contractpharma.com

CONTRACT PHARMA

For Pharmaceutical & Biopharmaceutical Contract Services & Outsourcing

DRY POWDER INHALATION MARKET & TECHNOLOGY TRENDS

SPONSORED BY EXPERIC

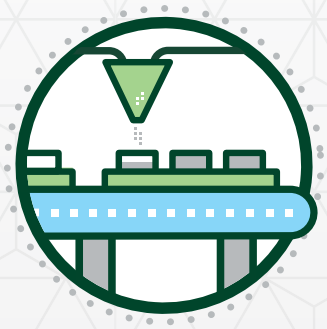
CONTRACT PHARMA
For Pharmaceutical & Biopharmaceutical Contract Services & Outsourcing

FEATURE ARTICLES

EXPERIC

Development and Support Services

Clinical Trial Supply Services



Specialized Commercial Manufacturing

Expert Dry Powder Inhalation Manufacturing

Experience It

Experic provides customized services for the development of dry powder inhalation products. With more than 15 years of experience dedicated to the formulation and development of inhaled products, the Experic team will support your project at every stage of development.

Experic's quality-by-design approach and scalable capabilities for precision filling, assembly, packaging, and logistics of reservoir-based and single-dose dry powder inhalation products ensure efficient delivery of the right solution for every DPI project.

Work with a partner that puts your project — and you — first. It's time to experience exceptional service. That's the Experic difference.

Visit EXPERICSERVICES.COM

Emerging Trends in Inhaled Drug Delivery

Inhaled drug delivery continues to evolve with groundbreaking innovations in technology, materials, and personalized medicine.

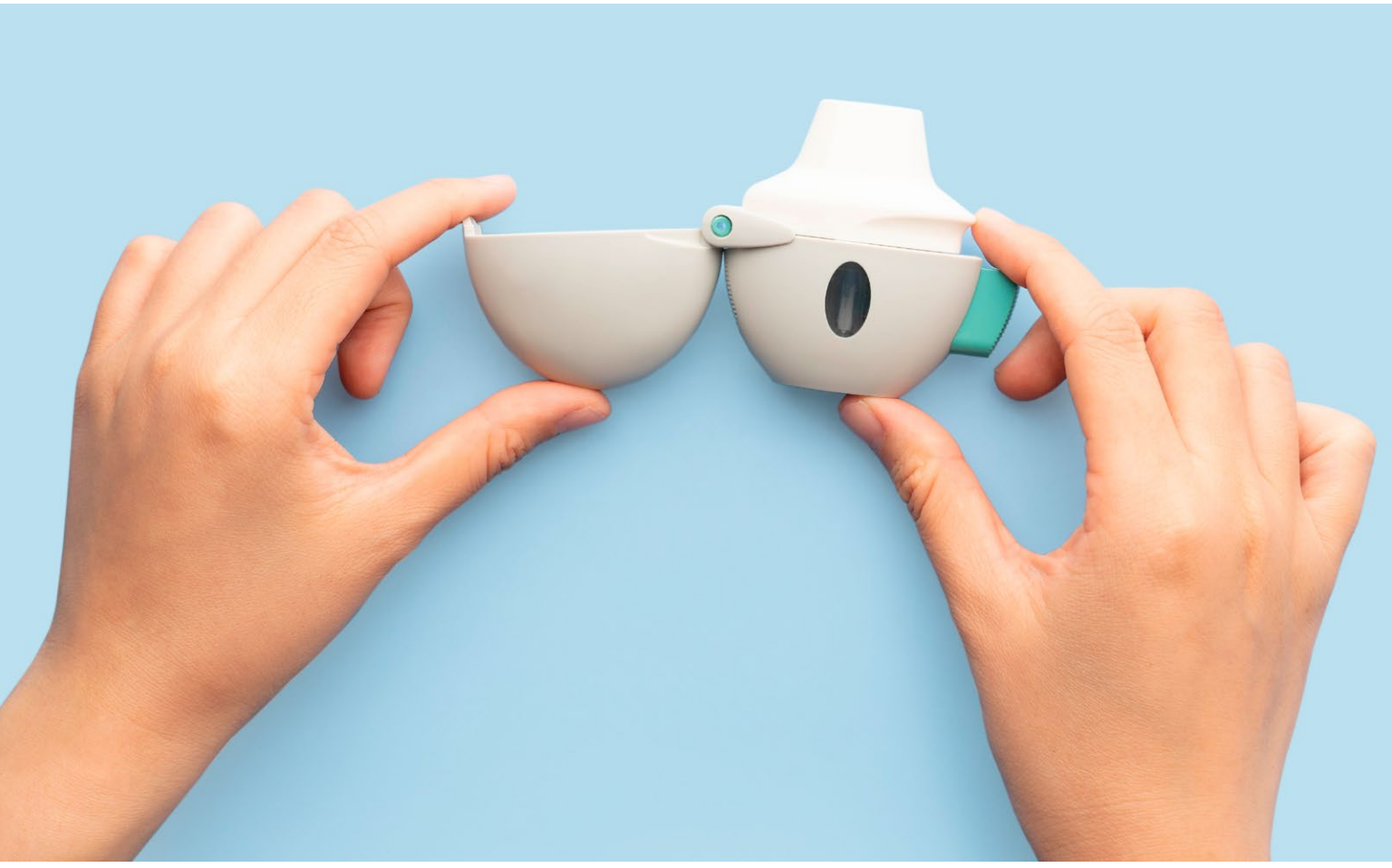
Inhaled drug delivery has been a critical and widely used route for administering various therapeutic agents, especially for the treatment of respiratory disorders like asthma and chronic obstructive pulmonary disease (COPD). Over the years, significant advancements in technology and research have improved the efficiency and effectiveness of inhaled drug delivery systems. This article explores the latest trends and developments in inhaled drug delivery, shedding light on the innovative approaches that promise to revolutionize this essential healthcare sector.

