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Optimizing Solid Dosage Manufacturing

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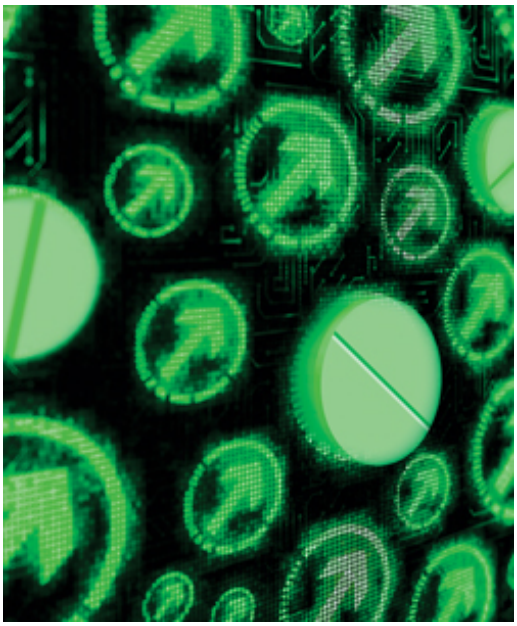
Quality-by-design methods aid process understanding and improvement.



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Solid-dosage manufacturing involves a range of processing technologies to take a formulated API through to a finished dose form (e.g., capsule, tablet). A thorough understanding of both the product and the process technology are required for optimization. “The more complex a therapy becomes, the more exacting the requirements of the process technology may be to achieve the required performance,” says Nicholas Johnson, strategic marketing director for Catalent’s Advanced Delivery Technologies.

In the past decade, the quality-by-design (QbD) initiative has brought a new focus on better understanding the raw material, formulation, and processing variables that influence the critical quality attributes (CQAs) needed to make a quality pharmaceutical product. QbD is really a synonym for process understanding, and greater understanding will lead to a better process with less out-of-specification material, said Conrad Winters, director of the Drug Product Development Group at Hovione FarmaCiencia, in a recent article discussing how to apply QbD methods in manufacturing-process development for a bulk powder and subsequent tablets (1). Because there are so many variables involved, process developers should use a risk assessment, based on prior knowledge, to determine which parameters are the most crucial to study further. “Expertise in the process ensures that a sufficiently broad study is completed,” says Winters. “A managed or limited study is of no value if you fail to capture the critical process parameters (CPPs).” Analyzing the results of these studies—by quantifying the impacts of the variables studied and evaluating the uncertainty or residual variability associated with them—allows process designers to establish a reliable design space and an operating space within the design space.

The focus on QbD has begun to break down the traditional barriers between formulation and process development, but even greater communication between these areas is needed to allow better optimization of the whole solid dosage process, says Tim Freeman, managing director of Freeman Technology. “As an industry, we are still challenged in understanding what attributes of the material are important regarding functionality during tablet manufacturing and attributes of the finished product,” says Freeman. Measuring powder properties, such as cohesion, permeability, density, and flow under gravity, is important for both designing and optimizing the manufacturing process. Powder characteristics must be understood to answer questions such as whether a

powder can be processed with direct compression, or if it will require dry or wet granulation.

Optimizing raw materials
Adequate raw-material specifications are currently a missing link in the quest for solid-dosage process optimization. A group from the National Institute for Pharmaceutical Technology and Education (NIPTE) began collaborating with FDA in 2011 on a searchable excipients knowledge database for excipient property measurement data to make more data available to developers (2). Better specifications for crucial raw-material powder properties, such as particle shape and flowability, would allow better control of material inputs and reduce the need to adjust the process to compensate for this variation, says Freeman.

Using PAT
Process analytical technologies (PAT) are now widely used to measure, understand, and improve the solid-dosage process. Real-time monitoring allows processors to identify a need for process adjustments more quickly, which improves process capability. Online monitoring methods, such as near infrared (NIR) analysis, can, for example, help identify the endpoint of the granulation process (3). In roller compaction, ribbon density and particle size distribution measurements can be measured on-line and used for process control, says Winters. In tableting, compression forces can be monitored online, and tablets can be rejected based on atypical compression events rather than actual testing, noted Winters in a webcast (4). Tablet properties such as weight, hardness, thickness, and content uniformity are now able to be measured online. Other important properties, such as powder flowability and particle shape, must be measured off-line or at-line, says Freeman, who notes that this engineering challenge is a focus for equipment and method development.

