A NOVEL POWDER FILLING TECHNOLOGY TO REDUCE DEVELOPMENT COSTS & TIMELINES

In this article, Simon Strothers, Director, and Dave Seaward, PhD, Projects Director, both of 3P Innovation, discuss the evolution of filling technology in the inhaled world, including a new technology and approach to filling which offers significant advantages over conventional filling systems.

The inhaled market place is in the midst of major new exploration and development of new therapies for a much broader range of indications compared with the well-established treatments for asthma and COPD. Inhalation is now seen as a viable alternative drug delivery route for a wide variety of drug groups, including vaccines, gene therapies, insulin, cannabinoids and antibiotics.

In this mix of new drug formulations, many are in dry powder form, but produced using advanced manufacturing methods, such as spray-drying, to create "engineered powders". These give a number of advantages including improved lung deposition, more potent dosing, greater drug efficacy and improved drug stability. However, this new generation of powders also brings a new set of challenges, which demand advanced manufacturing solutions for handling and filling of the powders.

In the early days of an inhalation product development programme, the target inhaler device may not be defined, so the powder is filled into standard capsules to satisfy preclinical and early clinical manufacturing. As a project progresses, however, pharma companies may wish to use specific inhaler devices for individual drugs and indications.

The challenge becomes sourcing scalable, highly flexible powder handling and filling processes that can satisfy the total lifecycle of a new drug, from preclinical to clinical to commercial production. Technologies like this, which help to shorten development and manufacturing lead-times, reduce costs and enable faster product launch.

> "Commercial pressures for high outputs, combined with tradition, have led to the vast majority of powder dispensing systems using inaccurate volumetric methods with a statistical process control check of actual weights. These checks are often counterintuitive as the actual weights are out of sync with the required weights."

OLD WORLD FILLING

Most liquid dispensed medicinal products are regulated by volume and therefore dispensed by volume, whereas most powder-based products are regulated by weight and yet are still dispensed by volume.

Mr Simon Strothers
Director
T: +44 1926 408 933
E: simon.strothers@3Pinnovation.com

Dr Dave Seaward
Projects Director
T: +44 1926 408 933
E: dave.seaward@3Pinnovation.com

3P Innovation Ltd
Welton Road
Warwick
CV34 5PZ
United Kingdom

www.3Pinnovation.com

DOSATOR	TAMPING DISK	VACUUM	CAPILLARY	AUGER	GRAVIMETRIC	
		•	•		•	1mg to 5mg
•	•	•	•		•	5mg to 50mg
•	•	•		•	•	50mg +
•	•	•	•	•	•	Free flowing Powders
•		•	•	•	•	Cohesive Powders
					•	Very cohesive powders / api
		•	•	•	•	Low Compaction
					•	100% weight Inspection
•	•	•	•	•	•	Low Speed 10s / minute
•	•	•				High Speed 100s / minute
•	•					High Speed 1000s / minute

Table 1: Matrix comparison of different types of filling system.

Powders by their very nature have dynamic physical properties and their density varies over time. Dispensing powder by volume does not deliver a truly accurate weight, neither at a development nor at a commercial level.

Commercial pressures for high outputs, combined with tradition, have led to the vast majority of powder dispensing systems using inaccurate volumetric methods with a statistical process control (SPC) check of actual weights. These checks are often counterintuitive as the actual weights are out of sync with the required weights due to fluctuations in powder density.

One of the most common styles of volumetric powder dispensing technology is the dosator which can typically dose 10-500 mg. The majority of existing commercially available dosators operate using the same basic technology.

Dosators are popular as they are relatively low-cost devices and they are widely used to fill capsules in solid oral dose applications. They are also used in inhalation applications but have a limited range both in terms of dose weight that can be dispensed and the types of powders that can be accurately handled.

Cohesive powders tend to have voids that create poor weight consistency. Very free flowing powders do not adequately "lock" within the dosator tube such that powder can fall out before the dispense position. In addition, the fines from inhalation blends can build up between the tube and the pin leading to seizure of the mechanical components. It should also be noted that the dispensed powder must be compressed, which can adversely impact bioavailability for inhaled applications.

