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Review

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Trends in the production methods of orodispersible films

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Abstract (max 200 parole)

Interest in orodispersible films (ODF) is growing day-by-day, since this dosage form overcomes some therapeutic obstacles, such as impaired swallowing, and offers several benefits, such as the possibility to adapt the dosing requirements for a subset of patients. As a consequence, technologies to produce ODF have risen attention for possible applications in the development of patient-centric formulations. This review critically discusses current trends in the technology platforms proposed to the production of ODF, including the innovation and opportunities to produce very small batches in a pharmacy setting. Although the main Pharmacopoeias recommend testing customized dosage forms for quality assurance, pharmaceutical assays are a matter of debate due to the complexity and high cost of conventional methods. Alternatively, non-disruptive online analytic methods can be proposed to assay ODF properties, above all to assure the uniformity of drug content.

Keywords (max 7):

Drug printing; Flexographic printing; Individualized medicine; Orodispersible films; Solvent casting

1 Introduction

Orodispersible films (ODF) are single or multilayer sheets of suitable materials intended to liberate rapidly the loaded active substance in the mouth, forming a fine suspension or solution in the saliva without mastication or water intake. ODF appear attractive for patients affected by functional or psychological dysphagia or, more in general, preferring a liquid dosage form, such as paediatrics (Orlu et al., 2017; Visser et al., 2017), geriatrics (Slavkova and Breitkreutz, 2015), bedridden and people who cannot have access to water. Indeed, ODF combines the dose accuracy typical of solid dosage forms and the ease of administration characteristic of liquid dosage forms (Cilurzo et al., 2018). ODF have the size of a postage stamp and are individually packed so that transportation and consumer handling is friendly. Furthermore, ODF can be advantageously used also as a carrier for other technologies, such as microparticles, nanocrystals and self-emulsifying systems (Lai et al., 2015; Musazzi et al., 2019; Talekar et al., 2019), which rule the drug release rate and, therefore, its bioavailability.

On the other hands, the main drawbacks are due to the limited formulation space (Borges et al., 2017) which implies a limited drug loading capacity. As an example, the highest dose available on the market is a 100 mg sildenafil ODF, but potent drugs are generally loaded. Palatability drives the compliance, but the formulation space limits the addition of excipients to taste mask; even if both astringent or bitter taste of drug can be opportunely reduced and/or eliminated (Cilurzo et al., 2010, 2011). Finally, the manufacturing process at the industrial scale is mainly based on solvent-casting technologies, which require production chains with specialized equipment which are common only to transdermal patches, and therefore, the number of manufacturers worldwide is limited. Nevertheless, similarly to the transdermal patches, the dose loaded in an ODF is defined by their size and, therefore, the same production chain could be used to prepare batches of different drug strengths. Because of this peculiarity, researchers are striving to optimize and/or to develop technologies to exploit this peculiarity in the extemporaneous compounding of small batches of

ODF in a pharmacy setting. Since the term "customized dosage form" should be related not only to a tailored dose but also to doses on-demand, shape and colour of a dosage form, this innovation would also allow end-users to easily identify their own medicine, improving the safety and adherence.

This review aims to describe the current trends in the ODF production by continuous manufacturing as well as for the preparation of small batches for an individualize therapy.

The references were extracted from SCOPUS and Web of Science databases using the following keywords: Disintegrant film, Orodispersible film, Fast dissolving film and Oral thin film.

2 Solvent casting

Solvent casting is the first and the most widely used method for the preparation of ODF (Mashru et al., 2005; Cilurzo et al., 2008a; Dinge and Nagarsenker, 2008). Since this technique is widely exploited at the industrial level due to the straightforward manufacturing process, it is also the first one investigated in laboratory settings (Allen, 2016). The solvent casting production process is mainly based on three steps: the preparation of a homogenous slurry mixture of components, obtaining a dried laminate by solvent casting and die cutting of laminate in desired films. For the first step, the active substance and excipients are dissolved and/or dispersed in an appropriate solvent (*e.g.*, water) using the equipment commonly used for the preparation of several liquid or semisolid preparations (*e.g.*, stirring tank at industrial level, beaker in a bain-marie in a laboratory/pharmacy setting). Then, slurries are cast and dried to give a film with a constant thickness which assures the uniformity of drug content. For the industrial continuous manufacturing, these steps require an apparatus able to control both the casting of the viscous slurry on a PET or a siliconized foil (*i.e.*, the carrier) and the solvent evaporation leads to the formation of a dried laminate which is, then, rolled up in jumbo rolls. The jumbo rolls are cut in reels whose length determines one of the two dimensions of the ODF. Afterwards, the reels are loaded in the

packaging machine, which unrolls and separates the film from the carrier before the die-cutting in the desired shape. At the same time, the packaging machine seals a bag usually made of three-laminates resistant to moisture material and inserts the dosage form to give the single packed ODF. To personalize the dose strength according to clinical needs, the patient can cut directly the tape ODF. In this context, the reel can be packaged or loaded in a device able to cut the film in the desired length to define the appropriate dose (Allen et al., 1987; Niese and Quodbach, 2019). However, since ODF is handled in a not-controlled environment, the humidity could affect the physical stability of the reel.

