# Maximise productivity in pharmaceutical high-throughput experimentation (HTE) with automated powder dispensing

Joanne Ratcliff, Mettler Toledo GmbH

In the pharmaceutical industry, the pressure to reduce costs and increase efficiency of drug development has fostered the growth of high throughput experimentation (HTE). This approach is only made possible by continuous developments and innovations in laboratory automation. HTE automation enables researchers to optimise route scouting and chemical development of new drug candidates, as well carry out solubility and stability screening more efficiently. One of the major bottlenecks encountered in HTE workflows is the time and effort necessary to manually weigh and prepare all of the samples and reaction materials required. Dosing a defined amount of powder is an increasingly important task in pharmaceutical R&D. Consequently, accurate automated weighing of small quantities of powders could have a huge impact on the efficiency of HTE workflows. Improvements in available technologies would benefit drug development by enabling more rapid screening, reducing lead time for new treatments and, ultimately, improve patient outcomes.

High Throughput Experimentation Requirements

A typical HTE workflow is screening in chemical development, which allows for the rapid, parallel evaluation of a large number

of variables in a timely and material-efficient manner, and can be applied to both active pharmaceutical ingredient (API) and formulation (Drug Product) research.
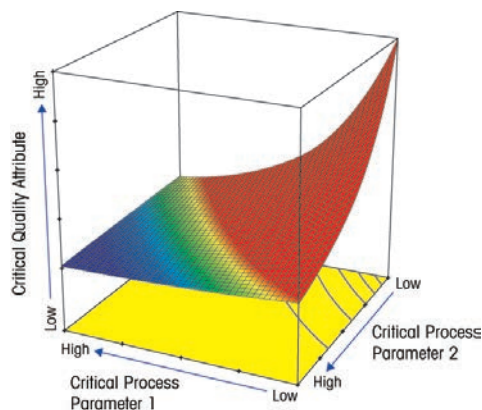
A statistical Design of Experiments (DoE) approach minimises the number of experiments that have to be performed in order to investigate a process, whilst sufficiently mapping the whole reaction space. This method is more efficient and effective, allowing the optimal conditions to be identified much faster, and at a much lower cost.

Figure 1: Optimisation of multiple parameters can be achieved simultaneously using a Design of Experiments (DoE) approach.

Screening and optimisation of reaction conditions is often carried out in 24, 48 or 96 vial plate format. It typically involves dispensing of 1 - 50 mg of multiple substances into each vial, according to a Design of Experiments (DoE) template, which can result in hundreds of doses being required to set up each experiment. There could be 20 different powder substances for each experimental design matrix.

Taking into account that some substances are particularly difficult to handle, and require dosing in small amounts (less than 10 mg) into vials of less than 8 mm diameter, it is clear that this task requires a great deal of time and concentration on the part of the researcher if this mundane and labour-intensive task is carried out manually with a spatula. However, for automated powder dispensing technology to successfully replace this tedious manual task, then it must be reliable, accurate, and easy for the laboratory researcher to use - not something requiring a highly-trained specialist user. Advances in automated powder dispensing technology would serve to increase R&D efficiency, resulting in reduced lead time for new treatments, and benefit patients and consumers alike.

Although the use of liquid handling automation is well-established in pharmaceutical laboratories, the development of automated powder dispensing has been much more challenging. Powder dispensing technologies have often been regarded as 'complex' and 'specialist', and some are only suitable for use with a limited range of powder types. Laboratory researchers have been put off by the fact that many commercial systems are complex to use, requiring hours of patient set-up and optimisation by a specialist for each powder, in order to achieve acceptable results. The wide range of physical properties exhibited by commonly used powders undoubtedly adds to the complexity of powder dispensing requirements for HTE. However, during the last decade, automated powder dispensing technologies are increasingly being integrated into pharmaceutical applications. These technologies have helped to increase research efficiency and productivity, as well as facilitating advances in data integrity (by automatic recording of all dispense information) and enhanced safety and ergonomics for the research scientists (by minimising exposure to unknown potency substances and reducing repetitive manual tasks).

