Is My Molecule Suitable for an Orally Disintegrating Tablet?

Review key attributes of orally disintegrating tablets and explore factors that influence their selection for new drug development or life-cycle maintenance.

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INTRODUCTION

An orally disintegrating tablet (ODT) is a tablet formulation that disintegrates completely in the mouth without chewing or sucking. Full disintegration must occur *in vitro* within 30 seconds according to the U.S. Food and Drug Administration (FDA) (1), or up to 3 minutes according to the European Pharmacopeia (2). Thus, the active pharmaceutical ingredient (API) is available for absorption almost instantly, depending on its solubility. Water is typically not required for administration, as the saliva in the mouth is usually sufficient for unit dispersion and API release.

These characteristics make ODTs particularly well-suited for patients with difficulty swallowing standard tablet forms of medication due to age, altered mental status or disability. Nonetheless, convenience and ease of use may lead to greater compliance, and thus improved clinical outcomes, even in the general patient population. Moreover, ODTs have the potential for oromucosal absorption for increased bioavailability.

PRODUCTION METHODS OF ODTs

ODTs can be formed by a variety of manufacturing processes. One process is loose compression, where a powder mix is blended and then compressed by various methods to form the final product. Excipients may include superdisintegrants to increase moisture penetration and facilitate tablet dispersion. A second process uses **3D printing technology** to create

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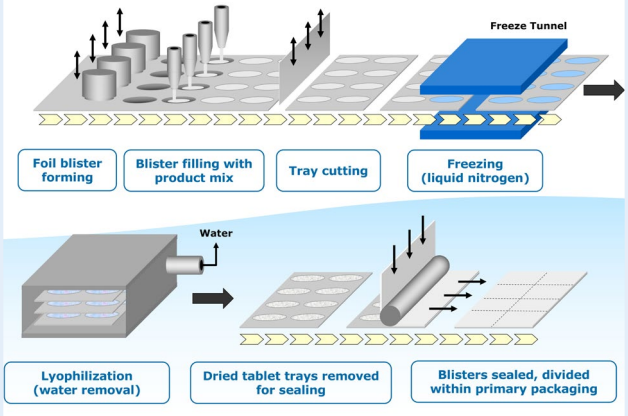
Figure 1: The freeze-dry manufacturing process for ZYDIS ODT.



layered tablets from a liquid mixture that is printed and dried one layer at a time to build the final solid tablet. Thin-film products are a related dose form, but are not ODTs in the strictest sense since they are not tablets. Another process is **lyophilization**, where a liquid mixture is dispensed into a mold and then freeze-dried to form the tablet. The resulting product is highly porous, allowing for increased moisture penetration.

The first commercial ODT to be approved by the FDA used the Zydis® ODT platform, a proprietary technology developed by Catalent (Swindon, UK) that creates lyophilized ODTs with a dispersion time of 3 seconds or less. The manufacturing process (FIGURE 1) is versatile and scalable, and the physical properties of the resulting ODT can be optimized for API stability and delivery. An aluminum tray with individual blister pockets acts as the mold for the product during manufacturing. With the addition of sealing foil, the molds also act as the final patient packaging, yielding an ODT that is resistant to damage during transport and storage since the tablet remains protected by the foil shell until the point of administration.

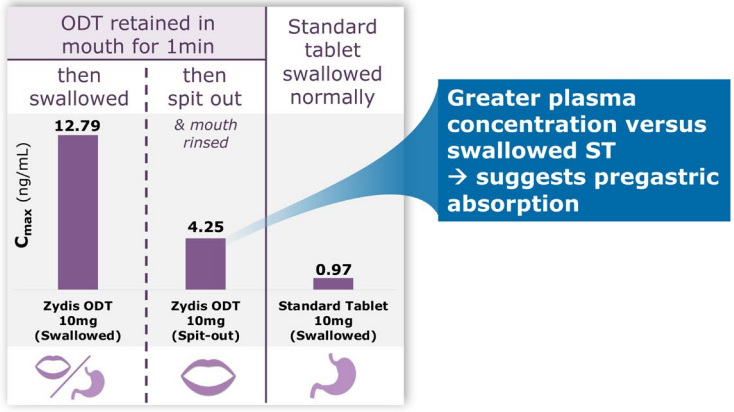
ODT SELECTION TO AVOID FIRST PASS METABOLISM

Standard tablet APIs are absorbed into systemic circulation from the gastrointestinal (GI) tract, which subjects them to conditions that risk degradation due to pH or enzymatic activity as well as first pass metabolism. Similarly, ODTs may have GI bioavailability comparable with that of a standard tablet; however, due to the oral disintegration of the ODT and fine dispersion of the API, patients may experience a faster onset of action compared with a standard tablet, which reaches the stomach intact.