Solvent casting can be also adapted to the production of small batches of ODF (Hoffmann et al., 2011; Niese and Quodbach, 2019) (**Figure 1**) and multi-layer films intended to administer fixed drug combinations (Niese and Quodbach, 2018). In particular, API with physicochemical incompatibility can be loaded at different strengths in different film layers in the same preparation process.

In case of ODF compounded in a pharmacy setting, machinery described above are generally too expensive and not easy to be adapted at the compounding processes. Alternatively, several methods have been proposed in the literature as summarized in **Table 1**. The simplest approach to compound ODF is based on the use of a Petri plate or proper slab, where a known amount of a drug-loaded polymeric slurry is casted and dried at an appropriate temperature (Dinge and Nagarsenker, 2008; Liu et al., 2017). However, the uniformity of content is difficult to assure since the Petri dish/slab has to be maintained perfectly horizontal in the oven to have a film with a constant thickness. To solve this issue, Foo and co-workers proposed a novel unit-dose plate filled by the desired volume of component mixture solution (**Figure 2**) (Foo et al., 2018). Alternatively, doctor-blade film coaters can be used (Allen, 2016): the slurry is spread onto a substrate homogeneously by a metering blade which removes the excess of mass and allows to achieve the desired coating thickness; these systems can also be connected with an oven to maximise the solvent evaporation

(Cilurzo et al., 2008a; Visser et al., 2015). Nevertheless, the rheological properties and the wettability of the carrier have to be in-depth investigate to assure the film uniform thickness (Cilurzo et al., 2008b). Thereafter, the obtained dried laminate is die-cut into pieces of the desired size.

Based on literature results, the solvent casting is a versatile and robust technology for both the industrial production and the compounding of ODF. The dose can be adjusted according to the patient's needs cutting the reel or laminate at the desired shape. This technology is also suitable to load a particular payload, such as nanocrystals dispersion which can increase the drug dissolution rate (Alsofany et al., 2018; Lai et al., 2015; Liu et al., 2017; Steiner et al., 2016), or microparticles which permit to obtain a gastroprotection or a prolonged drug release (Brniak et al., 2015; Musazzi et al., 2019; Speer et al., 2019). Obviously, nano- or microsystem might strongly impact on the film mechanical properties.

Generally, the formulation parameters strictly related to the film-forming material have to be monitored to avoid foaming during the mixing or the solvent evaporation, flaking during slitting, cracking during cutting or sticking to the packaging material. In this context, the ratio between the plasticizer and the film-forming material has to be rationalized (Cilurzo et al., 2010) or particular excipients can be added to maintain suitable film properties. As an example, the tendency of maltodextrin to stick to the primary packaging can be solved by adding a nanofiller (Franceschini et al., 2016).

3 Electrospinning

Electrospinning is another solvent-based technology explored to produce ODF characterized by a high-porous inner structure (Vasvári et al., 2018). Although differences among electrospinning machineries, the basic set-up consists in a metallic needle, through which the formulation is pumped with a controlled flow and charged under a high-voltage electric current in the 10–35 kV

range, above an opposite-charged collector (Huang et al., 2019). The active substance can be loaded both before and after the spinning process (Thakkar and Misra, 2017). In the former case, the main advantage is the improvement of the drug dissolution rate due to the huge surface area of nanofibers. In the latter case, placebo ODF can be embedded by the drug solution and dried, widening the possible applications of such technology.

Poly(vinyl pyrrolidone), gelatin and poloxamers (**Table 2**) are among the most studied materials to obtain electrospun ODF not only because these polymers are suitable to load both API and food supplements (Illangakoon et al., 2014; Rustemkyzy et al., 2015; Wu et al., 2015), but also they enhance the apparent solubility of drug. Indeed, PVP forming hydrogen bonds with the other component(s) (Cilurzo et al., 2007) allows to stabilize a supersaturated system and, therefore, improve the apparent solubility (Cilurzo et al., 2002); poloxamers offer improved wettability in addition to molecular dispersion (Ali et al., 2010).