SMART INHALERS

One of the most notable trends in inhaled drug delivery is the rise of smart inhalers. These devices are integrated with electronic sensors and connectivity features, enabling patients and healthcare providers to monitor medication usage and adherence. Smart inhalers can record the date and time of each dose, track inhaler technique, and provide real-time feedback to patients through smartphone apps. This technology enhances patient compliance, reduces the risk of medication misuse, and allows healthcare professionals to better tailor treatment plans.

NANOTECHNOLOGY

Nanotechnology has opened new possibilities in drug delivery, and inhaled drug administration is no exception. Nanoparticles can enhance drug solubility, stability, and bioavailability, leading to improved therapeutic outcomes. Additionally, they can target specific sites within the respiratory system, reducing systemic



side effects and increasing drug efficiency. Research is ongoing to explore nanoengineered carriers and their potential for personalized medicine in inhalation therapy.

DRY POWDER INHALERS (DPIS)

Dry powder inhalers have gained popularity over traditional metered-dose inhalers (MDIs) due to their eco-friendliness, ease of use, and cost-effectiveness. DPIs do not require propellants, making them more environmentally friendly, and they eliminate the need for hand-breath coordination, making them suitable for a broader patient population. The development of ultrafine particles and advanced powder formulations has further improved the performance of DPIs.

BIOLOGICS AND INHALATION

The use of biologics in inhaled drug delivery is an emerging area of research. Biologics, such as monoclonal antibodies, have revolutionized the treatment of various diseases, and efforts are being made to adapt them for inhalation therapy. Inhaled biologics hold promise for the treatment of lung diseases, such as cystic fibrosis and idiopathic pulmonary fibrosis, as well as non-respiratory conditions like diabetes and certain cancers.

PERSONALIZED INHALATION THERAPY

Advances in genomics and pharmacogenomics have paved the way for personalized medicine. Inhalation therapy is no exception, with researchers exploring the use of genetic information to optimize drug selection and dosing for individual patients. Personalized inhalation therapy has the potential to maximize treatment efficacy while minimizing adverse effects, tailoring treatments to patients' unique genetic profiles.

CONTINUOUS MONITORING AND TELEMEDICINE

Integration of inhalers with continuous monitoring systems and telemedicine platforms is an emerging trend in healthcare. These systems allow healthcare providers to remotely track patients' inhaler usage, symptoms, and lung function data. Timely insights into patient conditions enable prompt adjustments to treatment plans, reducing the risk of exacerbations and improving disease management.

CONCLUSION

Inhaled drug delivery continues to evolve with groundbreaking innovations in technology, materials, and personalized medicine. Smart inhalers, nanotechnology, DPIs, inhaled biologics, and personalized inhalation therapy are revolutionizing the way respiratory and other diseases are treated. These trends hold the potential to enhance patient outcomes, adherence, and overall quality of life, making inhaled drug delivery a promising field for both patients and healthcare providers. As research and development in this area progress, the future of inhaled drug delivery appears brighter than ever before. **CP**

EXPERIC

The Experic Difference
Experience It

Exceptional Development, Clinical Trial Supplies, and Specialized Commercial Drug Manufacturing Services

Tailored services are not a talking point at Experic; they are a reality. We work closely with our partners from tech transfer and development to clinical trial supplies and specialized commercial manufacturing. Our leading experts consult and guide you through every step of your product's journey with unrivaled white-glove service and innovative solutions.

We specialize in oral solid dosage and difficult-to-handle powders, navigating the right approach to the optimal performance of your pharmaceutical product based on dose, batch size, and critical quality attributes. With our experienced team, state-of-the-art facility, and cutting-edge equipment, featuring Harro Höfliger filling technologies, you are guaranteed a first-class experience from start to finish.

Work with a partner that puts your project – and you — first. It's time to experience exceptional service. That's the Experic difference.

Visit EXPERICSERVICES.COM

Trends in Dry Powder Inhalers

An overview of advancements, challenges, and future prospects in the dry powder inhaler market.

Dry powder inhalers (DPIs) have revolutionized the treatment of respiratory diseases, offering a user-friendly and effective means of delivering medication directly to the lungs. As the demand for improved respiratory therapies increases, the DPI market has witnessed significant advancements, challenges, and promising future prospects. This article explores the latest trends in dry powder inhalers, highlighting key developments, hurdles, and the potential impact on patient care.

