ThermoFisher SCIENTIFIC

CASE STUDY

MADE WITH
PROCESS & PURPOSE

# Thermo Fisher Scientific partners with orphan drug developer to resolve dissolution challenges

## Introduction

A Swedish pharmaceutical company focuses on identifying patent-pending small molecules with promising results in preclinical studies and further developing them for the treatment of aggressive lymphomas. This company's pipeline included a product formulated as a modified release (MR) multiparticulate (MUP). MR MUPs are developed to release drug according to specific profiles, including pulsatile, controlled, or delayed timing. Optimizing the drug release profile allows for control of the dose experienced by the patient and reduces the risk of dose dumping, toxicity, or bioavailability variations associated with gut transit time.

The customer was preparing to supply their MR MUP to a clinical trial of an orphan drug for the treatment of diffuse large B-cell lymphoma (DLBCL). This drug showed promising experimental and clinical results, but an important issue threatened successful use of the drug in a Phase III clinical trial.

## Situation

During formulation development of the investigational modified release drug for DLBCL treatment, the product showed instability. Specifically, the dissolution profile accelerated upon storage. A critical attribute of tablet quality, the dissolution profile is the percentage of the tablet that dissolves at various points in time. During storage, the dissolution profile should remain stable.

As in any clinical trial, providing patients with investigational drugs that retain their known strength for the required amount of time including storage is critical for accurately determining product safety and efficacy. The customer had to address the accelerating dissolution profile in order to have a product with suitable shelf-life to participate in the planned clinical trial.

Thermo Fisher Scientific worked with the customer to provide a solution that would result in stable drug product that can be dosed safely and consistently with minimal impact to their study timelines.

## Solution

With the dissolution profile problem identified, the customer and Thermo Fisher Scientific's team of experts focused on identifying a root cause so that a clear remedial pathway could be determined. Thanks to their strong links with local universities, the Thermo Fisher Scientific team took advantage of the best characterization analytical techniques possible to gain insight into the root cause of the dissolution behavior of the tablet. The team hypothesized that the hygroscopicity and solubility of the ingredients accelerated their migration from within the drug-loaded core to the surface of the multiparticulate. Using Micro Raman spectroscopy (see Figure 1) and Time-of-Flight Secondary Ion Mass Spectrometry (ToF-SIMS) (Figure 2) to determine API presence and localization

with respect to depth from the surface and spatial distribution at the surface where appropriate the team determined that the API was, in fact, present in the surface coatings of the MUPs, preventing controlled release through the functional MR coating system, as planned.

Figure 1. Micro Raman spectroscopy measured API levels at the surface of the MR MUP in various samples. Below are some of the data gathered from a single sample. The first panel includes measurements of API concentrations at various surface depths scaled at 0-100%. The xy map also shows concentrations of the API not scaled. The common least squares (CLS) algorithm reduced potential for large errors in results.

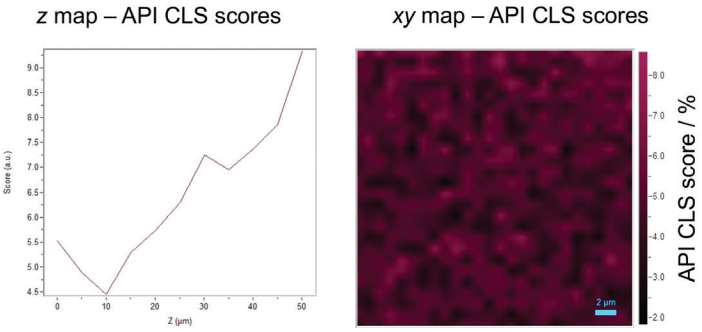
## Results

Based on the findings of the advanced imaging and stability studies, the Thermo Fisher Scientific team worked with the customer to implement strategies that would address the dissolution behavior. This included improving container closure to enhance stability, and adding more hydrophobic materials into the sub-coat to help prevent migration. The changes enabled the production of new stability data that could be used to assign a shelf-life to the drug product to cover the clinical trial.

Determining an accurate shelf life ensures that patients receive a product that retains its strength, quality, and purity. After identification and resolution of threats to their product's shelf life, the customer's clinical trial proceeded on time and as planned. Patients with aggressive lymphomas received the opportunity to try a new investigational product formulated to release drug according to the specific parameters being tested and with a suitable shelf-life to supply the trial as required.

## Summary

A pharmaceutical company developing small molecules for the treatment of aggressive lymphomas needed a partner that could help resolve an issue with a clinical trial drug. An accelerating dissolution profile threatened use of the drug in the trial. Thermo Fisher Scientific used sophisticated imaging techniques and stability studies to identify and address the root cause of the problem, enabling the customer to proceed with the trial on time and as planned. To learn more about how Thermo Fisher Scientific can help support your drug delivery project, contact us.

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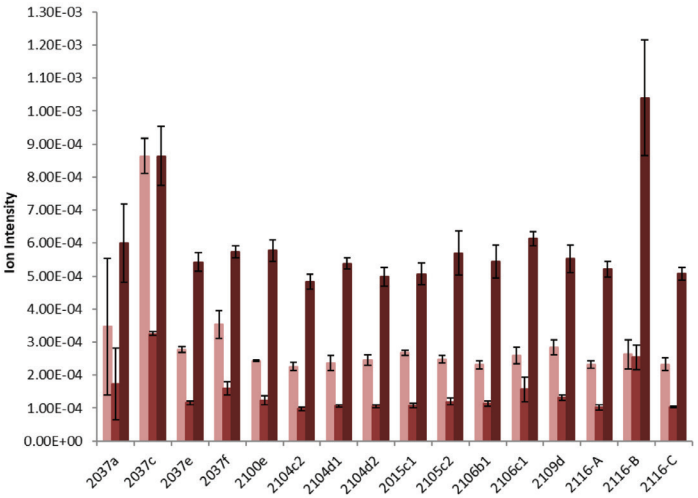


Figure 2. Time-of-Flight Secondary Ion Mass Spectrometry (ToF-SIMS) characterized presence of API at the surface of drug loaded pellets. The graph below shows ion of various marker ions for the API in various samples. An additional stability study focused on enhanced container closure and formulation to prevent migration.

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