, IvyFilm Kiddies® (Lamar-Forrester Pharma)	<i>Hedera helix</i> extract	Pullulan	Glycerin	31
Benadryl® Allergy quick dissolve strips (McNeill-PPC)	Diphenhydramine	Carragen Pullulan	Glycerin	24
Rx products				
Sildenafil Sandoz Orodispersible film® (Sandoz)	Sildenafil	HHPMC	Glycerin	30
Sildenafil IBSA Orodispersible film (IBSA Farmaceutici Italia Srl)	Sildenafil	DMaltodextrin	Glycerin Polysorbate Propylene glycol Monocaprylate	36, 37
Zuplenz® (VestiqPharmaceuticals)	Ondansetron	HHPMC	Polyethylene Oxide Colloidal Silicon Dioxide	24
Risperidon HEXAL® SF Schmelzfilm (Hexal AG)	Risperidone	HHPMC Maltodextrin	Glycerin	24, 38

method or electrospinning (8, 44). An ODF is designed to be placed on the tongue, where it is wetted with saliva in a few seconds, then the film-forming polymer is rapidly dissolved (up to 30 s) and the active pharmaceutical ingredient (API) begins to dissolve and release (45, 46). Most of the drug is swallowed with the saliva and then absorbed from the gastrointestinal tract; however, absorption of an API fraction through the oral mucosa may occur. Ideal ODFs should exhibit adequate elasticity, flexibility, softness, mechanical properties to facilitate their production, packaging and application, short disintegration time and pleasant taste. All these parameters have to be evaluated (15).

In recent years, there has been an increasing amount of newly developed poorly water-soluble APIs in pharmaceutical technology; new technologies were therefore introduced to improve their bioavailability (47). Administration of such drugs, especially at high doses, requires technological modifications enabling enhanced dissolution, which might be achieved by creating nanocrystals or nanoparticles (48). Reduction of the particle size results in an increase of their surface area, and thus provides increased saturation, solubility, fast dissolution and consequently improved bioavailability of APIs (49). Nanoparticles can be either in amorphous or crystalline state and amorphous material has a higher apparent solubility than crystals (50). Incorporation of nanocrystals or nanoparticles is now applied in the formulation of ODFs (51, 52) and might affect their mechanical properties. Young's modulus measurements suggest that nanocrystals or nanoparticles change film stiffness significantly (53).

EXCIPIENTS USED IN ODF PREPARATION

Film-forming polymers are key components in the manufacturing of ODFs. To strike a balance between mechanical properties and disintegration time of ODFs, proper selection of polymer type and concentration is an important issue (54, 55). Polymer properties are principally affected by their molecular mass (23, 56). To compare the effect of molecular weight on film properties, ODFs were prepared with low and high molecular mass maltodextrin. Results of the experiment revealed that films made of maltodextrin with high molecular mass were stiffer and less sticky than those obtained with lower molecular mass maltodextrin. Moreover, their tensile strength and elastic modulus were higher, whereas elongation at break was lower. Viscosity of the mixture provided by the polymer prevents API sedimentation, provides homogeneous dispersion of all ingredients and facilitates the manufacturing process. Ideal viscosity should be high enough to prevent sedimentation of particles, but at the same time not too high so as to avoid problems during the manufacture (57, 58). The most commonly used polymers are cellulose derivatives, polyvinyl alcohol and pullulan (Table III) (23, 59–62).

There are examples of films based on mixtures of different polymers such as: hypromellose and methacrylic acid copolymers (22); polyvinyl alcohol or polyvinylpyrrolidone and croscarmellose sodium (66–68); high molecular mass povidones and synthetic copolymers of macrogol-polyvinyl alcohol (Kollidon, Kollicoat) (69); carboxymethylcellulose, hypromellose and sodium alginate (70). Plasticizers are another major group of excipients used in ODF manufacturing (Table III). There are many publications on the influence of plasticizers on film characteristics, and the choice of a proper one or their mixture is a crucial issue (14, 23, 29, 38, 55, 71). As an example, macrogol with citric acid esters added should not be used to plasticize maltodextrin ODFs due to the lack of miscibility. Also,

