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## ORALLY DISINTEGRATING TABLETS - Patient-Centric Dose Design, Developments in Orally Disintegrating Tablets

### INTRODUCTION

The orally disintegrating tablet, or ODT, offers an easy-to-take alternative form to consumers of over-the-counter (OTC) treatments who perhaps do not have access to water, and patients of prescribed drugs who cannot, or will not, swallow standard oral dosage forms, such as tablets and capsules. It is not only patients at either end of the age spectrum – the very old and the very young – who suffer from an inability to swallow, or dysphagia, either, with a recent study indicating that 70% of younger people aged 16-34 who were surveyed reporting that they had difficulties swallowing tablets and capsules.<sup>1</sup> Pre-existing conditions may affect compliance too, and those with mental health issues may not want to take their medications, instead, secreting the tablets in their mouth before disposing of them later, or saving them for misuse or even self-harm in the form of an overdose. It can be easier to give a medication to a child using an ODT and of course, in the animal health arena, it can be a significant challenge to get pets or livestock to swallow tablets.

While liquid formulations can provide successful dosing options in some cases, the ODT can work in all of these situations. ODTs are designed to disperse quickly within the oral cavity, removing the need to swallow a solid tablet or capsule. When a drug is absorbed within the mouth, it enters the bloodstream directly, thus avoiding the first-pass metabolism by the liver, where side-effect-causing metabolites may be formed. It also gives a rapid onset of action, which may be advantageous before or during acute episodes of conditions such as migraine or psychiatric events.

A number of technologies are available to create ODTs. These include Catalent's Zydys® ODTs, which are made via freeze-drying technology, and others, such as loosely compressed tablets. Loosely compressed tablets typically take 15-20 seconds to disperse in the mouth, with a chalky, gritty mouthfeel, unlike Zydys tablets, which will normally disperse in less than 3 seconds with a smooth mouthfeel.

Zydys technology has been used to formulate a number of commercial products, particularly those for which a fast onset of action is beneficial. Recently, higher doses of up to 200 mg have been launched, and peptide and protein products formulated in this way are also available.

The structure of a Zydys tablet is key to its rapid dispersal properties, as the tablets are highly porous. This is achieved via a matrix of fish or bovine gelatin, or by using one of several non-gelatin polymers, plus structure-forming mannitol, which also aids in the solubilizing of the tablet. As well as the drug active, other ingredients, such as sweeteners, colors, flavorings, and acidity modifiers, are often incorporated to increase palatability.

The ingredients are all dissolved or suspended in water, accurately dosed into blister trays, and then frozen in liquid nitrogen freeze tunnels before being placed in freeze dryers. There, the water sublimates, leaving behind the porous matrix structure of the ODT, often referred to as a wafer. Figure 1 is an electron micrograph image of the matrix. The choice of packaging materials is important, and each blister strip is sealed using specially designed, multi-layer foils that are resistant to moisture ingress. Various options are available to optimize and tailor the patient's experience

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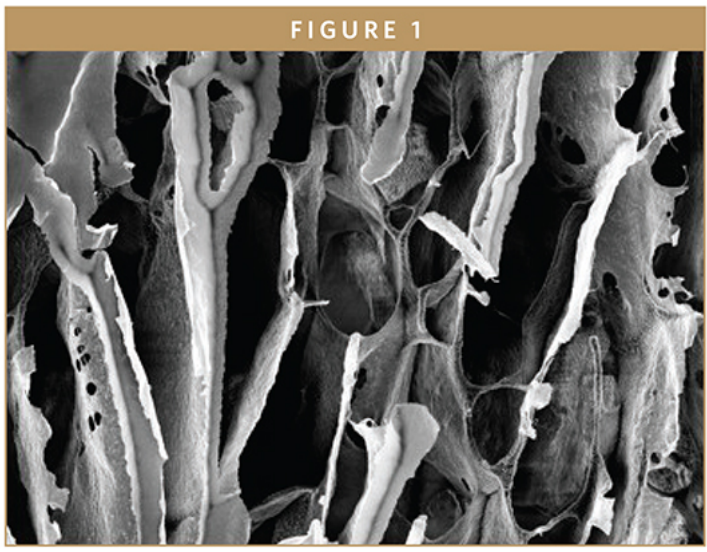
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of taking a medication that includes Zydis technology, for example, blister strips can be customized with multiple combinations of perforations, thumb-peel tabs to allow for easy opening, and printing options too, including helpful directions, regimen information or product branding. After "lidding" the blister strips may be packed into outer cartons.



