Orodispersible dosage forms: biopharmaceutical improvements and regulatory requirements

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Teaser

The technological and biopharmaceutical improvements of orodispersible dosage forms are reviewed in the light of the regulatory requirements.

Keywords

Biopharmaceutics, disintegration test, orodispersible, fast dissolving, patient compliance, regulatory affairs.

Abstract

Orodispersible dosage forms have a growing presence in the pharmaceutical market because their administration can improve the bioavailability of some drugs and their prescription can ameliorate the patient adherence and/or compliance. The current assessment reviews the main features of orodispersible tablets, including oral lyophilizates, and orodispersible films along with their main production technologies. The bioavailability data are summarized and the potentialities to improve the patient adherence and/or compliance are critically discussed. All these information is also revised in the light of both the EU and US regulatory frameworks, focusing on the differences in the definitions of such dosage forms and the requirements for marketing authorization.

Aiming to maximize the therapeutic potential of the active pharmaceutical ingredient (API) and facilitates its access to patients, different dosage forms have been proposed. Liquids (*i.e.* syrups, suspensions and solutions) can be easily swallowed and, in most of the cases, guarantee the largest bioavailability; even if the dose accuracy is limited using spoons or syringes to measure the volume to be administered. So, to solve this drawback, single dose sachets (*i.e.* a unit dose packaging) containing a defined dose as powder or granules or effervescent tablets dissolving and/or dispersing in water, have been introduced. However, the market is currently dominated by tablets and capsules. Indeed, both dosage forms allow delivering an accurate dose of the API and are capable of being economically mass-produced. Nevertheless, the administration of tablets or capsules is often associated to swallowing problems or fear of chocking so that there are a growing number of situations in which these products are not patient acceptable. Indeed, it is estimated that 20% of population have psychologic or physiologic impairments in swallowing tablets or capsules. This is particularly relevant for pediatrics, elderly and dysphagics [1]. Other groups that may experience problems using conventional oral dosage forms include mental ill, nauseated and uncooperative patients as well as people with reduced liquid-intake plans and travelers who may not have access to water [2]. To solve this issue and guarantee the benefits related to solid dosage forms, orodispersible dosage forms (ODx) are gaining increasing interest.

An ODx is defined as a dosage form intended to be placed in the mouth where they rapidly liberate the loaded active ingredient producing a fine suspension or solution of the API in the saliva. Thus, ODx improve the patient's compliance due to easily swallow without drinking or chewing and to assure an accurate dosing in comparison to liquid dosage forms. Beside the possible improvement of patient's compliance and/or adherence, ODx can modify the pharmacokinetic parameters according to the physicochemical features of the administered API. As examples, the extent of absorption of selegiline is significantly increased [2], while the bioavailability of piroxicam results unaffected after the administration by an ODx or an immediate release tablet [3].

Nevertheless, these two aspects are scantly discussed in literature, even if they are gaining an increasing impact on the requirements to grant a marketing authorization. In the present review, the main features of orodispersible tablets (ODT), including oral lyophilizates, and orodispersible films (ODF) are briefly described as well as their main production methods. The bioavailability data available in literature are summarized and the potentialities to improve the patient's adherence and/or compliance are discussed in the light of the EU and US regulatory frameworks. Reviewed articles were obtained from the PubMed, SciFinder and Scopus online databases.

1. The design of orodispersible dosage forms

The development of an ODx necessitates of specialized production methods and/or particular excipients, which are intellectually protected and/or required peculiar know-how. Two are the main ODx currently

available on the market: orodispersible tablets (ODT) or orodispersible films (ODF). Independently of the morphology, the common Achille's heel is related to the requirement for taste masking. Present methods of taste masking in ODx technologies include sweeteners and flavourings, microencapsulation or complexation [4]. Moreover, the balance between disintegration time and mechanical hardness of the ODx is intricate and affected both by process and formulation variables. Thus, the packaging design is usually optimized to protect the final dosage form from environmental moisture and/or mechanical stresses.