Table III. Excipients used in ODF formulation

Excipient	Excipient role	Excipient example	Reference
Polymers	<ul style="list-style-type: none"> • Enable rapid disintegration upon contact with saliva • Guarantee adequate mechanical properties and integrity • Provide the necessary elasticity and shape of the film 	Natural polymers starch, sodium alginate, pullulan, pectin, gelatin, maltodextrin, levan, zein, collagen, amylose, cellulose derivatives, chitosan Synthetic polymers polyvinyl alcohol (PVA), polyvinyl acetate, methacrylic acid copolymers	24, 38, 54, 63–65
Plasticizers	<ul style="list-style-type: none"> • Improve tensile strength and percent elongation • Prevent crushing, reduce glass transition temperature of the polymer • Reduce brittleness • Improve plasticity of the polymer which affects film flexibility • Improve API solubility and absorption • Affect mechanical properties • Some plasticizers improve taste masking efficiency (<i>e.g.</i>, sorbitol, mannitol, glycerol) 	Sorbitol, mannitol, glycerol, diethyl phthalate, triethyl citrate, tributyl citrate, sorbitol, macrogol, propylene glycol, citric acid esters	24, 38
Surfactants	<ul style="list-style-type: none"> • Solubilizing, dispersing, wetting agents • Enable films to disintegrate within seconds during contact with saliva 	Poloxamer 407, sodium lauryl sulfate, polysorbate	24, 38
Sweetening and taste masking agents	<ul style="list-style-type: none"> • Mask bitter or nauseating taste, especially important in case of pediatric population 	Flavored essences, aspartame, sucralose, cyclamate, glucose, fructose, oleoresins, ribose, sucrose, maltose, thaumatin I and II, sorbitol, mannitol	24, 38
Saliva stimulators	<ul style="list-style-type: none"> • Stimulate production of saliva in oral cavity 	Malic acid, tartaric acid, ascorbic acid, lactic acid	24, 38

*All excipients used in ODF manufacture have to be approved for use in oral pharmaceutical dosage forms.

increasing the glycerol or propylene glycol content in maltodextrin ODFs caused elastic modulus reduction and elongation at break boost. Their concentration in amounts higher than 18 % (*m/m*) caused ODF stickiness (57). *In vivo* organoleptic tests have shown that films with polyethylene glycol or a polyethylene glycol/glycerol mixture were characterized by unpleasant taste (72) and films plasticized only with glycerol had a more pleasant taste than those with propylene glycol (57). As ODFs are intended to dissolve or disintegrate in

the mouth, the taste of the formulation is a great challenge in this dosage form development. Unpleasant taste of APIs should be masked well enough to become acceptable both to children and adults, but the risk of overdosing a “candy-like” formulation (especially by young patients) should be kept in mind (73). However, it is known that “a spoon full of sugar helps the medicine go down”, as Mary Poppins, a character from a children’s book, used to say, which certainly applies to the designing of pediatric formulations (74).

TESTING METHODS

ODFs represent a relatively new drug dosage form. ODFs first became a part of the 7th Ph. Eur. edition in 2012, which included their general monograph. Only the release test is mentioned in Ph. Eur. to demonstrate the appropriate release of API and according to pharmacopoeial requirements ODFs “should possess suitable mechanical strength to resist handling without being damaged” (18).

Questions arising here include what the suitable mechanical strength means and exactly in what way a dissolution test should be carried out. As there are no standards of quality control methods in the pharmacopoeia, the logical assumption is that there is a need for unification of quality studies. Absence of standardized methods and equipment causes problems of how to develop a formulation characterized by optimal parameters (33). There is currently a tendency of using testing methods recommended for solid oral dosage forms (tablets and capsules), which in fact are not adequate for assessment of ODFs, since they do not relate to specific characteristics of ODFs and conditions to which they are subjected in the oral cavity (75). Also, the literature reveals a large number of individually modified methods and industrial directives (*e.g.*, for plastics and paints: DIN EN ISO 527-3, 2012; ASTM D 882-02, 2012) that may be utilized in quality evaluation of ODFs (76, 77). Therefore, elaboration of gold standard methods for assessing their properties and testing approaches is of the utmost importance (62, 78).

