

Orally Disintegrating Tablets

The Effect of Recent FDA Guidance on ODT Technologies and Applications

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Figure 1: Cross-section of a lyophilized ODT showing the highly porous structure.

The authors describe the various available technologies used in orally disintegrating tablets (ODTs). They also discuss the recent implications of the US Food and Drug Administration's *Guidance for Industry: Orally Disintegrating Tablets*.

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New drug-delivery technologies are often championed by contract manufacturing organizations. For new technologies that provide significant clinical as well as financial value, research and innovation in the contract-manufacturing and pharmaceutical segments lead to the emergence of numerous competing versions of the technologies.

Such a technology evolution has been evident for orally disintegrating tablets (ODTs). Designed to disintegrate rapidly on contact with saliva and enable oral administration without water or chewing, these formulations offer increased convenience and ease of administration with the potential to improve compliance, particularly in certain populations where swallowing conventional solid oral-dosage forms presents difficulties.

The Zydis (Catalent Pharma Solutions, Somerset, NJ) lyophilization technology provided the first approved ODT (Claritin Reditabs, Schering Plough, Kenilworth, NJ) in the United States in 1996. The earliest US regulatory definition for an ODT reflected the lyophilized ODTs that prevailed at the time. An ODT was defined as “a solid-dosage form containing medicinal substances which disintegrates rapidly, usually within a matter of seconds, when placed on the tongue (1).”

The emergence of multiple ODT technology platforms created some regulatory challenges due to increasing variance in the critical-product attributes of ODTs, notably disintegration time and tablet size. It can be assumed that the regulatory challenge was most acute for generic product applications. Hypothetically, in an abbreviated new drug application, the disintegration time of a generic product could be 30–45 s, and the disintegration time of a reference product 0–10 s.

Prolonged disintegration times may result in failure to meet the defining performance characteristics of the ODT dosage form, such that the product might require water for administration or chewing to facilitate swallowing. Where the patient or caregiver's expectation is for rapid dispersion in the mouth, larger units with slower disintegration times could result in confusion regarding the product quality and even present a choking hazard. Thus, in addition to product definition, patient safety is also a

significant consideration.

The US Food and Drug Administration responded to this challenge with the 2008 publication of *Guidance for Industry: Orally Disintegrating Tablets (2)*. Three main points stand out in the final guidance:

- ODTs should have an *in vitro* disintegration time of approximately 30 s or less (using *United States Pharmacopeia* disintegration test or equivalent).
- Generally, the ODT tablet weight should not exceed 500 mg, although the combined influence of tablet weight, size, and component solubility all factor into the acceptability of an ODT for both patients and regulators.
- The guidance serves to define the upper limits of the ODT category, but it does not supersede or replace the original regulatory definition mentioned. In other words, disintegration within a matter of seconds remains the target for an ODT.

The public comment process for the guidance provided valu-

Table 1: Target quality and performance attributes for orally disintegrating tablets (ODTs).

Attribute	Target	Comments
Disintegration	Disintegrates rapidly, usually within a matter of seconds, when placed on the tongue, without the need for chewing or liquids	FDA ODT guidance* recommendation
	< 30 s <i>in vitro</i> (USP)	FDA ODT guidance recommendation
Tablet weight	< 500 mg (finished product)	FDA ODT guidance recommendation
Dose range and accuracy	Meets requirements for drug product	As applicable to solid oral-dosage forms
Physical and chemical stability	Sufficient to provide adequate shelf life for the product	As applicable to solid oral-dosage forms
Robustness	Sufficient to ensure physical integrity during packaging, transport and patient handling	As applicable to solid oral-dosage forms
Drug delivery/ pharmacokinetics	Meets requirements for drug product (e.g., localized absorption, rapid absorption, enhanced bioavailability, and delayed-release)	Most ODTs are bioequivalent to conventional oral dosage forms, but some meet specific drug-delivery requirements.
Palatability	Appropriate for target patient population	Minimum bitter taste intensity and duration; absence of gritty texture desirable

*FDA ODT guidance is *Guidance for Industry: Orally Disintegrating Tablets (2)*.

able insight into the broad range of patient, regulatory, and industrial interpretation of the requirements for ODTs. One theme evident in the guidance document and the associated discussion is that patient acceptance is especially critical for ODTs. In addition to tablet size and disintegration rate, factors affecting patient acceptance of ODTs include palatability (i.e., taste, texture, and mouthfeel) and convenience (i.e., ease of handling). Patient acceptance can be harder to measure, quantify, and define appropriate limits for compared with other product attributes. What is regarded as acceptable is influenced by factors such as the condition being treated, frequency of dosing, and motivation of the patient.