However, a particular advantage of ODTs in comparison with standard tablets lies in the potential for pregastric absorption, which involves the transfer of the API through the oral mucosa and into systemic circulation. Applications of this route include scenarios where rapid uptake is desired, GI transit is compromised or where high first pass metabolic effects significantly reduce bioavailability. For example, the absolute bioavailability of a standard tablet formulation of the antipsychotic drug, asenapine, was less than 2%, while a formulation of asenapine as a sublingual ODT increased bioavailability over 17-fold to 35% (3). Avoidance of first pass metabolism through pregastric absorption of API can enable a lower dose of the ODT formulation.

Where a standard tablet API formulation has already been marketed, ODT-mediated pregastric absorption of an API may enable a

Figure 2: Selegiline case study demonstrates that greater plasma concentrations result from pregastric absorption.



Adapted from Clarke A, Brewer F, Johnson ES, Mallard N, Hartig F, Taylor S, Corn TH. A new formulation of selegiline: improved bioavailability and selectivity for MAO-B inhibition. J Neural Transm (Vienna). 2003 Nov;110(11):1241-55.

reduction of the unit dose while still achieving bioequivalence to the approved drug. This approach reduces the overall patient exposure to the drug and its metabolites, which may improve the safety profile. It may also avoid unnecessary API usage in production, which results in corresponding economic and environmental benefits. For example, increased bioavailability of an ODT formulation of the monoamine oxidase inhibitor, selegiline, enabled an 8-fold reduction in ODT API requirement compared to the original standard tablet formulation (4). As seen in FIGURE 2, peak serum concentration (C_{max}) was increased 4-fold relative to swallowing a standard tablet when patients kept an ODT in their mouths for 1 minute then rinsed without swallowing, indicating a significant pregastric contribution to total absorption of the ODT formulation. The reduced API requirement in the ODT formulation also resulted in a reduction in amphetamine-related metabolites (4), which may be associated with undesirable side effects.

ADDITIONAL BENEFITS OF ODTs

Additional studies have likewise demonstrated similar or increased bioavailability (5), comparable or improved safety profiles (6-10), and equivalent or improved clinical efficacy (9–11) of ODTs compared to their standard tablet API formulations. While pregastric absorption effects may be specific to the API and/or indication, these studies reflect the potential for improved safety and efficacy using ODTs due to superior pharmacokinetic or pharmacodynamic profiles as well as patient compliance.

ODT SELECTION FOR MUCOSAL DRUG TARGETING

ODTs may also be used where a local effect on the oral mucosa is desired such as the interaction of the API with receptors present on the mucosal tissues or on resident mucosal immune cells. Large molecules and biomolecules may also be employed as APIs in these ODTs since the goal is mucosal exposure, not systemic circulation, and therefore vascular absorption through the oral mucosa is not required. Examples include immunogenic vaccines, which stimulate an immune reaction against foreign antigens such as influenza, and

tolerogenic allergy vaccines, also known as allergy immunotherapy (AIT), where the goal is to induce the tolerance of molecules to which the immune system has previously become sensitized, such as grass pollen or house dust mite allergens.

