Automated Powder Dosing eases Pharma R&D bottlenecks

Mettler Toledo

The Enabling Technologies Consortium™ (ETC) is a group of major pharmaceutical and biotechnology companies who collaborate on issues related to pharmaceutical chemistry, manufacturing, and control (CMC) for the benefit of the pharmaceutical industry. The task of dispensing defined amounts of powders is increasingly important in pharma R&D, especially in the area of High Throughput Experimentation (HTE) such as screening applications, where it is currently considered a bottleneck. Therefore, improvements in automated powder dispensing technology would benefit API and drug product R&D, by alleviating the bottleneck. This will serve to increase R&D efficiency, resulting in reduced lead time for new treatments, and benefit patients and consumers.

In an effort to understand the relative merits and disadvantages of existing automated powder dispensing technologies, an independent evaluation was carried out by the ETC's High Throughput Experimentation (HTE) working group. This working group comprised of AstraZeneca (AZ), Bristol-Myers Squibb (BMS), GlaxoSmithKline (GSK), Merck & Co, and Pfizer. The study evaluated four commercially available automated powder dispensing platforms, including Quantos from Mettler Toledo, to assess their abilities to accurately weigh a wide range of different powder types into vials.

The results of this benchmarking study, entitled 'Collaborative Evaluation of Commercially Available Automated Powder Dispensing Platforms for High Throughput Experimentation in Pharmaceutical Applications', were presented at Pittcon 2018 [1] and published in OPRD [2].

Background

Although the use of liquid handling robots is well-established in pharmaceutical development, the history of automated powder dispensing has been much more challenging. The technology is often regarded as 'specialist' (only suited to a narrow range of powder types); or 'complex' (requiring a trained expert operator and hours of patient set-up for each different powder type).

Prior to this ETC study, it was believed that no existing automated powder dispensing technology could meet the needs for all materials or applications. So, the aim was to identify gaps in the current technologies, and target areas for technological advancement, in order to influence further development of a robust, universal solution to increase efficiency of HTE in pharmaceutical R&D.

ETC Benchmarking Study

The study compared four existing automated powder dispensing platforms to assess their capability to accurately dispense a series of reference powders into vials. The experimental strategy involved conducting objective, unbiased, systematic testing using standardised protocols. Tests were carried out by the five HTE group companies across seven different US and UK sites. The mass dispensed for each dose (in milligrams) and the dispense time (in seconds) were measured.

- Target dose weights: 2 mg, 10 mg and 50 mg
- 3 runs, 20 dispenses per run, per target dose

The powder dispensing tests were carried out in a number of different locations within the test laboratories involved: in a fume cupboard; in local exhaust ventilation (LEV); in a glove box; in a purge box; or on an open bench. This was simply due to the nature of the work normally undertaken by the individual lab.

Table 1: High Throughput Experimentation (HTE) working group collaborators on powder dispensing study.

Company	Site	Country
AstraZeneca (AZ)	Macclesfield	UK
Bristol-Myers Squibb (BMS)	New Brunswick, NJ	USA
GlaxoSmithKline (GSK)	Upper Merion, PA	USA
Merck & Co.	Kenilworth, NJ	USA
	Rohway, NJ	USA
	West Point, PA	USA
Pfizer	Groton, CT	USA

Selection of Reference Powders

Seven reference powders were carefully selected to represent a range of challenging physical properties typically encountered in a pharmaceutical laboratory. The seven powders, listed below, had varying flowability, particle size/shape, density and hygroscopicity characteristics.

- D-Mannitol – large particle size, particle shape described as laths
- Fumed silica – very low bulk density, high compressibility
- L-Proline – very high hygroscopic mass gain
- Limestone powder – high true density, least free-flowing powder (lowest flow function coefficient)
- Polyvinylpolypyrrolidone (PVPP) – highly hygroscopic, adsorbs moisture even at 0% RH
- Sodium chloride – very large particle size and the most free-flowing powder (highest flow function coefficient)
- Thiamine HCl – moderate powder flow, density and hygroscopicity; with a plate morphology

Particle size is an important factor in the flowability of a particular powder, where smaller particle size corresponds to lower flowability. However, other physical properties such as shape and irregularity also have an influence on the flowability.