Such deficiencies with dosators led to the development of alternative powder dispensers, many of which are fully customised for dry powder inhalers (DPIs). One of the more widely used systems is the vacuum dosator which is loosely based upon a standard dosator. In these systems, vacuum is applied to the base of the pocket into which the powder is placed. This removes air from the powder, which improves the dispensed weight consistency. However, it also compacts the powder, which can adversely impact bioavailability.

Broadly speaking, the formulation of powders via volumetric filling systems can sometimes be the business of guesswork. Often pharmaceutical firms improve flow characteristics via inventive methods of processing the powder or by adding flow-enhancing excipients.

Table 1 compares some of the key features of different types of filling system.

A MORE LOGICAL APPROACH...

3P's approach is to dispense powder by weight, rather than volume (i.e. by gravimetric means).

Gravimetric systems, in their purest form, have been available for several years, and until recently, the inherent slow response of weighing systems has restricted their use to lab and clinical supply applications. Xcellodose® (Capsugel, Morristown, NJ, US) and Quantos® (Mettler Toledo, Columbus, OH, US) are examples of low-speed, lab-scale, gravimetric filling systems.

3P has addressed this problem by creating the world-leading Fill2Weight technology (Figure 1) that reduces single dispense time to just a few seconds, making it suitable for high volume DPI manufacture.

Fill2Weight improves on the accuracy of volumetric systems by measuring, controlling and recording the weight of

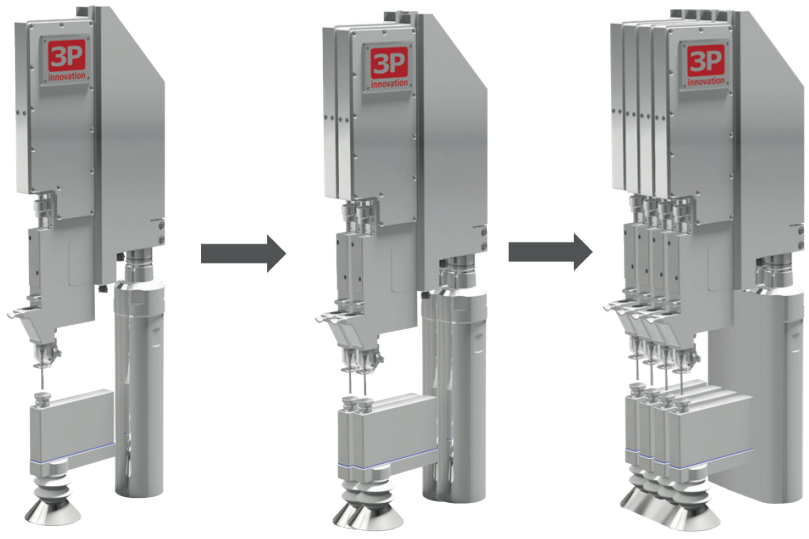


Figure 1: Fill2Weight is scalable and flexible, measuring, controlling and recording the weight of every dose, rather than dispensing a fixed volume.

every dose, rather than dispensing a fixed volume. This allows for compensation to changes in powder properties, such as density, in real-time, and without user intervention and re-calibration. Fill2Weight handles and fills a wide range of powders, including pure API, blended and spray-dried powders, engineered particles, biologics and lyophilised powders.

The benefits of the Fill2Weight gravimetric filling system are summarised in Box 1.

BOX 1: BENEFITS OF FILL2WEIGHT GRAVIMETRIC FILLING SYSTEM

- Highly versatile and independent of powder properties
- Easily scaled up for commercial manufacture
- Infinitely variable dose weight without tooling change
- No powder compaction and no particle shear
- 100% dose verification
- Tolerant to variations in powder properties
- Ideally suited to pure API

MEETING COMMERCIAL DEMANDS

In recent years, several big-name pharmaceutical product patents have expired, hitting large pharmaceutical firms hard and further accentuating the need to remain innovative and agile with new drug development.