ADVANCEMENTS IN DPI TECHNOLOGY

Improved formulations: Pharmaceutical companies have been working tirelessly to develop optimized drug formulations for DPIs, enhancing drug stability, aerodynamics, and overall performance. Novel excipients and carrier particles have been introduced to ensure accurate and efficient drug delivery.

Smart DPI devices: Advancements in sensor technology have facilitated the creation of smart DPI devices capable of tracking usage, providing dosage reminders, and transmitting data to healthcare providers. These innovations promote patient adherence and enable personalized treatment plans.

Breath-actuated DPIs: Traditional DPIs required a forceful inhalation to release the medication. Recent developments in breath-actuated DPIs have made drug delivery more reliable and consistent, especially for patients with compromised lung function.

CHALLENGES IN DPI DEVELOPMENT

Dosage consistency: Ensuring consistent and accurate drug dosage in DPIs remains a challenge due to various factors

such as humidity, particle aggregation, and patient inhalation technique. Researchers are striving to overcome these hurdles to guarantee uniform drug delivery.

Device complexity: As DPIs incorporate advanced technologies, device complexity increases. Ensuring user-friendly interfaces and clear instructions is crucial to avoid potential issues with device misuse.

Patient variability: Patients' inhalation patterns and lung functions differ, making it challenging to design DPIs that cater to all demographics. Customizable DPIs that adapt to individual needs may offer a solution.

ENVIRONMENTAL CONSIDERATIONS

Eco-friendly DPIs: Concerns regarding environmental impact have prompted the development of eco-friendly DPIs. Researchers are exploring biodegradable materials for DPI components to reduce plastic waste.

Propellant-free DPIs: DPIs that rely on propellants for drug dispersion may be phased out due to environmental concerns. Manufacturers are exploring propellant-free alternatives to align with sustainable practices.

REGULATORY LANDSCAPE

Harmonization efforts: Global regulatory agencies are working to harmonize standards for DPI development and evaluation, streamlining the approval process and facilitating international market access.

Post-market surveillance: With the advent of smart DPI devices, real-time data collection enables post-market surveillance, helping to monitor patient outcomes and device performance more effectively.

FUTURE PROSPECTS

Combination DPIs: Researchers are investigating the possibility of delivering multiple medications in a single DPI device, simplifying treatment regimens for patients with complex respiratory conditions.

Digital integration: Integrating DPIs with telemedicine and digital health platforms will enable remote monitoring and facilitate healthcare professionals in optimizing treatment plans.

Targeted drug delivery: Advancements in nanotechnology may lead to targeted drug delivery, allowing medications to be delivered precisely to specific areas of the respiratory system, enhancing treatment efficacy and reducing side effects.

CONCLUSION

As DPI technology continues to evolve, patients with respiratory conditions can anticipate improved treatment outcomes and enhanced convenience. With ongoing research, regulatory support, and environmental consciousness, the future of dry powder inhalers holds great promise in revolutionizing respiratory care. However, addressing challenges such as dosage consistency and patient variability remains vital to ensure optimal therapeutic benefits for all users. **CP**

EXPERIC

Expert Analytical Services
Experience It

Experience exceptional end-to-end analytical support.

Experic's team of analytical experts create sound strategies for your oral solid dose and/or inhalation products to safeguard your ability to meet regulatory requirements. Every project is a partnership, and we bring the full power of our robust analytical techniques, expanded GMP lab, and an experienced team to provide unmatched project support for your pharmaceutical product's path from the bench to market. A range of services can flex to accommodate both integrated development and manufacturing projects or stand-alone sample testing.

- Technology transfer
- ICH Q1A(R2)-compliant stability studies
- Method feasibility, development & validation
- Compendial testing (USP, Ph. Eur., BP, JP)
- Release testing
- Inhalation testing

Work with a partner that puts your project — and you — first. It's time to experience exceptional service.
That's the Experic difference.

Visit EXPERICSERVICES.COM

EXPERIC

WHITE PAPER

From Spray Drying to DP — Managing Particles for Optimal Delivery to the Lungs

The Benefits of Spray Drying

In recent years, spray drying has become a frequently used technique to convert liquid pharmaceutical formulations into powders. It is a fast and cost-effective technique, making it a desirable way to control the formation of consistent particles for dry powder inhaled (DPI) therapeutics. Spray drying can increase control over the resulting properties of the powder, including:

Particle Size

The size of the resulting powder can be adjusted by controlling the atomization process. This allows for the production of powders with specific particle size distributions, which can influence the dissolution rate, bioavailability, and other characteristics of the drug, well suited for DPIs. Additionally, smaller particle sizes can lead to an increase in specific surface area which can enhance solubility.

Stability

Spray drying can improve the stability of certain pharmaceutical compounds by removing water or other volatile solvents as compared to a solution-based formulation. The resulting dry powder can have a longer shelf life and increased resistance to degradation. In addition, the removal of water can reduce the requirements for aseptic processing in nonsterile applications due to the reduction in free water and thus, water activity.