Table 2: Physical characterisation data of the seven reference powders selected for testing.

Reference Powder	Flow function coefficient (4 kPa)	Bulk density (g/cc)	Tap density (g/cc)	True density (g/cc)	Particle size D[4,3]	Hygroscopicity: mass gain onset (RH%)	Hygroscopicity: mass gain max (wt%)	Hygroscopicity: mass gain final (wt%)	Morphology – SEM	Aspect ratio QicPic (A50)	Sphericity QicPic (S50)	Permeability (1.00 kPa)	Compressibility (0.5 kPA)
D-Mannitol	4.8	0.573	0.815	1.4825	122	10%	0.15%	0%	laths	0.57	0.76	2.11	4.32
Fumed silica	4.1	0.0325	0.0481	2.3437	17.9	30%	27%	19%	agglomerated, irregular particles	0.71	0.73	10.10	23.05
L-Proline	3.4	0.419	0.665	1.3698	94.6	50%	159%	19%	needles	0.45	0.71	0.90	2.21
Limestone powder	2.7	0.483	1.04	2.6798	4.23	50%	1%	0%	agglomerated, irregular particles	0.63	0.75	9.52	2.05
PVPP	6.0	0.343	0.458	1.2081	98.8	0%	44%	0%	agglomerated, irregular particles	0.72	0.81	1.95	2.77
Sodium chloride	>50	1.25	1.38	2.1543	348	60%	147%	0%	cubes	0.84	0.91	0.11	7.84
Thiamine HCL	6.5	0.241	0.448	1.3873	45.1	10%	35%	2.5%	plates	0.61	0.78	2.10	10.21

Test Results

A total of 17,797 powder dispensing data points were collected at the five pharmaceutical companies over a period of eight months. Following a data verification process, 16,175 valid data points were included in the statistical data analysis. 185 runs were performed with Quantos, with 3692 valid dispenses recorded in total. 1,622 data points were discounted from the analysis for reasons such as machine stalls or time-outs, zero readings, off-target anomalies, and algorithm learning phases. Only 0.2% of Quantos data points had to be discounted (6 readings out of 3,698).

Dispense Accuracy for Different Powder Types

Figure 1 shows the dispensing data for each of the seven reference powders, with accuracy (% error) indicated on the left y-axis (top row = target dispense 2 mg; middle row = 10 mg; bottom row = 50 mg). The different colours on the graph represent different platforms, and Quantos (Mettler Toledo) data points are displayed in green.

Note: Dispensing of fumed silica at 50 mg was excluded due to limitations of some automated platforms with this low density powder.

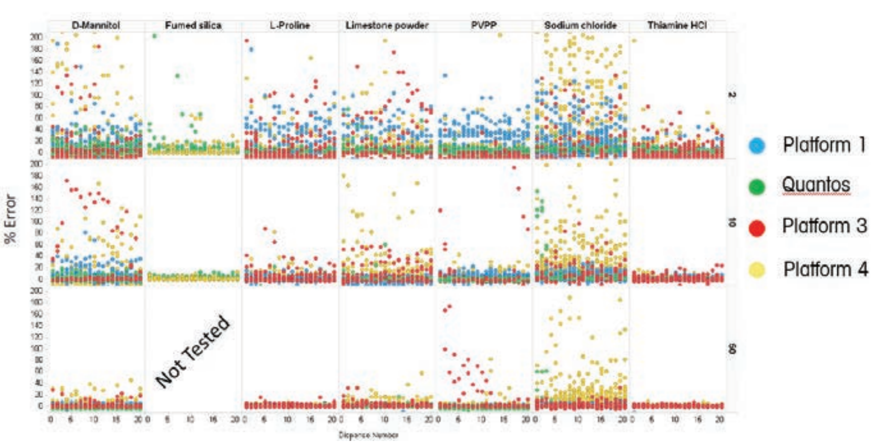

Figure 1: Dispense masses for all substances on all platforms tested with % error indicated. Quantos data is shown in green.