These pressures are not restricted to medium and large pharma companies. Firms of all sizes, from SMEs to multinationals, are under increased obligation to speed up the clinical trials phase and reduce the overall time to market. Then, once in the market, agreed commercial volumes have to be consistently realised without deviation.

At 3P, our *raison d'etre* is to help meet the above challenges for our clients and make them profitable while doing so. It's these commitments that have provided the blueprint for our latest R500 (Figure 2) and R1000 filling system derivatives.

Integrating the novel and powerful Fill2Weight dispensing technology and in response to market demands, 3P has now developed the R500 and R1000, the world's fastest gravimetric, fully automated powder micro-dosing machines. Our ongoing investment in gravimetric R&D has been driven by the evolving needs of the industry – not least the pressure on pharmaceuticals to reduce time-to-market.

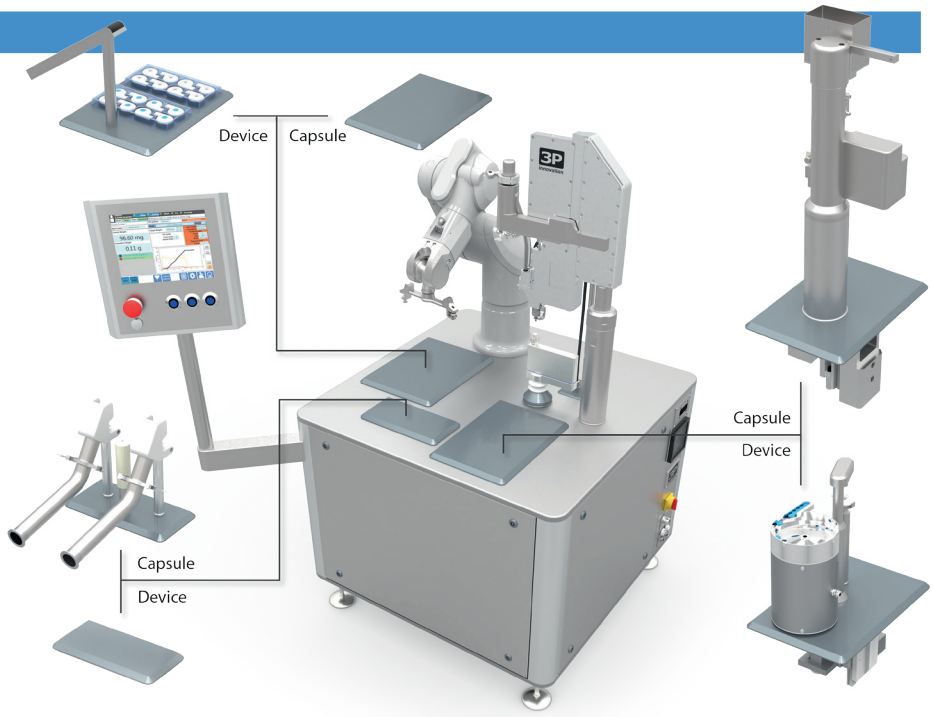


Figure 2: R500 – modular design for rapid changeover.

R500 and R1000 machines can now fill bespoke inhaler devices and other containers as well as capsules on the same machine. The machine achieves this high level of flexibility and minimum changeover times through the use of modular design principles combined with well-proven robotic automation methods.

WHY R500 / R1000?

Reduce Preclinical – Fast-Track to Phase III

During formulation development, additional processing steps are often required to achieve a powder form suitable for correct drug distribution, solubility, measuring and dosing (e.g. achieving flowability, fillability etc). Example processes include dry granulation, blending, roller compaction, micronisation etc.

Fill2Weight can handle and fill challenging formulations such as sticky, cohesive and fluffy powders, and offers the potential to simplify formulation by eliminating the need for additional "formulation for filling" steps. This reduces development time and associated costs and helps accelerate achievement of clinical Phase I and the first time in human (FTIH) milestone.