**FIGURE 1**

A significant amount of analytical work is required when developing a new ODT. X-ray diffraction is used to determine the crystalline state of the API and relevant excipients; whether it is crystalline or amorphous will have a bearing on the structural integrity of the final dosage forms. Differential scanning calorimetry is used to determine the melting point and other thermal events. This assists in calculating the necessary times for freeze-drying, while ensuring that the frozen product does not melt during the drying process.

Another technique, dynamic vapor sorption, is used to determine the moisture sorption and desorption profiles. This is important, as a freeze-dried formulation can be sensitive to highly humid environments and can shrink and lose its rapid disintegration characteristics. This helps inform the choice of packaging and formulation characteristics, allowing the products to be marketed in all geographic regions, including those where high humidity is common.

**A MORE PALATABLE OPTION**

As an ODT is designed to reside in the mouth for only a number of seconds; it cannot avoid the taste buds. If the taste of the active ingredient, or the sensation it generates on the tongue, is not too unpleasant, the simple strategy of including flavor ingredients and sweeteners in the formulation can be sufficient to make it acceptable to patients. For many other APIs, this is not the case. Many taste unpleasant, or can produce burning, numbing, or tingling sensations. If a patient-friendly ODT is to be created, then more creative formulation methods will have to be applied.

One way this can be achieved is via the Zydis Ultra formulation. The taste-masking is provided by the presence of a coating around particles of the API, which can be as small as 100 µm in size. This is less than half the size of the smallest particles that can be coated using more traditional coating processes. Smaller particles make for a better mouthfeel in an ODT; larger particles give a gritty sensation as the tablets disintegrate.

In place of a fluidized bed coating method, in the Zydis Ultra process, API particles are mixed with micronized polymer agglomerates in a vessel that has an acoustic vibrator. When the vibrator is activated, the contents begin to accelerate rapidly, and the polymer is deposited around the API. The vibration and collisions within the mixer result in a continuous polymer layer being formed. It is this layer that confers the desired taste-masking properties. No solvent is needed for this coating process.

In contrast to a traditional coating, the coated API inside is released slowly, a phenomenon that indicates that taste-masking has been achieved, while still meeting the US Pharmacopeial convention (USP) criteria for immediate release. The API still has 70%-85% potency w/w compared to uncoated particles. The difference between the release profiles of the two can be seen in Figure 2.

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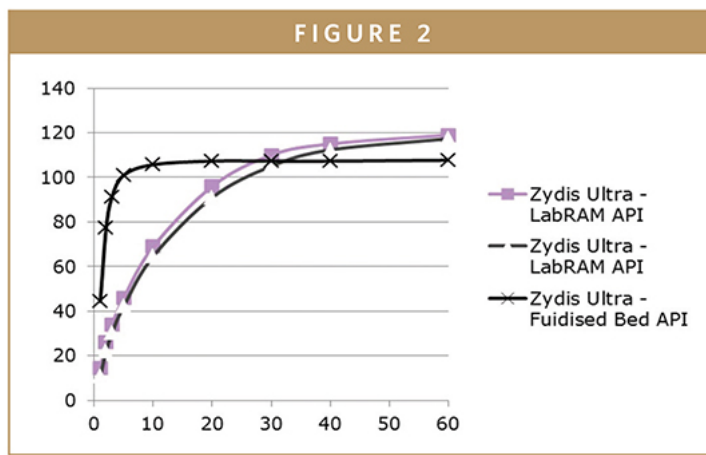
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A common alternative technique for taste-masking is the incorporation of cyclodextrin excipients. Cyclodextrins are sugar-based, ring-shaped macromolecules with holes in the middle that can trap smaller molecules inside if they are the right size. If the cyclodextrin has the appropriate size of hole, the API will become trapped, which prevents it from touching the taste receptors on the tongue.

As an example, a beta-cyclodextrin ODT formulation was created of the very bitter tasting antihistamine, cetirizine. More than three-quarters of a test group claimed its taste profile was acceptable and that the reformulated product incorporating Zydys technology was more pleasant tasting than the standard formulation.