Quantos performs extremely well in these tests, as observed by the lack of scatter in the green dots. Most are nicely clustered close the x-axis, indicating the lowest error of dispense (= the most accurate). In many cases, the green Quantos points are obscured by the red, blue and yellow points from the other platforms, which show a larger error.

Capability of Handling Different Powder Types

In this study, Quantos demonstrated the ability to handle a wide range of powder types accurately and reliably.

Free-flowing or Low Flowability Powders

- Sodium chloride has highest flow function coefficient (>50 4kPa), so is the most flowable powder
- Limestone powder is the least flowable powder (2.7 4kPa)

Sodium chloride is difficult for automated systems to handle because of the high flowability. However Quantos handles this substance well, with accuracy in the lowest reported band for the most challenging 2 mg target. Quantos copes with the low flowability limestone powder very successfully. Dispensing at all target weights are in lowest reported accuracy band (0-10% RSD).

High or Low Hygroscopicity Powders

- PVPP has a mass gain onset at 0% RH
- L-Proline has the highest maximum mass gain, 159 wt%

Both of these powders have challenging characteristics with respect to water absorption. PVPP starts to adsorb water at 0% RH, and L-Proline adsorbs as much as 159% water by weight (at 90% RH). Quantos dispenses both of these substances extremely well. Average dispenses for all target weights are in the lowest accuracy band.

High or Low Bulk density Powders

- Fumed silica has lowest bulk density, 0.0325 g/cc
- Sodium chloride has the highest bulk density, 1.25 g/cc

Powders with extreme values for bulk density are challenging for an automated system. However, Quantos copes with them well. 10 mg of fumed silica, with its low bulk density, was dispensed within the lowest accuracy band, whereas dispensing 2 mg of this substance was more challenging. Sodium chloride, with its high bulk density still delivered a dispense accuracy in the lowest band for both the 2 mg and 50 mg targets.

Variation in Particle Size

- Limestone powder has smallest particle size, 4.23 D[4,3]
- Sodium chloride has largest particle size, 348 D[4,3]

Particle size has a strong influence on the flowability of the powder. Quantos manages limestone powder very well. All dispenses are below 10% RSD (the lowest category reported). Sodium chloride is more difficult to dispense, due to the large particle size (and therefore high flowability), but Quantos still manages this substance well, as described above.

Variation in Particle Shape

- Thiamine HCl exhibits a plate morphology

Quantos handles thiamine HCl extremely well. All dispense data is in the lowest accuracy band reported. Thiamine HCl has moderate powder flow, density and hygroscopicity characteristics. In general, Quantos successfully handles a diverse range of particle morphologies, including cubes, needles, plates, laths and agglomerated irregular particles.

Dispense Time for Different Powder Types

Dispense time was the second parameter measured in the ETC study, because time also has a crucial impact on high throughput screening applications. The dispense time can be important if the powder properties have a propensity to alter during the course of a dispensing process (e.g. a tendency to adsorb water). However, primarily the dispense time has a direct impact on the throughput and overall productivity of the workflow. In simple terms, the faster a plate of powders can be dispensed the better, providing the accuracy is within accepted tolerances.

