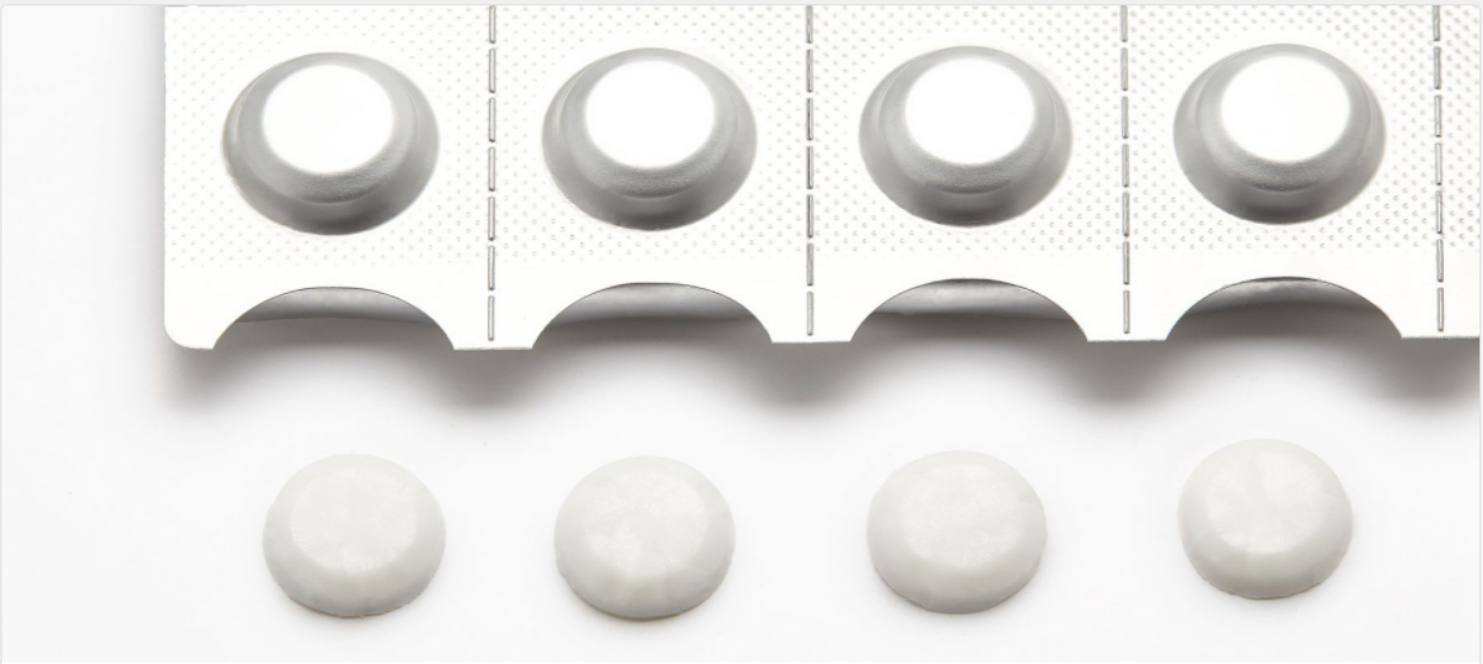

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Optimizing Oral Drug Delivery using Zydis® Orally Disintegrating Tablet Technology to Address Patient Challenges

Catalent Catalent

KEY POINTS

- Patients prefer oral dosing, but swallowing tablets can be a challenge for many patients.
- The Zydis® orally disintegrating tablet (ODT) platform addresses challenges associated with oral dosing, expanding benefits for patients and options for healthcare providers.
- A strong growth trajectory is expected for ODTs given therapeutic innovation and continued technology development.

Many patients prefer conventional tablets for the administration of medications, but some geriatric and pediatric patients and those with altered mental status and physical impairments find swallowing tablets to be difficult. Orally disintegrating tablets (ODTs), which dissolve completely without chewing or sucking, offer a patient-friendly dosage form for the administration of small-molecule drugs, peptides and proteins. With the potential for multiple sites of drug absorption, often faster onset action for the active pharmaceutical ingredient (API), and potentially greater bioavailability, ODTs are an attractive option for drug developers considering first-to-market formulations or product line extensions of existing drugs with compatible API. In this report, we look at how innovation in the industry-leading Zydis ODT platform is expanding oral formulation options and bringing benefits to patients.

