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ACCELERATING PHARMACEUTICALS' TIME TO MARKET: APPLICATIONS OF CAPSULE LOW-DOSING TECHNOLOGY

One of the key challenges of current pharmaceutical research and development is to offer utmost speed in the execution of development projects. This is due to the fact that more and more drugs fall in the category of unmet medical need and are granted abbreviated regulatory approval. Additionally, pharma innovators are committed to bring those therapies to the patients as fast as possible.

Trends in the global R&D pipeline suggest that the pharmaceutical industry is navigating a landscape of competing factors.[1] Though new pharmaceuticals are moving to market faster than ever, developers need time to optimize formulation for the sensitive or high-potency active ingredients that dominate the current pipeline of drug candidates.

The challenge of balancing speed and thorough development can be solved by choosing capsule microdosing technology. Manufacturers can dose small amounts of pure active pharmaceutical ingredients (APIs) or simple blends directly into hard capsules (figure 1). Micro doses less than 5 mg or low doses, which can range from 5 mg to 100 mg,[2] delivered in hard capsules are an accessible solution that enables manufacturers to bring new medicines to R&D or to market more quickly.

Figure 1: Standard hard-shell capsules can be precisely filled with low- or microdoses of an active pharmaceutical ingredient.

Courtesy of Aenova

SWAPPING TABLETS FOR CAPSULES

Low-dose pharmaceuticals are typically made by first blending a powdered API with several functional or nonfunctional filler materials called excipients and then compressing the powder into tablets. Excipients such as binding material and lubricants are necessary to form a stable tablet and enable good processability during manufacturing. Disintegrants ensure reliable API dissolution.

Tablets pose challenges as a dosage form for low-dose APIs. When they use less than 20 mg of API, some blending and segregation processes can lead to reduced dosage precision due to the high dilution. Tablets require a formulation process before they enter early-phase clinical trials, and optimizing formulation can increase development timelines.

To avoid time-consuming development trials for tablets, manufacturers often directly fill an API into hard-shell capsules and provide the capsules for early-phase clinical trials.[3] Modern filling machines can precisely fill low amounts of pure API (or premixes of an API with functional or nonfunctional filler material) into hard-shell capsules and ensure 100% dosage-control of each filled capsule (figure 2).

Direct, precise, reliable low-dose filling of hard-shell capsules can now be scaled to an industrial process. This means processes developed for initial studies can be used for commercial production, which eliminates some studies and development while moving a drug product to market.

Low-dose capsule production has low validation costs, involves no extra costs for process development, and "allows fast product change on the line," says Karl-Heinz Bannefeld, head of development at Aenova's site in Münster, Germany.

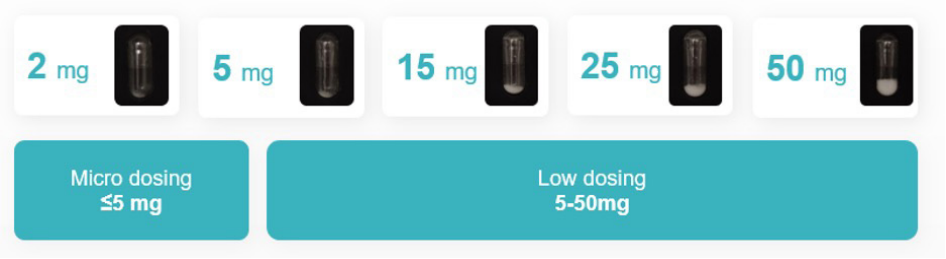

Figure 2: Standard capsules can be directly filled with pure active ingredient to create low-dose capsules, containing 5–100 mg. Microdose capsules contain less than 5 mg of active ingredient, which is often blended with just one nonfunctional filler material.

Courtesy of Aenova

PRECISE AND ACCURATE DOSING

Quality and safety requirements mandate manufacturing consistency in pharmaceutical manufacturing. Producers prepare low-dose capsules with the required consistency by using precision powder dosing followed by accurate measuring and monitoring of each filled capsule.