ETC 'Collaborative Study on High-Throughput Powder Dispensing Systems'

A recent collaborative study of automated powder dispensing systems, carried out by the Enabling Technologies Consortium™ (ETC), has helped to position Quantos automated powder technology as the most reliable and versatile powder dispensing technology for laboratory applications, based on both accuracy for a wide range of substances and ease of general use. Set-up in 2015, the ETC is a group of thirteen major pharmaceutical and biotech companies who actively collaborate on chemistry-related issues. Their aim is to develop new enabling technologies for the benefit of the pharma industry as a whole, working with 3rd parties such as vendors, universities and government labs where necessary. In this particular case, powder dispensing was identified as a common bottleneck in pharmaceutical R&D, so a working group of five leading pharmaceutical companies (GSK, Pfizer, AstraZeneca, Merck, and BMS) initiated a benchmarking study. The goals of this study were to compare and assess the capabilities of existing commercially available powder dispensing systems, in order to identify any gaps in the technology, with a view to driving research and innovation to meet the HTE needs of pharmaceutical scientists, and influence the development of robust platforms.

Table 1: ETC powder dispensing study parameters.

Test Substances:	Target weights:	Laboratory Environments:	Participating Companies:
• D-Mannitol	• 2 mg	• Fume hood	• AstraZeneca
• Fumed silica	• 10 mg	• Glove box	• BMS
• L-Proline	• 50 mg	• Local exhaust ventilation (LEV)	• GSK
• Limestone powder			• Merck
• Polyvinylpolypyrrolidone (PVPP)		• Purge box	• Pfizer
• Sodium chloride		• Open bench	
• Thiamine HCl			

The ETC automated powder dispensing benchmarking study involved four commercially available standard platforms, including the Mettler Toledo Quantos system. Seven reference substances were carefully selected which represent the range of challenging physical characteristics typically encountered in a pharmaceutical laboratory. These substances have varying flowability, particle size and shape, density, and hygroscopicity properties. Over the course of the study, almost 18,000 data points were collected by the five participating companies, in order to assess the accuracy and speed of dispensing powder into vials. Tests were carried out on each instrument, with target weights from 2 mg – 50 mg for each powder, in a variety of different laboratory environments (fume hood, glove box, local exhaust ventilation (LEV), purge box, on open bench). Preliminary results were presented at Pittcon 2018 [1]. The full findings of this ETC study are published in Organic Process Research and Development [2].

Figure 2: Quantos QH012-LNMP dosing head (2.5 mm diameter dosing pin with pushing stirrer and Pinocchio 1 mm nose, specifically designed for dispensing into small receptacles).

Powder dispensing data collected during the ETC study demonstrated that the Mettler Toledo Quantos equipped with a single dosing head type (QH012-LNMP - see *Figure 2*) was generally suitable for all powders, at all target masses evaluated. Quantos could achieve accurate dispensing of a diverse set of powder types, in an acceptable time (*Figure 3*). Even at the lowest and most challenging target dose (2 mg), dispensing was broadly accurate and repeatable without any optimisation of dosing parameters. For screening workflows, the real advantage of automated powder dispensing is being able to dose below 10mg with high accuracy and precision, which allows many more experiments to be performed than previously feasible and therefore allows a much more comprehensive DoE.
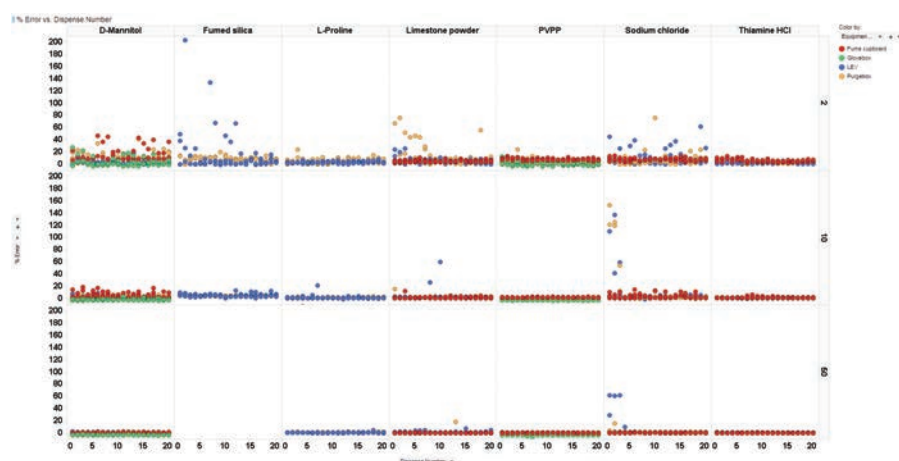

Figure 3: Dispense accuracy data collected on Quantos during ETC case study.

