Innovative Excipients in Solid-Dosage Manufacturing

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This article looks at key considerations in excipient selection during formulation development and their impact on the performance of the finished drug product.

Oral formulations, which form the largest category of pharmaceutical dosage forms, tend to require more excipients than other preparations. As a result, trends in oral solid-dosage forms have a significant impact on excipient demand (1).

Trends in oral solid-dosage forms

While the high number of poorly soluble APIs continues to be a challenge in the formulation of tablets and capsules, there is now a wider range of options available for these drugs, observes Paul Titley, business development director, Aesica. "Approaches such as spray drying, hot-melt extrusion, lipid-based drug delivery, and multiparticulate systems are increasingly being used in both drug development and the manufacture of solid dosage forms," notes Anil Kane, PhD, global head of formulations at Patheon.

Randy Wald, senior research fellow at Bend Research, part of Capsugel Dosage Form Solutions, adds that the demand for specialized dosage forms, such as pediatric/geriatric, abuse-deterrent, and controlled-release formulations, has also grown over the past decade.

"More than ever before, pharmaceutical companies are looking to take a holistic approach that places the patient at the center of everything they do," says Verena Garsuch, PhD, pharmacist and senior manager of formulation development, Hermes Pharma. "A recent survey (2) highlighted that more than 50% of people find it hard to swallow traditional solid tablets. This presents exciting new opportunities to better meet consumer needs, for example, by making pharmaceuticals more user-friendly."

"Dosage forms such as orally disintegrating granules (ODGs), effervescent tablets, lozenges, instant drinks, and chewable tablets are specifically designed to be easier to swallow and offer a more pleasant experience," explains Martin Köberle, PhD, senior manager of analytical development, Hermes Pharma. "By creating medicines that people 'want to take' rather than 'have to take,' we have the opportunity to improve treatment compliance while boosting product differentiation and brand recognition."

Continuous processing, QbD, and PAT

Wald observes that another major trend has been towards continuous processing, where multiple continuous unit operations are coupled into an integrated system. "The genre includes the primary processes in oral solid-dosage form manufacture such as direct blend, wet and dry granulation, tableting/encapsulation, and film coating. Drivers include streamlined development, lower and more flexible manufacturing, higher quality product, and lower net costs," says Wald. "Moreover, with quality by design (QbD) and process analytical technology (PAT) becoming more mainstream, manufacturers are placing increasing emphasis on raw materials and process controls."

The adoption of QbD continues to improve pharmaceutical development. Garsuch notes that more companies are moving away from traditional, empirical methods towards a rational, systematic approach. "QbD enables a more robust approach and more accurate decision making, as it is based on data and facts rather than relying on trial and error or instinct," Köberle comments. "The adoption of QbD across the industry is still in progress, but with regulatory authorities demanding that more processes meet QbD requirements, this trend is expected to continue."

"Excipient manufacturers are implementing the concepts of QbD in their manufacturing processes to improve the quality and consistency of the excipients. There is also an improvement

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in the quality from the perspective of higher purity and lower impurities in the excipients," Kane points out.

Excipient selection

Excipients make the bulk of a solid-dosage form and they play a crucial role in the properties and performance of the finished formulation, such as its stability, drug release, bioavailability, taste, and texture. Garsuch and Köberle emphasize that excipient quality is not only essential for meeting the requirements set out in the pharmacopeias, but it is also necessary for creating reliable products and enabling the production process to proceed unhindered. "It is, therefore, essential to characterize and understand your excipients as comprehensively as possible, including particle size and shape," they remark.

"Primarily, pharmaceutical excipients need to be GRAS-listed (i.e., generally regarded as safe), have a bovine spongiform encephalopathy (BSE)/transmissible spongiform encephalopathies (TSEs) free certification, well-established specification sheets and control test procedures, and quality control," explains Kane. "The key consideration in selecting excipients in solid oral-dosage forms is its global acceptance. Most of the products developed are intended for global markets and seldom do we see any products focused on a selected market. Hence, raw materials, excipients, packaging formats, and stability requirements are considered for global filing. Beyond its global regulatory acceptance is the functionality of the excipients. The functionality of an excipient and its lot-to-lot consistency in meeting the quality specifications are critical in vendor selection and qualification."

Wald adds that excipient selection needs to take into account the API chemical and physical properties (e.g., solubility, permeability, chemical stability, particle properties, and physical form); dosage form; and manufacturing process preferences or constraints. "It is also important to consider the required pharmacokinetic performance (especially the required absorption profile and plasma-time targets, as predicted from pharmacokinetics-pharmacodynamics modeling) and functional excipients used for enhanced absorption, controlled or modified release, chemical stability, taste masking, or commercial manufacturing process viability" continues Wald.