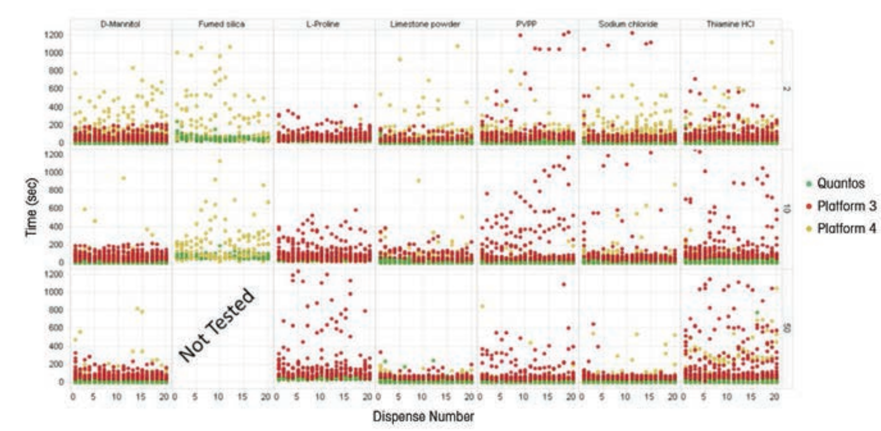

Figure 2: Dispense time (in seconds) for the seven different powder types at 2 mg, 10 mg and 50 mg target doses, measured for three of the platforms tested. Quantos data is shown in green.

Figure 2 indicates that Quantos has superior dispensing speed compared to the other platforms, by the fact that the green dots are positioned close to the x-axis and are mostly obscured by the other colours.

Note: Platform 1 recorded very few dispense times, so the blue data is not included in this graph.

ETC Observations

The ETC study concluded that there are several critical factors affecting the performance of automated powder dispensing system in general:

- The installation location plays a role in successful powder dispensing for certain materials.
- Most automated systems perform better at higher dispense targets, so the lowest target (2mg) is the most challenging.

- Environmental conditions affect powder dispensing, and higher humidity generally has an adverse effect on dispense accuracy due to the effect on the powder flow characteristics.

Summary

This study has demonstrated that the Quantos automated powder dispensing technology, from Mettler Toledo, is capable of handling a wide range of different powder types, even those with extreme physical characteristics. Quantos can successfully dispense at low target weights, and in a variety of containment systems. Accurate results can be achieved without set-up or optimisation time for a specific powder type, or training of an expert user. Quantos can be a general walk-up application in the laboratory, easy enough for anyone to use. It also offers significant safety benefits, in terms of minimising user exposure, and most importantly can help to alleviate the bottlenecks in pharmaceutical R&D screening and formulation workflows.

Key Benefits of Quantos Technology

Accuracy, at low target weights with challenging substances

In the ETC study, Quantos demonstrated a superior dispensing performance in terms of accuracy and dispense time, for almost all powders and target weights compared with the other systems evaluated. Quantos proved extremely capable of delivering robust and reliable data for all types of powders, with a range of challenging physical characteristics. Quantos showed a significant advantage when dispensing the smallest target weights of 2 mg.

Ease of use, no set-up time or expert user required

The results obtained by ETC are particularly impressive considering that the standard dosing head type was used throughout the study and the standard algorithm was used, with no optimisation of dosing parameters for the different powder types involved. This proves that the Quantos system is very easy to use in a simple standard set-up with no expert user required.

Safety, minimising user exposure by operating reliably within various containment systems

Powder dispensing data collected during the ETC study on the Quantos system was consistently reliable and accurate across all the challenging locations tested - in a fume cupboard, in a glove box, in a LEV, and in a purge box. This means that the Quantos system is a safe option for successfully dispensing toxic substances in any suitable environment.

References

1. *ETC presentation, Pittcon, 1 March 2018, Matthew Bahr (GlaxoSmithKline) 'A Collaborative Study on High Throughput Powder Dispensing Platforms'. http://www.etconsortium.org/pittcon2018*

2. *Collaborative Evaluation of Commercially Available Automated Powder Dispensing Platforms for High-Throughput Experimentation in Pharmaceutical Applications", Matthew Bahr, David Damon, Simon Yates, Alexander Chin, David Christopher, Samuel Cromer, Nicholas Perrotto, Jorge Quiroz, and Victor Rosso, Organic Process Research & Development 2018, 22 (11), pp 1500-1508. https://pubs.acs.org/doi/abs/10.1021/acs.oprd.8b00259?journalCode=oprdfk*

Footnote on ETC

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