Disintegration time and release tests

In the pharmaceutical technology, both from the drug development and quality control perspective, disintegration time and drug release tests are essential tools to estimate dosage form properties (79, 80). In the case of ODFs, disintegration and release procedures are difficult to distinguish due to the short time in which they occur (81). According to the International Pharmaceutical Federation/American Association of Pharmaceutical Scientists (FIP/AAPS) guidelines for ODT (which may be applied to ODFs), a disintegration test may be used instead of a dissolution test if it is shown to be a good discriminating method (75). If API appears as molecular dissolution in the ODF, then the released API rate depends only on the disintegration time of the film. However, if API is dispersed in the film, both disintegration time and dissolution tests are recommended (82). Properly conducted disintegration time examination is crucial for evaluation of orodispersible dosage forms. Reference to ODT disintegration time, which is up to 3 min according to the Ph. Eur. (83) and 30 s or less according to the FDA and USP guidelines (20, 84), is recommended. The test is usually performed using pharmacopoeial apparatus for studying the disintegration time of conventional solid dosage forms (tablets and capsules) (85, 86). As the apparatus requires large volumes of solution to perform the test, it does not mimic the oral cavity conditions. More-

over, the mechanical force of the tongue is not reflected either (24, 87). Therefore, some modifications, like using a sample holder to keep ODF vertically in the disintegration tester with attached weights to facilitate observation of the disintegration endpoint, are proposed (38, 88). However, using disks or weights may disesteem the disintegration time because of additional forces exerted on the ODF while carrying out the test (89). As the volume of saliva in the oral cavity is less than 2 mL (90), tests under conditions similar to those prevailing in the oral cavity conducted in a small volume of medium, usually 2–7 mL, are recommended (72, 91, 92). ODF might be placed on the liquid surface in a Petri dish and its disintegration time is measured using a stopwatch (the dish may be shaken constantly in order to imitate the movement of the tongue in the mouth) (73, 93). This method allows for ease of application and simple test setup. Nevertheless, the endpoint detection creates some difficulties, especially for transparent ODFs and it is very difficult to implement process automatization. Further, neither the adhesion of the film to the oral mucosa nor the influence of the force of the tongue are considered during the test (94). Another approach is the fixing of an ODF in slide frames and placing it horizontally over a Petri dish; a small amount of medium (usually about 200 μ L) is then piped onto the ODF surface. The time until the fluid penetrates through the film making a hole is observed and measured with a stopwatch (92, 95). This method seems to be appropriate for observing the disintegration time of thin films. For thicker films, a standard volume of medium (200 μ L) might be too small to disintegrate a thick film layer, which might prolong disintegration time. Obtained results do not correlate with the data of *in vivo* disintegration, since during the test the films are wetted only from one side, which is not comparable with physiological conditions (9, 94). In the method utilizing a wire mesh, the ODF is placed on a stainless steel wire metal mesh where its bottom is wetted by contact with distilled water. The time taken to pass through the mesh is considered as disintegration time (55, 59). To improve assessment of the ODF disintegration endpoint, a disintegration test unit (DTU) was developed (Fig. 1). DTU is a modification of the pharmacopoeial test and is used as an accessory to the pharmacopoeial apparatus for disin-

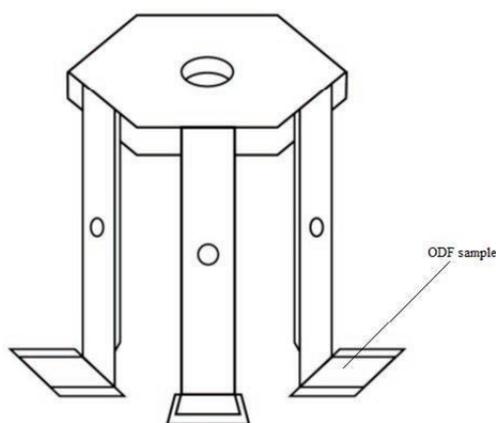


Fig. 1. Schematic illustration of the disintegration time unit for determination of disintegration time endpoint (modified from reference 96).

