

MICRO-DOSING EQUIPMENT FILLS NICHE IN R&D, CLINICAL TRIAL MATERIALS

Lab work often involves repetitive, tedious tasks that are better handled by automation. This article looks at micro-dosing equipment from three manufacturers. The equipment speeds dosing, reduces errors, and frees personnel to pursue other activities, all of which lead to cost savings.

The three principal suppliers of equipment for micro-dosing powders are Capsugel, Greenwood, SC; Mettler-Toledo, Columbus, OH; and Symyx Technologies, Sunnyvale, CA. Each offers a unique platform to suit different requirements.

Capsugel supplies Xcelodose, which is typically dedicated to filling two-piece capsules with neat APIs or API-excipient blends. Mettler-Toledo supplies Quantos, which uses disposable dosing heads that prevent cross-contamination of the APIs or blends. Symyx supplies Powdernium, a robotic workstation that allows you to select source and destination modules to suit the material and dosing task.

While each machine has unique characteristics, all of them can dispense neat API, which allows end-users to bypass the formulation stage and thus launch clinical trials more quickly. The machines also improve the speed and accuracy of preparing samples and simplify recordkeeping.

Xcelodose

When Xcelodose was under development in the late 1990s, it was called "Project Pepper Pot" because its method of dispensing powders resembled the action of a pepper shaker. "If you turn [a pepper shaker] upside down, some pepper comes out and then stops. If you tap it, more comes out," said David Edwards, Capsugel's director of pharmaceutical technology. "Our engineers and scientists decided that the amount that came out the holes was reproducible, and it was a function of the number of holes, the diameter of the holes, and the powder." That simple con-

cept—coupled with a high-accuracy balance and a feedback algorithm to control dosing—was the basis for the company's first machine.

Today's Xcelodose equipment retains that concept and is available in two versions. The 120S is a semi-automatic machine that fills capsules, vials, tubes, blisters, and other containers. The 600S is fully automatic and dedicated to capsule filling. It rectifies, opens, fills, and closes as many as 600 capsules per hour, about 10 times faster than manual filling.

Fill amounts range from 100 micrograms to more than 100 milligrams, and relative standard deviation is 2 percent. "Most companies will not fill amounts of 10 or 15 milligrams by hand because attrition is too high," Edwards said. "You can make a lot of

mistakes, and the amount you throw away can be quite high." The machine handles all powder types. "We've seen about every powder under the sun and, to date, we have not found a powder that we cannot dispense," Edwards said.

Xcelodose came to market 7 years ago, and adoption was initially slow. Today, there are several dozen in operation worldwide, and nine of the top 10 pharmaceutical companies use the machine, Edwards said. Last year, the company upgraded the equipment and sold machines into China and India for the first time.

Filling pure API eliminates the need for excipient studies and other formulation tasks, slashing 3 to 6 months from development time. The machine costs "several hundred thou-



Capsugel's Xcelodose 600S fills as many as 600 capsules per hour with as little as 100 micrograms. Its 120S semi-automatic machine also fills vials, blisters, cassettes, and other receptacles.

sand dollars," but that sum can be recouped with one project, Edwards said. He cited one project in which a contract research organization spent 10 months filling 90,000 capsules by hand. "That is still our biggest competitor, hand filling."

Quantos

The introduction of Quantos last spring builds on Mettler-Toledo's long history of expertise in weighing equipment and on an industry shift toward potent APIs, small-scale operations, and "green" chemistry, said Tom Butta, business area manager of laboratory solutions.

According to Butta, the equipment satisfies three principal concerns of lab and R&D work: speed, safety, and controlling costs. "Weighing at the milligram level, to be accurate to within 3 to 5 percent, is a tedious process, whether it's for HPLC standards, or filling an API," he said. "To improve speed, you need to take the

human factor out of traditional weighing practices." The same is true when it comes to potent APIs. "No matter how careful you are, there is always some risk of operator exposure or cross-contamination." The cost saving comes from reducing labor and minimizing or eliminating product loss. "A couple milligrams of a new API can run thousands of dollars."

