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Precision Powder-In-Capsule Micro-Dosing Accelerates Drug Product Development

INTRODUCTION

Advancing active pharmaceutical ingredients (APIs) through the drug product-development lifecycle is fraught with challenges. Development timelines are tight, so it's crucial to determine early in the process if an API is a viable candidate for clinical testing. Given the increased complexity of most API molecules in development pipelines, it's likely that these new compounds may have physicochemical or environmental constraints that require extra processing steps to produce a viable dosage form.

A key tool that has emerged to address these combined issues of tight timelines and complex molecules is precision powder micro-dosing in capsules. This development tool makes it possible to quickly get formulations to the clinic, saving time, money, and use of limited API, while avoiding premature termination of otherwise promising APIs.

This paper describes the use of precision micro-dosing to prepare API powder-in-capsule (PIC) dosage forms for oral or pulmonary administration. These PIC dosage forms reduce early-stage evaluation time (in Phase I and II) in part by reducing the need for formulation steps, such as excipient compatibility testing or tablet development. PIC studies have also proven a useful evaluation method for high-potency, low-dose applications where accurate micro-dosing is required. Case studies are presented.

PRE-FORMULATION

API synthesis and drug product development both are complex, multistep processes, full of inherent risk. Drug substance manufacturers must address such issues as lot-to-lot variability and scale-up concerns as they work to bring forth high-purity, stable drug candidates. Risk factors may crop up as development proceeds—such as changes in API particle or flow properties—that also affect the ultimate dosage form.

An important first step, therefore, is to develop a full understanding of the physicochemical properties of the API. Synthesis chemists and drug product-development teams must examine API characteristics such as dosing range; potency; solubility; flow properties; and sensitivity to light, moisture, and oxygen. Characterization tests may cover morphology (scanning electron micrography), particle time-of-flight (aerodynamic particle size distribution), particle size distribution (laser diffraction analysis), thermal characteristics (differential scanning calorimetry), water uptake (dynamic vapor sorption and Karl Fischer titration), and crystalline properties (powder x-ray diffraction) to gain an accurate picture of potential problem areas and to select the best dosing regimen.

THE MICRO-DOSING APPROACH

When timelines are tight, micro-dosing may provide the most expeditious route to quickly introduce a dosage form into clinical testing. Basically, micro-dosing involves the precision weighing and dispensing of powdered API using various platforms or techniques. The approach has gained significant traction in recent years, particularly for high-potency compounds for oncology and other indications. The approach has two clear advantages.

(1) ***Minimal API Usage.*** Depending on API characteristics, API doses as low as 100 µg can be encapsulated, with minimal weight variance. This material-sparing approach is well-suited particularly because in early-stage work, API supplies are limited and in high demand (e.g., for analytical test development). Extensive early formulation tests can deplete the API supply, stalling development efforts.

(2) ***Speed To Clinic.*** By directly incorporating API (or blends and other formulations) into a usable dosage form (i.e., capsules), viable prototype formations can be quickly identified and tested. Efficient API use can jump-start dosage form development, at times leapfrogging to the clinic while other conventional development steps are still in the planning stages. For instance, use of speciality capsule materials can bypass time-consuming steps of devising coatings for enteric protection and/or modified drug release.

In micro-dosing, the neat API or a powder blend can be encapsulated, used for analytical tests, or even used to start stability studies, while other approaches are evaluated in parallel. For work involving powders blends or other formulations, some dose-ranging studies may be required, but

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it may be possible to use micro-dosing to test multiple strengths of the same formulation.

PRECISION MICRO-DOSING

The advantages of the PIC approach are shown by Lonza's Xcelodose® Precision Micro-Dosing Systems, which have been widely adopted for early-phase PIC studies. Figure 1 shows the Xcelodose technology design, in which powder is dispensed into a capsule through a mesh screen at the base of the dispensing head. Powder is released by the tapping action of a solenoid on the tapper arm, which cradles the dispensing head. The parameters of the tapping process can be tightly controlled by varying dispensing head type, mesh hole size, number of holes, tapping frequency, and dispensing rate. A balance is used to continuously monitor the net weight of API that has been dispensed. The system accurately controls dosing by continuously monitoring the net weight being dispensed in real time and automatically adjusting the tapping rate during dispensing. As the weight approaches the target fill weight, the rate of powder delivery is reduced and then eventually stopped when the fill weight range is reached. Xcelodose systems identify and reject capsules that are over or under the filled weight range and generate comprehensive documentation for the process parameters, including individual weights for each filled capsule.

