Delivered Dose Uniformity Testing the FIA Way

Automated but Agile

The founders of AB FIA have worked with automation of the delivered dose uniformity (DDU) testing of inhalers for almost 30 years. No single system can fit every customer; factors such as flexibility, regulatory expectations and costs must be considered. FIA's systems are customized for every project but are built on well-established modules[1] that have been implemented in bench-top, semi-automated and fully automated systems.

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Techniques and Methodology

The most challenging part is to develop a sensitive but reproducible and robust method. Our solution for drug collection and recovery builds on a fritted glass collector, an impinger[2], inserted into a round-bottom glass flask (Figure 1).

This apparatus gives superior visibility for the analyst and has proven to be chemically compatible with most API's we have come across (other materials are available). The mouthpiece of the inhaler is inserted into the impinger's dynamic inlet which is activated during dosing to achieve a leak-tight fit (Figure 2). The impinger is connected to a highly advanced but compact vacuum system that helps attaining the critical flow condition (P2, P3 ratio with a sufficient vacuum source). During testing the system monitors the pressure drop over the device (P1). Additionally, the flow rise-time is maintained at patient realistic values by keeping the flow path distances at a minimum, something usually overlooked in other automated system designs. The volumetric air flow and P1-P3 of the dosing are recorded in the software and presented in reports. Since the air flow is sensed by a robust laminary flow element downstream of the impinger, the FIA systems minimize influences from evaporated solvents from previous work-ups.

The dose is collected on the glass frit of the impinger in the flask, which is connected to a solvent distribution system served by FIA's individually controlled pneumatic dispensers. These dispensers give unsurpassed precision and accuracy, combined with a very long life-time. The pneumatic drive of the dispensers delivers solvents with high pressure through highly sophisticated nozzles for efficient recovery. The absence of electrical power minimizes explosion risks (ATEX zones can be designed upon request). After solvents have been dispensed onto the glass frit, in portions and with different solvent composition, the solution is sucked through the filter and drug is automatically quantified by an in-line spectrophotometer or is injected into an on-board H/UPLC system. Collection of aliquots into vials is also possible for off-line analysis. Availability of several generic water- or alcohol-based analysis methods will help the customer get started with their own development. The collector station can optionally be combined with a waste station, with the benefit of dosing the device in essentially the same way as in the dose testing. The dosing is performed in a horizontal orientation, by rotating or lifting the collector of interest.

The system can also be configured for abbreviated impactor measurements (AIM).[3,4] The dose aerosol is separated into two size-fractionating components by two standard Fast Screening Impactors (FSI) from MSP,[5] Figure 3, that are mounted above the impinger dose station (Figure 2) from which the drug product is

Figure 1. *Sampling apparatus for the delivered dose (principle described in reference 1).*

Figure 2. *An example of a combined dose and waste collection station.*

Figure 3*. Two FSIs used alternating on top of the sampling apparatus in Figure 2.*

collected on the impinger frit and worked-up in the same way as in the delivered dose example. By automatically alternating which of the two FSIs are aligned above the impinger and by the proper choice of the size-fractionating components, the recovered fine particle dose (FPD) can be either the large particle mass (LPM) or the small particle mass (SPM).

Without human intervention, dosing can consequently be done for AIM, dose and waste on the same device throughout the full dosing regime, on all inhalers in the magazine! Such a system configuration is shown in Figure 4. Because of the efficient work-up and cleaning of the impinger, an astonishing cycle time of ONLY THREE MINUTES per dose is commonly achieved.

One additional option is to equip the system with a holder for an NGI or Andersen impactor (ACI) for FPD, using the same dosing position as the AIM, which is removed when doing FPD. This semi-automated function brings the opportunity to dose the impactors automatically and get meta-data such as P1. The user manually replaces the NGI cup tray or ACI with a new one. Fully automated delivered dose or waste dosing can be performed with the next dosing regime or inhaler before the next impactor is dosed.
Automation is the easy part; movement of the device is done by an over-head Gantry (on the right-hand side in Figure 4) or by an articulated robot arm, which collects and returns the device to a magazine. The overall storage capacity is between 60-240 inhalers depending on need and the device. Numerous DPI and pMDI actuators have been produced for customers with various levels of control and monitoring. The quantification system is configured according to the customer's needs and positioned to the left of the dosing station in Figure 4. The system is surprisingly compact, with a length and height of roughly 2 m and a depth of 1 m, it fits into a standard lab room with little need for re-arrangements. The system is connected to a local or central vacuum, solvent and waste distribution system.

Figure 4. *FIA's full automation system principle which can be configured according to the device and customer's need.*

What are the Key Factors for Success of Lab Automation?

We would stress simplicity and that the system should be intuitive to both the analyst and technician[6].
Our staff is available for technical and application support before, during and after the implementation. FIA has an outstanding track-record working according to GAMP 5 and having an integrated development team of engineers and analysts. Through FIA's membership in MVIC (www.mvic.se) we have direct access to world-leading expertise within performance testing, drug characterization, validation and regulatory advice, including writing automated analysis methods to be included in the submission file. We have access to test laboratories where we can perform factory acceptance testing and method development with our own chemists, before delivery of the system to the customers! This service minimizes the long lead times often seen between system delivery and having an analytical method in place.

Summary

- An agile and compact system with a small foot-print but with a very high throughput
- Intuitive and simple methodology based on a fritted glass filter impinger
- Advanced solvent delivery and vacuum system
- At-line direct UV and H/UPLC analysis
- Fully automated DDU, waste and AIM and combinations thereof
- Semi-automated NGI and ACI dosing
- Engineering and delivery according to GAMP 5 principles
- Project support from chemists and validation experts

References

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