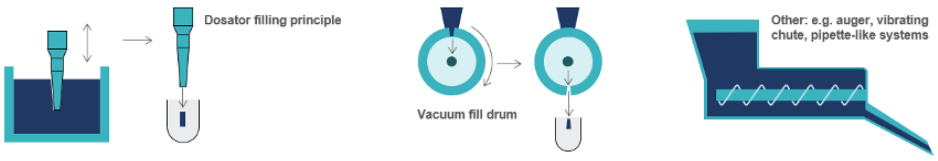

Figure 3: Common methods of precision powder filling for low-dose capsules include a dosator, a vacuum fill drum, and an auger.

Courtesy of Aenova

Technologies for precision powder dosing include dosators, vacuum fill drums, and vibrating feeder systems (figure 3). A dosator essentially works like a pipette for powder: It descends into a bed of powder, picks up powder, and transfers the powder into the capsule body. This volumetric dosage can be varied by adjusting the dosage chamber of the dosator.

Dosing via vacuum fill drum is based on volumetric dosing as well. The drum contains cavities with a precisely defined volume. Powder is raked into the cavities and held via negative pressure until it is ejected into the capsule body. Augers and vibrating chutes are common powder-handling methods for preparing low-dose capsules for preformulation tests.

How do manufacturers confirm that each capsule has the same amount of powder? Due to differences in the mass tolerances for the empty capsules and the low doses of powder, weighing each filled capsule is not a reliable method of quality control.

As an example, take a mass tolerance of ±3 mg for a size 3 capsule. If the tolerance for the filling mass is 5%, that means the allowable variance for 2 mg of API is ±250 µg—less than 10% of the capsule tolerance. Any variation in powder filling would be undetectable within the capsule tolerance.

Advances in precision powder filling ensure 100% control of each capsule's content at a variety of production volumes. To achieve that level of control during low-dose capsule production, manufacturers use the net weight control method on a production line. They check empty each capsule, dose the powder into the capsule, and recheck the capsule. A gravimetric or capacitive sensor rapidly and accurately detects the mass difference from the powder dose. This complete control means no empty or deficiently filled capsules leave the production line, according to Bannefeld.

Aenova, a contract development and manufacturing organization, has established filling capacity for low-dose capsules at its Münster site.[4] "We can produce pure API-, powder- or granulate-filled capsules, and even optionally combinations of two of these forms," says Gereon Rau, head of low-dosing technologies at Aenova Münster.

A SOLUTION FOR MANY CHALLENGES

Low- or microdose capsules will ease many of today's pharmaceutical development and manufacturing challenges, according to Rau. Global trends in drug research and development include accelerating production timelines, developing products for areas of unmet need, and optimizing the bioavailability of poorly soluble APIs.[1] Low- or microdose capsules enable manufacturers to eliminate formulation steps, move faster to preclinical and clinical trials, and take optimal doses from trials directly to commercial production.

Compared with preparing low-dose tablets, directly filling capsules shortens the timelines for developing formulations and processes and for the scaling-up phases of the drug pipeline. Monitoring production by weight filling streamlines the set-up for a manufacturing line, makes the validation process straightforward, and enables production with any batch size.

When determining optimal dosage during development, manufacturers can use low-dose capsules to rapidly produce a range of dosages to test in clinical trials. The same batch of powder can be used to create different dosages just by changing the filling weight of powder in the capsule. The optimal dose—or doses—that emerges from trials can be moved directly to commercial-scale production with the existing process.

Low-dose capsules also provide a fast route to preparing drug products in various sizes according to patient needs. For example, small capsules such as size 3 are easier for pediatric or older adult patients to swallow.[5]

In contrast, it is more complex to prepare low-dose tablets in multiple dosages and form sizes. Each dose requires a new formulation and new blending and compression processes. Additionally, full line clearance is required to switch dosages during tablet production.

Low-dose capsules have an advantage over tablets for APIs engineered to optimize bioavailability. When an API is insufficiently soluble, manufacturers can transform it into particles with a surface and structure engineered to improve bioavailability. Directly filling a capsule with a particulate API preserves the particles' surface treatment and morphology, which are critical to its therapeutic effect. In addition, Bannefeld says, the sheering and compression forces that help create tablets can cause damage that could affect the API's performance. Capsule filling can also be beneficial if an API is unstable when mixed with excipients.

Finally, low-dose capsules simplify packaging for shipping and delivery. Standard blistering or bottling can be used, and only one tooling is needed because the capsule size is identical for different dosages. "It's just a standardized container," Rau says. "You can put whatever you like inside a capsule."

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