tegration time evaluation. It is designed for testing 6 samples simultaneously. DTU is placed in a basket-rack assembly from the top and allows to follow ODF in the vertical plane in the bath (it holds the ODF in horizontal position, allowing a top view of the ODF during testing). DTU moves together with the device for raising and lowering the basket in a 1000-mL beaker and enables easier ODF observation and more precise definition of the endpoint (96).

Another approach is the use of a texture analyzer equipped with a special disintegration rig (used for ODTs), which mimics *in vivo* conditions in the human mouth. In this test, a flat-ended cylindrical probe penetrates into the ODF immersed in the medium. As the ODF disintegrates, the instrument is set to maintain a small force for a defined period of time. Plots of the distance traveled by the probe, generated with the instrument's software, provide a disintegration profile of the ODF as a function of time. These plots are used to calculate the start and the endpoint of ODF disintegration (97). Another method utilizing a texture analyzer is fixation of ODF to a special platform and setting the probe to mimic the oral cavity forces. At the moment when the film is touched by the probe, 1 mL of artificial saliva is administered to the film (98). Disintegration behavior can be also analyzed with a newly developed SFaB ("Slide Frame and Ball") device, which is an adjustment to the slide frame method. The main advantages of the device are the indication of the clear endpoint (the ball falls on the bottom of the vessel after complete disintegration) and the consideration of the mechanical stressing component representing the tongue force as well as physiological properties in the mouth (0.9 mL of distilled water is utilized). The measurement starts when the fluid drop is dropped on top of the film. Afterwards, the ball (4 g) is placed in the middle of the film. The test ends when the ball falls through the film. To overcome the difficulties connected with unintended rolling of the ball on the film surface during the disintegrating process, an insert to the SFaB keeping the ball constantly in the centric position was implemented (53, 94). Another novel and robust test method enabling clear endpoint detection is the PharmaTest[®] film disintegration tester PT-ODF (Basket Add-On to Test Orodispersible Films). This is a simple device with a sample holder facilitating assessment of disintegration time. Six ODFs are simultaneously held by clamps in transparent glass tubes. Small weights (3 g) are fixed to the lower periphery of each film (simulating mechanical force of the tongue) and fall down once the film has disintegrated. The weights clipped on the bottom of the films are considered to simulate the force provided by the tongue. PT-ODF connected to the disintegration basket moves up and down in the medium (900 mL of distilled water, at 37 ± 0.5 °C) in the test vessel. After disintegrating, the weights hit the split metal sieve of the basket and close an electrical circuit. The endpoint is detected automatically and the instrument logs the disintegration time. However, the medium volume used in the test is much larger than in the oral cavity (94, 99). In addition, the contact angle (measured by a goniometer) is a parameter indicating the susceptibility of ODF to wetting in contact with the liquid. Angle values below 90° mean that the film moistens easily, which is indirectly related to disintegration time (15, 44, 48). However, as none of the methods mimic the physiological conditions adequately, the most reliable disintegration time test is the *in vivo* measurement performed on volunteers – ODF is placed directly on the tongue and the time required for complete disintegration is recorded (100).

The choice of medium is a very important parameter in ODF assessment, for it influences the disintegration and dissolution process (83). Human saliva is a natural biological fluid, characteristics of which are affected by personal differences, concomitant diseases, time of the day and diet (101, 102). As no saliva substitute is defined in the Ph. Eur., it is hard to decide which medium mimics this fluid best (103). Artificial salivas – stimulated