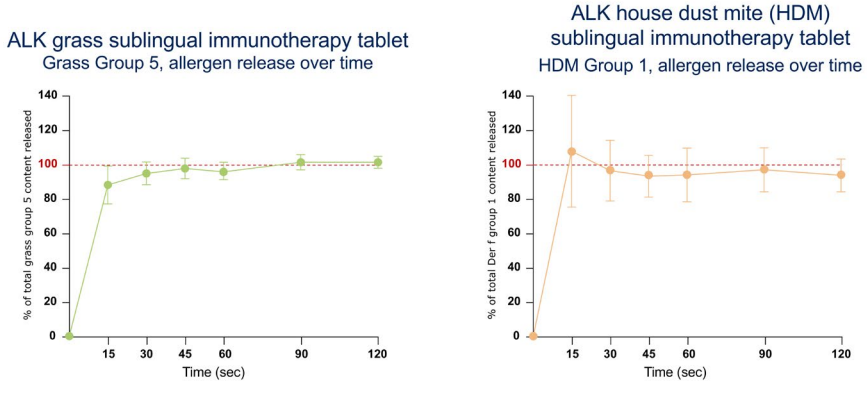
CASE STUDY: ALLERGY IMMUNOTHERAPY

Subcutaneously injected immunotherapy (SCIT) requires both in-clinic administration and careful up-dosing to reduce risk of systemic reactions. Allergen extracts typically contain a mixture of biomolecules, which may include proteases. Therefore, SCIT products prepared as a suspension for injection require refrigeration to remain stable and have a limited shelf life. ALK (Hørsholm, Denmark) used the Zydis ODT platform to develop sublingual immunotherapy (SLIT) tablets using multi-molecule allergen extracts. Lyophilization results in high chemical and physical stability of the allergen extract proteins (12), granting the ALK SLIT tablets a shelf life of up to 5 years without refrigeration. Disintegration time of SLIT tablets was approximately 1 sec *in vitro* (13), with complete molecular release in 15–30 seconds (FIGURE 3), allowing uptake of the allergen extract by target effector cells within the oral mucosa prior to the patient swallowing or salivary washout. Unlike SCIT injections, SLIT tablets generally have not been found to require up-dosing and have very low risk for systemic reaction (14), so after an initial clinical administration, SLIT tablets may be taken by the patient at home, resulting in increased compliance and patient satisfaction. From a commercial perspective, the ODT formulation has enabled ALK to obtain full registration of 5 SLIT tablet products with an allergen range covering 70% of patients with respiratory allergies requiring AIT treatment, with high growth in customer acceptance and clinical use over the past 5 years (15).

CHARACTERISTICS OF ODT-COMPATIBLE API

Formulation of an API as an ODT is dependent on both the physicochemical properties of the API and the target product profile (see FIGURE 4), although two key limits exist. First, due to direct mucosal exposure to the API,

Figure 3: Suitability of Zydis ODT for administration of allergy immunotherapeutics. Data suggest complete allergen release within the recommended sublingual holding time *in vitro*[1,2].



[1]Lund K, et al. The importance of tablet formulation on allergen release kinetics and efficiency: comparison of freeze-dried and compressed grass pollen sublingual allergy immunotherapy tablet formulations. Clin Ther 2019;41(4):742-53.
[2]Ohashi-Doi K, et al. Bioavailability of house dust mite allergens in sublingual allergy tablets is highly dependent on the formulation. Int Arch Allergy Immunol. 2017;174:26-34

Figure 4: Summary of general API criteria for Zydis® ODT platforms.

	ZYDIS® ODT				ZYDIS ULTRA® ODT
Delivery target	Systemic			Local	Systemic
API criteria	Oral		Sublingual / Buccal	Mucosal	Oral
EHS classification	OEB 1–3 (of 4) (Limited low end OEB4 potential subject to individual review)				OEB 1–2 (of 4)
	No cytotoxic, ß-lactam antibiotic or sex / corticosteroid hormone (other hormone activity subject to specific review).				
Aqueous solubility	<10mg/ml	>10mg/ml	Min ~50% target dose/ml		No specific limit identified to date
Unit dose	Max ~300mg	Max <100mg	Max ~20mg	Subject to site / mechanism of action	Max ~400mg
Log P / Log D (at pH6.8)	No specific requirement		>1		No specific requirement
pKa	No specific requirement		None or in range 5–9		No specific requirement
Molecular weight	Typically <~1000Da		Lower mw (<~500Da) increases absorption potential		Small molecule
API particle size	D_{90} <25µm		D_{90} <25µm (if not fully dissolved)		~90% within 75–250µm
API stability (aq. sol^n / suspen^n)	≥ ~48hrs at RT				No specific limit identified to date
Taste masking options	Sweeteners and/or flavors; ion-exchange resin or cyclodextrin for lower doses.		Sweeteners and/or flavour only to maintain API availability		Coated API ± sweetener and/or flavor

ODT formulation is contraindicated for certain classes of drugs. Second, API compatibility with excipient materials is an absolute requirement. For example, in the original Zydis ODT technology, the basic formulation platform is gelatin, which provides structure, and mannitol, which is both structural and related to taste and mouth feel.

API solubility affects the amount that can be incorporated whether for systemic or local delivery since very soluble APIs generally have a more significant impact on the lyophilization process than do those in suspension. APIs that are liquid at room temperature (e.g., oils) will typically be no more than half of the drug mix by volume due to the impact on the finished product characteristics and stability, and may need additional excipients for incorporation, depending on the nature of the liquid. In addition, APIs must not be volatile to avoid loss during the lyophilization process. ODT formulation is most appropriate for small molecules (<1000 Da), with APIs smaller than 500 Da generally demonstrating increased pregastric absorption potential. However, molecules of 5,000 Da or larger may also be used depending on a variety of factors. For oral-mucosal delivery targets, API solubility limits are determined by the targeted dose. Peptides and proteins are typically compatible with lyophilized ODTs, and since absorption is not necessarily required, the molecular weight limit is dependent on the desired site and mechanism of action, with increasing size generally associated with greater difficulty reaching systemic circulation. While maximum API dosages are limited by API physicochemical characteristics and acceptable tablet sizes, minimum API dosages are affected by issues of dose uniformity during manufacturing as well as handling constraints; for lyophilized ODTs, microgram dosages may be achieved.

