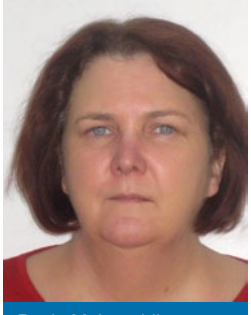
A Q&A

Zydis® — The Versatile Orodispersable Tablet (ODT) Technology



Rosie McLaughlin
Director Scientific Affairs, Zydis
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Catalent's ODT platform is ideal for sublingual delivery of proteins, peptides, and vaccines.

Rosie McLaughlin, Director Scientific Affairs, Zydis, Catalent Pharma Solutions

Since they were first launched in 1986, orally disintegrating tablets (ODT) have become an important part of the industry's oral dose form tool kit. Based on current global growth trends, the ODT market is expected to reach $12 billion by 2018.[1] Zydis®, the ODT technology from Catalent Pharma Solutions, is a freeze-dried oral solid dosage, fast-dissolve formulation that disperses almost instantly. To date, more than 20 products in 60 countries have been launched with Zydis. *Pharmaceutical Technology* recently spoke with Rosie McLaughlin, Catalent's Director of Scientific Affairs—Zydis, about the advantages of Zydis technology and its versatility in helping to treat a range of therapeutics areas.

Pharmaceutical Technology: What aspects of the Zydis formulation and process make the dose form so widely applicable?

Rosie McLaughlin: Zydis is amongst the fastest dispersing ODT with greater versatility than conventional loosely compressed ODTs. The rapid disintegrating properties are related to both the formulation excipients and the process itself. In Zydis, gelatin is the main polymeric structure former and, in combination with mannitol, provides increased robustness and elegant appearance. Both gelatin and mannitol will readily dissolve in saliva, contributing to the rapid disintegration and the "melt-in-the-mouth" experience. During lyophilization, ice crystals leave behind a multitude of air pockets within the ODT structure once dried. This results in a highly porous structure, which helps to wick up the saliva and assists in tablet disintegration.

Zydis is being applied to achieve bioequivalence to existing conventional tablets, to avoid first-pass metabolism in the sublingual delivery of small molecules and to the sublingual delivery of proteins, peptides, and vaccines. As a freeze-dried ODT, Zydis is ideally suited to provide stable, room-temperature formulations for proteins, peptides, and vaccines. In addition, Zydis is being used as a platform for *in situ* generation and stabilization of nanoparticles for improved bioavailability of BCS Class II and IV compounds.

So, you can see that the technology platform has great versatility across the range of pharmaceutical products.

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Pharmaceutical Technology: Are there any changes in the nanoparticles on storage?

Rosie McLaughlin: Fenofibrate as a model compound was nano-sized to a d90 of approximately 400nm and d50 of 200nm in a Zydis matrix, freeze dried and placed on stability for 6 months at 25/60% RH and 40/75% RH. No significant change in particle size distribution was noted at either condition demonstrating that nanoparticles can be successfully stabilized in the Zydis platform.

Pharmaceutical Technology: Is there a limit to the size of the peptide that can be delivered with Zydis through the sublingual route?

Rosie McLaughlin: Size is an important consideration in the sublingual delivery of peptides. From the literature, the most commonly studied peptides for oral delivery include calcitonin, which is about 3.4 kilodaltons, GLP1, which has a similar size, insulin with a molecular weight of approximately 5 to 6 kilodaltons, and even human growth hormone at 22 kilodaltons. Based on this an upper limit in the region of 10 kilodaltons could be in envisaged. However, the actual tertiary structure, the molecular size and charge can also influence the amount that can be absorbed. In animal PK studies, Catalent has demonstrated an increase in bioavailability in calcitonin delivered sublingually using Zydis compared to that delivered orally to the GIT.

Pharmaceutical Technology: What types of vaccine antigens are suitable for delivery using Zydis?

Rosie McLaughlin: Many different vaccine antigens can be used in Zydis, including live attenuated, whole inactivated, and split virion. Using whole inactivated flu virus as a model antigen, protective immunity was demonstrated in a mouse model. Split virion or sub-unit vaccines often require an adjuvant, and the inclusion of adjuvants in Zydis has also been demonstrated.

Pharmaceutical Technology: How did you determine the extent of absorption by the sublingual route?

Rosie McLaughlin: In animal studies, the sublingual dose is compared to a Zydis unit that has been resuspended in water and administered by gavage (the dosage is delivered directly to the GIT). The PK profile of the sublingual dose (area under the curve, Tmax and Cmax), can then be compared directly to the dose delivered to the GIT.

In humans, the PK profile of Zydis tablets swallowed, and those delivered sublingually, can be compared. In some instances, the patient receiving the sublingual dose may be instructed not to swallow for a few minutes.

Pharmaceutical Technology: Is there a limit to the amount of peptide that can be formulated into Zydis?

Rosie McLaughlin: In general, peptide APIs tend to be quite potent, therefore, the dosage required is often small. Most are readily soluble in aqueous medium or form a colloidal solution, so there is no limitation in terms of low doses that can be included. If a high dose is required, some proteins and peptides can form gels, and if too viscous, could impact the dispersion properties of the products. However, in practice, this has never been a limiting factor.

Reference

1. Orally Disintegrating Tablet and Film Technologies 7th Edition, Technology Catalysts, http://technology-catalysts.com/wp-content/uploads/2016/02/ODT7_brochure.pdf, accessed June 29, 2016.