The role of the excipient is a key consideration, according to Titley. "For example, you would ask, what do we expect this excipient to achieve? Do we understand the differences between the various grades? Are we using it in the correct manner? What weight will we need per dosage form—is it too high for the target size?" However, familiarity is also one of the factors in excipient selection, Titley points out. "The drug developer or formulation scientist will consider, have we used this excipient before; is it on our database; has the quality assurance manager approved the source?"

"Other factors, such as batch-to-batch variation, stock limitations, and price fluctuations, can also have an impact on the supply of trustworthy, well-characterized excipients," notes Köberle. "In these cases, it is essential to know if the excipients that you select will perform as expected, will continue to be reliably available, and whether they can be easily replaced should the need arise."

Garsuch explains that taking a QbD approach to selecting excipients involves a rational and systematic process that evaluates these risk factors. Often this approach includes conducting compatibility studies or applying design-of-experiment (DoE) approaches to collect the data needed to better understand how the excipients will perform during formulation development and manufacture. "If pharmaceutical companies fail to pay close attention to excipient quality, they run the risk of creating products that are outside of specifications. This can ultimately lead to manufacturing downtime, supply shortages, increased costs, and damage established business relationships," says Garsuch.

Impact of excipients on drug product performance

"QbD has always been used to understand the variation of the properties of an individual excipient," observes Titley. "Excipient properties can affect critical quality attributes (CQAs) of the drug product, such as flow, compaction, and content uniformity. The most obvious one is the variation in particle size of a particular excipient, especially in solid-dosage forms. Excipient manufacturers and formulators have used QbD to show that the particle size variance is not an issue from batch to batch. If there is variation from batch to batch, then the critical process parameters (CPPs) can be investigated to make the product more robust."

"Although the selection of the excipients with the proper functionality and their corresponding levels in the drug product formulation are critical to drug product performance, a deeper understanding of how variability in the excipients can affect drug product performance and the proposed control strategy has also been identified as an important component of improved drug product development," comments Kane, citing a study by Kushner et al. (3). "A number of drug product recalls identified excipient variability, and, therefore, a lack of an adequate control strategy, as a contributor to failure of the drug product, further underscoring the need for improved excipients variability understanding." Evaluating the impact of excipient variability on drug product performance, however, has presented a greater challenge to date than evaluating API and process impacts on drug product performance, according to Kane. "This is partially because of the pharmaceutical manufacturer having more internal capability to manipulate the API and the manufacturing process for experimental study. For excipients, the observed lot-to-lot variability for an individual grade is a function of the control strategy put in place by the excipient supplier. Because of the scale of excipients manufacture and the broader industrial application of many pharmaceutical excipients, it can be difficult for pharmaceutical manufacturers to easily obtain an ideal set of samples to adequately investigate the impact of

excipient material properties on drug product performance," he explains.

"The science- and risk-based approach to regulating pharmaceutical manufacturing, developed in 2004 by the Office of New Drug Chemistry in the United States Food and Drug Administration, focuses on the impact of chemistry, pharmaceutical formulation, and manufacturing processes on drug product CQAs and their impact on safety and efficacy. In 2012, FDA released a guidance for abbreviated new drug applications (ANDA) that further affirmed the role of excipient material property understanding (along with drug substance and manufacturing process understanding) as a significant aspect of QbD drug product development. As a direct result of these regulatory expectations, the impact of excipients on the manufacturability and performance of new drug products has recently received increased scrutiny in the pharmaceutical industry," Kane elaborates.

Methocel DC2 for direct compression

Excipient choices for a formulation are typically driven by functionality requirements and compatibility with the API, observes Ali Rajabi-Siahboomi, PhD, chief scientific officer, Colorcon. "Excipient grade choices are most important when deciding which manufacturing process will be used," he stresses, and further explains that direct compression (DC) may not always be suitable for formulations due to several reasons.

The primary reasons typically revolve around the API and its particular properties, according to Rajabi-Siahboomi. "Many times, APIs are very fine powders, sometimes below 10 microns in size. Small particles do not flow well and good flow is essential in the tableting process to achieve low tablet weight consistency. Both wet and dry granulation techniques can be used to agglomerate fine powders and improve flow," says Rajabi-Siahboomi. "Another main reason DC may not be suitable is the compactibility of the API; as poor compactibility results in low tablet hardness. Wet granulation techniques are typically used to resolve this issue."

DC grades of excipients facilitate both direct compression and roller compaction processes, producing robust tablets that are also suitable for subsequent film coating, notes Rajabi-Siahboomi. "Some of the factors to consider when choosing grades of excipients are particle size, flow properties, density, and compactibility."