Table IV. Different compositions of SSFs

	Media proposed in the literature: Composition and concentration (g L ⁻¹)	Reference
SSF ₁	KCl (0.72), CaCl ₂ ·x2H ₂ O (0.22), NaCl (0.6), KH ₂ PO ₄ (0.68), Na ₂ HPO ₄ (0.866), KHCO ₃ (1.5), KSCN (0.06), citric acid (0.03)	107, 108, 109
SSF ₂	CaCl ₂ ·x2H ₂ O (0.228), NaCl (0.017), Na ₂ HPO ₄ (0.204), MgCl ₂ ·x6H ₂ O (0.061), K ₂ CO ₃ (0.603), NaH ₂ PO ₄ ·xH ₂ O (0.273), submaxillary mucin (1.0), alpha-amylase (2.0)	107, 108
SSF ₃	KCl (0.149), NaCl (0.017), NaHCO ₃ (2.1), alpha-amylase (2.0), gastric mucin (1.0)	107, 108
SSF ₄	NaCl (8.0), KH ₂ PO ₄ (0.19), Na ₂ HPO ₄ (2.38)	109, 110
SSF ₅	Albumin (0.01), methylcellulose (0.025), KCl (0.0062), K ₂ HPO ₄ (0.0034), NaF (0.001), MgCl ₂ (0.0005), dextrose (0.469), methylparaben (0.02)	109, 110
SSF ₆	NaCl (1.256), KCl (9.639), KSCN (1.892), KH ₂ PO ₄ (6.545), urea (2.0), Na ₂ SO ₄ (7.632), NH ₄ Cl (0.178), CaCl ₂ ·x2H ₂ O (2.278), NaHCO ₃ (6.308)	111, 112
Commercially available media		
SSF ₇ (AFNOR)	NaCl (0.7), KCl (1.2), Na ₂ HPO ₄ (0.26), NaHCO ₃ (1.5), KSCN (0.33), urea (1.3)	113, 114
SSF ₈ (Fusayama Mayers)	NaCl (0.4), KCl (0.9), CaCl ₂ ·xH ₂ O (0.795), NaH ₂ PO ₄ ·x2H ₂ O (0.69), urea (1.0)	108, 113, 114
Phosphate buffers pH 6.8		
SSF ₉	Na ₂ HPO ₄ (71.5), C ₆ H ₈ O ₇ (21.0)	109, 112, 115
SSF ₁₀	KH ₂ PO ₄ (50.0), NaOH (0.2 M)	116

salivary fluids (SSF) – occur as solutions or suspensions containing organic and inorganic compounds. They differ in elemental composition, ionic strength, pH, conductivity or enzyme content (104). In the literature, there are many examples of SSF created by scientists for their laboratory needs, as well as ready-made products (Table IV). However, pharmacopoeial phosphate buffers pH 6.8 are still the most often used media (105, 106).

Drug release from ODFs is usually carried out according to the pharmacopoeial requirements for solid oral dosage forms using a basket or paddle apparatus in medium (phosphate buffers pH 6.8 or SSFs) heated to 37 °C (117–119). However, pharmacopoeial apparatus have some disadvantages (120). Basket apparatus problems may arise with the adhesion and mesh clogging by the film, while paddle apparatus presents phenomena of ODF flotation in dissolution media or local adhesion to the bottom of the vessel, which makes it difficult to achieve data reproducibility (27, 57, 121). In order to avoid floating and to mimic the *in vivo* adhesion, sinkers and double-slide tapes are used (each film is fixed to a rectangular glass slab and placed at the bottom of the dissolution vessel) (89). As a result of rapid disintegration, complete release of API takes place very quickly and samples of the analyzed fluid are taken in a short time. FIP/AAPS guidelines for the *in vitro* release test of novel/special dosage forms suggest using a basket apparatus with higher sampling

frequency at earlier time points. Determination of the released dose at a time point is also suggested (75). Other approaches involve the use of the Franz diffusion cell (122, 123), a syringe with 10 mL of medium (124) or the microfluidic device (covered by the patent). The microfluidic device mimics physiological conditions of the mouth by the laminar tangential solvent flow with a rate of 1 mL min^{-1} and low hold-up volume (1 cm^3). ODF is placed on the bottom surface of a dissolution cell, where it is exposed to tangential solvent flow. Samples are collected at the exit of the cell at different time intervals, filtered and analyzed using an appropriate technique (125). Use of a device based on flow-through cell with a limited amount of dissolution fluid and collecting samples at short time intervals lead to more realistic dissolution profiles (126). Two methods based on paddle apparatus with different dissolution setups utilizing a UV-fiber optical probe as data point detector were described by Krampe *et al.* (9). Release test might be also performed in a pharmacopoeial dissolution apparatus V (paddle over disk) (127, 128).