ODT TECHNOLOGY OFFERS MULTIPLE PATIENT BENEFITS

ODTs offer several key advantages over other dosage forms. Their rapid disintegration improves the oral drug delivery experience for many patients from young children to seniors to patients suffering from dysphagia.

Zydis ODT formulations are ideal for:

- Acute conditions where treatment is required “on the go”

- Patients experiencing nausea and vomiting
- Patients with liquids restrictions
- Pediatric patients who have not learned to swallow traditional tablets

Additionally, the instant dispersion of the tablets in the mouth prevents patient "cheeking"—holding tablets in the cheek for later disposal or redirection—offering particular benefit where compliance may be resisted, such as psychiatric patients or addiction treatments administered under supervision. "Every time I introduce someone to Zydis ODT, they are blown away by the speed with which it disperses—consistently less than three seconds," said Ralph Gosden, Head of Product Development at Catalent, the experts in Zydis technology.

Such ease of use, combined with improved mouthfeel, and taste masking of bitter APIs can help to make it easier for patients to stick with their dosing regimen. And stronger patient compliance may ultimately translate to improved clinical outcomes—a win for everyone.

The **Zydis® ODT platform** consists of three technologies:

Zydis® ODT is a unique freeze-dried dosage form that disperses within 3 seconds without the need for water.

Zydis® Ultra technology offers enhanced taste-masking capabilities, increased drug loading and the potential for functional coating while maintaining the fast dispersion characteristics of Zydis ODT.

Zydis® Bio technology offers a formulation strategy for oromucosal delivery of peptides, allergens and viral vaccines.

ZYDIS FUNCTIONALITY

Used in the first commercial ODT to receive U.S. FDA approval, the Zydis ODT platform has a long history of innovation. This family of proprietary technologies offers a range of capabilities, with three targeted formulations. Zydis ODT technology can be utilized for the delivery of small molecule APIs, peptides and allergens. The Zydis ODT is a unique freeze-dried dosage form that disperses within three seconds, without the need for water, and is ideal for the delivery of small molecules whether targeting pre-gastric or gastrointestinal absorption. Zydis Ultra technology offers enhanced taste-masking capabilities, increased drug loading and the potential for functional coating, while maintaining the fast dispersion characteristics of Zydis ODT.

Zydis Bio technology allows for the buccal or sub-lingual (oromucosal) delivery of large-molecule peptides and allergens. It is also uniquely positioned as a vaccine dosage form, as the manufacturing process preserves vaccine stability and allows for long-term storage and shelf life. Zydis ODT rapid disintegration and API release are ideal for sublingual vaccine applications. Together, these attributes offer many advantages for the potential oral delivery of vaccines, such as ease of delivery and cost—important considerations for those focused on patient safety, public health and supply chain issues.

With Zydis ODT and Zydis Bio, there exists the potential for pre-gastric absorption, where the drug is absorbed oromucosally into systemic circulation. This channel avoids first pass metabolism and gastrointestinal degradation, thereby potentially translating to lower doses and a reduction in the formation of metabolites and improving a drug's safety profile. Catalent is currently engaged in a program with Aston University, U.K., to create a predictive tool to determine optimum levels of absorption enhancer to boost pre-gastric absorption.

IS ODT THE RIGHT FIT?

ODTs are appropriate for a wide range of therapeutic areas, from allergy and gastrointestinal treatments to anti-psychotic medicines and anti-depressants. New products can benefit from the outset, while existing products can be reformulated as an ODT for line extensions and differentiation for a valued brand. Feasibility evaluations are an important first step for developers considering ODTs, as the API must be suitable for oral administration. Some classes of drugs may be restricted from ODT development due to their requirement for specific handling facilities. Otherwise, the suitability of an API for ODT formulation relates to its physicochemical properties and target product profile.

The Zydis research and development team fully characterizes each API and associated Zydis formulations throughout the development process to mitigate potential pitfalls and provide a robust data package in support of regulatory filings. This process includes:

- Consideration of the relevant API characteristics identified during the technical evaluation of important preformulation data, solubility and aqueous stability factors
- Consideration of dose, lipophilicity, and molecular weight, especially when targeting oromucosal drug absorption

- Creation of a range of prototype formulations prepared under different processing conditions
- Use of analytical techniques to determine the compatibility of a candidate API with the Zydis technology
- Short-term accelerated physical stability studies

Certain medications have characteristics that are challenging for ODT technology. For example, high-dose formulations and extremely bitter API's have previously presented difficulties. Zydis Ultra helps to address these challenges by allowing for improved taste masking so that, through a specialized coating process, a higher amount of API can be incorporated into the rapidly dispersing tablet.