Solubility

Spray drying can be employed to improve the solubility and dissolution properties of poorly soluble drugs. By formulating the drug in an amorphous solid dispersion with certain excipients, the drug's bioavailability can be enhanced.

Using Quality by Design (QbD) for Multivariate Process Optimization

Dry powder inhaler (DPI) systems to deliver drugs via inhalation to the lungs have advanced dramatically in recent years. Combination products, such as DPIs, require product developers to have a deep understanding of the complex formulation–device–patient interrelationship to ensure delivery of the precise inhaled dose. As a result, a methodical focused approach to quality is essential for developing products that are consistently safe and effective for their intended users. Development of DPIs requires the integration of QbD principles for formulation (including spray drying) and process development with design controls and human factors.

QbD is a proactive systematic approach to build quality into product development and enhance development capability, speed, and formulation design. It is a technique that increases efficiency by focusing on the most important interactions — a priority for all stages of combination product development and manufacturing.

In terms of mitigating risk, process development informed by risk analysis techniques, such as failure mode and effects analysis (FMEA) in conjunction with QbD can be used to determine risks involved in certain parts of manufacturing and development processes. The more information obtained during process development, the better the yields and quality.

Applying QbD techniques to process development also requires the establishment of an acceptable quality target product profile (QTPP). Establishing QTPP is achieved by defining product attributes and patient needs in critical quality attributes (CQAs). These needs are mapped to critical material attributes (CMAs), evaluating the quality impact of critical process parameters (CPPs), and evaluating both metrics together. Since spray drying optimization requires evaluating multiple factors that interact with each other, QbD is an appropriate approach to process development activities whereby statistical methods can be utilized to design and analyze experimental data that increase process understanding and the impact of process controls. Partial-factorial and definitive study experimentation (i.e., tools within the Design of Experiment [DoE] toolbox) can help to reveal interactions of parameters while concurrently reducing consumption of valuable materials and the number of experiments.

Within the context of spray drying, multiple factors can impact the critical quality attributes (CQAs) of the dry powder. Particle size distribution, density, morphology, and flowability are important when formulating powders for inhaled delivery. The goal is to have a stable dry powder with an acceptable glass transition temperature (Tg) while minimizing product degradation.

Excipient selection can impact the CQAs of the resulting dry powder, such as powder rheological properties, and reduce powder aggregation during encapsulation or device filling — and eventual drug delivery. For DPI products, sugars and amino acid excipients such as lactose, trehalose, mannitol, and leucine have been commonly used, with lactose capable of producing a narrow fine particle size distribution and enhancing the shelf life of the spray dried powder. Polymers such as HPMCAS and PVP-VA are used to create amorphous dispersions. Spray drying can also include suspended nanoparticles and nanoemulsions. Additionally, buffered salt solutions, sugars, lipids, polymers, and oligopeptides can be used with certain biological molecules.

Solvent selection is also critical. Preformulation studies should be conducted to assess the compatibility of the API and excipients with the chosen solvent system. These studies can include solubility determination, stability studies, and compatibility testing (e.g., physical and chemical interactions) to identify any potential issues and optimize the formulation. Additionally, the solvent's latent heat of vaporization, heat capacity, thermal diffusivity, and bubble point can also affect spray drying capacity and drying kinetics. The solubility and mass diffusivity (relative to evaporation rate, drying kinetics) of the drug substance and excipients can affect the structure of particles leading to surface enrichment, hollow particles, dense particles, and other

morphological changes. Degradation of the API must be assessed post-processing (a function of the temperature, residence time, and the quantities of chemical species present), and stability studies will be conducted to assess the long-term stability and shelf life of the spray dried product. Based on the solvent selection and preformulation studies, a formulation can be developed by selecting appropriate concentrations of the API and excipients in the solvent system to provide a stable and homogenous solution for spray drying.

Spray Drying Equipment Factors

Spray drying pumps a liquid formulation through a spray nozzle or atomizer, where it is broken into small droplets. Regardless of the type of atomizer used, the atomization process is affected by complex interrelated factors such as shearing and inertial forces, surface tension, droplet viscosity, and droplet size distribution, all of which affect the angle and velocity of the atomized spray. There are several types of atomizers used in spray drying, such as high-pressure nozzles, rotary atomizers, two-fluid nozzles, and ultrasonic atomizers. Each type has its advantages and limitations and the selection depends upon factors like desired particle size, feed properties, and production requirements.

The properties of the liquid feed, including its viscosity, surface tension, solids content, and temperature, can affect atomization. Understanding feed properties is crucial for selecting an atomizer that can effectively disperse the liquid into droplets of the desired size range. Adjustments may be necessary to optimize atomization based on the characteristics of the feed.

The design and configuration of the atomizer also play a significant role in achieving the desired droplet characteristics. Factors such as the geometry of the atomizer, nozzle size, atomization pressure, and placement within the drying chamber need to be considered since these parameters impact droplet size, spray pattern, spray angle, and spray cone, which in turn influence the drying kinetics and product quality.