Alternatively, to the use of a solvent- and polymeric-based dispersion, the spinning of melted materials was investigated using a complex spironolactone-hydroxypropyl-β-cyclodextrin as model system (Nagy et al., 2013). Furthermore, aiming to prepare a fixed-dose combination, the combination of electrospinning and inkjet printing (paragraph 5.1) was proposed as a valid alternative to the solvent-casting of multi-laminates (Thabet et al., 2018a). Palo and co-authors demonstrated the feasibiliy to deposite lidocaine on the electrospun and cross-linked gelatin substrates by inkjet printing, whereas piroxicam was incorporated within the substrate fibers during electrospinning (Palo et al., 2017). The analysis of solid-state of piroxicam, which is a low soluble drug with a monohydrate and three polymorphic forms (Cilurzo et al., 2005), evidenced that the amorphous state was stabilized by gelatin. Although electrospinning is proposed for large scale-application (Nagy et al., 2010), this technology appears promising for the preparation of small batches due to low operative flow rates from 0.5 to 2.0 mL/h (Illangakoon et al., 2014; Yu et al., 2010). However, even if the equipment seems simple to use, some drawbacks limit the application

for the preparation of ODF in a pharmacy setting. Indeed, the formulation to spin has to be carefully characterized to assure the reproducible formation of nanofibers and the process parameters optimized; the use of solvents can generate hazardous waste and the yield is low electrospinning process requires low viscosity fluid (Chou et al., 2015; Thakkar and Misra, 2017).

4 Hot-melt extrusion

In order to avoid the use of solvent(s) in the ODF production, the feasibility of extrusion technologies has been investigated (Jani and Patel, 2014). In particular, hot-melt extrusion (HME) can be used for both continuous manufacturing and preparation of different dosage forms (Wilson et al., 2012). In general, HME consists of an apparatus in which a mixture (i.e., API and excipients) is melt and extruded through a die. In the case of film production, their final thickness and wideness is controlled not only by the die dimension but also by the geometry and rotational rate of the calendrer which differently stretches the extrudate during the formation of the reel. The extrusion apparatus can be ram- or screw-based. The first configuration consists of a ram compressing the melt material in a heated barrel and pushing them through a die for the high pressures. The second one consists of one or two rotating screws inside a heated barrel. The twin screw-based design provides a more uniform mixing with respect to the other two configurations. As casting technique, HME can be easily adapted to operate in continuous and to mount process analytical technologies (Wilson et al., 2012).

Despite the possible advantages of such technique, the HME application to ODF preparation is limited to few examples (**Table 2**) because polymers used for the preparation of ODF (e.g., polysaccharides) are generally heat sensible and/or exhibit high value of glass transition temperature that cannot easily tuned by adding a plasticizer. Indeed, the addition of large amount of plasticizer can give too sticky or ductile ODF (Cilurzo et al., 2008a). In 2008, our research group demonstrated the possible application of screw-extrusion technology in the production of

maltodextrin ODF (Cilurzo et al., 2008a). Using the design of experiment, Low and co-workers investigated the effect of drugs and excipients with different physicochemical and technological properties on the performance of ODF made by hydropropyl cellulose (Low et al., 2013). They also showed that the disintegration and dissolution profiles can be modulated by the addition of solubilizing polymers. The addition of the API to the basic formulation has not only an impact on the extrudate processability but also on the mechanical properties of the final films. Finally, Pimarande et al. focused the attention on starch matrices plasticized by glycerol, demonstrating that ODF with a very fast disintegration time (6-11 s) can be prepared by single-screw HME (110 °C) (Pimparade et al., 2017). The results also highlighted that a devolatilizing system was needed to remove the vapour created by the melt of the materials and, therefore, to obtain non-sticky, homogeneous extrudates.

With respect to other solvent-based preparation technique, HME allows preserving better the physicochemical stability of API sensitive to water. However, the higher operating temperatures limited the number of API that can be processed using this technology.

5 Printing technologies

Printing of pharmaceuticals refers to two different deposition models both of which can lead to the fabrication of ODF (Alomari et al., 2015; Scarpa et al., 2017). 2D printing requires the use of an edible carrier ("substrate") that would hold/sorb the deposited ink in a digitally predefined pattern; 3D printing enables also printing in the Z direction by adding material layer-by-layer, resulting in a 3D dosage form. However, despite efforts to move from a discontinuous towards continuous printing process (Thabet et al., 2018b), most of the methods described in literature appears more suitable for the preparation of small or very small batches. Furthermore, since the ODF are produced using a preformed film or formed directly with the required surface and shape, the relevance of mechanical properties in the definition of the quality attributes is limited since the

dosage form should comply only with the stresses generated by the patient handling and not by those generated by the unrolling of the reels.

5.1 Ink-jet printing

Through ink-jet printing (IJP), there are potentially only three main stages of the manufacturing of ODF: (i) the preparation of the ink containing an API as solution or suspension, (ii) the jetting of the ink on an edible substrate in a programmed way and (iii) the drying (**Figure 3**). As exemplified in **Table 3**, this technology enables the deposition of several API with high potency (Buanz et al., 2011) and/or a narrow therapeutic index (Vuddanda et al., 2018).

