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Key Considerations in Excipients Selection for Solid Dosage Forms

Randy Wald, senior research fellow at Bend Research, part of Capsugel Dosage Form Solutions shares insights on trends shaping the evolving solid dosage manufacturing landscape, including advances in excipients and the impact on formulation development and manufacturing processes.

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The majority of pharmaceutical drugs are still produced as solid dosage forms because of the acceptability and convenience of the oral route as well as the good patient compliance it offers in general. As solid dosage forms do not require sterile manufacturing conditions, the overall production costs are less expensive. Moreover, the pharmaceutical industry has years of experience developing solid dosage forms with well-defined and known processes, equipment, and technologies.

To gauge emerging trends in solid dosage manufacturing, *Pharmaceutical Technology* spoke with Randy Wald, senior research fellow at Bend Research, part of Capsugel Dosage Form Solutions about key drivers shaping the pharmaceutical drug development and manufacturing landscape.

PharmTech: How has the manufacture of solid dosage forms changed over the past decade?

Wald: The manufacture of solid dosage forms continues to evolve, with key drivers including functional improvements, safety, and overall cost of development and commercial manufacture.

Several key trends can be noted, all of which continue and include increased partnership of CDMO/CMO with pharmaceutical companies, increased demand for specialized dosage forms (pediatric/geriatric, abuse-deterrent, fixed dose combinations), higher potency APIs in the development pipeline and in commercial production, the maturation of solubility-enhancing technologies, increasing prevalence of continuous manufacturing processing displacing legacy batch processing, and continued advances in excipients including ready-to-use and co-processed.

The outsourcing of pharmaceutical development and/or manufacturing to CDMO/CMOs has become mainstream given the continued trends of pharmaceutical company downsizing and focusing on molecule discovery and marketing functions, the increasing role of small/virtual pharmaceutical companies in drug discovery and development, and the demand for increasingly innovative drugs using specialized technologies.

Continuous processing, where multiple continuous unit operations are coupled into an integrated system, improves overall productivity and costs of production and is complimentary with ICH and other quality-by-design paradigms. Continuous processing, such as continuous coating, has been implemented in immediate-release capsules and tablets (initially in the health & nutrition segment and, in past few years, there has been fast growth in Rx/OTC). It will continue to find applications in the pharmaceutical segment inclusive of more specialized areas such as extended-release drug products.

We are also seeing functional improvements using existing pharmaceutically approved excipients. Given the prohibitive cost of developing and gaining approval for a new excipient, suppliers have coupled processing advances for the development of innovative dosage forms. Several examples can be cited:

- Coupling of processing and polymer chemistry to greater effect, e.g., melt-spray-congeal processing to encapsulate API in a lipid matrix, the architecture of which is tailored to meet the functionality required whether it is bioavailability enhancement, controlled release, and/or taste masking.
- Use of functional capsules incorporating approved enteric polymers to eliminate previously required coating steps to provide gastric resistance or fully enteric protection for solid oral dosage forms. The elimination of functional coating can speed up and de-risk the development process for actives requiring enteric protection and/or targeted release in the upper GI tract.
- Use of existing excipients and processing to provide abuse resistance for opioids and other often-abused drugs, which is increasingly required by regulatory authorities. By understanding the typical routes of abuse, resistance is being built into drug products using a range of excipient functionality inclusive of thickening agents, waxy or high melting point excipients and taste modifiers.
- Additional functionality built into existing excipients, e.g., additional grades of pharmaceutically approved excipients to provide more tailored functionality and/or improved supply-chain performance such as shelf life. Examples include new polymer grades for hot-melt extrusion and spray dry dispersion processing (e.g., more molecular weight and viscosity grades for cellulosic polymers). Co-processing of approved excipients for greater functionality and simpler manufacturing is another trend.
- Drug design and manufacture for specialized populations including pediatric

and geriatric applications where patient compliance is a challenge. Reducing the number of medications and/or dosing frequency, coupled with improving the ease of swallowing, is increasingly factored in and drives more fixed dose combinations, extended release, and multiparticulate formulations.

PharmTech: Excipients make the bulk of a solid dosage form and they play an important role in properties of the finished formulation, such as its stability, drug release, bioavailability, taste, and texture. When it comes to formulation development, what are the key considerations when selecting your excipient for a solid dosage form?

Wald: Functional excipients form the foundation of most solid oral dosage forms and as such, careful consideration must be taken in their selection. The possible consequences of sub-optimized excipient selection can include reduced bioavailability, compromised stability, manufacturing complications, and increased chance of side effects, which affect the overall commercial success of the drug. We have developed decision trees and models, based on more than a thousand compounds, to guide the choice of appropriate technology and excipients for key challenges such as bioavailability and controlled release.

Key technological considerations include:

- The product's desired pharmacokinetic performance (PK modeling)
- Functional excipients for enhanced absorption, controlled or modified release, API stability, etc.
- Dose levels
- API physical/chemical properties

Commercial considerations are also factored in, such as the desired finished dose presentation. This process greatly narrows the choice of excipients preferred for the technology and manufacturing processing.

PharmTech: In terms of excipients for solid dosage forms, what are the key advances that have significantly impacted the formulation development and manufacturing process of solid dosage forms?

Wald: Excipient suppliers continue to respond to both regulatory and industry trends by providing additional grades of existing excipients as well as new and/or co-processed excipients. Key requirements include enhanced excipient functionality and range to assist in repositioning existing compounds for greater efficacy and/or new indications. For preclinical evaluations, speed, and de-risking are key considerations. And simplified formulation and processing approaches are increasingly important. A few examples are listed in the following:

- Additional grades of hypromellose acetate succinate (HPMCAS) have been developed to expand the range and applicability of spray dry dispersion technology for addressing low solubility.
- Lipid multiparticulate (LMP) technology has been developed to provide the functionality of lipid-based formulations and the benefits of the multiparticulate format—an example of leveraging lipid-based formulation and melt-spray congeal processing know-how to achieve innovation with existing excipients.
- New polymers and grades have been developed specifically for hot melt extrusion processing, based on increased understanding of the process and requirements.
- Dry dispersion formats of existing polymers have been developed for ease of processing and reduced costs.
- Functional capsule technology developed to intrinsically provide enteric protection, eliminating the need for functional coatings and the complexity and risk associated with their application.
- Co-processing to provide multi-functionality and/or improved functionality using a single excipient for early stage development through commercial production.

PharmTech: Do you see a need for novel excipients and if so, what excipients?

Wald: Continued advances—not necessarily novel excipients—in excipient formulation and processing technology are required to keep pace with the increasing challenges in drug product formulation and production. As an example, the drug pipeline challenge continues with an increasing percentage of poorly soluble and higher molecular weight molecule candidates. Thus, excipient functionality that provides both enhanced absorption and extended release is a promising area. Another example is the move towards continuous processing. Excipient vendors will increasingly need to supply excipient types and grades amenable to new processing versus historic batch processing.

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