Spray drying process parameters, such as inlet temperature, atomization pressure, and feed rate, also need to be optimized to achieve the desired particle size, morphology, and drying efficiency. The process optimization approach may involve multiple trial runs and adjustments to achieve the desired product characteristics. The combination of solvent evaporation rate and diffusion rate of the solute from the inner core to the outer crust of the particles has been shown to significantly affect the final morphology of the particles. Lower solid contents and smaller nozzle tips can lead to smaller droplets and thus finer final particles, while a higher feeding rate can produce a larger particle size.

Atomized droplets are then introduced into a drying chamber or tower, where they come into contact with a stream of hot air or gas for rapid evaporation of the liquid component, leaving behind solid particles. Drying air flow needs to be controlled for effective drying and factors such as airflow velocity, temperature, and humidity influence the drying rate and thus particle size, particle density, and particle morphology. Various methods can be used for particle collection depending on the specific requirements of the product.

Typically, the control of a spray drying process relies on setting of inlet temperature and controlling the outlet temperature as function of the spray rate. As evaporation consumes thermal energy within the spray drier, the drying air cools, reaching the outlet temperature as the material completes drying and exits the drying chamber. During this process, continuous monitoring and adjustment of the process parameters are necessary to ensure consistent and optimal spray drying performance. Online monitoring tools, such as laser diffraction particle analyzers, can provide real-time feedback on droplet size distribution, enabling adjustments to be made that allow the desired product characteristics to be achieved.

Careful consideration of these multiple variables can result in improved product quality, particle size distribution, and overall process efficiency.

Post-Spray Drying, Filling, and Optimization Considerations

The processing of the spray dried materials can include secondary drying, roller compaction, and filling or tableting of the final product. The need for secondary drying is a function of what is achievable within the spray dryer. If the spray drying results in excess moisture or residual solvents, which can affect glass transition temperature, stability, and product performance, secondary drying may be required.

For inhalation products, where post-processing (excluding blending and filling) is atypical as it damages the engineered particles, connecting the spray drying experimentation to filling feasibility studies is important. Spray dried materials tend to be highly compressible, cohesive, adhesive, and hygroscopic. Because creating an ideal powder from a performance perspective may lead to complications on the filling side, it is highly recommended that filling studies be incorporated into process development activities.

Increasing the manufacturing scale of spray drying may be necessary as projects progress from early phase work to pilot and pivotal batches. Scale-up will require a partial redevelopment of the spray drying process (or at least the process understanding) as some critical ratios may be hard to maintain from scale to scale. However, there is more flexibility on batch size with spray dried materials because the processes are essentially continuous. If a batch needs to be twice its current size, it may be possible to run the spray dryer twice for twice the amount of time under the same conditions. There are practical considerations for how long to run a spray drying batch that relate to the amount of risk of a potential batch failure.

While initial goals of spray drying are to create quantities of material for clinical trials and stability, the ultimate goal (through QbD) is to create a complete understanding of the phase space of the process and formulation controls of the spray drying process and how it affects any downstream processes. This will be accomplished through design of experiments and risk analysis and will lead to a more robust control strategy and clear pathway for manufacturing, process validation, and commercialization.

Working With A CDMO

Regardless of how advanced a project may be, sponsors and CDMOs can benefit from working together closely and collaboratively from the beginning of any DPI formulation and development project. From a QbD perspective, this means communication of project goals, critical quality attributes that need to be understood or defined, an understanding of completed development work, the phase of the project, the target scale of the batches, and any other relevant details related to the project scope. Well-defined project goals, scope, and an understanding of CQAs are the key elements for delivery of a successful project.

EXPERIC

Expert Packaging, Labeling, and Distribution of Clinical Trial Supplies

Experience It

Experience the speed and agility of Experic's personalized service.

Experic specializes in expedited end-to-end services that will help you meet important milestones for your clinical study. From planning to closeout, Experic project managers provide complete product accountability, freeing you to focus on what counts most — patients. Experic has what it takes to provide comprehensive clinical supply solutions and unrivaled client-focused care.

Planning

- Expert Advice
- Procurement of Packaging Materials, Labels, & Commercial Drug

Packaging

- Bottling
- Blistering
- Carding
- Labeling
- Kit Assembly

Storage & Logistics

- Temperature Controlled & Monitored Storage
- Global Logistics
- Direct to Site
- Direct to Patient

Work with a partner that puts your project — and you — first. It's time to experience exceptional service. That's the Experic difference.

Visit EXPERICSERVICES.COM

EXPERIC

CASE STUDY

Mitigate Risk by Conducting Filling Assessments During Formulation Development

Overview

A small-sized pharmaceutical company had worked with a variety of other contract manufacturing organizations (CMOs) and had no success achieving the necessary product yields to advance the development of their highly cohesive product formulation.

The client approached Experic to determine if one of the company's technologies could effectively and consistently fill their formulation with the goal of reproducibly metering powder into single dose containers and achieving an adequate yield.

