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Automated inhaler testing

Fully and semi-automated systems for inhaler tests save labor, money, and time

Mark Fish
RTS Life Science

As the popularity of inhalation devices increases, so does the burden of testing in pharmaceutical development and quality control. Numerous tests may be performed during product development, with especially large volumes occurring during late stage clinical trials, stability trials and, ultimately, batch release. Changes in the manufacturing process, in the formulation, or in the device design require additional in-depth studies to determine the safety, stability, and clinical effectiveness of the product.

A large-scale development project may require testing of up to 7,000 devices and, in most cases, pharmaceutical laboratories test tens to hundreds of inhalers in a single day. Companies such as manufacturers or contract research organizations (CROs) that perform large numbers of inhaler tests are under pressure to boost productivity and reduce turnaround times while ensuring reliability and data quality.

Regulatory requirements for inhaler testing

The US Pharmacopeia describes testing requirements for aerosols, nasal sprays, metered dose inhalers, and dry powder inhalers, and the European Pharmacopeia (0671 and 0523) documents testing of preparations for inhalation and of pressurized pharmaceutical preparations respectively. Two types of testing are of particular importance:

Delivered or emitted dose testing, which quantifies the total amount of drug emitted or delivered by the inhaler. For multi-dose inhaler products, the pharmacopeias specify the need for a profile of drug delivery through the life of the device, known as content uniformity or uniformity of dosage units.

Particle size distribution testing, which determines the size of the particles or droplets in the delivered dose in order to assess the proportion of active ingredient that reaches the desired areas of the lung during inhalation, those particles of 5 µm or less commonly referred to as the fine particle fraction.

The challenges of manual testing

Although testing regimes vary depending on regional pharmacopeia requirements, laboratories typically analyze only doses taken at the start, end and, if required, middle of the total shots fired from an inhaler. For all shots, even waste shots, the device must be actuated according to the patient information, including shaking or agitation if specified.

For a 160-dose device, a lab might typically collect up to 10 shots for analysis of through device content uniformity, meaning that 150 shots will be fired to waste for every device tested. Release in the US market requires through batch dose content uniformity testing of batches of 10 devices for every batch of product released, so analysts may fire 1,600 shots, with 1,500 fired to waste, for every batch. With typical production lines producing several batches per week, the number of test and waste fired shots can easily reach 3,000-5,000 per week and could be higher.

Even if an analyst could maintain a firing rate of one device actuation every 10 seconds, which would be a difficult rate to achieve, firing 1,600 shots would still take more than 4 hours of intense physical activity. In reality, a single lab analyst working manually to perform delivered dose content uniformity testing might be expected to complete through device life testing on 10 devices in a typical 8-hour shift.

Because inhaler testing protocols feature multiple repetitive manual operations such as device shaking and actuation, analysts who perform these tests manually risk developing health problems such as repetitive strain injury (RSI) and work related upper limb disorder (WRULD). Manual firing can also expose lab analysts to solvents and drug products that could result in long-term health effects. Not only does the fear of injury limit throughput, actual injury could result in significant financial damages. The costs of dealing with a single event vary dramatically but could potentially reach hundreds of thousands of dollars in lost productivity, health or retirement costs, and expensive litigation.

Aside from the challenges imposed by the sheer number of tests, the variability inherent in manual testing can greatly affect the accuracy and reliability of the results. Analyst technique, type and condition of equipment, environmental conditions, procedural method, and the quality of the product being tested can all introduce variation. Even minor changes in the experimental conditions during the testing of a device can dramatically affect its performance and the associated analytical results.

These variations can make discriminating between product quality and testing issues extremely difficult, possibly leading to unnecessary additional tests. Time wasted on investigations of out of specification results can lead to low staff morale and add avoidable costs to the development project or quality assurance process.

Automation alternatives

Fully automated systems perform every aspect of dose content uniformity testing or particle size analysis, from shaking and waste firing to cascade impaction and preparation of samples for analysis without any intervention by an operator. Automated systems present no risk of repetitive strain injury, and they feature waste collection and containment solutions to protect the operator and environment from the risk of exposure to drug products.

A fully automated testing system can easily perform 5 times as many sample preparations as a human analyst over the same 8-hour shift and can free up the analyst to perform other tasks that require more problem solving. An automatic system can continue working through the night, potentially making it 15 times more productive than a one-shift manual operation.