EVALUATION OF MECHANICAL PROPERTIES

Mechanical properties play a crucial role in physical integrity of ODFs (53, 61, 81, 129, 130). They provide information about the resistance to stretching or pulling, which is important during removal, cutting, packaging, transport and patient handling (11). ODFs are tested for the following factors: tensile strength, tear resistance, percentage of elongation, Young modulus, folding endurance (29). As no standard methods for determining their mechanical strength are provided, a wide range of tools and methods are applied (18, 19, 84).

Tensile properties

Tensile strength is defined as the maximum stress needed to stretch the film – it is used to measure its mechanical strength as diametric tension or tearing force. In Ph. Eur. and USP, the tensile strength test is mentioned only for surgical sutures and patches (18, 116); therefore, methods recommended for plastic industry are used as templates, *e.g.*, DIN EN ISO 527, ASTM D 882 (76, 77). The ASTM D 882 test is one of the more widely used tests in industry to properly identify and characterize plastic films and thin sheeting materials for control and specification purposes. Both methods are used to investigate the tensile behavior of test specimens and for determining tensile strength, tensile modulus, elongation and other aspects of tensile relationships (78). According to the above tests, ODF is held between two parallel clamps and pulled. One of the innovations is the texture analyzer, used in food, cosmetics and pharmaceutical industry, due to the fact that texture significantly affects physicomaterial properties (strength, elasticity, durability, *etc.*) (131). The texture analyzer equipped with a load cell holds ODF between two clamps positioned at a distance of a few cm. A strip is pulled by the top clamp until the film breaks (132). Influence of the cross-sectional area of the sample and the speed of upper clamp movement are recorded (133). To evaluate the tensile properties, a microprocessor based advanced force gauge tensiometer with a motorized test stand might also be utilized (134).

Tear resistance

The ODF material strength and ability to withstand rupture is defined as tear resistance (122). Tear resistance is the stress that corresponds to the greatest tensile force (F_m) obtained

during the static stretch test, referring to the original cross sectional area of the sample. The film is subjected to deformation at a constant rate. Maximum force required to rupture the film is measured in Newtons (39). Measurement might be carried out according to DIN EN ISO 527 and ASTM D 882 – the sample is held between two holders and a uniform pulling force is applied until the aforementioned deformation occurs (24, 76, 77, 124).

Percent elongation (% E) and percent elongation at break

When a sample is subjected to tensile stress, deformation of the sample occurs, resulting in sample elongation and hence stretching. Elongation measurement is primarily done to estimate the polymer plasticity. This parameter indicates the material ability to stretch without being damaged. Use of the following formula allows calculating percent elongation by measuring the increase in film length after tensile measurement:

$$\% E = [L - L_0] \times 100/L_0$$

where L is the final ODF length and L_0 is the initial ODF length. The point at which the film breaks after increase in its length is defined as percent elongation at break (24, 39, 132).

Young modulus

Young modulus (elastic modulus, linear modulus) determines film stiffness. This parameter expresses the characteristic of the material relative to its linear deformation by the stress occurring in the range of elastic deformations. Test methods used for tensile strength determination can be also utilized in relation to the Young modulus (135).

Percentage elongation, tear resistance as well as Young modulus, may be evaluated by a texture analyzer, which is the most commonly used equipment for the assessment of mechanical properties. ODF is fixed in an individual sample holder. When the probe is in contact with the surface, the measurement starts. Movement of the probe proceeds at constant speed until the film is damaged (34).