Although these additional factors may determine patient preference for the product and potentially influence compliance as well as the overall commercial success of an ODT, they are not considered the key defining characteristics of the dosage form. The inclusion of palatability criteria was debated during the guidance-consultation process, but its eventual omission suggests FDA recognition of this. Nevertheless, patient-acceptability considerations are evident in all aspects of the FDA guidance document, which sets the precedent for future growth and innovation in the ODT sector.

Despite the publication of the FDA guidance for ODTs, this category of dosage form lacks globally harmonized nomenclature and criteria. For example, the *European Pharmacopeia* defines orodispersible dosage forms as having a disintegration time of less than 3 min (3). It is the authors' experience that such differences do not result in inconsistent regulation of ODTs in different regions, but greater harmonization would be preferable.

Pediatric application of ODTs

Although ODTs in general offer improved convenience and are frequently preferred over conventional solid oral-dosage forms, ODTs may lead to significant improvements over current treatment options for specific patient groups, for instance, pediatric patients. The European Medicines Agency's Committee for Medicinal Products for Human Use (CHMP) described orodispersible dosage forms as having "great promise for children" (4). The use of an ODT formulation of ondansetron has been found to be helpful in the treatment of children as young as 6 months of age suffering from gastroenteritis and dehydration (5).

To enable the potential benefits of ODT formulations to be fully realized, the additional requirements of this group also need to be considered, and the ease with which the different types of ODT can be adapted to meet these requirements will affect their overall application and commercial potential. Clearly, size and disintegration time are particularly important. A fast disintegration time will reduce any potential choking hazard and will also make it harder to spit out the dose. Similarly, the taste and texture of pediatric formulations are critical to facilitate compliance in children, particularly for chronic conditions where repeated administration may be an issue. Specific consideration needs to be given to the type and level of flavors and sweeteners used in pediatric formulations, especially where artificial ingredients are used. The choice and level of other excipients requires similar review for pediatric formulations, where there may be established limits for children or where there is a lack of excipient safety data

for this population.

As solid-unit doses, ODTs generally offer improved dose accuracy, storage, and stability advantages over liquid preparations. However, for pediatric applications, ODTs also need to be able to accommodate a wider range of doses, particularly at the lower end. ODT technologies that can offer low-dose accuracy will be of particular benefit to this group. In addition, clinical studies in pediatrics are required to confirm acceptable safety and efficacy in the target patient group, but the initial selection of an ODT for pediatric indications and compliance with the FDA ODT recommendations would help to eliminate the risk of unsuccessful administration.

ODT technologies

As discussed, the need for the ODT guidance was precipitated by the range of available ODT technologies and their differing product characteristics. The formulation and process considerations of these different technologies and the product characteristics relevant to their performance as an ODT are reviewed in the following section. Thin-film technology, while not falling under the definition of an ODT, is designed to meet the same objective of oral delivery without administering water or chewing, and is also mentioned. The product attributes desirable for ODTs are summarized in Table I.

Current commercially available ODT technologies can be broadly categorized according to their method of manufacture as follows:

- Lyophilized tablets
- Compressed tablets
- Other (including molded tablets, spray-dried powders, and sugar floss).

Examples of each ODT technology platform are provided in Table II.

The ability of a particular ODT technology to meet the desirable ODT quality and performance attributes, including the recommendations of the FDA guidance document, largely depends upon the formulation and process approach on which the ODT is based. A brief overview of each technology platform is further discussed in this article, and a comparison of product process requirements and attributes is provided in Table III. Examples of specific product performance are also given in Table IV.

Lyophilized products

Zydis. The Zydis technology is an example of a technology platform for lyophilized ODT products. The basic formulation and process for lyophilized ODTs are all similar, but there are some important differences between each lyophilized ODT technology, which result in significant variation in performance.