1.1. Orodispersible tablets

ODT present similar in appearance to conventional tablets, the rapid penetration of water through capillary action into the porous framework leads to disintegration in the 30 s - 3 min range [5, 6]. The main production strategies include lyophilisation, moulding or direct compression using peculiar excipients. Freeze-drying can be considered one of the key processes in the production of ODT. The solvent sublimation from a frozen solution or suspension of an API with matrix-forming excipients generally results in a porous and lightweight product, which dissolves instantly to release the API when placed in the mouth. In case of poorly water-soluble API, freeze-drying can also aid in achieving a final product with the desired physical or chemical characteristics by reduction of crystal size or the conversion from the crystalline to the amorphous form [7]. Moreover, since low-operation temperature allows to minimize the API thermal degradation, this technology has recently proposed also to develop ODT containing vaccines [8]. One of the most famous patented drug product, namely Zydis® tablets, is produced by freeze-drying after dispersing/dissolving the API in a water-soluble material directly in the blister [2]. Typical matrix forming excipients are gelatin, dextran or alginates. Mannitol is often used to increase the fluffy volume of the lyophilizate and glycine to prevent its shrinking during freeze-drying. The ideal drug candidates possess low water solubility, with fine particles (< 50 μm) and good aqueous stability in the suspension. For water soluble API, the maximum drug loading is around 60 mg [1].

Compression and heat moulding are the main approaches to prepare ODT using a moulding technique. The former involves moistening of the powder blend with a hydro-alcoholic solvent, followed by compression into mould plates to form a wetted mass. The wetted mass is, then, air-dried. In the heat moulding process, a molten mass containing a dispersed and/or dissolved drug is directly poured onto blister packaging. Then, the dispersion is solidified at room temperature.

In both cases, moulded tablets possess highly porous structure, which increases disintegration and dissolution rates. However, the addition of binders is often required to provide sufficient mechanical resistance and prevent tablet breaking. The dissolution and/or dispersion time of the API depends on its physical state in the matrix. On the other hand, the API can also dissolve partially or totally in the molten carrier, forming a solid solution, or a dispersion in the matrix, respectively [9].

Compression is a straightforward method of producing ODT with good mechanical strength. However, the relatively low porosity of a tablet matrix may reduce the water penetration, prolonging the disintegration time. The formulation methodologies to produce mechanically acceptable ODT include the use of excipients which can induce fast disintegration (e.g. effervescent agents or super-disintegrants [10]) or sublimation agents (e.g. menthol, camphor, thymol and ammonium bicarbonate [11]) or melting binders (i.e. binders that melt at body temperature [12] Among the market available products, Durasolv® and Orasolv® technologies are based on direct compression with or without effervescence excipients which allow to load a dose ranging from 0.125-500 mg and 1-750 mg, respectively.

Crystalline transition methods involving low compression forces to ensure high tablet porosity followed by post-manufacture treatment (i.e. heat or humidity) were also proposed to produce hard tablets without compromising disintegration time [13, 14]. However, possible variations on the drug solid state limit the application of these approach [12].

Particle engineering by means of blending [15], co-grinding [16] and freeze-drying [7] allows the design of new multifunctional excipients with improved mechanical or disintegration properties without developing a new chemical entity. As an example, the granulation of a low compressibility saccharide, such as mannitol which provides fast disintegration, with a high compressibility saccharide, such as maltose, produces strong compacts with high tensile strength and fast disintegration time [15]. And again, when freeze-dried amorphous sucrose mixed with mannitol was compressed at low compression strength, crystallization of the amorphous sucrose in the tablet occurred, increasing the tablet tensile strength without altering the original tablet porosity [13]. Moreover, spray-drying is considered a valuable tool for the development of tableting multifunctional excipients with improved flowability and porosity [12]. Similarly, freeze-drying produces hybrid excipient with high porosity and specific surface area [7].

1.2. Orodispersible films

ODF are gaining attention as a valuable alternative because they allow overcoming the fear of chocking and extending the patentability of ODx [17]. ODF are generally constituted of plasticized hydrocolloids or blends [18, 19] laminated and dried by a solvent casting technique and sealed in moisture-protecting packages [20]. Problems that may occur during the manufacturing process include entrapped air bubbles, inappropriate viscosity of casting solutions, insufficient uniformity of content, batch-to-batch variability and the effects caused by organic solvents (e.g. fast evaporation, residual solvent) [20, 21]. Hot melt extrusion (HME) is a suitable solvent-free alternative [19], even if the melting and thermal stability of the formulation have to be preliminary evaluated [22]. A promising manufacturing technique is printing of the API onto a plain film using inkjet printers, flexographic printers or a combination of both techniques [23, 24].

The restricted space of the oral cavity limits the size of the dosage form: ODF with a size of 2×2cm^2 and a thickness of 100 µm as well as a size of 2×3 cm^2 and a thickness of 350 µm are judged as acceptable [25].