Folding endurance

The folding endurance value determines film flexibility. Examining the number of folds gives an indication of ODF brittleness and is important for their storage and administration without being broken. Literature data most often indicate 300 folds per film as excellent flexibility. Measurement is taken by repeated folding at the same point at an angle of 180° until the film breaks (136). Flexibility of ODF can be also determined by adapting the ASTM Bend Mandrel Test D 4338-97 (137). The film is bent over a mandrel and examined for cracks over the area of the bend under strong light. The film is assumed to be flexible if no cracks are visible at a 5× magnification (135).

MOISTURE CONTENT

Residual amounts of water or other solvents remaining in the films affect significantly their brittleness, friability, mechanical properties, stability, tackiness and adhesion. Films with high residual water can be tacky and sticky, whereas films with low water

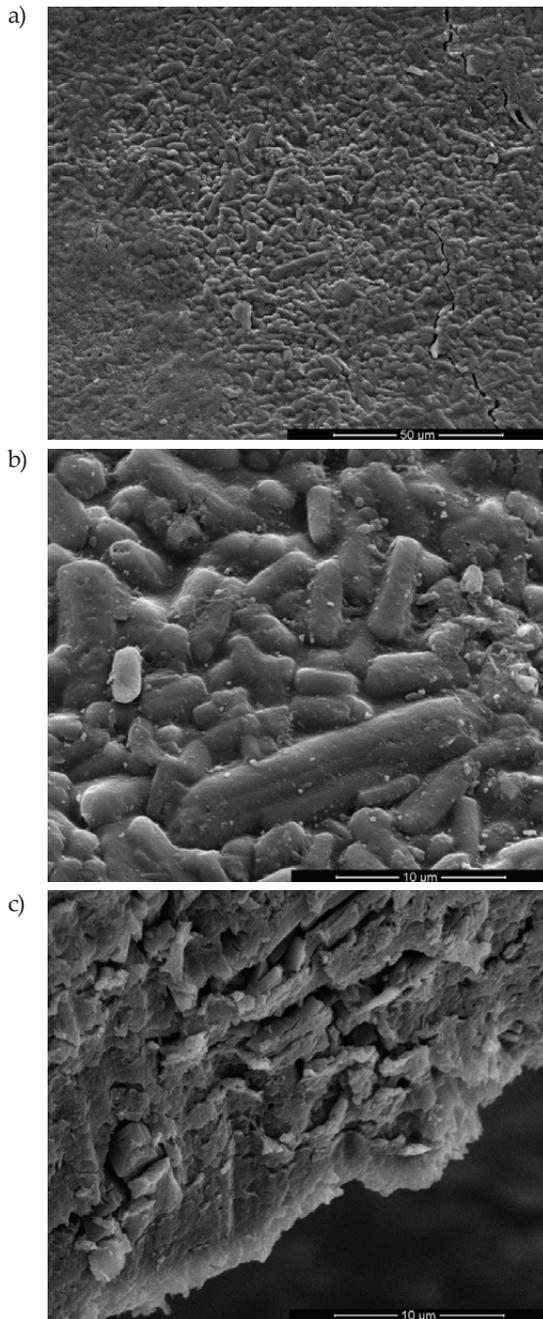


Fig. 2. Scanning electron microscope images of ODF with HPMC and loratadine under magnification: a) 2000× b) and c) 10000×.

content tend to be brittle (24, 138). Therefore, residual water content has to be controlled and suitable packaging should be provided (8). Moisture is assessed by moisture content testing equipment, Karl Fisher titration method, dynamic vapor sorption or the most widely used weighing method. ODF is pre-weighed and heated above 100 °C until a constant mass is obtained and then re-weighed (24, 121, 139, 140).