For both systemic absorption and local targeting, micronization of less water-soluble API molecules is typically required to ensure homogeneity and promote ODT dissolution *in vivo*. Additionally, for lyophilized ODTs, APIs generally must maintain physical and chemical stability in aqueous solution or suspension for a minimum of 24-48 h to allow for the commercial manufacturing process; most formulations are processed at controlled room temperature, but lower temperatures can be used to improve API stability, if required. Taste masking options include sweeteners, flavors, ion exchange resins or cyclodextrins, depending on the target absorption route. Multiple formulation strategies can be adopted to promote pregastric API absorption, including addition of excipients for pH adjustment, permeation enhancers or mucoadhesives.

For APIs that are not targeting pregastric absorption, newly developed ODT platforms such as Zydis Ultra® ODT may offer additional benefits and further extend the potential ODT product range. Zydis Ultra ODT uses resonance acoustic mixing to generate a continuously coated, free-flowing API, which provides improved taste masking and enables increased drug loads, while potentially reducing restrictions due to API aqueous solubility or stability (see **FIGURE 4**). Micronization of the API is not required, although spherical morphology and particle size of 75–250 micrometers are preferred.

SUMMARY

ODTs are a patient-preferred dose form that offers additional potential benefits related to pregastric API delivery and absorption. While new drug products may benefit from ODT formulation beginning with product launch, ODT formulation can also play a role in life cycle management of approved products, through 505(b)(2) or similar regulatory pathways. API suitability for an ODT is dependent on multiple factors, including delivery target and physicochemical profile. New advances are also being developed to expand the potential of this technology.

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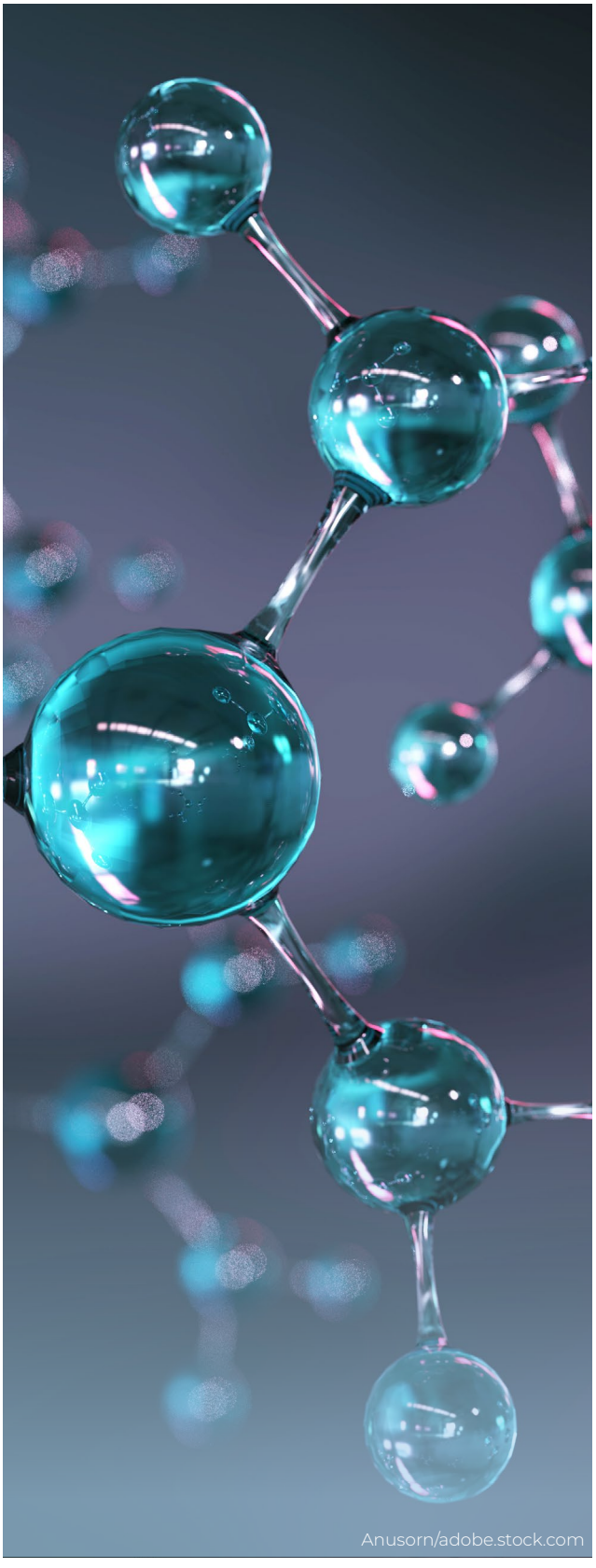

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