However, different dose strengths may be obtained from the same formulation cut in different shapes so that ODF have been recently proposed as extemporaneous preparations for personalized use [26, 27]. Since the ODF weight is lower than 200 mg, the formulation space is reduced with respect to the ODT which can load up 500 mg of API and their use is limited to potent active ingredients. Moreover, both the loaded drug itself and the taste masking agent can influence the mechanical properties of the films [28, 29] so that the molecular weight of the film forming material should be accurately evaluated [30] or peculiar excipients added to the formulation [31, 32].

2. Drug bioavailability

ODx are intended to disperse rapidly upon contact with saliva after being placed in the mouth. Thus, it is generally perceived that the API administered by these dosage forms is more rapidly absorbed through the pre-gastric route from the mouth, pharynx and oesophagus providing a faster onset of action than the conventional immediate release tablets or capsules. Nevertheless, it should be kept in mind that the residence time of the drug on the pre-gastric mucosae is quite short. Indeed, the transit time of saliva from the buccal cavity to the stomach is in the order of seconds independently of the age [33]; while after swallowing the residual volume of a liquid in the oral, pharyngeal, and oesophageal tracts is about the 10% [34]. This value does not significantly change after the intake of an acidic liquid bolus [35]; while after the ingestion of a paste bolus, only the residues in the oesophagus significantly increases up to 50% [34]. Thus, the swallowing process leads to a complete removal of the disintegrated and/or dissolved ODx within 5 to 10 min [2]. In other words, an increase in the bioavailability occurs only if the drug has a (i) high solubility in the saliva; (ii) adequate water/octanol partition coefficient to diffuse through pre-gastric mucosae; (iii) pK_a to assure the presence of the undissociated form at the saliva pH. The most outstanding example is the case of selegiline since its administration by using an ODT improved both the AUC and C_{max} of about 5-folds with respect to a conventional dosage form [2]. This marked improvement of bioavailability allowed the reduction of the dose from 10 mg to 1.25 mg. Moreover, since the pre-gastric absorption avoids the first-pass metabolism, the side effects caused by metabolites were also reduced. However, the improvement of drug bioavailability is confined to a very limited number of API, e.g. flupentixol [36] or ketoprofen [37], and often to reach this goal, ODx is combined with a technology to improve the drug dissolution rate, as in the case of meloxicam [38].

Many reports underline that the intake of water can significantly affect the extent of API absorbed due to the washing of the pre-gastric mucosae. As an example, the bioavailability of vardenafil resulted slightly improved with respect to a conventional tablet only assuming ODT without drinking [39]. However, this trend cannot be considered a rule since in the case of rizatriptan the t_{max} was reached 0.67 h after drinking water, while the C_{max} was reached in 1.33 h in absence of water. This delay was attributed to decrease the transit time from the mouth to the GI tract where the drug is absorbed [40].

The influence of these dosage forms on the rate of drug absorption appears less relevant and it was described only in few and often very preliminary studies. As an example, the administration of piroxicam, as a freeze-dried tablet, gave a much faster absorption rate during the first hour after dosing (t_{lag} = 21.6 min) than the capsule formulation (t_{lag} = 59.4 min), although the bioavailability of the two formulations was similar [3]. Moreover, a significant reduction of the t_{max} values was found as in the case of valsartan [41] or sumatriptan [42]. **Table 1** compares the main pharmacokinetic effects related to the administration of conventional dosage forms or ODx.

The recovered data not only confirm that the improvement of the bioavailability is strictly related to the API physicochemical properties, but also that the technologies used to produce an ODx do not influence the biopharmaceutical performances. As a matter of fact, the bioavailability of rizatriptan administered by an ODT produced by freeze-drying or direct compression using calcium silicates was comparable [43]. Similarly, the bioavailability of ondansetron administered by an ODT or ODF is essentially the same, independently of the ingestion of water [44].

3. Improvement of patient compliance and medication adherence

The lack of compliance related to the intake of solid dosage forms (*i.e.* tablets and capsules) is particularly relevant in patients who do not like or have difficulty taking tablets or capsules. Effectively, swallowing problems can be due to psychological or objective reasons. The latter can be related to abnormalities of the head and neck, age-related degeneration of the oesophagus, trauma or surgery, neurogenic or muscular disorders, as well as the side effects of some API as in the case of anticholinergic effects responsible of dry mouth [45].

The issue of swallowing tablets or capsules involved all general populations, even if it appears more evident in special subpopulations. Beside paediatrics and geriatrics who can present an altered acceptance of dosage forms with respect to adults [46], dysphagia is particularly relevant in patients with mental health disorders due to a variety of causes such as psychiatric medication side effects or comorbid neurologic conditions [47].