To create ODTs using the Zydis lyophilization technology, the active pharmaceutical ingredient (API) is dispersed in a matrix

Table II: Orally disintegrating tablet technology platforms.

Technology Platform	Proprietary Technology	Company	Examples of commercial products*
Lyophilized	Zydis	Catalent	15 commercial products, including Grazax and Claritin
	Lyoc	Cephalon	7 commercial products, including Proxalyc and Loperamide Lyoc
	Pharmafreeze	SPI Pharmaceuticals	Unknown
	Quicksolv	Janssen	Risperdal
Compressed Tablets	AdvaTab	Eurand	AdvaTab cetirizine Lactimal ODT
	Orasolv/ Durasolv	CIMA Labs	Remeron Soltab Zomig-ZMT Niravam FazaClo Orapred
	Flashtab	Ethypharm	Prevacid Solutab Ibuprofen
	Pharmaburst	SPI Pharmaceuticals	Not known
Sugar floss	Flashdose	Biovail	Ralivia
Molded tablet	WOWtab	Yamanouchi/Astellas	Benedryl FastMelt

*Proprietary technology and product examples are trademarks and registered trademarks, except for ibuprofen.

consisting of a polymeric structure former (e.g., gelatin) and a saccharide (typically mannitol) dissolved in water. In the finished product, the glassy amorphous structure of the polymeric component imparts strength and resilience while retaining some flexibility. The specific grade of gelatin typically used and its associated dissolution characteristics ensure a smooth, rapid melt in the mouth. Mannitol crystallizes during freezing, thereby providing an elegant appearance and rigidity and ensuring that the product is robust to handling and transport. Because mannitol is readily soluble, it also has the function of improving texture, taste, and mouthfeel.

Depending on its solubility, the API may be dissolved in the matrix or dispersed to form a homogenous suspension for dosing. The liquid dosing process ensures good dose uniformity and can accommodate extremely low-dose strengths (i.e., micrograms), particularly important for low-dose pediatric applications.

For suspension products, dose strengths of up to 400 mg can be accommodated, and the API is typically micronized. Particles in excess of 50 μm may feel gritty, so particle size is an important consideration. For solution products, due to the depression of freezing point by the soluble API, dose strengths of up to 60 mg are achievable. In both solution- and suspension-based products, the API is finely dispersed in the dried unit, contributing to rapid dispersion and smooth mouthfeel.

In addition to the basic structure-forming components and API, other excipients may be included in the formulation such as pH-modifying agents for optimal stability or taste-masking effect, and flavors and sweeteners for palatability. If necessary, other taste-masking strategies such as complexation with ion-exchange resins or encapsulation of the API may also be consid-

ered, though the larger particle sizes and need to maintain the integrity of taste-masked particles during the mixing and dosing steps are more challenging with this technology.

The active mix is dispensed into preformed blister packs, which travel through a tunnel cooled with liquid nitrogen to freeze the product rapidly. After freezing, the product is lyophilized, and the dried blisters are sealed.

The freezing process results in a network of ice crystals that are sublimed during lyophilization to produce a highly porous structure (see Figure 1). The matrix components maintain the structure of the dried unit, but on contact with moisture, the high porosity leads to rapid penetration of water. The matrix quickly dissolves, resulting in the fast disintegration characteristics of Zydis products. *In vitro* disintegration times of less than 10 s are typical of Zydis products and are clearly well within the FDA ODT guideline of 30 s.

The product is dosed and dried in an all-aluminum blister pack, which offers good physical and environmental protection. The product slightly adheres to the pack, resulting in minimum movement of the product within the blister pockets to ensure robustness during transportation. The product is a wafer-like structure but of minimum friability and of sufficient strength to be removed from the packaging without breakage.

The wafer-like structure and high porosity of Zydis formulations reflect the fact that water is typically the major component of the dosing formulation, so that the weight of the dried product is significantly reduced and often dictated primarily by the dose of the API. The recommended 500-mg weight limit for ODTs is only likely to be approached for the very highest doses in Zydis formulations, and would be offset by the rapid disintegration. The generally low-exipient load is also advantageous for pediatric formulations.