### ODTS OF THE FUTURE

Recent developments have made it possible to formulate a number of different types of medicine as ODTs that at first sight, one might think would not be compatible with this type of oral dosage form. For example, ODTs can be made from very lipophilic APIs, by way of using an oily emulsion in place of the aqueous solution or suspension that is normally the starting point for an ODT formulation.

Although no products made in this way are yet marketed, tablets have been formulated using a mass fraction of 15% olive oil-in-water emulsion. This has allowed ODTs containing 15 mg of the oil to be created, and an oil-soluble API could be dissolved in this before the tablet is formed. This has been proven with ibuprofen, which, if formulated as an ODT, could offer significant advantage to consumers in speed of onset.

Another innovative possibility is the prospect of formulating a two-layer ODT that would allow two different ingredients to be incorporated within each dose. This could be particularly beneficial if those ingredients were otherwise incompatible, whether it were two different APIs or an API and an excipient, for example, vitamins B and C; and the artificial sweetener, aspartame, which is unstable above pH 6.5 and so is incompatible with many basic excipients and APIs, such as calcium carbonate.

The prospect of formulating biologics as ODTs offers even more promise for the dose form. Biologics usually have to be dosed via injection or infusion, because the complex structures can rarely withstand the highly acidic enzyme-containing environment in the gastrointestinal tract. If they can be delivered through the mucous membranes in the mouth, they could enter the bloodstream undamaged as the acidity of saliva is normally close to neutral, and none of the protease enzymes that digest proteins are present.

There are regional variations in the thickness of the epithelium that can be exploited; the sublingual epithelium is typically 100-200  $\mu\text{m}$ , while the buccal membrane is thicker, at 500-800  $\mu\text{m}$ . Absorption enhancers and bioadhesives can be included in the ODT formulation to promote absorption. Catalent's Zydys Bio technology was developed as a way of achieving oral delivery of biologics.

There are various other advantages, such as room-temperature stability, whereby cold chain distribution will not be required. This is particularly important for biologic products, such as vaccines, that are destined for developing countries, where access to refrigeration cannot be relied upon, and in pandemic situations, where speed of distribution is key to success.

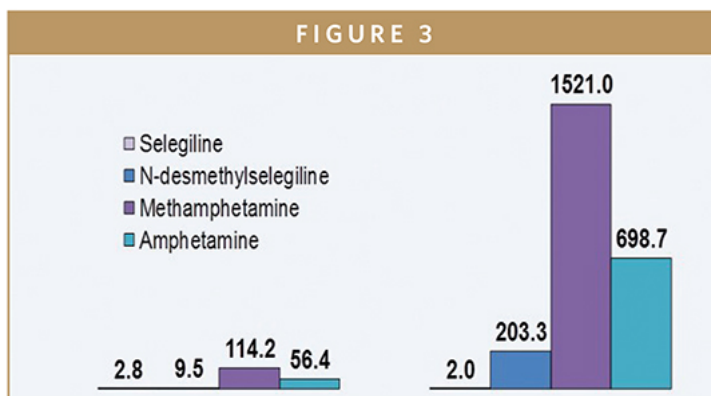
The peptide drug calcitonin has been successfully formulated in this way, and vaccine ODTs could be particularly important in the future. By avoiding the need for injection, there would be none of the pain, and potential for injection site reactions, that can engender reluctance to immunization among patients and parents. The mucosal response that can occur is a further benefit in immunizations against infections, such as human papillomavirus, influenza, and pneumonia.

Preclinical studies in mice have shown the potential of an ODT influenza vaccine. The loss of bodyweight is indicative of disease severity, and those mice infected with influenza but who were unvaccinated lost significant amounts of weight. In contrast, those who were given the oral vaccine showed no significant loss in bodyweight, even after they were challenged with the influenza virus.