Thus, challenges exist in the development of formulations for these special populations that, beside the assurance of a predictable drug absorption, should improve both the safety of the treatment (*i.e.* accuracy in dose regimen with respect to liquids) and patient compliance (*i.e.* to overcome the swallowing issues of solid dosage forms) [48]. In this sense, ODx, along with some multi-particulate dosage forms, can represent a valid solution. However, it should be considered that palatability is one of the main critical attribute for the success of the therapy by ODx. Moreover, the taste sensation of paediatric or geriatric populations is quite different from that of adults adding a further issue in the pharmaceutical development [46]. Thus, the combination of a taste masking technique with the production of ODx with a predefined dose is often mandatory, especially for paediatric drugs [4]. The widely used approaches for selecting taste masking

214 agents, namely flavours and sweeteners, are both *in vivo* panels of volunteers or *in vitro* tests (*i.e.* the
215 electronic tongue) [28, 30]. In any case, these studies are typically conducted in or calibrated on adults and
216 can obviously fail. The end-user acceptability is mainly studied in adults and very few data are available for
217 paediatrics [49]. A very recent work aimed to compare the attitudes towards dosage forms of school
218 children and adolescents, underlined that ODx and chewable tablets were the most accepted dosage forms,
219 even if it was not possible distinguish a preference between ODF and ODT [50].
220 Beside the possible therapeutic improvements, which can be achieved in subjects with swallowing issues,
221 ODx solve the administration of drugs in patients who are non-cooperative, or prone to spitting out drugs,
222 or suffer from diseases requiring restricted fluid intake, *e.g.* oedema or heart failure [51]. Moreover, the
223 convenience of ODF in being portable dosage forms is an advantage compared to ODT and liquid dosage
224 forms that can demand a special package for transportation or are only available in large bottles,
225 respectively [21].
226 In summary, patients with physical swallowing issues can perceive several benefits, which could improve
227 the medical adherence. As a matter of fact, in a crossover study, more than 75% of the sample group
228 reported willingness to swallow the ODT formulation in comparison to the conventional tablet and this
229 percentages resulted significantly greater in patients with neurologically-based swallowing problems [52].
230 This data suggested behavioural therapy and dysphagia management are usually necessary to address the
231 underlying cause of the disorder [45].
232 The relevance of ODx in the treatment of neurologic disorders was confirmed by many clinical studies
233 performed on olanzapine, risperidone and sodium valproate. As an example, a significantly greater
234 proportion of schizophrenic patients (92.9%) were compliant (>75% adherent by pill count) with their
235 olanzapine ODT with respect to the conventional tablet formulation (78.5%; P=0.015) [53].
236 Another subpopulation of patients who can benefit using ODx are bedridden patients, due to the reduced
237 likelihood of suffocation or choking. ODx would be also preferred by people affected by nausea, or
238 subjected to limited liquid intake, *e.g.* patients on dialysis or with severe urinary incontinence [45].
239 Moreover, patients who have to assume drug products that require frequent dosing may improve adhesion
240 to the therapy since ODx lead to a reduction of discomfort when water is not readily available. Such
241 hypothesis is supported by a study which compared the patient preferences when choosing conceptually
242 between taking a tablet once-a-day or an equally safe and effective, but significantly smaller, soft gel
243 capsule twice per day: the 82.8% preferred the soft gel capsule [54].
244 All these advantages improve the medication adherence and result in a beneficial cost-effectiveness. A
245 survey aimed to compare the medication compliance and safety profile of voglibose ODT and conventional
246 tablets, revealed the tendency of more than half of enrolled patients to switched from conventional tablets
247 to ODT, even if only the 1% patient were diagnosed dysphagia confirming the general improvement of the
248 compliance [55].

As reported above, the use of antipsychotic ODx may facilitate medication adherence reducing the risk of relapse and hospitalization. In a relative recent pharmaco-economic study based on model projections, olanzapine ODT therapy was costlier ($ 9,808 vs $ 9,533), but more effective in terms of a lower hospitalization rate (15% vs 16%) and better quality-adjusted life years (0.747 vs 0.733) than olanzapine conventional tablet therapy. This data confirmed that olanzapine ODT was more cost-effective than olanzapine conventional tablet [56].