Key Strengths of Quantos powder dispensing technology

The strengths of Quantos powder dispensing technology compared to other systems tested were:

• High accuracy (low % error)

• High precision (low % RSD mass)

• Fast (low dispense times)

• Suitability for all powder types

• Minimal effect of environment (robustness of results - equipment used in multiple different containment devices and locations with minimal effect on results)

Quantos automated powder dispensing technology has proven success in accurately dispensing a wide range of different powder types, even those with extreme physical characteristics. Particle size has a strong influence on the flowability of a powder, and Quantos is able to successfully dispense free-flowing, high or low density powders, statically charged or hygroscopic powders, as well as powders with varying particle sizes, varying morphologies, and oxygen-sensitive materials, such as catalysts, that require handling and storage under nitrogen or in a glove box. The Quantos dosing technology is reportedly able to handle 90% of powders used in a pharmaceutical laboratory.

Automated dispensing of low target weights, in a variety of laboratory situations or containment systems, is possible without any significant impact on either the accuracy or speed of dispensing. The importance of reliable dispensing of a wide range of different powder types, in challenging laboratory environments, such as within a glove box or fume hood, with minimal impact on accuracy or speed, cannot be underestimated. Crucially, accurate dispensing can be achieved without the need for a trained expert user to invest time in dosing head selection, or complex system set-up and optimisation for each specific powder type, as the Quantos system is as intuitive as a balance - easy enough for anyone to use.

These critical factors - accuracy for wide range of powder types, suitability for low target weights, robustness in different environments, and ease of use - make Quantos technology feasible for use in general laboratory applications.

Automated Powder Dispensing into 96 Well Plates

One of the key requirements of many HTE workflows is the ability to dispense into 96 position plate formats. The most recent innovation in the Quantos powder dosing product portfolio now provides this capability. The fully automated CHRONECT Quantos platform combines the intrinsically accurate and efficient Quantos powder dispensing technology with a state-of-the-art 6-axis robotic arm, to achieve many-to-many powder dispensing operations into a range of vial sizes (*Figure 4*). Up to 32 different powder substances, each with a dedicated dosing head to avoid cross-contamination, can be accommodated on the CHRONECT Quantos platform at any one time. Dispensing can be performed into three 12 - 96 position format plates at a time, with a maximum capacity of 288 vials or tubes (1 ml volume, 6 mm diameter).

Figure 4: Chronect Quantos for many-to-many powder dispensing into 12 - 96 position plate formats.

Looking ahead

Accurate and reliable powder dispensing will reduce both the time and the sample quantity required for a wide range of drug discovery and drug-efficacy screens, which will help to alleviate the bottlenecks in pharmaceutical R&D screening and formulation workflows. Increasing pressure on the pharmaceutical industry is only likely to further increase the demand for powder dispensing in the lower mass range, due to screening earlier in development programs, where less material is available. Continuous developments in accurate and reliable powder dispensing automation, such as Quantos, can support these requirements.

Read more at: www.mt.com/cs-quantos-powder

Additional Links:

1) ETC presentation: "A Collaborative Study on High Throughput Powder Dispensing Platforms", Bahr M., http://www.etconsortium.org/pittcon2018

2) ETC publication: "Collaborative Evaluation of Commercially Available Automated Powder Dispensing Platforms for High-Throughput Experimentation in Pharmaceutical Applications", Bahr M., Damon D., Yates S., Chin A., Christopher D., Cromer S., Perrotto N., Quiroz J., Rosso V., Org. Process Res. Dev. 2018, 22 (11), pp.1500-1508, https://pubs.acs.org/doi/abs/10.1021/acs.oprd.8b00259?journalCode=oprdfk