DC grades of excipients facilitate both direct compression and roller compaction processes.

Methocel (The Dow Chemical Company) DC2 is a polymeric hydroxypropyl methylcellulose (HPMC) excipient that provides an alternative to wet granulation in matrix tablet production. "Methocel DC2 has been specially engineered, by The Dow Chemical Company, with particle morphology to facilitate the flow of the material, as compared to the controlled-release (CR) grade of Methocel," explains Rajabi-Siahboomi. "Improved flow properties may allow for simpler and less costly manufacturing techniques, such as DC. These changes must be balanced with the other properties and functionalities of the polymer, compactibility of the blend, and controlled-release performance of the final tablet."

Rajabi-Siahboomi highlights that several case studies showing the improvement in flow properties and the impact on tablet properties have been published (4–6). "These studies have ranged in scale and looked at API concentration and solubility, and process technique. The outcome of these studies has demonstrated tighter tablet weight and hardness, as well as more consistent drug uniformity when Methocel DC2 is utilized as the controlling polymer," adds Rajabi-Siahboomi.

According to Rajabi-Siahboomi, Colorcon and Dow have generated a cost-comparison spreadsheet to facilitate analysis of tablet manufacturing costs. "When comparing a wet granulation process to a DC process, the model shows a potential reduction in costs of around 60%, when utilizing a direct compression process enabled by Methocel DC2," says Rajabi-Siahboomi.

Affinisol polymers for solid dispersions

"Affinisol (The Dow Chemical Company) HPMCAS (hydroxypropyl methylcellulose acetate succinate) has a number of properties that make it ideal for formulating poorly soluble drugs as solid dispersions," says Robert Schmitt, PhD, fellow, R&D, Dow Pharma & Food Solutions. "The polymer is soluble in a range of organic solvents, which provides a wide latitude for developing spray-dried dispersions from solvents most compatible with a specific API. The glass transition temperature (Tg) of the polymer is high enough to produce a stable dispersion for many APIs and the water uptake of the solid dispersion is low, which leads to a solid dispersion with good shelf stability. Finally, the polymer can be tailored via control of both the succinate and acetate groups as well as the molecular weight in order to optimize the performance of the dispersion both in the solid state and upon dissolution," explains Schmitt. "This high level of control allows for the development of a stable dispersion that has the optimum dissolution and super-saturation performance *in-vivo*."

According to Schmitt, there are many factors to consider when selecting the best formulation for a specific API. "The choice of polymer family is typically driven by the drug class and the desired release profile," he asserts. "We currently combine a review of the API physical properties along with high throughput screening to define which polymer is most effective for a particular API." Schmitt observes that HPMCAS is a suitable choice for highly crystalline compounds, "provided enteric performance is consistent with the delivery goals," he says.

"If HPMCAS is selected as the lead polymer, we then evaluate a series of

custom produced polymer grades, which allow for the optimization of the API performance. This effort is primarily focused on optimizing the drug-release rate and super-saturation performance as the solid-state properties of the polymer do not vary much over the composition range available," continues Schmitt. "The API to polymer ratio is driven by the dose requirements as well as the stability of the API in the polymer. We find stable formulations in the range of 10–50% API are typical. One of our goals is to provide solubility-enhancement polymers that don't require additional excipients for optimum performance. This leads to more predictable performance while providing stable formulations."

Dow has also designed a novel cellulosic polymer with improved thermal properties for hot-melt extrusion (HME) applications. Affinisol HPMC HME can be readily extruded over a wide range of temperatures without the need to add plasticisers. The standard pharma grades of HPMC have high Tg's and very low melt flow, observes Schmitt. "To process these polymers via HME, it is critical to add high levels of plasticizers. However, the plasticizers tend to increase the mobility of the API within the solid matrix leading to lower API stability."

According to Schmitt, the Affinisol HPMC HME grades have been tailored to reduce the Tg of the material and significantly improve the melt flow of the product. "With Affinisol HPMC HME, it is possible to extrude the neat polymer, which represents a breakthrough because it is now possible to use this excipient in the highly efficient extrusion process," he explains. "By eliminating the need for plasticizer in the formulation, a simple binary system can be utilized, providing good shelf stability. While greatly improving the processability of HPMC within the HME processing space, the Affinisol HPMC HME maintains good sustainment properties already known for HPMC."

Eudragit polymers for controlled-release formulations

Evonik's poly(meth)acrylates, better known as Eudragit, represent a versatile toolbox for controlled-release formulations, remarks Ann Gray, market segment manager oral excipients, Evonik Pharma Polymers & Services.