4. Data requirements from a regulatory point of view in Europe and USA

In the attempt to compare the definition of the dosage forms able to disintegrate in short time in the buccal cavity in the European Union and the United States of America, several differences catch the readers' eye. Indeed, the FDA defines orally-disintegrating tablet [57] what the European Authority classifies as orodispersible tablets and oral lyophilizates [6] (**Table 2**). Likewise, the European term "orodispersible film" corresponds to "oral soluble film" in the US (**Table 3**). Some dissimilarities are also present in the quality, safety and efficacy data requested by the EMA and FDA to grant a marketing authorization. In general, the *in vitro* studies required to demonstrate the product quality are those reported in the Pharmacopoeia monographs. In the case of Ph. Eur., the "Tablets" and the "Oromucosal preparations" monograph arethe reference font for ODT [6] and ODF, respectively [58]. The USP reports the definition of both ODT and ODF in the "Pharmaceutical Dosage Forms" monograph [57]; while the product quality tests are indicated in the monograph on oral and mucosal dosage forms, respectively [59, 60]. The quality requirements of ODT are different from those of ODF: the disintegration of ODx is required by both the pharmacopoeias, whereas only the Ph. Eur. expressly indicates the dissolution test of ODF (**Table 2**; **Table 3**). Nevertheless, a great variability in the acceptance limit for the disintegration of an ODT is reported : it is less than 3 min in Ph. Eur. [6] and approximately 30 seconds or less for the FDA [5], although more stringent (10 seconds) [61] or wider acceptance time limits (1 min) can also be found in the USP monographs [62].

According to all the regulatory sources, disintegration and dissolution testing are carried out by using the compendial disintegration and dissolution apparatus and protocols intended for oral dosage forms [63, 64]. The use of sinkers, or other supports, is acceptable to avoid floating. However, the experimental set-up cannot be considered an accurate model of the physiological condition in the buccal cavity [65]. For example, the medium volume generally used is significantly larger (up to 0.5 L) than the few millilitres of saliva present in the buccal cavity. Hence, several strategies were proposed to evaluate the ODx disintegration in static or dynamic conditions (*e.g.*, shaking or swirling) [65], or using small volumes (from 2 to 25 mL) in Petri dish instead of the common vessels and sample holders as supports [66]. Especially for ODF, alternative test endpoints (e.g., film break, swelling, hydration patterns) was suggested to be more reliable than the complete disintegration as reported in the compendial assay [65, 66]. Although

disintegration is one of the most critical attribute in the development of an ODx, the dissolution of the API particles in physiological fluids should be also considered in the light of the possible repercussions on its pre-gastric absorption. No saliva-model medium is officially available and the dissolution media currently indicated in the pharmacopoeia monographs (*e.g.*, water, pH 6.0 phosphate buffer, 0.1 N hydrochloric acid, pH 4.0 sodium acetate trihydrate buffer) vary according to the physicochemical properties of API to be tested [61, 62, 65-69]. In this context, it is noteworthy that pH 6.0 phosphate buffer solution is proposed as dissolution medium as it is already reported for medicated chewing gums by the Ph. Eur. [70]. In addition, to better model physiological buccal conditions (*e.g.*, mechanical stress induced by tongue, saliva flow, small volume of fluids), different methodological approaches were used to characterize ODF and ODT [65]. Recently, in the attempt to propose a novel biorelevant method to study API dissolution, a common paddle dissolution apparatus was adapted with an additional device, designed to control the medium volume in contact with ODF, imitating the saliva flow (0.22-0.82 mL/min) and the mechanical stress of tongue. Using such apparatus, the dissolution rate of a drug-loaded ODF was slower than by using conventional dissolution methods [71].

The impact of ODx on patient compliance and adherence along with the possible modification of the API bioavailability, especially if subjected to pre-gastric absorption, guided the regulatory agencies to upgrade the regulatory frameworks [72-74] and adopt specific product guidelines regarding the clinical aspects [75]. These regulatory interventions are particularly relevant for new drug products containing an API which is a component of an already granted medicinal product. The clinical studies required to support the marketing authorization of an ODx can be reduced in presence of a proof of bioequivalence, as already established for all other solid dosage forms [76, 77].

