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Understanding How Excipients Affect Drug Quality

At CPhI North America 2017, an AbbVie scientist will discuss how excipient property variability affects quality for amorphous solid dispersions and extended-release products.

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By Pharmaceutical Technology Editors

In implementing quality by design for drug formulation, it is crucial to identify the critical properties of excipients and understand how their variation affects the final drug product. Yihong Qiu, senior research fellow for Oral Drug Products, Manufacturing Science & Technology, AbbVie, Inc., is giving a presentation at CPhI North America titled, "Understanding Critical Excipient Properties to Ensure Consistent Quality of Amorphous Solid Dispersion and Extended-Release Products [1]." The presentation is scheduled for Wednesday, May 17, at 4 pm. *Pharmaceutical Technology* spoke with Dr. Qiu, who shared some of his insights on the topic.

PharmTech: What are the critical excipient properties that can have a "natural variability" in what is supplied for pharma processing?

Qiu (AbbVie): Physicochemical and mechanical properties of an excipient are known to impact quality, performance, or processing of the final drug product. Properties of excipients generally show different degrees of inherent or 'natural' variability due to variations of the starting materials and manufacture of the excipients. Criticality of certain properties is usually determined by its essentiality to the function of a particular excipient. Criticality of a specific excipient property is also often defined by its possible influence on drug product quality, which is controlled by the characteristics of API, formulation, and process. Therefore, assessing critical properties of an excipient needs to be based on understanding of the excipient as well as the API, product, and process.

High excipient variability can become detrimental when certain excipient properties have been shown to affect potency, purity, or even processing of a particular product (e.g., pH, moisture, residual metals, or peroxides). This variability may also become detrimental when consistent properties of functional excipients are crucial to achieving reproducible product performance and quality, especially for more sophisticated delivery systems, such as modified release (MR) or amorphous solid dispersion (ASD) products. The extent of supplier-to-supplier and/or batch-to-batch inherent variability of an excipient often depends on the variations in the starting raw materials (e.g., source, specifications), manufacturing technology (e.g., batch vs. continuous processing), process parameters and controls, scale, equipment, systems, operators, environmental conditions, and even characterization tests (e.g., sensitivity, selectivity). The source of an excipient (i.e., natural, naturally derived, synthetic, or semi-synthetic) typically plays a key role in its inherent variability. For example, feedstock for naturally derived polymeric excipients often varies with species of crop, growing conditions, and/or harvesting location. Due to a broader natural variation, batch blending is sometimes required to meet product specifications, resulting in greater composition variations. In contrast, synthetic excipients are manufactured from purer starting chemicals and thus generally exhibit lower variability when manufacturing is well controlled. Its variability is more often manifested by variations in residual starting materials, byproducts, or synthetic impurities, for example, though excipient properties can still fluctuate. Lastly, impact of excipient properties can also be related to sensitivity (robustness) of formulation, process, and even test methods of a product to excipient variability.

PharmTech: Which critical quality attributes of a drug product are affected by these excipient properties (as well as by other raw materials and processing conditions)?

Qiu (AbbVie): How properties of an excipient may affect drug product performance and critical quality attributes (CQAs) depends highly on the function of the excipient in the formulation and the relationship between excipient quality and the drug product. For example, variability in the rate-controlling polymers for MR products can significantly influence drug-release performance and reproducibility, but dissolution performance of an immediate-release product containing soluble API is often capable of tolerating greater variability of an excipient used as processing aid or diluent. Impact of chemical properties (e.g., substitution, trace impurities) and physical properties (e.g., particle size, flowability) of an excipient on product CQAs may also differ depending on API, product design, and process. For instance, stability of a drug that is prone to hydrolysis could be sensitive to variability in pH and moisture content, but not variation in residual peroxides whereas the opposite can be true for a different drug that primarily undergoes oxidative degradation. Drug release of an extended release product may exhibit high variability between the rate-controlling polymer batches or suppliers even though variations of the apparent viscosity and/or substitutions of the polymer remain within specifications. This variability could be a result of variation in excipient properties that can affect drug-release performance but are not controlled by the specifications, such as polydispersity or homogeneity of the substitution. Excipient properties and its interplays with certain processes or unit operations can also impact processability or quality of the drug product. For example, variability in glass transition temperature of a polymer used to form ASD using a hot-melt extrusion process may affect reproducibility of the extrusion process and residual crystallinity. However, the spray-drying process would be more forgiving to this type of variability.

PharmTech: What are some of the solutions for handling this variability?

Qiu (AbbVie): Not all excipients or all properties are critical to product quality and performance. Each drug product and associated manufacturing process is unique and influenced by individual excipients to a different extent. Therefore, a risk- and science-

based approach is required to manage and address excipient variability. For many excipients, appropriate tests and specifications are in place to ensure consistent quality and reliable performance at an acceptable risk level associated with the general end-use applications. For excipient properties that are critical to critical quality attributes of drug products, especially more sophisticated products (e.g., MR and ASD) with higher level of risk and impact, a more in-depth understanding is required by closely linking excipient attributes to the intended function and by determining how excipient functionality can be controlled and whether additional product-specific specifications should be added based on formulation and process understanding. For example, understanding excipient's critical role in a product or reactivity between the trace impurities with a specific API can help provide a solution tailored for a particularly sensitive API or formulation. To develop a robust formulation and/or process that is capable of tolerating excipient variability, pharma companies and excipient suppliers need to closely collaborate and exchange information. Pharma companies need to share details on the end-use application of the excipient, required functionality and attributes, and problems encountered or anticipated at the early stage of development. The excipient manufacturers need to share their knowledge and expertise to help evaluate excipient properties critical to the drug product by providing in-depth characterization and historical data and identifying raw material and manufacturing variables or changes that can potentially affect these properties and functionality. This type of cooperation can help develop an effective and practical approach to predict and control future batch-to-batch variability within acceptable ranges. In short, to control, reduce or minimize possible negative impact of excipient variability on products and processing, a collaborative effort among pharma companies, excipient suppliers, the US Pharmacopeial Convention, and regulators is essential.

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[1] http://schedule.cphinorthamerica.com/session/understanding-critical-excipient-properties-to-ensure-consistent-quality-of-amorphous-solid-dispersion-and-extended-release-products