MORPHOLOGY

An important issue is to ensure suitable API distribution and its uniformity in a film. The morphological state of ODF may alter its mechanical strength, *e.g.*, by crystal growth. Interaction between API and polymers as well as the crystalline nature of API may result in the formation of a rough surface of films, their brittleness and loss of transparency (138, 141, 142). API incorporated in the film might also cause recrystallization and affect mechanical or disintegration properties; it is therefore crucial to assess the texture and morphology. In order to investigate the stability of API, it is recommended to observe crystals at time zero and after storage – at possible API crystallization time (24, 133, 143, 144). Evaluation can be conducted by the following techniques: dissecting microscope, optical polarization, near-infrared spectroscopy imaging (NIR), transmission electron microscopy (TEM), X-ray diffraction or scanning electron microscopy (SEM) (Fig. 2), which appears to be the most reliable method for surface examination and evaluation of the role of composition on the crystallinity, morphology and texture of the film. These methods also provide data about ODF stability, since they reveal recrystallization of API particles in the film and possible interactions between drug and excipients. Macroscopic observation should not exhibit any bubbles, cracks or aggregates and film texture should be homogenous and smooth (39, 122, 145).

THICKNESS, MASS EXAMINATION, CONTENT UNIFORMITY

Thickness uniformity is directly correlated with the dose contained in a single film and appropriate thickness affects comfortable administration (122). Thickness can be measured with a calibrated digital micrometer, Vernier caliper, screw gauge, microscope (with specialized software), digital camera or SEM images (146). Different number of repetitions (usually 2 to 5 at different locations, *e.g.*, in the corners and in the middle of the film) is recommended (14, 123). In human volunteer studies, ODFs with a size of 2 × 2 cm² and 100-μm thickness as well as size 2 × 3 cm² and 350 μm were judged as acceptable (119, 147).

To determine whether each film contains the same amount of drug, to be sure of the dose accuracy, weight examination is also performed. Mass variation is calculated by weighing an individual film three times and calculating the average mass for each. A deviation from average mass signifies inefficiency of the applied method and high possibility of non-uniformity in the API content (57, 139). To assess content uniformity in individual films, 20 films are usually examined. Drug content should be in the range from 85–115 % (4).

DRYNESS TEST/TACK TEST

In order to check if ODFs are not tacky, easy to take out of the package and to keep their plane form without rolling up, the tack test is conducted. The tack is defined as film

tenacity (related to adherence). This study aims to determine the ability of adhering to any piece of paper that is pressed into contact with the strip. The test was used primarily in the paint industry, but has also found application of evaluating ODF adherence (27, 39).

TASTE EVALUATION

Due to direct contact of API particles with taste buds and the necessity of product acceptability by the patient, the taste and palatability of ODFs are crucial factors (9). Under *in vitro* conditions, biochemical, biomimetic or ion selective detectors are utilized (148–150). There has recently been an increasing use of special panels dedicated to taste evaluation – “electronic tongues” (multisensor taste detectors with pattern recognition systems) (71, 151–153), which seem to be good alternatives to pre-testing of the formulation. Taste masking properties can be also evaluated *in vitro* using a dissolution test (148, 154). The most reliable, but ethically problematic, is the *in vivo* test in human volunteers. Before the examination, subjects evaluate their sensory sensibility thresholds for respective tastes, using four standard substances: tartaric acid (sour), sucrose (sweet), sodium chloride (salty), quinine (bitter). It is proposed to conduct the study in the following stages: rinsing the mouth with distilled water, placing the required amount of drug and then a film sample with the same drug content on the tongue for 30 seconds, spitting the drug and rinsing the mouth with water. For taste evaluation, the scale with the following values is usually utilized: 0 – free of bitter taste, 1 – slightly bitter, 2 – moderately bitter, 3 – very bitter (155).

CONCLUSIONS

ODFs are considered to be an attractive oral solid dosage form especially for patients struggling with swallowing difficulties and mental disabilities, as well as children and the elderly. Compared with traditional dosage forms, they seem to be a convenient and self-administrable drug delivery platform, enhancing patient adherence and compliance. Despite monograph insertion of ODFs in the pharmacopoeias, special directions and requirements for their quality assessment have not been specified. Traditional pharmacopoeial apparatus or their modifications, as well as innovative approaches are currently utilized for their characterization. The challenge is to develop test methods that would enable carrying out unified, accurate and optimal research. Suitable and standardized methods are crucial issues to face the difficulties associated with quality evaluation; hence, this review presents conventional and modified test methods utilized to determine the characteristics of ODFs.

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