Among parameters that can influence the API pharmacokinetic, its aqueous solubility, absorption site in the gastrointestinal tract and administration modalities should be taken in consideration during clinical studies. According to the EMA guideline on bioequivalence, the modalities of administration (*e.g.*, with or without water) is also crucial in the design of the bioequivalence study [72] and, therefore, three are the possible scenarios to compare the performances of a new ODx and a marketed reference medicinal product. First, the reference product can be administered with or without water and the bioequivalence study should be performed without water, which is considered the most critical condition by the EMA. Secondly, the reference product is taken only in one way (*i.e.*, with or without water) and the bioequivalence study should be performed in the same way. Finally, if the reference product is taken only in one way (*e.g.*, with water) and the product under evaluation is proposed to be administered in the other (*e.g.*, without water), then the new product should be tested in both modalities of administration with respect to the reference product administered in only one way. Moreover, it should be underlined that for high soluble API (*i.e.*, BCS class I and III) with prevalent absorption in the stomach and intestinal track, the dissolution profile of the drug product can be considered as the bottle-neck factor to predict and compare the biopharmaceutical

performances of a test product with respect to the reference. In this case, both the Regulatory Authorities accept the use of biowaivers as surrogate of the bioequivalence studies for drug products containing API not absorbed at pre-gastric level [72, 73]. For example, the FDA states that biowaiver studies can be used to compare the biopharmaceutical performances of dosage forms characterized by a very rapid (85% within 15 min) or rapid (85% within 30 min) *in vitro* dissolution profile [73]. Otherwise, when the active ingredient is absorbed in the oral cavity (*e.g.*, selegiline) or is poorly soluble in water, a bioequivalence study is required at least. Indeed, the faster API release by ODx can alter its pharmacokinetics and, consequently, its therapeutic efficacy.

Beside such critical aspects related to the design of the bioequivalence study, the identification of the reference product could be also challenging. Indeed, due to the relative novelty of such dosage forms on the market, an already-on-the-market ODx can be not available. As a consequence, conventional immediate release dosage forms are generally used as references. In this context, two possible situations can emerge: (i) the bioequivalence between ODx and the reference product is demonstrated and, therefore, the ODx can be considered a generic product; (ii) the two products are not bioequivalent and appropriate preclinical and clinical studies may be required to obtain the marketing authorization. In EU, this condition falls in the hybrid procedure described by Article 10(3) of Directive 2001/83/EC. In US, a similar approach is represented by 505(b)(2) NDA application [78]. In both the cases, although the preclinical and clinical data are generally less than those required by the Agency to applicants for a first-in-man drug product, the authorization dossier should appropriately support the safety and the efficacy of the new ODx.

5. Conclusions

The assessment of the literature underlines that ODx can be advantageously exploited to improve the compliance of patient population with special needs. On the other hands, the claimed improvement of bioavailability cannot be generalized, since it is strictly depended on the main features of the loaded drug and, sometimes, the modality of administration.

The role and peculiarities of ODx in the pharmaceutical scenario is also indirectly recognized by the regulatory Authorities who are updating the relative pharmacopoeia monographs. However, the definitions reported in the EU and US differ in some points and, therefore, it is highly desirable a process of harmonization to favour the procedure for market authorization avoiding the development of drug product that, otherwise, should satisfy different specifications in different markets. In order to reach this goal, the development of specific compendia assays is also advisable. In particular, novel disintegration and dissolution tests should be appositely developed to improve the biorelevance of *in vitro* data obtained, taking advantage from the biorelevant strategies already proposed in literature for both ODT and ODF. Until now the attention of regulatory agencies is mainly focused on the clinical aspects rather than on the

upgrade of the disintegration and dissolution tests used for controlling the quality of ODT and ODF. This regulatory gap is particularly critical since the disintegration and dissolution of an ODx are two of the most critical attributes studied during the pharmaceutical development of a novel drug product and included in the quality controls at batch release. Moreover, the definition of peculiar experimental protocols would also improve the correlation between *in vitro* data included in the quality part of authorization dossier and the *in vivo* data of bioavailability and other factors that may affect the patient compliance (*e.g.*, a bad tasting sensation due to a slow dissolution of a bitter API).

Finally, from the market standpoint, it is relevant underline that while ODT are consolidate dosage forms, the number of ODF reaching the market is still limited, even if the first over-the-counter product (*i.e.* Chloraseptic® Relief Strips, a bilayer film loaded with benzocaine intended for the treatment of sore throat) was launched in US in 2003. This can be due to different reasons, a mong which, technological issues could play a key role. Indeed, the production of ODF required both specialized production equipment and manufacturing area with humidity controls. Furthermore, the formulations are still covered by intellectual properties and this could be considered a strong point for industries and, therefore, a future diffusion of ODF on the market, but also their weakness.

Conflicts of Interest

Paola Minghetti and Francesco Cilurzo are members of the board of directors of Pharmafilm srl – Spin Off of University of Milan involved in the development of ODF.