Based on the mechanism generating the drops, IJP technologies are classified as continuous jetting printing (CJP) and drop-on-demand (DOD) printing (Alomari et al., 2015). In the first case, there is a consistent ejection of a liquid through a nozzle which produces a continuous stream of ink primary drops "steered" to a landing site to produce the printed pattern. This is obtained by applying an electric charge on some of the drops that deflect the stream from the main axis under an electrostatic field (Karki et al., 2016). The jetting of the ink through the nozzle forms a liquid stream, or column, which becomes an elongated tail and ends up in a single primary drop able to impact on the substrate guaranteeing the good quality of printing. In DOD printing, the production of individual drops takes place rapidly under the response of a trigger signal. The drop ejection occurs due to the kinetic energy of drops generated from the source located in the printhead nearby to each nozzle (Daly et al., 2015) and the two main technologies are piezoelectric and thermal printing. In both cases (i.e., CJP and DOD), the printhead apparatus may be based on a single nozzle or multiple nozzles ranging from 100 to 1000 in number. The thermal IJP uses brief heat pulses generated by a resistive element to the jet fluid. Each print head contains a micro-resistor which heats up rapidly on receipt of electric pulses, forming a superheated vapour bubble. The vapour bubble expands, forcing out the fluid from the nozzle and producing a droplet. Then, the

vapour bubble collapses creating a partial vacuum that pulls fluid from the ink reservoir to refill the thermal ink-jet chamber. In piezoelectric IJP, each nozzle is surrounded by a piezoelectric element usually made from lead zirconate titanate. When a voltage is applied to the element, it deforms, creating pressure waves leading to the ejection of the fluid. Once the element returns to its normal shape, the nozzle is filled with ink, ready to be reactivated (Alomari et al., 2015). Moreover, the droplets can also be dispensed with a high spatial resolution in a given pattern so that IJP can be exploited to print the precise amount of a drug (i.e. haloperidol) in the form of a QR code on an edible substrate (Edinger et al., 2018). Afterwards, drying can be carried out to reduce the solvent content. When an organic solvent (e.g., ethanol) is used to solubilize the API, the drying step is essential to fulfil the threshold standards currently in force for the solvent specification; in case of an aqueous solvent, a drying step should reduce the water content to avoid microbial contaminations or improve the ODF stability over time. There are two main mechanisms: absorptive drying at ambient conditions (Alomari et al., 2015) and evaporative drying using hot air convection (Voura et al., 2011). In both cases, it is important to investigate the effect of drying on the physical state of the active, if any, and its effect on the therapeutic outcome of the drug.

IJP demands precise control of the process and formulative parameters (Azizi Machekposhti et al., 2019). The solution volume has to rationalized based on the substrate (Lee et al., 2012): varying the volume of solution jetted and/or changing the concentration of the feed determines the amount of drug deposited so that this technology is especially valuable in minimizing wastage of expensive drugs (Alomari et al., 2015). Moreover, the printing process and the distance between the support and the nozzle should be properly set up in order to avoid any smearing effects, especially when multi-layers are printed on the same support (Genina et al., 2013b).

Hence, the formulation of a printable ink depends the printer system and the mechanism of drop generation (Azizi Machekposhti et al., 2019; Genina et al., 2013b). The ink should be optimised at least in terms of viscosity, surface tension, boiling temperature (especially for thermal IJP), solvent

evaporation rate (De Gans et al., 2004). In particular, the surface tension (e.g., ~ 33 mN/m for thermal IJP) should be high enough to enable the formation of spherical droplets and to resist leakage from the print head when the printer is not in operation. The viscosity (≤ 20 mPa s) should be low enough that the fluid can be jetted out, but sufficiently high that the fluid is not ejected too early, which can lead to the formation of a tail, producing satellite droplets (Içten et al., 2015; Pardeike et al., 2011). When such parameters are not optimized, the fluid tail (i.e. CJP) can break off on its way toward the substrate causing the formation of different drops and resulting in a bad quality print (Raijada et al., 2013) or the nozzle can clog (Azizi Machekposhti et al., 2019). It is important that drops land in their designated coordinate on the substrate, because otherwise dose uniformity cannot be assured. Viscosity and surface tension also affect the refilling phase of the drop generator as the solution passes through spouts into the nozzle firing chambers (Alomari et al., 2015). Therefore, an ink formulation comprises surfactants and viscosity modifiers (Daly et al., 2015). Glycols such as polyethylene glycol (PEG) and glycerol are commonly used as viscosity modifiers (**Table 3**), but also humectants to avoid the clogging of the nozzle due to the rapid solvent evaporation. Moreover, a colourant can be added to the ink formulation to probe the drug distribution onto the ODF (Niese and Quodbach, 2018; Thabet et al., 2018c; Vakili et al., 2016; Wickström et al., 2017) or to easily differentiate the drugs upon dual deposition of drug fixed combination (Alomari et al., 2018).