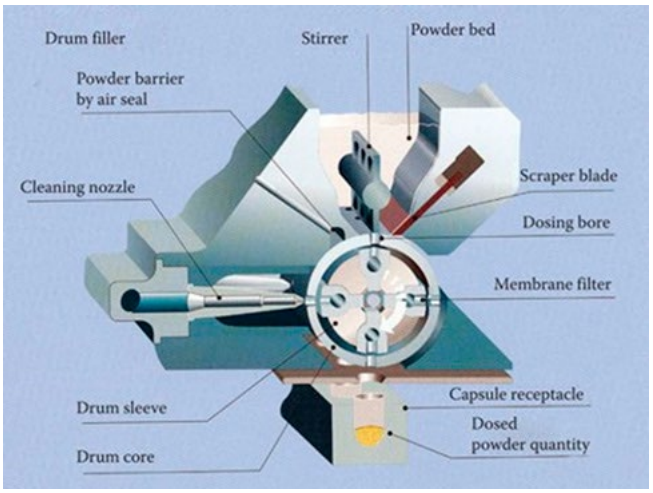
Understanding the Powder

Prior to coming to Experic, the client had invested a great deal of time developing a gravimetric filler that used a vibratory filling mechanism. Unsurprisingly, they found that their blended formulation segregated at certain parameter settings and they could only achieve, at best, a 70% yield of finished product.

Due to this experience, Experic recommended conducting a formulation filling feasibility study to gain the valuable information needed for the client to decide the course of action for future development of the product.

Experic also suggested a drum filling strategy since it is capable of handling cohesive powders without using vibration, which can lead to formulation segregation. Additionally, drum filling is a volumetric process which is generally favored over gravimetric filling for small doses due to its scalability. The Drum Lab was specifically selected because it does not require much formulation for each experiment and can be quickly cleaned and reassembled to increase the experimental throughput.

Harro Höfliger Drum Lab



Integrating the Technology

The Drum Lab features a single-dose volumetric filling drum with a set of precisely machined bores used for metering the powder. A hopper, which contains a powder bed, sits directly above the drum.

The system meters powder by drawing air by vacuum through the filter at the bottom of the bore of the drum as the powder bed is stirred. The dosing bore then rotates to a position above the target container and an impulse of air deposits the powder into a single-dose receptable such as a capsule. Dosing consistency is a function of filling the precise volume bore at a reproducible density. Net fill weight of each dose is measured to determine yield, which is critical in formulation and manufacturing development.

Filling Study Observations

Experic conducted several experiments to determine if the product formulation could be filled at its target weight of 6 milligrams. The highly cohesive nature of the powder resulted in significant fill weight variability. To observe the behavior that was causing fill weight variability under different filling conditions, a camera was positioned above the powder bed. We were able to capture a number of phenomena: bridging, which occurred at higher fill levels of the hopper at fast stir rates; rathole formation, which occurred after the volume in the hopper decreased; and stirrer adhesion, which was seen intermittently throughout the study.

Bridging

At fast stir rates, powder bridged across the top of the hopper, which was surprising because the initial charge of powder filled less than half of the hopper. As the stirrer turned, the powder was transported from the bottom of the powder bed to the hole above the stirrer where powder is typically added, leaving the powder bed starved for product. This lack of available powder resulted in inconsistent fill weights.

Bridging

Rathole Formation

Stirrer Adhesion

Rathole Formation

After the hopper volume was decreased, the powder bed remained at the bottom of the hopper; however, the fill weights were still inconsistent. This was caused by the formation of voids in the bed directly above the dosing bore. In this case, although the powder was directly adjacent to the bore, it did not flow into the bore due to its cohesiveness. Again, inconsistent powder availability led to inconsistent filling.

Stirrer Adhesion

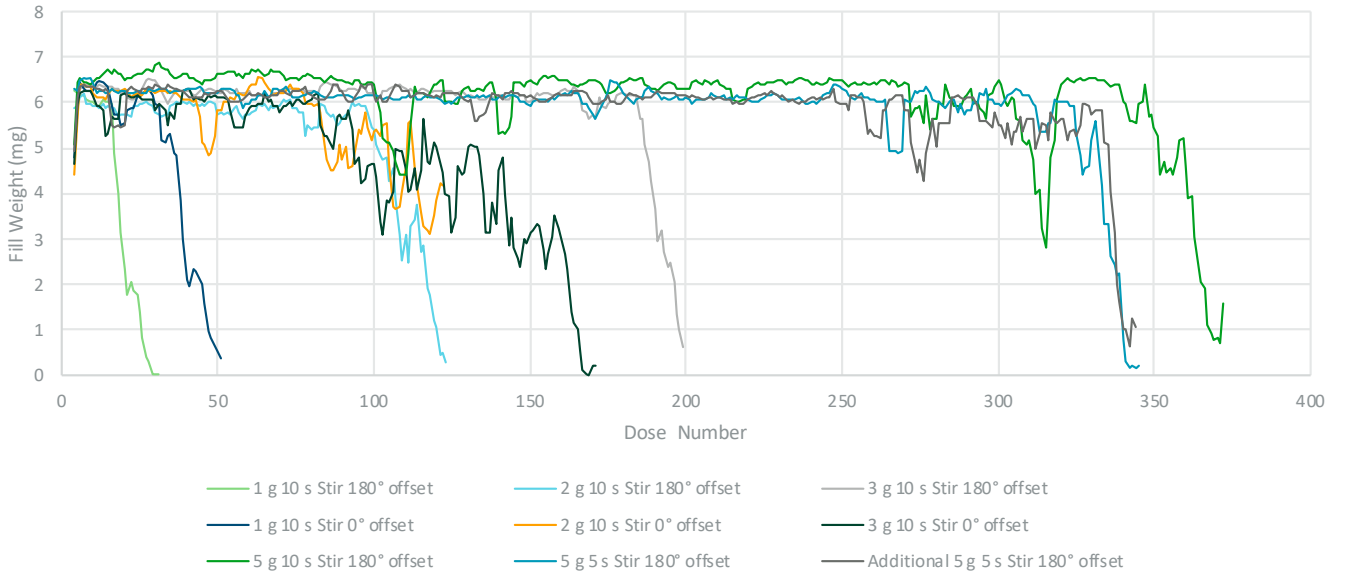
This phenomenon was observed when the stirrer passed through the powder bed and adhered to the powder, even though the stirrer was made from polished stainless steel. This effectively reduced the quantity available for filling and again showed the mechanism for creating cohesive bridges above the stirrer.