Not only does R500/R1000 support faster achievement of Phase I, the fact that reduced formulation for filling is required may also mean that costly and time-consuming stability trials necessary to evaluate these additional processes are reduced accordingly.

The system is highly flexible – system parameters can be quickly and easily adjusted to suit different powders, varying environments and varying bulk properties between batches. The settings are captured as "recipes" which are stored and can be quickly called up for future batches.

Meet Regulatory Challenges: PAT, Online Inspection & Feedback

Powders possess inherently variable properties, such as bulk and tapped densities, which can vary both throughout a batch and from one batch to another. The Fill2Weight system incorporated in R500 / R1000 is a dynamic system that compensates for this unstable, changing nature of powders and provides 100% real-time process control.

Fill2Weight also provides 100% verification of dosed drug weight and fill parameters. Every dose is recorded, including actual fill weight and fill time. This makes it suitable for continuous processing applications; for example, feeding powders into a processing vessel. As closed-loop weighing is used, so the system will fill until the target weight is achieved. If powder properties change, the system will adapt to this, modifying settings as necessary to maintain control of the process between defined limits. Changes and trends are recorded so a full history of the production parameters is maintained. This is adaptive, real-time control of the process.

ABOUT THE AUTHORS

Simon Strothers, MSc, joined as a Director of 3P innovation in 2013 and is responsible for Business Development and Marketing. His background is in mechanical engineering. He qualified with a Bachelor's degree in Mechanical Engineering at the University of Manchester (UK) and has a Masters Degree in Business Management from Warwick University (UK). Mr Strothers' career started with Lucas Aerospace, where he worked as Design Engineer, Systems Engineer and Programme Manager, responsible for flight control and engine actuation systems for aircraft. He then worked as a management consultant for four years, driving business improvement projects across a wide variety of industries including paper making, railways and aerospace. For the past 14 years he has worked in the field of custom automation and engineering consultancy for the life sciences and FMCG sectors, initially as senior project manager and since 2006 as business development director.

Dave Seaward, a founding director of 3P, is a chartered engineer with a first degree in joint electrical and mechanical engineering and a control theory PhD. His PhD focused on the application of servo motors to packaging machinery. This early work has led to a career spanning 30 years associated with the development of custom automation for a variety of industries. These include the pharmaceutical and medical device sectors. Many of his projects have included advanced powder or liquid dispensing. Seaward is named inventor on multiple patents. He has worked on 14 dry powder inhaler programmes and nine different injectable drug delivery and auto-injector projects. At 3P, he developed high speed gravimetric powder dispensing technology capable of dosing pure API including biologics into devices and capsules for inhaled and injectable applications. More recently he has helped develop the processes to manufacture a number of drug eluting polymer/modified release products.

Manage Potent Drugs

The trend towards smaller, higher-concentration doses and more potent NCEs is being driven by both the demand for more targeted treatments (and hence fewer side-effects) and less-frequent administration to patients. This trend is driving pharma companies to explore dose forms comprising pure API or higher concentrations of API, with either no, or more limited, excipient. Non-uniform particle morphology (shape), triboelectric charge and small particle size are some of the challenges associated with pure API that present powder-handling and -dosing challenges. In addition, filling pure API often means lower dose weights (<5 mg). Fill2Weight is designed to meet these challenges and provide a flexible, versatile tool to support next-generation powders and formulations of the future.

Support Biological Drug Development

Fill2Weight is designed to handle and fill delicate, spray-dried and freeze-dried (lyophilised) powders without damaging powder particles. The technology also offers the opportunity to pharma manufacturers to fill tray (or bulk) lyophilised powders that can reduce the overall costs associated with in-vial lyophilisation, and which opens up a whole new world of choice with regard to container or device type.