For CROs or large-scale manufacturers who must test numerous batches, the additional testing capacity of provided fully automated systems, typically equivalent to 4 to 5 additional lab analysts, easily justifies the cost. However, for many laboratories whose lower or unpredictable testing requirements make justifying the cost of fully automated inhaler testing difficult, semi-automation, available at a fraction of the cost, is emerging as a popular alternative.

Semi-automation involves separate machines for specific repetitive activities such as waste firing, device conditioning, and sample recovery, requiring the analyst to perform some portion of the operation, at minimum by transferring devices or samples between stages. These systems may have the capability to handle multiple inhalers simultaneously, or they may handle only one inhaler at a time. Like their fully automated counterparts, semi-automatic testing systems help laboratories to reduce data variance and improve operator safety. The systems offer flexibility, allowing labs to add additional automation in the future by adding systems for additional tests as needed.

Multi-device semi-automatic systems

Firing of inhalers to waste or for dose collection requires actuating them into a fume hood or collection system and for pressurized devices, as well as for some DPIs, may include shaking the devices in a prescribed way before actuation. While an analyst performing the tests manually typically handles one device at a time, and could at most handle two devices at once, a semi-automated inhaler testing device (Fig. 1) can simultaneously process 10-30 devices in parallel, in a highly configurable and reproducible manner, completely freeing analysts to perform other operations.

Figure 1

Semi-automatic pMDI Waste Shot Firer

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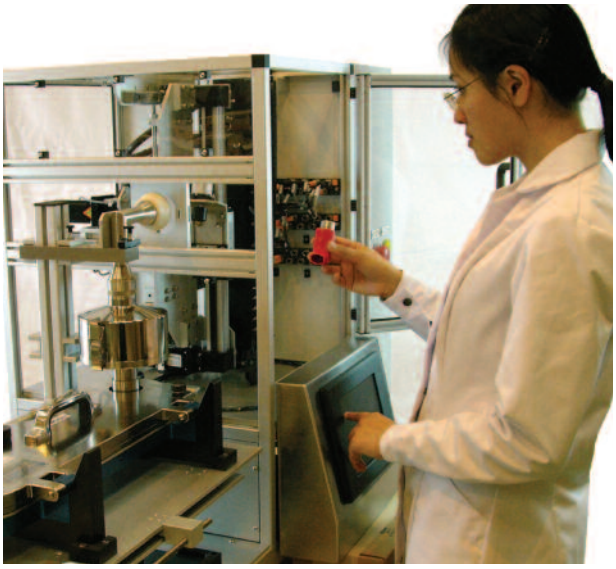
Easy to load input racks accommodate multiple device types, and linear and inversion shaking programs, which are adjustable for varying amplitudes and frequency, can adapt to different shake requirements, completely negating the need for manual shaking. Automated shaking and actuation eliminates variation in analyst technique, providing more accurate results. In semi-automatic particle size analysis, the machine fires the inhaler to waste until it reaches the necessary dose and then fires the inhaler to dose collection tubes or to a cascade impactor. Versions using either Andersen or Next Generation cascade impactors are available, as are other types of particle size analyzers. Some models also prepare samples for analysis by HPLC.

Figure 2

Tabletop Test Shot Firer



In addition to improving reproducibility and confidence in testing, some features of automation help meet the US FDA guidance on MDI and DPI chemistry, manufacturing, and controls documentation requirements for the accuracy, precision, specificity, sensitivity, and ruggedness of each test method. Shot detection technology, along with automated logging of method variables and environmental parameters, allows analysts to measure and document all aspects of the testing methods.

Many of these systems also feature integral waste collection and filtration that shields the operator from exposure to drug products while safely collecting waste materials for later disposal. The machine enclosure simultaneously reduces the amount of human interaction with potentially dangerous compounds and protects against contact with moving parts.

Single device semi-automatic systems

Single device systems are usually designed to mimic shaking and hand actuation of inhalers or nasal spray pumps and come in the form of benchtop instruments mounted on a standard lab bench. These instruments are ideal for laboratories with low throughput requirements, especially where space is at a premium (Fig. 2). Single device units generally allow for adjustment of shaking and actuation parameters, and some more complex machines include shot detection and the ability to interface with other analytical instruments for particle analysis or plume geometry measurement.

Mark Fish is Business Unit Director for the Drug Delivery Automation Business at RTS Life Science, Northbank, Irlam, Manchester, M44 5AY, UK. Tel.: +44 161 777 2000. lifescience.info@rts-group.com

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