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Another challenge that the industry is currently engaged in solving is moving beyond process monitoring to using PAT data to actively control the process. Processors are addressing issues such as integrating instrument software with plant equipment and ensuring that PAT measurements are quick enough to allow control of process fluctuations (5).

Continuous processing
The use of continuous operations in solid-dosage manufacturing is growing rapidly. “Process development in a continuous process is much easier and faster than in a batch process,” notes Freeman. “Because the process has a low residence time, you can change variables and explore the results very quickly, in minutes or hours instead of days.” Scale-up is also easier, because the process can be run for a longer time rather than in larger equipment. Continuous processing, combined with PAT, allows for the possibility of closed-loop control. The aim is to have a process that can compensate for variation in inputs, such as water content in the raw materials.

Hot-melt extrusion (HME) is inherently continuous, and continuous processes for wet or dry granulation (with continuous drying and milling) and direct compression are also in use. GEA Pharma Systems, for example, introduced the ConsiGma continuous, high-shear, wet granulation process using a twin-screw extruder in 2013. In January 2014, GEA and Freeman Technology announced a collaboration to advance the use of continuous wet granulation and drying technology. Data from Freeman Technology’s FT4 Powder Rheometer are being used to quantify the influence of the ConsiGma operating conditions on the bulk characteristics of granules, and these data are then correlated to attributes of the tablets. “The study rigorously investigated the impact of changes in water addition level, granulator screw speed, and powder feed rate,” according to a press release (6). “The results show how it is possible to produce granules of closely defined quality using a series of different operating conditions, and demonstrate how the design space for the ConsiGma can be mapped efficiently for a given tableting blend. Dynamic powder measurements provide the information needed to effectively specify optimal operating conditions. Within a commercial manufacturing environment, they would also provide the information needed for operational decision making within the design space.”

L.B. Bohle is building a technology center, expected to be completed in mid-2014, to develop and demonstrate continuous wet and dry granulation. At the center in Ennigerloh, Germany, L.B. Bohle processing experts will work with specialists from the Universities of Dusseldorf and Graz and experts from Siemens on measuring, monitoring, and controlling the continuous production process, and these developments will be used to produce new equipment and optimize current machinery, the company said in a press release (7).

Optimizing manufacturing processes for improved solubility
With the increasing use of APIs with low solubility or bioavailability, processing technologies for improving solubility are being developed and optimized to meet this growing need. Spray drying and HME for pharmaceutical

applications, for example, have evolved over years of research and are now established processing technologies with market precedence for improving solubility, notes Dan Dobry, vice-president at Bend Research, part of Capsugel's Dosage Form Solutions (DFS) business unit. The QbD methodology is especially relevant to bioavailability-enhancement products because each molecule presents its own unique challenges, which are identified and mitigated using risk-based approaches and by designing quality into the product from the beginning, says Dobry. Optimization of spray drying and hot melt extrusion, for example, involves understanding performance, stability, and manufacturability for a specific API and target product profile. "Performance can be optimized by understanding the dissolution mechanism of a specific formulation and pairing that understanding with a mechanistic biomodel to predict absorption," explains Dobry. "Stability is optimized by understanding the physical state of amorphous materials and development of predictive models to screen out unstable formulations before they are advanced. Manufacturability is optimized by using first principles and multivariate statistical models that correlate critical quality attributes to key process parameters."

Although understanding this interdependence of the formulation and process operating space has influenced the most significant advances in optimizing the manufacture of amorphous dispersions, equipment innovations have also played a role. In spray drying, important innovations have been in drying chamber geometry, nozzle choice, and process parameter ranges, notes Dobry. Future equipment innovations are expected to tackle the cost of goods for "very" poorly soluble compounds and the handling of potent compounds, predicts Dobry.