Filling Trial Results

Filling trials were conducted on the Drum Lab with varying stirrer speeds and hopper fill levels. Initial filling of the powders on the Drum Lab was done operating the stirrer at conventional speeds (0.5 revolution in 300 milliseconds). It was quickly learned that these fast stir speeds caused the bridging effects, mentioned above, leading to a nearly immediate loss of fill weight consistency (less than 30 doses). Due to this result, the other extreme was explored, reducing the speed of the stirrer to only 0.5 revolution in 5 to 10 seconds. This improved the consistency over the short term (60 doses).

After establishing that a consistent fill could be achieved for 60 doses, Experic turned its focus to trying to increase the total number of doses that could be consistently filled. This is largely influenced by the amount of powder that is added to the hopper and the rate at which powder is refreshed. Hopper fill levels of 1, 2, 3 and 5 grams were then tested, and results can be seen below. It was expected that the amount of material that remained in the hopper would be constant, filling in all dead zones of the hopper. This would mean that adding a larger amount to the hopper should result in less waste.

However, during the trial, a maximum of only 250 doses (~1.5 grams) could be consistently filled from a 5-gram hopper fill. This is only a 30% yield, meaning that 3.5 grams of formulation in the hopper were not available. This 30% yield was the same as the value seen at the 1-gram fill level, which was unexpected. Though the cause was not investigated further, it is hypothesized that it related to compression of the formulation resulting from stirring.



During filling trials for cohesive powders, varying the level of the powder bed typically can be used to control cohesive bridge effects that affect mixture segregation and the overall consistency of the filling process. However, in this case, powder bed management was not a primary determinant due to the highly compressible and cohesive nature of the powder.

Following these initial trials and analysis of the results, Experic suggested alternative filling experiments for the client to consider, including changing the powder bed geometry and type of stirring or filling technology. However, the client had already invested heavily trying to make this formulation work, and in the end, decided to reformulate the product.

Conclusion

While we were not able to find a perfect filling solution for the client's formulation, this case study demonstrates the importance of introducing filling studies during formulation development. Early filling trials can determine if there is a critical linkage between filling process parameters and the product design, assess the impact of lot variation and help in understanding the day-to-day variability in powder density and characteristics. These considerations can influence the robustness of filling and consequently the timelines of a development project as it transitions from lab scale to manufacturing.

EMIL W. CIURCZAK
Contributing Editor, Contract Pharma

That's About the Size of It

Particle sizing is critical in all forms of pharma products.

No matter what your product, from injectables to tablets to freeze-dried materials, the size of the particles is critical. From "there shouldn't be any in clear injectables" through micronized low solubility APIs through the effects of excipient particle sizes on solid dosage forms, knowing (by actual measuring) the size (and/or presence) of particles is a critical piece of data.

Being able to qualify the particles is as critical, too, however, this column will stick to the measurement of the size, not any physical attributes. There are several techniques for estimating/measuring the mean particle size of a solid material. Some are old and some newer, namely:

1. Nested sieves (e.g., USP method)
2. Coulter counters
3. Microscopy (photo-microscopy)
4. LASER-light scattering (in a suspension)
5. Diffuse reflection (e.g., NIRS)
6. Spatially Resolved Dynamic Light Scattering (SR-DLS)

The "tried and true" method of sieving a portion of the powder has been around for more than 50 years. The bulk material is poured onto the largest-holed sieve and the stack of steadily decreasing hole sizes is shaken/tapped for a set period of time. The amount (weight) of material retained on each sieve is measured and the weight-averaged particle size mean is calculated. One potential source of error is that the amount retained on the bottom pan is designated "less than the smallest sieve size." That, alone, skews the actual value of the mean size.

Another flaw is a one sieve measurement—as per several USP monographs—for a raw material. The pass/fail criterion might

read, "no more than 1% is retained on a 100-mesh screen." When I was early in the process of generating my library of raw materials for NIR qualification, I examined a sample of Na Pentobarbital that had just passed QC. My newly minted NIR algorithm failed the sample. Upon examination, it was found to be micronized, not granular, The criterion for particle size? Less than 1% retained on a 100-mesh screen—easy to pass when micronized.