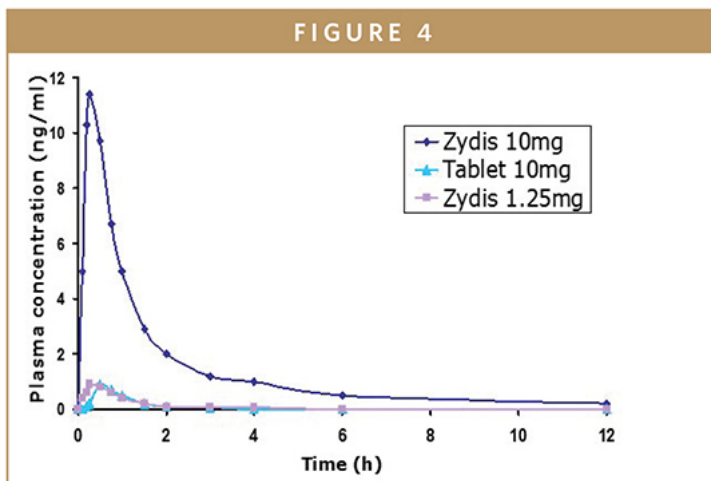
Regardless of the type of API that is being delivered, the fact that ODTs offer a route to pre-gastric absorption instead of parenteral delivery can offer some significant benefits to patients. Not only does it offer the potential for a faster onset of action, but by removing that first-pass metabolism of the liver, side-effect profiles can be greatly improved.

The ability to deliver pre-gastrically depends very much on the molecular weight, lipophilicity, and required dose level of the API. Some APIs, even if these properties are favorable, are still not suitable for pre-gastric absorption. But where it is feasible, if the ODT is designed correctly, then it is possible to ensure that the active will be absorbed buccally or sublingually, without being swallowed.

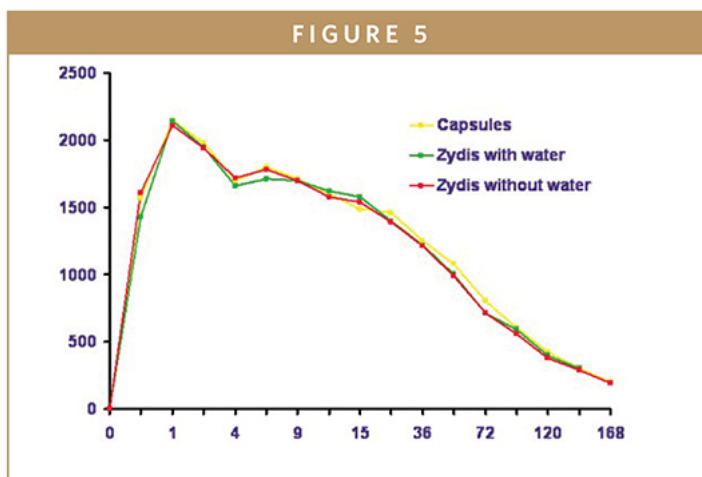
As an example, the monoamine oxidase B drug selegiline, used in Parkinson's disease and depression, may cause patients to suffer side-effects. These result from some of the active metabolites generated by liver enzymes, including methamphetamine. Therefore, if the drug enters the bloodstream directly, these metabolites are not formed and the side-effects they cause cannot occur.



The graph shown in Figure 3 shows the comparison of metabolites formed in a standard 10-mg selegiline tablet, and a 1.25-mg ODT formulation of the same active. Figure 4 shows that the lower-dose ODT produces the same area under the curve (AUC) as a conventionally formulated selegiline tablet. And, importantly, the two are bioequivalent. As can be seen in the graph in Figure 5, the AUC for the ODT, taken both with and without water, is essentially the same as a standard 10-mg formulation.







ODTs have become a standard dosage form for a number of medicines, where the fast onset of action or ease of dosing are important. They offer significant advantages to both patients and consumers of OTC medications, and although their advantage over conventional tablets is perhaps more obvious when thinking of the young and old, there are many people outside of these groups who have difficulty swallowing tablets and capsules and would welcome an ODT alternative dose form. Recent developments in ODT technology have widened the range of actives that can be formulated and product types that are possible. In particular, the promise of formulating biologics and ODT vaccines that do not require a healthcare worker to administer them, as with many that are injected, or that do not require cold storage and transit, often to the less accessible parts of the world where so many vaccines are required, is hugely exciting.

#### REFERENCE

1. In a study commissioned by Hermes Pharma and conducted by Spiegel Institut Mannheim based on 2,000 individuals in Germany and North America ([www.epmmagazine.com](http://www.epmmagazine.com) accessed Sep.23, 2016).

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