The solvent should be selected as a function of drug solubility and the printing technology used. Aqueous solutions are more easily jetted out by thermal IJP since their boiling point generally falls in the optimal temperature range (90-95 °C) for this technology; on the contrary, piezoelectric systems can also be used with organic solvents since the drop formation depends on the mechanical stimuli produced by the piezoelectric sensor (De Gans et al., 2004). When an aqueous-based solvent system is used, the homogeneity of active substance dosing and deposition on the substrate may be challenging. However, the use of organic solvents has to be carefully evaluated in light of the

accepted regulatory threshold specification. Volatile solvents may also induce a rapid API recrystallization after jetting, producing an inhomogeneous deposition and nozzle clogging (Genina et al., 2013b). On the other side, the use of suspended API or the addition of surfactants can increase the payload of low-soluble active substances. Generally, the particle size of suspended API lower than 1-5 μm is a pre-requisite to avoid clogging (De Gans et al., 2004; Pardeike et al., 2011). In this context, nanocrystals or nanoparticles, were loaded into inks to improve the drug apparent solubility without affecting the ink printability (Pardeike et al., 2011; Planchette et al., 2016). For example, 10% nanocrystals of folic acid, a BCS class IV drug, were homogeneously deposited on a common edible paper (Pardeike et al., 2011).

In this type of contactless printing, ODF can be obtained on any pharmaceutical grade substrates, such as polymer-based films or placebo ODF (Genina et al., 2013b). However, the nature of substrate (**Table 3** determines the contact angle and the wettability (Wimmer-Teubenbacher et al., 2018), other than the disintegration time and the patient acceptability. The contact angle between the ink and the substrate influences both the payload and API physicochemical stability (Azizi Machekposhti et al., 2019). In presence of a high contact angle between the jetted drops and the substrate, API cannot be absorbed efficiently before the solvent evaporation and, therefore, it may be crystallized on the film surface with the risk of the API transfer onto the packaging material during storage (Buanz et al., 2013; Genina et al., 2013a, 2013b). Excipients able to improve the substrate porosity (e.g., crospovidone) was added to improve the absorption of API solution into the substrate if the contact angle cannot be further reduced (Genina et al., 2013b).

As an alternative to IJP, flexographic printing technology (FPT) was also proposed. FPT is an offset, rotary printing process in which the ink is metered by an anilox roller onto an unrolled placebo ODF obtained by casting (Janßen et al., 2013). Subsequently, the solvent is removed by a fan and the film is rolled up again. As an example, Janßen and co-workers successfully printed onto the drug-free ODF using both an API solution (i.e. rasagiline) suspension (i.e. tadalafil) (Janßen et

al., 2013). To improve the dose accuracy and/or tailor the drug release, Genina and co-workers combined jet-printing of an API solution on paper which was subsequently coated by a polymeric dispersion using FPT release (Genina et al., 2012). However, the use of FTP presents two problems regarding the filling of the cells of the anilox roller with ink and the transfer of the ink from the cell to the ODF. Formulation aspects connected to the solution viscosity, contact angles and, in case of suspension, crystal size (Genina et al., 2013a) are the most critical attributes.

Both IJP and FTP allow to maintain the main characteristics of placebo ODF/substrate and obtain ODF differing in terms of mechanical properties and stability compared with films prepared by casting (Janßen et al., 2013). Moreover, these technologies are more versatile and easier-to-use than other solvent-based ones (i.e. solvent casting, electrospinning). In addition, personalized ODF can be compounded by IJP in a pharmacy setting since the printer is generally adapted from common inkjet printer and is governed by common writing software (e.g., Microsoft Word®) (Genina et al., 2013b). However, the main IJP drawbacks can be identified in the narrow ink formulative space and API payload, together with the availability of placebo ODF to use as a substrate for the printing.

5.2 Fused deposition modelling

The possibility to adapt the fused deposition modelling (FDM) to the production of ODF was also explored. FDM involves the deposition of molten thermoplastic polymer filaments, usually with a diameter of 1.75 mm, through two heated extrusion rollers with a small orifice in a specific 3D laydown pattern which subsequently solidifies on a building plate (Chia and Wu, 2015; Goole and Amighi, 2016; Skowyra et al., 2015). The technology consists of a software-controlled print head that moves within the x- and y-axes; while the platform, which can be thermostated, moves vertically on the z-axis, creating 3D structures layer-by-layer with a thickness of 100–300 μm by fusing the layers together (Korpela et al., 2013; Skowyra et al., 2015). The critical parameters are related to the speed of the extruder, the infill density, the height of the layers and the temperature of

both the nozzle and the building plate. As summarized in **Table 3**, the literature describes only the preparation of polyethylene oxide (PEO) loaded by ibuprofen or paracetamol and poly(vinyl alcohol) and paracetamol (Ehtezazi et al., 2018; Jamroz et al. 2017). However, its application is limited by the availability of drug loaded-filaments made of a pharma-grade polymer, which are generally preliminarily prepared by hot-melt extrusion (Melocchi et al., 2016).