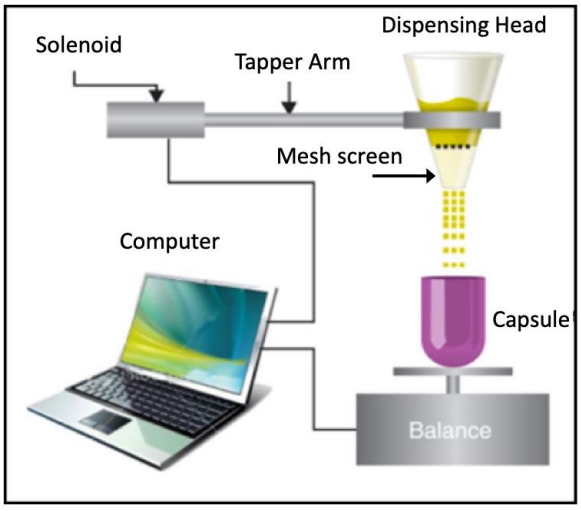

Figure 1
Xcelodose micro-dosing system design

This micro-dosing system accommodates use of a wide range of capsule types and sizes. Factors such as particle size, powder densities, salt correction factors, API moisture sensitivity, and enteric protection needs may help determine capsule composition, as well as processing and storage conditions.

While gelatin capsules are typically the default choice for micro-dosing, numerous speciality capsules are readily available, depending on API characteristics and the preferred dosing method, and the target drug delivery profile.

CASE STUDY SUMMARIES

The following case study summaries provide brief examples of how precision PIC micro-dosing can be useful in a variety of applications.

High-Potency, Low-Dose API. This case involved a high-potency, low-dose application for initial clinical testing on an aggressive timeline. The target dose was 0.1 mg to be dosed in a size 1 capsule. Several fill evaluations were performed under containment to determine the best dispensing head and to set tapping frequency and other process parameters on two scales of equipment: the small-scale Xcelodose 120S (nominal capacity of 120 capsules per hour under containment) and the higher-capacity Xcelodose 600S (nominal capacity of 600 capsules per hour under containment) for Good Manufacturing Practice (GMP) manufacturing. The yield was only 46%, which was as expected because the fill weight was so low, but with overage enough capsules were successfully produced with minimal loss of API. Despite the aggressive timeline of 3 months (from preliminary evaluations to release of clinical dosage form), program targets were met.

Dry-Powder Inhaler (DPI) Application. Micro-dosing can be used to prepare PIC dosage forms pulmonary delivery using a DPI. This case involved encapsulation of API that had been spray-dried to achieve the correct particle characteristics for pulmonary delivery (in the 2.5- to 3-µm range with a tight particle-size distribution and the right particle morphology). Tests were performed at three different fill weights. As Figure 2 shows, the Xcelodose system produced reliable results, with yields ranging from 78% to 95% as the average fill rate increased from 4.97 mg to 20.03 mg. The relative standard deviation (RSD) was consistent and the particle size distribution was well-defined. Using PIC micro-dosing to deliver spray-dried API can rapidly advance dosage form development, by using the same principles across multiple dosing ranges.

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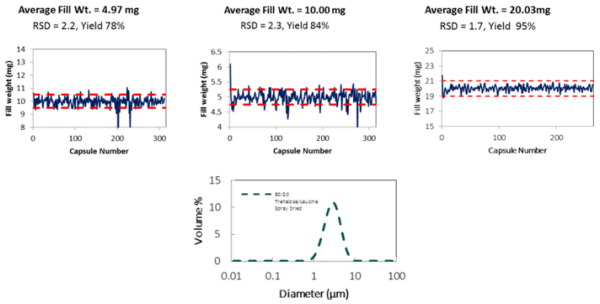

Figure 2
Multiple dosing fill weight ranges using micro-dosing for a DPI application

SUMMARY

Precision PIC micro-dosing approaches are invaluable tools that pharmaceutical companies can use to increase speed to clinic and gain competitive advantage. They can quickly assess new drugs in their pipelines, while remaining cognizant of development costs for formulated dosage forms. Lonza has extensive experience in PIC micro-dosing with its proprietary Xcelodose systems, which are available in a range of phase-appropriate sizes and capabilities inclusive of containment. In addition, we have extensive in-house expertise in speciality capsule types, as well as micronizing and spray-drying across an array of drug substance and particle engineering challenges. We also provide integrated product development, pre-formulation and formulation services, analytical method development, and manufacturing services inclusive of phase-appropriate encapsulation. To learn more, please visit our website.

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