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Table 1 – Main pharmacokinetic parameters after the administration of orodispersible films (ODF) or tablets (ODT) in humans with respect to conventional dosage forms. The reviewed publications were identified by searching Scopus, PubMed and Web of Science and combining the following key words: orodispersible or fast-dissolving or fast-disintegrating and bioavailability or pharmacokinetics or C_{max} or AUC.

API	Dosage form	Process (peculiar excipient)	Water Intake	$AUC_{0-\infty}$ (CV%) (ng x h/mL)	C_{max} (CV%) (ng/mL)	t_{max} (h)	Ref.
flupentixol	ODF	Casting (HPMC E5)	N	11.73±6.72	0.144±0.046	1.5	36
	IR	Tablet	N	7.76±2.94	0.115 ± 0.016	4.0	
olanzapine	ODF	Casting (API as solid dispersion)	-	2.75±0.50	14.22±2.95	2.8	79
	ODT	Freeze-drying (Zydis®)	-	125.34±34.18	12.96±2.64	3.8	
rizatriptan	ODT	Freeze-drying	N	75.5±22.2	20.8±11.4	1.33	43
	ODT	DC (calcium silicate)	N	76.9±25.8	20.3±9.5	1.29	
	IR	-	Y	69.88	27.29	0.7	40
	ODT	-	Y	69.94	29.07	0.7	
	ODT	-	N	66.13	20.04	1.3	
sumatriptan	ODF	Casting	-	43.70±12.23	10.78±4.14	0.3	42
	IR tablet	DC	-	39.84±12.01	8.59±3.17	2	
	Sublingual ODT (25 mg)	DC (co-processed excipient)	-	51.29±4.91	2.5	10.0	80
	IR (25 mg)	DC	-	39.84±5.39	2	8.6	
	ODT (50 mg)	-	-	103	30	0.8	81
	IR (50 mg)	DC	-	199	52.2	1.0	
	ODT (100 mg)	-	-	105	29.1	1.0	
	IR (100 mg)	DC	-	175	52.3	1.0	
sumatriptan	ODF (25 mg)	Casting (anti-nucleant agent)	-	43.70±12.23	10.78±4.14	0.3	42
	IR (25 mg)	DC	-	39.84±12.01	8.59±3.17	2.0	
sildenafil	ODF		N	685.65 (4.37)	267.21(4.68)	-	82
	FCT	-	N	666.28 (4.60)	285.97(5.32)	-	
sildenafil	ODF (100 mg)	Casting	N	2000.10±1000.96	645.30±281.83	0.75	83
	FCT (100 mg)	-	Y	1932.13±987.70	664.96±317.91	0.75	
amlodipine	ODT	-* (mannitol)	N	481.4 (162.3)	-	8.0	84
			Y	495.9 (149.7)	-	8.0	
	Capsule	-	Y	498.6 (133.0)	-	8.0	
meloxicam	ODT	DC (API as solid dispersion)	N	40.189±7.430	1.589±0.159	3.5	38
	IR	Tablet	Y	37.830±9.879	1.242±0.203	5.8	
valsartan	ODT	Freeze-drying	-*	14710 ± 4437	2879 ± 244	1.1	41

	IR	DC	-*	10870± 1300	1471 ± 553	2.2	
ondansetron	ODF	Casting	N	203 (51.2)	28.4 (39.6)	2.0	44
	ODT	Freeze-drying (Zydis®)	N	214 (47.5)	28.7 (37.4)	2.0	
escitalopram	ODT (1x20 mg)	-*	N	650±221	20.7±4.5	3.0	85
	ODT (2x10 mg)	-*	N	628±213	20.0±4.2	3.0	
	IR (2x10 mg)	DC	Y	658±218	22.0±5.6	3.0	
ketoprofen	ODT	Freeze-drying	N	3347 (18.0)	1490±316	0.3	37
	IR	DC	Y	2038 (21.2)	1020±240	0.5	
piroxicam	ODT	Freeze-drying	-	134967 (13.6)	1812 (4.4)	4.8	3
	IR	Capsule	-	135031 (12.6)	1900 (5.1)	5.2	
granisetron	ODT	-*	-*	47.27±14.73	7.42±2.19	1.3	86
	IR	Capsule	-*	41.54±10.84	7.32±2.35	1.4	
vinpocetine	ODT	Freeze drying (API in β-CD)	-	488.72±12.82	39.18±8.71	0.8	87
	ODT	Freeze drying (solid dispersion)	-	428.71±9.35	34.41 ± 8.24	1.1	
	IR	DC	-	249.43±14.67	25.20±8.09	1.5	
terbutaline sulphate	Sublingual ODF	Casting	-	176.12±8.45	12.525±2.04	2.5	88
	Tablet	--	-	86.298±5.51	8.143±1.10	3.5	

DC: direct compression; IR immediate release (conventional) dosage form; FCT: film coated tablet; * unknown; **after drug product administration.