Following administration and rapid dispersion on the tongue, the Zydis formulation effectively reverts to the original API solution/suspension. Therefore, the Zydis ODT provides all the convenience of a solid oral-dose form with the advantages of a

solution/suspension product.

The Zydis product has found wide applicability to achieve a range of clinical applications such as:

- Products bioequivalent to conventional tablets
- Products suitable for pregastric (buccal and sublingual) uptake to enhance bioavailability and avoid first-pass metabolism, thereby minimizing undesirable metabolites
- Stable protein and peptide products
- Vehicles suitable for the delivery of oral vaccines
- Physical and chemically stable products with shelf life comparable to conventional tablets approximately two to five years.

Quicksolv. The Quicksolv technology (Janssen, a subsidiary of Johnson & Johnson, New Brunswick, NJ) process is similar to the Zydis technology in that an aqueous dispersion of the API and matrix components is first formed and then frozen. Water removal from the frozen matrix can be performed either by lyophilization or submerging frozen product in alcohol (solvent extraction) to produce a dry unit (7). The product formed has uniform porosity and adequate strength for handling. The product has similar properties to that of the Zydis product (7).

Lyoc. The Lyoc process differs slightly in that an oil-in-water emulsion is prepared and placed directly into blister cavities followed by freeze-drying. To maintain homogeneity during freeze-drying, it is necessary to include polymers to increase the viscosity of the matrix to an almost paste-like consistency to prevent sedimentation. The increased viscosity of the matrix reduces the porosity of the product, thereby increasing freeze drying times and having a negative impact on disintegration.

Compressed tablets

The basis for compressed tablet ODTs is the use of super disintegrants, effervescent agents, or high aqueous soluble ingredients or combinations of each.

OraSolv. CIMA Labs' (a subsidiary of Cephalon, Frazer, PA) OraSolv product combines taste-masked active drug ingredients

Table III: Comparison of product characteristics of various technologies for orally disintegrating tablets.

Technology platform	FDA Guidance (2)	Lyophilized		Compressed tablet			Sugar floss
		Zydis and QuickSolv	Lyoc	AdvaTab	OraSolv	DuraSolv	
Product Characteristic*		Zydis and QuickSolv	Lyoc	AdvaTab	OraSolv	DuraSolv	FlashDose
Disintegration Time	< 30 s	< 10 s	< 30 s	< 30 s	< 40 s	< 50 s	< 15 s
Maximum tablet weight and dose range	< 500 mg	400 mg	500 mg	750 mg	750 mg	500 mg	600 mg
Taste-masking	Not specified	Flavors, sweeteners, pH adjustment, ion-exchange resin		Flavors, sweeteners, taste-masked particles			Flavors, sweeteners
Mouthfeel	Not specified	Smooth		Variable (some gritty)			
Clinical applications	Not specified	BE** Buccal Oral Vaccines	BE	BE Modified release	BE†	BE†	BE

*Product characteristics are trademarks and registered trademarks.

**BE = bioequivalent to conventional solid oral-dosage form.

†CIMA / Cephalon have also developed Oravescent, an ODT designed to facilitate oral transmucosal delivery.

Table IV: Disintegration times for orally disintegrating tablets (6).

Product*	Technology*	Diameter (mm)	Start** (seconds)	End** (seconds)
Alavert 10 mg	CIMA	10.0	22.7	32.8
Benadryl Fast Melt	-	11.2	10.9	15.7
Claritin Reditabs	Zydis	11.1	00.0	03.8
Exedrin Quicktabs	-	17.5	11.8	25.8
Maxalt MLT	Zydis	11.0	00.0	01.8
NuLev	CIMA	14.0	07.9	13.9
Remeron Soltab	CIMA	09.7	22.3	56.6
Xilopar (1.25 mg)	Zydis	11.0	00.0	02.8
Zofran Zydis	Zydis	09.0	00.0	02.2

*Products and technologies are registered trademarks.

