Case study
Drug product

Fixed dose combination drugs

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A large, multinational pharmaceutical company was seeking a CDMO partner with the expertise and technological capabilities to combine three drug substances into a fixed dose combination (FDC) product suitable for adult and pediatric dosing.

The incompatibility of one of the APIs with the other two and the need for flexible dosing for a diverse patient population were key challenges. These were overcome using a combination of multi-layer tablets for adults, mini-tablets for pediatric patients, and polymer coating technologies. In a second case, microparticulate technology was used to meet a customer's needs for combining two APIs with different release profiles.

Meeting the challenges for FDCs

When companies are looking to combine two or more APIs into a single FDC product — whether for the purpose of improving convenience and patient compliance, reducing manufacturing costs, repurposing proven compounds, or extending a product's patent life — several factors require consideration, including:

- Are the APIs chemically compatible or prone to interact when combined?
- Do the APIs differ in their need for immediate-, delayed-, or sustained-release?
- Would the company benefit from being able to choose from a wide variety of oral dosage forms (e.g., tablets, mini-tablets, encapsulated powder for resuspension) and formulation options (such as taste masking) to accommodate the different needs of various patient populations, including infants and other pediatric patients who may have difficulty swallowing?

In the complex cases described here, the customer companies recognized the advantages gained with the broad range of choices, flexibility, advanced knowhow, and technology that Cambrex offers. The companies were able to explore different formulation options with Cambrex scientists and leverage the expertise and capabilities of an established CDMO, including:

- Proven capabilities in blending, compression and coating
- State-of-the-art equipment for producing mini-tablets, multilayer tablets, and tablet-in-tablets
- Microparticulate technology for controlled-release formulations

Overview

Two companies wanted to create FDC formulations that contained multiple drug substances to enable single dosing. They were looking for a CDMO partner that had the flexibility to provide a broad range of formulation options that would be appropriate and beneficial for a variety of drug types, delivery needs and indications.

Challenge

The first case required combining three different APIs into one formulation. One of the APIs was not compatible with the other two, necessitating an FDC design that ensured API segregation to avoid potential interactions. The second case involved two drug substances with different release profiles to be administered as one FDC drug.

Solution

In both cases, the companies were able to benefit from Cambrex's extensive range of equipment and technological expertise that allowed them to design and develop FDC strategies that met their needs.

Results

Cambrex produced a multilayer polymer-coated three-API tablet for adult indications to overcome the complex challenges in the first case study, and dual mini-tablets combined in a capsule for pediatric patients. To meet the demands of the second case study, Cambrex leveraged its microparticulate technology to combine two drug substances into one FDC product, using polymer coatings to achieve differential drug substance release.

- Specialization in dry and wet granulation, roller compaction, extrusionspheronization, ion exchange technology, and hot melt extrusion manufacturing technologies to enhance drug substance solubility and bioavailability
- Experience working closely with regulatory agencies from preclinical development through to approved products
- Extensive FDC pipeline including products submitted to the US FDA and currently on the market

A three-in-one FDC

When faced with the challenge of combining three APIs — one incompatible with the others — into an FDC drug product, Cambrex developed two different types of drug products targeting adult and pediatric indications. The design of the adult FDC drug product involved combining the two compatible APIs into a single tablet and coating it with a polymer. That tablet was then coated with the third API. The polymer coating segregated the third API from the first two. The newly formed three-API multi-layer tablet was then polymer-coated.

For the pediatric indication, mini-tablets were the ideal solution since they could be sprinkled from a sachet. Cambrex compressed the two compatible APIs into one mini-tablet and manufactured the third, incompatible API in a separate mini-tablet. Combining the two mini tablets into an FDC product solved the incompatibility issue.

Polymer-coated microparticulate technology

The main challenge presented by this customer was the need to formulate an FDC drug that contained two APIs with different release profiles. One API was targeted for release in the duodenum, immediately after the drug exits the stomach, whereas the second API was intended to release farther along in the intestinal tract. Working in close collaboration with the client, Cambrex designed an innovative solution in which microparticulates were coated with either the first or the second API, and each set of microparticulates was then coated with a polymer specifically selected for its controlled-release properties at different pHs.

Analytical challenges

The development and validation of analytical methods for FDC products is especially challenging due to the presence of multiple APIs with various strengths in the finished dosage form. Cambrex's analytical team has many years of valuable experience developing innovative analytical methods. By applying modern technologies and techniques, including ultra-high pressure liquid chromatography (UPLC), Cambrex can combine three separate API assays and the detection and quantification of impurities into one analytical procedure for finished FDC products. This saves significant time and cost. In addition, Cambrex's analytical team has overcome challenges of sensitivity and solubility in developing a single dissolution method that greatly speeds up the FDC development program.

"Cambrex is very open to work in a collaborative way with our customers. It's not 'we do what we think and if we fail, we do it over.' Instead, we work together, getting the customer's input, and we do it right the first time."

Maryse Laliberte
General Manager

About Cambrex

Cambrex is a leading global contract development and manufacturing organization (CDMO) that provides drug substance, drug product, and analytical services across the entire drug lifecycle.

With over 40 years of experience and a growing team of over 2,200 experts servicing global clients from North America and Europe, Cambrex is a trusted partner in branded and generic markets for API and finished dosage form development and manufacturing.