Cambrex

Case study
Analytical services

Overcoming limitations to achieve uniform dosing

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Challenges in blend formulation of a low-dose capsule to meet urgent clinical demand.

Dose adjustment: Meeting clinical demand

Drug companies often consider the value of CDMOs in terms of process development to meet milestones for regulatory filings and scale-up efforts for commercialization. However, specific needs in the clinic can also drive new efforts in method development and drug product formulation. Choosing the right CDMO with the proper experience and facilities can make or break the ability to deliver swift modifications to a formulation.

Formulations of low-dose drugs require a careful balance of several factors to ensure that each dosage has an acceptable blend and content uniformity. Determining the right methods and equipment specifications to pair with the selected material requires expertise across multiple areas of the development process. In this case, an immediate need for lower dose capsules in the clinic posed several challenges in blend formulation with very tight timelines for delivery. With the equipment already optimized to deliver the smallest dose, Cambrex targeted modifications to the formulation to solve the client's needs. The analytical team worked on multiple fronts while also supporting the manufacturing team, and delivered qualified methods to support release testing of batches of the new formulation.

Glide past barriers: A chemical solution to a physical problem

The use of automated equipment to maximize throughput capabilities offers flexibility in transferring specific doses to capsules, but there are some limitations. When doses are low, transfer accuracy can be compromised and lead to a higher reject rate. Here, the challenge was to add components to the formulation that would not alter the potency or safety profile of the drug substance, while improving the flowability of the product during capsule filling.

An existing method for the neat powder in capsule was used as a starting point, but recovery using that method was not adequate. The team theorized that the sample diluent was not breaking up the blend sufficiently. One of the excipients, methyl crystalline cellulose (MCC), may have accounted for this by creating a complex with the API that filtered out during sample preparation. A key deliverable for the client was the development of a validated method for maintaining content

Dependable diagnosis.

Our experts get to the root cause to deliver the right solution.

About Cambrex

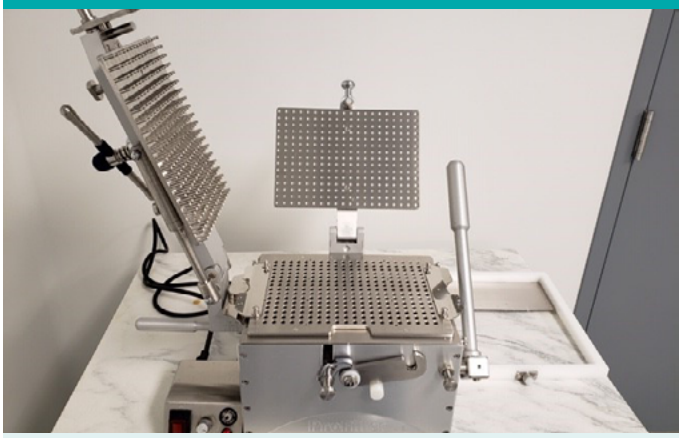
Cambrex is **the** small molecule company that provides drug substance, drug product and analytical services across the entire drug lifecycle. Enjoy working with our experts to accelerate your small molecule therapeutics into the market.

With over 35 years' experience and a growing team of over 2,000 experts servicing our global clients from our sites in North America and Europe, we are tried and trusted in branded and generic markets for API and dosage form development and manufacturing.

uniformity using a new diluent to disrupt the complex formation. By selecting a new diluent during method development and using a "flood fill" encapsulation method to accommodate the increased bulk of the formulated material, accurate content uniformity testing was achieved for the drug substance.

It takes expert knowledge of the chemical process in order to trace a physical limitation during manufacturing back to its chemical origin. Here, the limitations of the ProFiller® "flood fill" encapsulator during the filling operations were addressed by adding the glidant silicon dioxide to improve the flowability of the drug substance. This allowed the equipment to produce reliable low-dose capsules to meet the clinical demand.

Balancing blend formulation with equipment specifications



Using automated equipment to increase throughput for capsule filling must meet uniformity standards.

Low-dose capsules can push the physical limits of the equipment to deliver an accurate and uniform dose of API to each capsule. The correct modifications to blend formulation and use of a "flood fill' encapsulation machine can overcome this barrier and ensure accurate delivery of dosages during high throughput filling.

Finding the right blend: Methods to ensure uniformity

Uniformity is a critical attribute in drug product formulation because it will ultimately impact the clinical effect on the patient by affecting drug dissolution, absorption and bioavailability. Thorough testing of formulations is critical to determine the uniformity after blending and after encapsulation, and to assess the potency of the material. It also serves to demonstrate to regulatory authorities that the process is controlled to ensure the same amount of drug substance in each dosage.

Rather than relying on a single form of analysis, Cambrex uses several methods to ensure quality, including Karl Fisher (KF) water content and related substances methods. These methods are redeveloped as needed according to the unique attributes of the drug substance. For example, after adding the excipients to the formulation in this case study, the water content increased dramatically. The existing KF method for the neat powder had to be modified for a different level of standard and melting temperature in order to yield valid results for the new blend formulation.

Chromatography is used to measure content and blend uniformity across several samples, and to quantify potency when performing the assay method. When the team detected excipient interference using the original method, they adjusted the wavelength to isolate the API. In this case, the experts also developed a dissolution method for the material from scratch. Samples of the acidic media were pulled across various time points to assess the timing of drug product release while the dosage form disintegrates in the dissolution batch. Dissolution methods can be especially powerful because they mimic the drug activity in vivo.

Beating the clock: Testing in parallel with manufacturing

All four of these methods were developed in parallel to dramatically compress the timeline. With validated methods available, batch release testing was able to take place as product came off the manufacturing line, and Cambrex was able to deliver the low-dose capsule formulation on time.

Achieving uniformity in formulation development not only satisfies regulatory requirements, it reduces lost revenue caused by rejected product. Low-dose drugs in particular can pose challenges during filling due to physical limitations of the equipment as well as challenges in achieving blend homogeneity. CDMOs must apply expert knowledge of the root causes to address both chemical and physical challenges. Cambrex leverages our top analytical and formulation teams to meet these challenges under aggressive timelines.

Strategy over shortcuts.

There is no shortcut to a quality product, but working strategically saves time.

Developing 4 methods in parallel means 4x faster delivery.

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