Table 2 – Definitions, quality controls of an ODT and in vivo studies required to support the equivalence to a conventional drug product.

	Ph. Eur. 9.1	**EMA guidelines**	**USP 40**	**FDA guidelines**
	Orodispersible tablet [6]; *oral lyophilizates* [6].	*Orodispersible tablets*	*Orally-disintegrating tablet*; *Lyophilized oral products* [57]	*Orally-disintegrating tablet* [5]
			Definition	
	Orodispersible tablet: uncoated tablets intended to be placed in the mouth where they disperse rapidly before being swallowed; Oral lyophilizates: solid preparations intended either to be placed in the mouth or to be dispersed (or dissolved) in water before administration [6].	Not available	Preparations intended to disintegrate rapidly within the mouth to provide a dispersion before the patient swallows the resulting slurry where the API is intended for gastrointestinal delivery and/or absorption [57].	Solid oral preparations that disintegrate rapidly in the oral cavity, with an in-vitro disintegration time of approximately 30 seconds or less, when based on the USP disintegration test method or alternative [5].
			Quality controls	
Disintegration	< 3 min in water [6].	Not available a specific guideline on quality.	Variable as function of drug product. For example: < 10 s [61]; < 30 s [67]; << 60 s [62].	≤ 30 s USP disintegration test Alternative methods can be used only if they demonstrate to be equivalent to USP methods [5].
Dissolution	Not reported an ODT-specific assay [6].	Not available a specific guideline on quality.	Variable as function of drug product. For example: ondansetron > 80% in 10 min [61]; donepezil > 80% in 30 min [62]; clonazepam > 75% in 60 min [89].	Not reported an ODT-specific assay.
Water content	Only for oral lyophilizates [6].	Not available a specific guideline on quality.	Only for lyophilized oral products [59].	Not reported an ODT-specific assay.
			Equivalence to another marketed oral immediate release product	
Pre-gastric absorption	-	Bioequivalence study; Appropriate non-clinical and clinical studies in the case of a not-bioequivalent product [72, 75].	-	Bioequivalence study; Appropriate non-clinical and clinical studies in the case of a not-bioequivalent product [73].

Only Gastrointestinal absorption	-	Biowaiver studies for rapid and very rapidly dissolving drug products containing API included BCS class I and III are admitted [a]; Bioequivalence study; Appropriate non-clinical and clinical studies in the case of a not-bioequivalent product [72].	-	Biowaiver studies for rapid and very rapidly dissolving drug products containing API included BCS class I and III are admitted [a]; Bioequivalence study; Appropriate non-clinical and clinical studies in the case of a not-bioequivalent product [74].

[a] test and reference drug products contain the same salt, ester, ether, isomer, mixture of isomers, complex or derivative of an API. The preparation is considered “very rapidly” dissolving when more than 85 % of the labelled amount is dissolved within 15 min, using paddle or basket methods, in pH 1.0 – 1.2, pH 4.5, and pH 6.8 [72, 73].

Table 3 – Definitions, quality controls of an ODF and in vivo studies required to support the equivalence to a conventional drug product.

	Ph. Eur. 9.1 *Orodispersible film [58]*	**EMA guidelines** *Orodispersible film*	**USP** *Oral films [57]*	**FDA guidelines** *Soluble film [90]*
		Definition		
	Single- or multi-layer sheet of suitable materials, to be placed in the month where they disperse rapidly [58].	Not available.	Thin sheets that are placed in the oral cavity. They contain one or more layers. A layer may or may not contain the API [57].	A thin layer or coating which is susceptible to being dissolved when in contact with a liquid [90].
		Quality Controls		
Disintegration time	Not reported an ODF-specific assay [58].	Not available a specific guideline on quality.	Not reported an ODF-specific assay [57].	Not available a specific guideline on quality.
Dissolution profile	Suitable test to demonstrate the appropriate release of API [58].	Not available a specific guideline on quality.	Required, but the assay is not indicated [57].	Not available a specific guideline on quality.
Mechanical properties	Required, but the assay is not stated [58].	Not available a specific guideline on quality.	Required, but the assay is not stated [57].	Not available a specific guideline on quality.
		Equivalence to a marketed drug product		
	-	The same approaches indicated in **Table 2.**	-	The same approaches indicated in **Table 2.**