To overcome this limitation, hot-melt ram extrusion 3D printing was proposed for the preparation of small batches of personalized therapy (Musazzi et al., 2018b). This technique is based on three simple operations: (i) preparation of the mixture, (ii) feeding the mixture in the chamber of the ram extruder and heated and (iii) printing ODF directly onto the primary packaging material (**Figure 4**). Considering the small amounts of an extemporaneous batch, the low performances in terms of mixture homogeneity can be by-passed using ram extruders since all components are mixed before starting the extrusion. Promising results were obtained by loading high amount of paracetamol in a maltodextrin based ODF (Musazzi et al, 2018b).

6 Conclusion

Different technological solutions, available to prepare ODF, can be potentially chosen according to the physicochemical properties of the API and the batch size. Even if solvent casting is the only consolidate technology at industrial level, HME can be considered as a possible alternative despite the risk of detrimental effects of temperature on API chemical and physical stability.

The advent of printing and electrospinning technologies opens new solutions towards the personalization of the drug dose loaded into ODF: changes in shape and/or dimension would allow have a dose tailored for a specific patient or group; variation of colour would allow end-users to easily identify their own medicine, improving medication safety and adherence. Among printing technologies, IJP is the most investigated technique, even if the ink formulation and availability of edible substrates need to be evaluated case-by-case.

However, which quality controls and how to perform them remain a matter of debate as no clear regulatory requirements are defined in the main Pharmacopoeias, probably because of the novelty of this dosage form. As an example, in the Ph. Eur monograph of orodispersible films, the technological characterization includes only a dissolution test and the evaluation of mechanical strength, to assure ODF handling without any damages, but in both cases specific methods are not reported. It should be also mentioned that the assurance of quality is particularly critical in case of compounded ODF because the safety and quality remain under the responsibilities of pharmacists (Selmin et al., 2019).

The development of non-destructive methods enabling the determination of the uniformity of content in the production of ODF by the continuous manufacturing or by compounding magistral preparations on the basis of prescriptions, is highly desired. Among colorimetry and spectroscopic assays, near-infrared (NIR) spectroscopy appears the most promising since its use is widely adopted as a quality control tool in the pharmaceutical industry and hand-held devices are affordable.

The definition of non-destructive methods for quality control and the availability of printers suitable for the use in a pharmacy setting could open new and real perspective to tailor the dose by ODF.

The future of these production technologies depends also on the introduction of a regulatory pathway that permits the development and use of personalized medical products.

Figure captions

Fig. 1. Schematic view of the pilot-scale coating bench for continuous oral film manufacturing equipped with the optical probe for wet-film thickness measurement [reprinted from Niese and Quodbach (2018), with permission].

Fig 2. Unit-dose (UD) plate for casting ODF. (A) Top view. (B) Side view of casting solution confined in the casting well encircled by bank structures [reprinted from Foo et al. (2018), with permission].

Fig. 3. Schematic representation of a conventional drop-on-demand piezoelectric inkjet printing system for fabrication of drug-loaded microparticles [reprinted from Lee et al. (2012), with permission].

Fig. 4. The main features of hot-melt ram extrusion 3D printer for ODF (reprinted from Musazzi et al. (2018b), with permission].

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Table 1 – ODF prepared by solvent casting technologies, main components and features.

Apparatus	Film-forming polymer(s)	Plasticizer(s)	Solvent	Other formulative notes	Ref
Automatic film applicator	HPC, HPMC	GLY	Water	Tragacanth, xanthan gum or Arabic gum used as thickening agents	(Woertz and Kleinebudde, 2015)
Automatic film applicator	HPC, HPMC, PEO, SC	GLY, PG, PEG	Water	β-cyclodextrins for taste masking of donepezil	(Liu et al., 2018)
Automatic film applicator	HPMC	GLY	Water	Loading of prolonged-release diclofenac sodium micropellets	(Speer et al., 2019)
Automatic film applicator	HPMC	GLY	Water	Dissolution of the risperidone nanocrystals are carefully evaluated	(Steiner et al., 2017)
Automatic film applicator	HPMC	GLY, PEG 200	Water	Loading of prednisolone microparticles	(Brniak et al., 2015)
Automatic film applicator	HPMC	GLY, TPGS	Water	Loading of tadalafil nanocrystal	(Vuddanda et al., 2017)
Automatic film applicator	HPMC	PEG 1500	Water	Films cut using a rotary blade	(Khadra et al., 2019)
Automatic film applicator	PVA	GLY	Water/ethanol	Mesoporous silica nanoparticles as dissolution enhancers	(Şen Karaman et al., 2018)
Automatic film applicator + air-forced oven	MDX	GLY	Water	Loading of melatonin lipid microparticles.	(Musazzi et al., 2019)
Automatic film applicator + air-forced oven	MDX	GLY	Water	Improving film tensile strength by PVA nanoparticles	(Franceschini et al., 2016)
Automatic film applicator + air-forced oven	MDX	GLY	Water	Loading of quercetin nanocrystals	(Lai et al., 2015)