R500 / R1000

Suitable for all clinical phases and commercial production, R500 combines fully automatic functionality with high speed gravimetric filling, with the aim of reducing preclinical development and clinical production time, costs and risk.

The enhanced scalability of the R500 enables drug manufacturers to double production with the simple addition of a second Fill2Weight head. The twin-head configuration, known as the R1000, incorporates duplex tooling on the robot to double the machine output from 500 capsules per hour (CPH) to 1000 CPH.

The R500 and R1000 are the fastest and most flexible gravimetric powder fillers for capsules available. At 1000 CPH, 100% weight verification and 21CFR11 compliant, this system represents a highly competitive package across the lifecycle of a product, from lab R&D to cGMP Clinical Manufacturing to commercial-volume production.

The R500 / R1000 can be supplied in a number of formats:

1. Capsule filling only
2. Device filling only
3. Combined capsule and device filling.

For the combined capsule and device system, changeover between formats is achieved quickly and easily through swap-out of modules. The Fill2Weight module and robot remain in place as common modules for all applications. Figure 2 illustrates how the system is configured for each format. For device or container filling, a Transfer Isolator is available for loading and marshalling devices in and out of the machine. This enables higher throughput whilst maintaining operator safety.

Full environmental control is available if required, including air extraction, humidity (RH) and temperature control.

R500 / R1000 is also designed for sterile filling if required and can withstand hydrogen peroxide vapour (HPV) sterilisation, and Wash in Place (WIP) and Clean in Place (CIP) processes using a variety of cleaning agents.

CONCLUSION

This article has summarised how the challenges of dispensing small and exact amounts of inhaled formulations into DPI devices and capsules are being overcome by technology. Volumetric systems are becoming less viable when it comes to dispensing complex powders accurately and efficiently at both clinical development and commercial production phase.

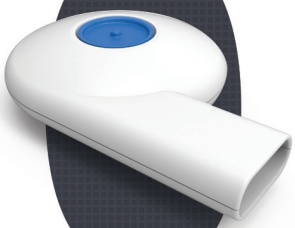
The R500 and R1000 provide automated, high-speed and accurate gravimetric filling solutions which enable critical clinical trial data to be obtained without the need for costly "formulation for filling" iterations. The technology is available now, to de-risk and cut out much of the inflated cost and time involved with dispensing new and current inhaled powders into DPIs.

ABOUT THE COMPANY

3P innovation, the home for **P**roduct, **P**rocess and **P**roduction Innovation, is a successful engineering company with a reputation for delivering innovative solutions to major pharmaceutical, medical and fast-moving consumer goods companies. The company develops custom automation, usually associated with product launches. Its approach ensures robust products are manufactured on efficient machines. From low speed laboratory equipment to high speed assembly lines 3P can develop an appropriate custom solution. It also has a range of standard machines, products and technologies. All 3P's standard systems have been designed to reduce the time to market associated with new product developments.

R500

Fill capsules and inhaler devices on the same machine...



R500 / R1000 - A Time Compression machine. Reduces drug development and clinical manufacturing lead times. ***Fill2Weight*** gravimetric dispensing technology significantly reduces pre-clinical and clinical timescales by negating the need for time-consuming formulation steps for processing and filling.

R500 - Capsule Filler Configuration

R500 – Device Filler Configuration

Transfer isolator option for automated device infeed / outfeed

Device Filler with Transfer Isolator

- **Rapid changeover**
- **Scalable, high-speed filling applies from lab-scale to commercial production**
- **Handles spray-dried, pure API, blended, freeze-dried and biological powders**
- **500 – 1000 cph on same machine footprint**
- **100% weight verification and 21CFR11 compliant**
- **Mobile; easy to move between clean room and labs**
- **Compact; 1m x 1m floor space**
- **Fully GMP compliant**
- **Suitable for sterile manufacture**

For more information on ***R500*** and ***Fill2Weight***, please contact Simon Strothers at 3P Innovation, on **+44(0)1926 408933** or email **info@3pinnovation.com**

www.3pinnovation.com

3P innovation