**Start and end refer to disintegration time.

with a low-effervescence system. On contact with saliva, the effervescent system promotes disintegration of the tablet. The OraSolv process typically involves blending the microencapsulated API with magnesium oxide and mannitol to aid in the release of the drug from the polymeric coating. These microparticles are further blended with other excipients and loosely compressed to maintain some degree of tablet porosity to aid dispersion. Compression forces need to be kept to a minimum so as not to disrupt the API taste-masking coating. The resultant tablet is relatively weak and friable and requires specific patented packaging technology (PakSolv, CIMA Labs) and use of aluminum blisters to protect the drug from moisture. Disintegration times are typically less than 40 s.

DuraSolv. The DuraSolv (CIMA Labs) technology is similar to OraSolv technology but uses increased compression forces during tableting such that the product is sufficiently robust to be packaged into traditional push-through blister packs or bottles. Durasolv technology incorporates the taste-masked active drug ingredients but may or may not contain the low-effervescence system. A consequence of increasing compression to improve robustness is a compromise in drug loading, which limits the product to fairly small doses. Both OraSolv and DuraSolv products are sensitive to moisture due to the presence of the effervescent system and must be packaged appropriately.

FlashTab and Pharmaburst. FlashTab (Ethypharm, Saint Cloud, France) and Pharmaburst (SPI Pharma, Wilmington, DE) technologies rely on the use of super disintegrants. FlashTab is a combination of wet and dry granulation before compression. Microparticles of taste-masked API are blended with conventional tableting aids and disintegrants such as polyvinyl pyrrolidone or crospovidone (cross-linked PVP), cross-linked sodium carboxymethyl cellulose (cross-linked CMC) and swelling agents such as starches or microcrystalline cellulose. Disintegration times are typically less than 1 min.

The Pharmaburst ODT uses a proprietary disintegrant (Pharmaburst) that is based on mannitol blended with conven-

tional tableting aids. The excipient system is claimed to be of good flow characteristics and highly compressible such that robust tablets can be produced while maintaining disintegration times of 30 s or less depending on the drug loading.

Other excipients promoted for the formulation of ODTs using conventional tableting technology include BASF's (Florham Park, NJ) Ludiflash, a mannitol/crospovidone/polyvinyl acetate combination, and Fuji Chemical Industry's (Toyama, Japan) F-Melt, a cospray-dried powder combining inorganic excipients and disintegrants dispersed in a carbohydrate complex.

AdvaTab. The AdvaTab (Eurand Pharmaceuticals, Dayton, OH) system incorporates the microencapsulated API (Microcaps, Eurand Pharmaceuticals) for taste-masking purposes. This ODT platform relies on the fact that AdvaTab tablets are compressed using a patented external lubrication system in which the lubricant is only applied to the tablet surface. AdvaTab tablets can be manufactured using low-compression forces and permit ingress of moisture on contact with saliva. AdvaTab tablets are claimed to be robust and to disintegrate rapidly in the oral cavity. The tablet-compression step does not lead to breakage of the drug particles.

The advantage of the compressed tablet ODT platforms is that they are able to accommodate taste-masked APIs, either by microencapsulation or within a taste-mask matrix, with relative ease. However, the compression forces used need to be carefully balanced to avoid compromising the taste-masking coat or rapid disintegration time while still achieving sufficient cohesion within the tablets for adequate handling robustness.

As indicated in Tables III and IV, disintegration times for the compression ODTs tend to be longer. The levels of excipients required (including taste-masking materials) in the finished product are typically higher than for the ODT technologies using lyophilization.

Sugar-floss systems

Biovail's (Mississauga, Canada) Flashdose system is an example of a sugar-floss system. This system involves producing fibers from molten saccharides (sucrose, dextrose, or lactose) or polysaccharides. The floss fibers are blended with API and other excipients and compressed into tablets. There is usually a conditioning step at elevated temperature and humidity to ensure complete conversion of amorphous sugar fibers to crystalline material. This system relies on the highly soluble nature of the sugar components as well as the formulation porosity to achieve rapid disintegration.

Molded tablets

Molded tablets are based on a technology platform that uses water-soluble ingredients such as saccharides (lactose, mannitol, or maltose) that cause the tablets to disintegrate and dissolve rapidly. Typically, the powder blend is moistened with a hydroalcoholic solvent and molded into a tablet using low-compression pressure. The wet-compressed mass is air dried.