The referee method for the quandary was photo microscopy. The drawbacks to this technique are obvious: a) it is slow and b) it only shows a tiny portion of the sample. Most sampling techniques are suspect, anyway, but taking less than one gram from a multi-kilo sample hardly gives a credible value for mean particle size. It will remain a nice referee technique, but unlikely to replace other QC methods anytime soon.

These counters, where the slurry of particles flows through a "gate" are estimated as to size and number. This was popular in the 1970s but had several flaws, not the least of which was that an elongated crystal could be counted as several particles as it passed through the portal. These were supplanted by a LASER-light scattering device (Malverne) where the slurry of particles is stirred, and the diffusion of light is captured on concentric rings (light scatters more as the size decreases).

LASER-light scattering (LLS) instruments really came into their own in the 1980s. They were simple, but effective. The sample is suspended in a saturated solution of that same material to avoid dissolution and errors in measurement, stirred gently to assure distribution and avoid precipitation, and measured. While this was far better than earlier methods, there were still several caveats to consider, based, as always, on physics.

Anyone who has performed gravimetric analyses knows that you allow the precipitate and supernatant to sit overnight before filtering and measuring the material. This "digestion" is, in reality, the kinetics of dissolution and re-precipitation. This dynamic is continuous, but, based on surface area, the smaller particles disappear while the larger one gather mass. This process occurs in the LLS instrument. Timing is critical when measurements are being made—the longer you stir and measure, the more the mean shifts. In addition, since there is no primary reference for these data, scrupulous attention to technique will allow precision on sample-to-sample measurements.

The other mechanism involved is mechanical; in the stirred sample, larger particles will be beaten to smaller and smaller particles. This skews the measurement and the major reason for non-reproducible results.

The only alternative to measure dry powders by sieve analysis would be to use diffusely scattered light. My experience with NIR allowed me to graphically estimate the mean particle size of a powdered sample.[1] The method works assuming a) a well-sampled bulk material and b) an equation, previously generated, is in place. The calibration, in this case, was made by sieving a bilk sample and measuring the cuts via an LLS device and creating a calibration graph (Absorbance at a specific wavelength versus the reciprocal of the mean particle size; A v. 1/μ). The Absorbance of the QC sample is then measured, and the particle size calculated. While there are, again, no reference standards, although there are sources for "known" polymer beads that could be used for reference, there are two advantages: a) the sample is stable and b) multiple readings (shake sample and re-read) may be made and multiple samples taken, since the method is so fast and non-destructive. At the recent IFPAC conference (N. Bethesda, MD), I came across another method for testing that was impressive. Spatially Resolved Dynamic Light Scattering (SR-DLS), recently developed as the NanoFlowSizer, employs SR-DLS, based on Low-Coherence Interferometry (LCI). It provides new possibilities for non-invasive, real-time, and continuous inline measurement of size characteristics in flowing and quiescent nano-dispersions. In Conventional Diffuse Light Scattering (DLS) measurements need to be performed under static conditions ensuring that particle movements are solely caused by Brownian motion and not influenced by other factors like liquid flow.

Additionally, conventional DLS cannot be applied to relative turbid suspension without dilution, while these are often encountered in industrial or process environments. Since nano-suspensions are in motion during processing and vary in turbidity levels conventional DLS is unsuitable for process analytical (PAT) applications.

Low Coherence Interferometry (SR-DLS) allows particle size characterization in process flows since it can measure highly turbid suspensions without dilution. The technology is based on low coherence interferometry providing light scattering information as function of optical pathlength (pathlength or depth in the sample). The sample is illuminated by low coherence light from a broadband source instead of a laser, and back scattered light interferes with light split from the source with a specific optical pathlength. The interferometer part of the technology allows to resolve backscattered light for specific path lengths in the sample simultaneously. The depth resolved light scattering data holds information on particle movement caused by both Brownian motion as well as flow rate and pattern. The contribution due to Brownian motion is extracted by smart algorithms and used for calculation of the particle size characteristics, while the flow rate information is obtained instantaneously for every measurement as well.

Nanoparticles are often seen in vaccines, where the size of the materials are critical in having the proper bioavailability and dosage levels. Since the process cannot be stopped for each measurement, SR-DLS allows real-time measurement and, if needed, changes to the process. The particle size data may be plotted over time to generate a "process signature" for each lot. The effectiveness of each lot is determined, and the 3-D plot may be used as a template for later batches.

So, in short, there are numerous ways to check your incoming materials for mean particle size. Depending on how they are to be used will determine the preferred technique. If, for example, you are to dissolve the materials, a rough measurement will allow the operators to estimate the time it takes to make the solution. If, however, you are making a suppository—as we were with my early example of NIRS—granular will work, while micronized materials will float on the surface and not make the product.

So, choose your "poison" and do your best work. **CP**

References

1. Determination of Particle Size of Pharmaceutical Raw Materials Using Near-Infrared Reflectance Spectroscopy", Spectroscopy 1 (7), 36 (1986). Co-Authors: R.P. Torlini, M.P. Demkowitz.