THE ZYDIS MANUFACTURING PROCESS

For those APIs determined to be compatible with Zydis ODT technology, the manufacturing process is well defined and scalable, consisting of four main steps:

- Mixing of the API and appropriate excipients to form a solution or suspension
- Precisely filling the liquid into preformed blisters before freezing the mixture
- Freeze-drying to remove the water and create a solid, dispersible tablet
- Sealing of the blisters to protect the dosage form from light and moisture

The lyophilization process results in a porous, moisture-penetrable product surface. Unit dosing the liquid mix allows for precise control of the tablet's size and weight, ensuring dose uniformity. The excipients and manufacturing process work together to create the rapid disintegration properties of Zydis ODTs.

The process for Zydis Ultra, which effectively taste masks most bitter APIs, differs in that the API must be polymer-coated in an acoustic mixer before it is incorporated into the Zydis matrix. Formulation strategies such as use of flavors, sweeteners and ion exchange resins are effective when the API is moderately to reasonably bitter, but poor taste can remain for extremely bitter compounds. The acoustic coating technology employed to create Zydis Ultra provides a barrier around each drug particle to ensure that the bitter taste does not break through. The polymer coating provides effective protection in the aqueous environment of the mouth, but is quickly removed in the gastrointestinal tract, ensuring that bioavailability is maintained versus conventional oral delivery methods.

Biological molecules are often less stable than their small-molecule API counterparts. Zydis Bio therefore uses polymers capable of maintaining a low solution viscosity at low temperatures, allowing the product suspension to be dispensed into the blister pockets while maintaining stability.

ZYDIS TECHNOLOGY AT WORK: MAKING IMMUNOTHERAPY CONVENIENT

Using its Zydis ODT technology, Catalent supported Denmark-based ALK-Abello A/S (ALK) in the formulation, development and manufacturing of ALK's sublingual immunotherapy (SLIT) tablets for the treatment of respiratory allergies. An alternative to regular subcutaneous injections, which need to be administered by a clinician, the SLIT tablets offer patients extraordinary convenience by delivering solubilized allergens to immune cells embedded within the mucosae under the tongue. The freeze-dried tablet technology effectively encapsulates the allergens without impacting their stability, then rapidly releases and solubilizes them with a small amount of saliva.

Product test results were compelling: "*In vitro* evaluations of Zydis ODT encapsulated allergens show[ed] the tablet disintegrates within one second, solubilizes the allergens in a limited volume of fluids and releases all its content within 15-30 seconds."[1,2] By contrast, compressed sublingual tablets lagged, taking 31 seconds to dissolve, and released only 8.7 percent of allergens after one minute, with particulates left behind.

ALK's Executive Vice President of R&D Henrik Jacobi credits Zydis ODT as a major contributor to the success of his company's SLIT treatments: "Fast-dissolving technology is used across ALK's SLIT tablet range, which has delivered consistently strong results throughout its clinical development. We believe that the tablet formulation technology is an important factor in this success."

STRONG GROWTH PROSPECTS FOR ODTs

Leveraging 25 years of research, development and production, the Zydis platform continues to overcome challenges associated with oral dosing, and to expand benefits for patients, and options for healthcare providers. “As new treatments are identified for existing and newly characterized indications, I believe that ODTs will continue to feature strongly across the range because of the specific patient benefits offered,” said Dr. Susan Banbury, Head of Zydis Formulation at Catalent.

With well-established and readily scalable manufacturing processes, ODTs present a significant opportunity to benefit many more patients with rapidly dissolving oral formulations. With new classes of therapeutic entities, the Zydis ODT formulation and process may also offer certain technical advantages such as low temperature processing and enhanced product stability. “The combination of therapeutic innovation and continued ODT technology development means a bright future for Zydis ODTs,” added Dr. Banbury.For more information, visit https://www.catalent.com/oral-dose/oral-technologies/orally-disintegrating-tablets/ or contact:

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