The manufacturing process for the WOWtab (Astellas Pharma, Yamanouchi, Japan) product involves granulating highly soluble low-moldable sugars (e.g., mannitol, lactose, glu-

Table V: Examples of products using thin-film technologies.

Supplier	Product*	Active ingredient (dose strength)
Novartis	Various products under Theraflu and Triaminic brands	Phenylephrine hydrogen chloride (HCl) (2.5 to 10 mg) Dextromethorphan hydrogen bromide (5 to 20 mg) Diphenhydramine HCl (12.5 to 25 mg)
Pfizer	Benadryl	Diphenhydramine HCl (12.5 mg and 25 mg)
Pfizer	Sudafed	Phenylephrine HCl (10 mg)
MedTech Products/ Prestige Brands	Chloraseptic	Benzocaine (3 mg) Menthol (2 mg)

*Products are registered trademarks.

cose, sucrose) with high moldable sugars (e.g., maltose, maltitol, and sorbitol). Following compression, there is a humidity conditioning step to increase product robustness.

Thin-film technology

Thin-film technology is a relative new area of interest with respect to oral fast-dispersing products. Although not strictly an ODT, the oral thin-film platform provides an alternative to traditional tablet approaches.

Oral thin films generally consist of hydrophilic polymers of varying thickness (50 to 200 nm). The manufacturing process is based on liquid casting to control film and weight variability. The dosage required is achieved by manipulating the API concentration in the bulk solution and/or the film-thickness produced. The films are dried by passing through oven(s) to evaporate the solvent used to prepare the film. The dried film is cut into single unit doses before packaging. During manufacture, the dried film must be protected from heat and humidity. The final packaging of the strips also needs careful consideration to protect the product from moisture. Taste-masking options include the use of sweeteners, flavors, and ion-exchange-resin complexes. Encapsulated APIs for taste-masking purposes is challenging because the larger particles can give rise to uniformity issues.

Although disintegration of thin films are rapid (< 30 s), their limitation is drug loading (approximately less than 30 mg). Increasing film-thickness or using multiple layers may increase drug loading, but greater thickness can have a negative effect on disintegration. The specific packaging requirements also add complexity and cost to these products, though specific packaging technologies such as Catalent's DelStrip pack are being developed to suit the thin film strips. To date, the majority of products have been in the over-the-counter sector (see Table V).

Summary

The 2008 FDA industry guidance on ODTs (2) provides recommendations that clarify the expectations of the ODT dosage form. ODTs were originally developed for, and are mostly associated with, good patient acceptance and compliance. The FDA guidance reinforces such thinking by focusing on disintegration time and unit size in the context of what does and does not constitute an ODT because these two parameters heavily influence ODT patient acceptance and compliance.

Lyophilized ODTs were the first ODTs to market and have been successful in terms of sales value, sales volume, and number of worldwide product approvals. Lyophilized ODTs have proven to be versatile, by spanning a range of clinical applications (e.g., bioequivalence, buccal uptake, and stable formulations of macromolecules.) Having set the original standard for ODTs, the lyophilized products provide the additional assurance of compliance with the FDA guidance.

Compressed ODT formulations provide the convenience of using standard

tableting technology and taste-masked APIs. Specialty companies can apply this technology, but the availability of super-disintegrants also make this technology accessible for in-house pharmaceutical development. Products made *via* compressed tableting and with sugar-floss systems can also meet the FDA ODT guidance by going through some further product optimization with respect to disintegration time. Possible compromise on upper-dose strength (i.e., tablet weight) may be required. The tablet size and weight may be negated if it can be demonstrated that all components are soluble and leave minimal residue. Thin films provide a potential alternative to ODTs which, if the dose limitations can be resolved, may also find wider application. In all cases, overall patient acceptability remains a prime consideration.

In addition to meeting the FDA guidance recommendations, palatability remains a factor that may influence the choice of ODT technology for a specific API. The relative importance of these factors in meeting the overall product criteria needs to be established on an individual basis and prioritized accordingly. However, if the defining characteristics of disintegration time and unit size cannot be met, it should be recognized that an alternative, non-ODT dosage form may need to be developed.

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