Automatic film applicator + air-forced oven	MDX	GLY, amino acids	Water	Used of amino acids as non-traditional plasticizer of maltodextrin	(Selmin et al., 2015)
Automatic film applicator + air-forced oven	Poly-sodium methacrylate, methyl methacrylate	PEG 400	Water	Evaluation of the residual water on film mechanical properties	(Musazzi et al., 2018a)
Automatic film applicator + air-forced oven	SC	Sorbitol	Water	QbD:	(Mazumder et al., 2017)
Continuous manufacturing apparatus	HPC, HPMC	GLY	Water, ethanol or acetone	Comparison with discontinuous process	(Thabet and Breitkreutz, 2018)
Continuous manufacturing apparatus	HPC, PVA	GLY	water/ethanol	Multilayer ODF	(Thabet et al., 2018a)
Continuous manufacturing apparatus	HPMC, PVA, HPC	GLY, triethyl citrate, citric acid	Water	Personalization of the dose by a cutter which allows the unroll of the loaded reel	(Niese and Quodbach, 2019)
Plate (acrylic)	Gelatin, SC	Sorbitol	Water	ODF as supplement carrier	(Garcia et al., 2018)
Plate (glass)	Guar gum	Sorbitol	Water	Prolonged release by alginate beads	(Castro et al., 2018)
Plate (glass)	HPMC	PG	Water	Disintegrants	(Zhang et al., 2015)
Plate (glass)	HPMC, PVA	PEG 400	Water	Lacidipine loaded as nanoparticles	(Chandra et al., 2018)
Plate (non-stick baking tray)	PVA/CMC	GLY	Water	Comparison with printed loaded with clonidine	(Buanz et al., 2015)
Plate (polypropylene)	HPC, Pectin	Not specified	Water	Loading of olmesartan nanocrystal	(Alsofany et al., 2018)
Plate (polypropylene)	HPMC E5	PG, GLY	Water/ethanol	poloxamer 407 and hydroxypropyl-β- cyclodextrin to improve the solubility of triclosan	(Dinge and Nagarsenker, 2008)

Plate (polypropylene)	PL/pectin (tamarind)	Sorbitol, GLY, glucose	Water	Taste masking of aprepitant by tamarind pectin	(Sharma et al., 2016)
Plate (Teflon®)	HPMC/chitosan	GLY	Water	Mannitol as drug release modifier (data on animal model)	(Singh et al., 2018)
Plate (Teflon®)	Kollicoat IR	GLY	Water	Optimization by QbD: orthogonal array Taguchi design	(Adeleke et al., 2018)
Plate (unit-dose)	HPMC E5	GLY	Water	Defined unit-dose	(Foo et al., 2018a)
Slab (glass)	HPMC	PEG400	Water	Loading of a self-emulsifying system	(Talekar et al., 2019)
Slab (glass) + polyester liner	MDX	Xylitol, sorbitol	Water	Addition of superdisintegrant in the film base	(Pechová et al., 2018)
Suction film applicator (Erichsen, Hemer, G)	PL/trehalose	GLY	Water	Loading of proteins, Drying by evaporation or sublimation	(Tian et al., 2018)
Vacuum film applicator (Erichsen, Hemer, G)	HPMC: Carbopol, HPC, sodium CMC	GLY	Water	Loading of poorly water-soluble diazepam	(Visser et al., 2015)

CMC: carboxymethyl cellulose, GLY: glycerol, HPMC: hydroxypropyl methylcellulose, HPC: hydroxypropyl cellulose, MDX: maltodextrins, QbD: quality by design, PEG: polyethylene glycol, PEO: polyethylene oxide, PG: Propylene glycol, PL: pullulan, PVA: polyvinyl alcohol. SC: pregelatinized starch.

Table 2 – ODF prepared by electrospinning, and HME technologies, main components and features.

Apparatus	Polymer	Solvent	Other notes	Ref
Electrospinning	Eudragit®E	-	Melt electrospinning	(Nagy et al., 2013)
Electrospinning	Gelatin	PG, water	Single and combination of lidocaine HCl and piroxicam loaded by inkjet on electrospun as a substrate	(Palo et al., 2017)
Electrospinning	PEO	Water	potassium iodate nanocrystals	(Rustemkyzy et al., 2015)
Electrospinning	PVA	Water	Riboflavin/caffeine fixed combination	(Li et al., 2013)
Electrospinning	PVA, Kollicoat IR, HPMC	Water	Solid dispersion of donepezil with improved dissolution	(Nagy et al., 2010)
Electrospinning	PVP	Ethanol	Amlodipine/valsartan fixed combination	(Bukhary et al., 2018)
Electrospinning	PVP K30	Ethanol	Solid dispersions of ketoprofen with improved dissolution	(Yu et al., 2010)
Electrospinning	PVP K30	Ethanol	Solid dispersions of ibuprofen electrospun with improved dissolution	(Yu et al., 2009)
Electrospinning	PVP K60	Ethanol	Paracetamol/caffeine fixed combination	(Illangakoon et al., 2014)
Electrospinning	PVP K90	Water/ethanol	Solid dispersions of irbesartan with improved solubility and dissolution	(Adeli, 2015)
Electrospinning	PVP K90, PVP K10	Ethanol	Taste masking of helicid with improved dissolution	(Wu et al., 2015)
HME	HPC	Triethyl citrate	Effect of Kollidon® VA 64 (KOL) and Soluplus® (SOL) on film dissolution and mechanical properties	(Low et al., 2013)
HME	MDX	Glycerol	Cellulose microcrystalline as an anti-sticking agent	(Cilurzo et al., 2008a)