Quantos is essentially an automatic balance for free-flowing powders. What makes it unique is its disposable dosing heads, which fit on sealed vessels that double as transportation and storage containers. The pre-sterilized components dispense 25, 75, or 250 doses in amounts of 1 to 250 milligrams using a channeled pin in the dispensing head. The in-out motion of the pin and its rotation speed determine how much powder is dispensed. Weight measurement resolution is to the nearest 0.005 milligram, meaning statistical error does not exceed the USP standard of 0.1 percent for doses of 10 milligrams or more.

The dispensing head also contains an RFID chip that stores the algorithm and the protocol for dispensing the material. "After dispensing a material just a few times, the dispensing head has learned to optimize," Butta said. The chip also stores downloadable data, such as lot number, product number, test date, fill date, and the initial and remaining weights. The disposable heads make sense, Butta said, because they are inexpensive and eliminate sterilization tasks and the need for cleaning solvents. "The safety of using a closed head is justification enough in many cases," he added.

The company offers auto-samplers that hold 15 or 30 capsules size 3 and larger, thereby converting the Quantos from a one-to-one oper-



Mettler-Toledo's Quantos uses disposable dispensing heads that eliminate the need for sterilization and cleaning solvents. Each dispensing head includes an RFID chip that controls dosing and stores data.

ation to a one-to-few operation. "This is not production machinery that produces in bulk, but for the clinical trial market—dispensing just API in small batches—it is ideally suited," Butta said. "We have a customer right now using it for a clinical trial and they have to produce a batch of 10,000, which they deem to be pretty small." That company expects to reduce filling time to one-fourth what its previous method required.

Butta said the company plans to introduce a version of Quantos to handle microgram quantities. A base version of the machine sells for about \$50,000. Equipped with an auto-sampler and HEPA filtration, it costs \$100,000 to \$110,000.

Powdernium

Symyx added Powdernium to its product line in 2006 when it acquired Autodose, the Swiss company that invented it. Symyx knew the equipment well because it had been using it on behalf of customers since 2000. "We took the technology they had on powder and merged it with our technology," said Eric Carlson, vice president of product development within the company's tools division.

The equipment is a robotic platform that picks up materials from one or several sources and dispenses the material(s) into one or several destinations. "You can fill up several hoppers and [Powdernium] knows how much is in each. It may only have several milligrams and make sub-milligram dispenses," Carlson said. "Its flexibility allows us to fill not just capsules, but vials and a variety of different types of receptacles. It really is a multipurpose tool," Carlson said.

In operation, a robotic arm transfers a plate holding an array of capsules or other vessels onto a deck equipped with a high-accuracy balance. Once tare weight is established, dispensing begins. The dispensing head has a hopper shape and a valve at the bottom. The valve opens and closes while a whisk turns within the hopper to keep the powder flowing. When the target weight is reached, the process repeats until the entire array is filled. Fills can range from ultra-fine powders, to fluffy enzymes, to millimeter-scale beads and pellets.

Self-regulating software uses algorithms to optimize the filling routine. "Based on that, it learns how to get faster and faster. The first fill might take 2 minutes, but on average, over

the entire array, it might take 20 to 25 seconds," Carlson said. Software also tracks which capsules or containers may, for whatever reason, fall outside the weight tolerance.

Using stacks of trays called hotels, Powdernium can store and fill 2,000 to 3,000 size 000 to 4 capsules, and the company offers an apparatus for sorting, separating, and closing the capsules. Capsule filling, however, is only one of its applications. "One reason companies buy our instrument is that when they're just starting out, they're not going to dedicate a machine to filling capsules 100 percent of the time. Ours is a multipurpose platform that allows them to do a variety of things."

The company launched its SV line of shaker powder dispensers in January 2009. The dispensers act as a hybrid vial hopper and storage vessel and include a disposable valve cap. The cap eliminates cleaning and minimizes the risk of cross-contamination.

The company has 120 to 150 machines in the field worldwide, most of them at pharmaceutical companies. The equipment costs \$180,000 to \$250,000, depending on the accessories it includes. T&C

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Symyx's Powdernium is a multipurpose robotic platform that can dose from one or many sources to one or many destinations. It comes with a variety of accessories to suit the micro-dosing task.