Maximising Effectiveness of DPI Capsules

Figure 1: Xcelodose® 600S precision powder micro-dosing system

Capsugel's Xcelodose® precision powder micro-dosing systems produce capsules for effective use in dry powder inhalers

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Industry Requirements

Finding efficient drug delivery methods is becoming increasingly important as the pharmaceutical industry looks to improve the performance of its new compounds and extend the applications of existing drugs. One option that has long been used to successfully treat respiratory conditions and provide compounds with a fast-acting route into circulation is drug delivery via inhalation using a dry powder inhaler (DPI). The two-piece capsule is commonly used to contain a drug dose in a DPI, and Capsugel's Xcelodose® precision powder micro-dosing system, with its unique method of dosing capsules for R&D, is being routinely chosen by pharmaceutical and biotech firms to automate filling of DPI capsules.

Automatically filling DPI capsules requires equipment that can dose powders without compaction, as it is essential that powder particles freely de-aggregate when the DPI is used. Filling systems must also be able to dose at low weights, while also ensuring the amount of powder in the capsule is precise and reproducible. The system needs to be easily sanitised and work accurately in temperature- and moisture-controlled environments – another important step in preventing powder aggregation so it flows freely in the capsule. Finally, during the early stages of drug development, high dose flexibility is needed with limited process development. Traditionally, automated methods of dosing capsules have relied on producing a powder plug to fill the capsule. However, this can cause powder compaction, and though traditional automated filling technologies generally dose accurately in the 10 to 40 mg range (the dose range of many new drug formulations for use in DPIs), they are set up to manufacture larger batches. Unfortunately, their operation usually requires a minimum amount of bulk product which is often not available in the early stages of development.

Technology

The Xcelodose® 600S and Xcelodose® 120S systems can rapidly fill high-quality DPI

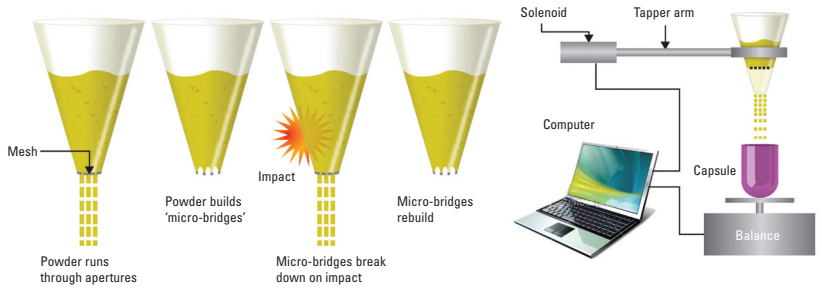
capsules for many forms of inhaled drugs. The Xcelodose® system works on the 'pepper pot' principle, dispensing a uniform amount of powder each time according to the number of times the pot is agitated and the size of the holes in the pot, without compacting the powder in the capsule.

The Xcelodose® system has a dispensing head that contains a mesh of holes with precise diameters. The dispense head is filled with powder, and with the aid of tapping the powder passes through the mesh via gravity directly into a capsule shell. The capsule base is placed on a seven place microbalance, tared to zero, and dispensing begins. After each discreet dispensing event, the powder forms 'micro-bridges' and is not released from the head unless it is tapped again. The amount of powder dispensed is a function of particle size and flow properties of the drug formulation, the size and number of holes in the dispensing head, and the number of taps the dispensing head receives. The weight being dispensed is monitored several times per second during the fill process and the number of taps is adjusted accordingly. When the capsule has reached its target fill weight, the motion stops and the final fill weight is logged by the control system, allowing full traceability of the capsules. The capsule is then automatically moved and replaced by an empty capsule on the microbalance, while the filled capsule is sealed and sorted into an 'acceptable weight' bin, or a reject bin if it is out of the set weight range.

Using an Xcelodose® system, high quality capsules made of either gelatin or Hydroxypropyl Methylcellulose (HPMC), such as Capsugel's Vcaps® Plus capsules, can be accurately dosed with powder weights as low as 0.1 mg and up to several hundred milligrams, in capsule sizes from 000 to 5. The RSD of the Xcelodose® system is around two per cent and it can dose up to 600 capsules per hour. The system can also be fitted with an Xcelodose® system RH control unit which controls the relative humidity to levels as low as five per cent with a tolerance of +/- 1 per cent. This helps prevent hygroscopic compounds from absorbing moisture during dosing, making powders less likely to form aggregates and more likely to remain free flowing in the capsule.

Images: Capsugel

Figure 2: Xcelodose® system methodology



Benefits of the Xcelodose® System for Dosing DPI Capsules

The Xcelodose® system's ability to accurately dose very small amounts of expensive or potent active pharmaceutical ingredients (APIs) without compaction makes it ideal for dosing DPI capsules during product development – helping to ensure the free flow of powders, increase the dose percentage emitted, and saving money. The Xcelodose® system can also be easily cleaned with all the parts being able to be quickly removed and sanitised prior to the next day's run. The system can also be kept clean during runs with operators being able to access and swab all the machine parts and clean the dispense heads with isopropyl alcohol (IPA).

Application

Two Xcelodose® systems, an Xcelodose® 600 and an Xcelodose® 600S, are being used at the major drug development services company, Aptuit, to routinely dose HPMC capsules for use in DPIs. Since 2002, Aptuit has used the Xcelodose® system to produce extensive campaigns of DPI capsules for use in clinical phases f or several pharma and biotech clients, sometimes producing as many as 80,000 capsules in a batch.

After assessing a variety of tamp and dosator technologies, Aptuit chose the Xcelodose® systems for automatically filling DPI capsules, primarily because of the system's ability to dose capsules without compressing the powders inside. The company has filled DPI capsules with 10 to 40mg of approximately eight different blended formulations or spray dried powders for use in respiratory DPIs. Operators at Aptuit prefer to dose blended or spray dried formulations using the Xcelodose® system as its method of loose filling minimises the risk of aggregation – a critical feature to ensure optimum clinical performance of DPI capsules. To date, they have observed no segregation of the components of the blend that has prevented GMP manufacturing. Typical production rates for DPI capsules at Aptuit are 300 to 400 capsules per hour with their Xcelodose® 600S system and 200 to 300 capsules per hour with their Xcelodose® 600 system.

The Xcelodose® system is ideally suited for accelerating production of high-quality capsules for DPIs as Aptuit's sustained use of the technology for many different clients' inhaled drug formulations clearly demonstrates.

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