HME	Modified starch	Glycerol	Continuous manufacturing with a degassing port attached to the extruder to avoid air bubbles.	(Pimparade et al., 2017)

HPMC: hydroxypropyl methyl cellulose, HPC: hydroxypropyl cellulose, MDX: maltodextrin, PEO: poly(ethylene oxide); PG: Propylene glycol, PVA: poly(vinyl alcohol), PVP: poly(vinyl pyrrolidone).

Table 3 - ODF prepared by printing technologies, main components and features.

Apparatus	ODF				
	Polymer/substrate	**Plasticizer**	**solvent**	**Other notes**	**ref**
Solvent-based methods					
Inkjet	Edible paper	-	3% Tween 20, water	Combination of nanocrystal and inkjet printing technologies	(Pardeike et al., 2011)
Inkjet	Edible substrate	-	PG/water (Caffeine ink), PG/ethanol (Loperamide ink).	Recrystallization of printed caffeine was observed on carrier surfaces; loperamide did not recrystallize on any substrates	(Genina et al., 2013a)
Inkjet	HPMC/GLY substrate	-	Ethanol	HPMC/HPC Structured template ODF prepared by casting	(Steiner et al., 2019)
Inkjet	HPMC/GLY substrate	-	Ethanol, DMSO, PG	Combination therapy	(Alomari et al., 2018)
Inkjet	HPMC/GLY substrate	-	PG, water	Impact of contract angle between jetted drop and substrate on printing homogeneity	(Genina et al., 2013b)
Inkjet	HPMC/GLY substrate	-	Polypropylene glycol, propylene carbonate and blue Milliyet dye 28 colourant	Stand-alone and continuous printing of ODF	(Thabet et al., 2018c)
Inkjet	HPMC/GLY substrate + mesoporous fumed silica	-	Lactic acid, ethanol, erythrosine	Quick response (QR) code generation	(Edinger et al., 2018)
Inkjet	PVA/CMC/GLY substrate	-	Methanol, water, GLY	Comparison with casting containing the same drug	(Buanz et al., 2015)

Inkjet	Rapidfilm® (Tesa Labtec)	-	Sodium picosulfate ink, polymeric nano-suspension ink, polymeric coating inks	Non-contact printing system that incorporates both piezoelectric and solenoid valve-based inkjet printing	(Planchette et al., 2016)
Inkjet	Sugar-sheet substrate	-	Ethanol, PG	Printing of poorly soluble drugs on a sugar-based substrate	(Eleftheriadis et al., 2018)
Thermal Inkjet	commercial potato starch film	-	Water, GLY	Salbutamol sulphate; 40 μg/cm^2 per print pass	(Buanz et al., 2011)
Thermal inkjet	Edible rice paper (Easybake®); sugar paper	-	Yellow edible ink (Deco Enterprises)	Printing on edible substrates and dose differentiation by ink colour intensity	(Wickström et al., 2017)
Thermal Inkjet	HPMC/GLY substrate	-	water	Ink was obtained by dissolving spray-drying microparticles of HPMC and warfarin in water;	(Vuddanda et al., 2018)
Solvent-free methods					
FDM	PEO; starch or PVA	PG	-	Single and multi-layered films printed with addition of superdisintegrants	(Ehtezazi et al., 2018)
FDM	PVA	-	-	Addition ethanol to moist the PVA/aripiprazole blend	(Jamróz et al., 2017)
Hot-melt ram extrusion 3D printing	Maltodextrin	GLY	-	API and film components prepared as paste; no solvent system used.	(Musazzi et al., 2018b)
Semisolid extrusion 3D printing	PVA; HPC	-	-	The polymeric component is wetted with a hydroalcoholic solution to allow the printing, no information on drying	(Sjöholm and Sandler, 2019)

CMC: microcrystalline cellulose, DMSO: dimethyl sulfoxide, FDM: fused deposition modelling, GLY: Glycerol, HPC: hydroxypropyl cellulose, HPMC: hydroxypropyl methylcellulose, PEG: polyethylene glycol, PEO: polyethylene oxide, PG: Polyethylene glycol, PVA: polyvinyl alcohol.