Laboratory-based methods have also improved to the point of being able to predict success in improving bioavailability. "There is enough basis of work to be able to provide good guidance as to whether to continue the development process with an SDD, for instance," explains Jeffery Basham, vice-president of business development at Metrics. When a CMO uses QbD principles in exploring and documenting chosen formulations, the client has a basis for explaining what and why various decisions were made during the development process, explains Basham.

Hot-melt extrusion

Extrusion is a well-understood mixing process in several industries, and this understanding is being applied to optimize the pharmaceutical HME process. Commercial adoption rates of HME are expected to increase as it becomes even more accepted as an effective means to address drug solubility challenges, predicts Nicholas Johnson, strategic marketing director of Advanced Delivery Technologies at Catalent. The company expanded its OptiMelt HME capabilities at its Somerset, NJ facility in September 2013 in response to increased customer interest, particularly in the post proof-of-concept stages of process development and scale up. The OptiMelt technology platform was developed to optimize the HME process through an alliance with polymeric-excipient producer BASF, which involved developing the most effective ways to screen drug candidates and identify the most applicable polymers early in the development process. The technology platform also incorporates Catalent's experience to effectively integrate the HME extrudate into the most appropriate finished-dosage form (e.g., tablets, capsule and granules, and controlled-release technologies) for customers' end requirements.

HME has the potential to become more widely applied to a greater variety of formulation challenges, over and above bioavailability enhancement, because of several advantages. These benefits include being solvent free, able to operate as a continuous process, and having relatively compact equipment that allows a more effective use of infrastructure. "One of the largest-scale products we manufacture using hot-melt extrusion is not for bioavailability enhancement but rather addresses a specific formulation challenge for an over-the-counter product that was most readily addressed through hot melt extrusion with downstream processing into a convenient dose form," says Johnson. "We fully expect to see more such opportunities for the wider employment of hot-melt extrusion in the future."

Softgels and liquid-filled capsules

Amorphous dispersions (made using HME or spray drying) can be compressed into tablets or filled into capsules. Another option for improving solubility is using a liquid or semi-solid approach that incorporates combinations of lipids, water-soluble surfactants, and co-solvents in a softgel or liquid-fill hard capsule (LFHC) finished dosage form. "The choice of delivery platform is based on a combination of many factors, including dose/potency, the API's physicochemical properties, and customer preference on dosage-form presentation," comments Dobry. "Lipid technology can be especially useful for extremely lipophilic compounds and where there is a need for induction of fed-state, reduction of efflux, promotion of lymphatic absorption, or decrease in hepatic or luminal metabolism."

Liquid filling offers a more straightforward manufacturing process with more reliable scaleup than dry-powder filling or tableting, adds Stephen Brown, managing director of the Capsugel DFS Livingston, Scotland site. For LFHC, Capsugel has developed a specialized liquid-filling and sealing process that eliminates product leakage. The

capsule design has two capsule ring-barriers at the top of the sealing zone and eliminates dimples to remove low cap–body contact areas that could affect the sealing process. Capsugel's proprietary Licaps Fusion technology system lowers the melting point of gelatin, which allows fusion at moderate temperatures. "The combination of capsule design and the use of fusion technology results in fewer capsules removed during post-vacuum inspection and zero subsequent leaking capsules during pre-bulk packaging inspection," says Anthony Macci, senior vice-president of Global Operations at Capsugel DFS.

Catalent's new OptiShell technology increases the range of excipients that can be used in softgels, and further advances are expected to provide more options (8). Traditionally, limits to soft-gel encapsulation include use of fill temperatures below 40 °C, neutral or acidic fill formulations, and excipient limitations. OptiShell non-gelatin shell technology, however, allows fill temperatures up to 70 °C and semi-solid and highly viscous fills. The OptiShell shell is less susceptible to crosslinking and can accommodate a wider range of excipients and surfactants, as well as more basic pH fill formulations, explains Ted Andrew, product manager for Catalent's RP Scherer Softgel. Softgel technology is well optimized with the experience gained over 80 years of formulating and manufacturing, says Andrew.

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