"Eudragit L 30 D-55 and L 100-55 are used for enteric coatings that dissolve quickly after stomach transit. For drug release in lower sections of the small intestine, Eudragit L and S can be used in variable mixtures to target specific dissolution pH values. Eudragit S or FS grades with a dissolution pH of 7 are recommended for pharmaceutical forms that are intended for colonic drug delivery," explains Gray.

According to Gray, the insoluble Eudragit polymers enable a variety of formulation strategies for controlled-release dosage forms. "Eudragit RL/RS and Eudragit NE/NM 30 D are insoluble, independent of pH, and swell in physiological media, thus releasing the API in a diffusion-controlled manner," she continues. "Eudragit polymers of different functionalities can be combined to achieve release profiles tailored to the API and therapeutic requirements, for example zero-order, circadian, and pulsatile release. They may be applied in one layer or also as multiple layer coatings."

"Eudragit polymers form inert matrix structures from which the active is released through (pore) diffusion. Depending on the physicochemical properties of the active and the desired release profile, both pH-independent and pH-dependent Eudragit grades can be used to develop extended-release matrix formulations," says Gray, adding that conventional granulation technologies can be used, as well as direct compression of the polymer powders. She also highlights that the added advantage of these matrix systems is their higher resistance to the influence of alcohol.

Gray also mentioned that the company's Eudragit E PO and its customized ready-to-use variant, Eudragit E PO ReadyMix, form protective coatings of low water vapor permeability that dissolve quickly in acidic media leaving disintegration and release behavior in the stomach unaffected, even when used in thicker polymer layers.

When asked about Evonik's QbD approach, Gray said that in general, as fully-synthetic polymers, Eudragit does not have the high variability that is inherent in excipients manufactured from natural substances. She emphasizes that quality is planned into the manufacturing processes of Eudragit polymers by means of well-established chemistry, highly controlled processes, and tightly specified raw materials from backward vertical integration. "Evonik offers in-depth knowledge of polymer properties to customers so they can achieve robust formulations that meet QbD requirements," adds Gray.

Other innovative excipients on the market

One of the key advances in excipients is the development of coprocessed products for solid-dosage forms, observes Titley. "These products are a combination of two or more standard excipients, which speeds up the formulation development process. Typically these coprocessed excipients are already standard ingredients used in the pharmaceutical market, hence, the acceptability of the product is a key advantage for formulators," Titley adds. "An example of a co-processed excipient is Prosolv Easytab from JRS Pharma, which combines four standard excipients into one product. All the formulator has to do is add the API." Prosolv Easytab is an all-in-one, ready-to-use, high functionality, excipient composite that combines binder/filler, glidant, superdisintegrant, and lubricant for rapid formulation development and convenient tablet manufacture.

GalenIQ, a multifunctional excipient from Beneo-Palatinit for oral solid dosage forms, is available in a variety of particle sizes and morphologies. This non-hygroscopic, physically and chemically stable excipient serves as an anti-caking agent, anti-humectant agent, stabilizer, and taste-masking agent among its various functions.

Roquette has developed Pearlitol Flash, a mannitol–starch compound with unique disintegrative properties

for the formulation of orodispersible tablets. The company recently introduced a new range of directly compressible polyols—maltitol, xylitol, and sorbitol—that can be used to create a variety of tastes and textures for all types of tablets. Kleptose Linecaps (maltodextrin) has been developed as a taste-masking agent, particularly for pediatric formulations. It masks the bitter taste of the API by decreasing the overall amount of drug particles exposed to the taste buds. Roquette's Lycatab C-LM is a low-moisture partially pregelatinized maize starch, used as a hard capsule filler for moisture-sensitive APIs to add stability to the formulation.

Advances in spectroscopic and imaging technologies

"Advances in spectroscopic and imaging technologies allow us to better analyze excipients in a way that is not possible using chemical analysis alone," observe Garsuch and Köberle. "For example, we can now photograph 60 to 70,000 particles in a single, rapid analysis that provides deep insights into particle size distribution and shape, all key characteristics that influence excipient behavior during formulation development and manufacture," remarks Köberle. "Modern DoE approaches also utilize powerful, multivariate data analysis methods that allow us to systematically screen and select excipients in a way that is faster and more informative than traditional, univariate methods."

"New PAT systems are also enabling us to improve the formulation process in real time, both during development and later during manufacture. In this case, spectroscopic methods can be used to monitor the process inline and in real-time without the need for sampling, allowing us to rapidly fine-tune and troubleshoot the process. Some of these technologies can even provide data without needing to be in contact with the product, reducing the chances of contamination," adds Garsuch.

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