Excipient quality: Beyond the pharmacopeia monograph

Excipients are anomalies of pharmaceutical science. They typically do not treat a disease or improve the patient’s quality of life, but without them, many of the therapeutic advances of the last 100 years or so would not have happened. Excipients, along with the product manufacturing process, help convert bulk active pharmaceutical ingredients (APIs) into medicinal products that patients can use, since most APIs administered unformulated would not be acceptable to the patient or caregiver and/or would not provide the required therapeutic benefit.

Ensuring excipient quality requires extra-monograph testing and specifications, which should be agreed upon between the excipient end user and supplier. This article discusses how application of Quality-by-Design (QbD) principles can help to define such extra-monograph testing and specifications.
We rely on excipients to perform a variety of tasks relating to the patient and their treatment, including:

- Allowing us to make the API molecule into a form from which it can be absorbed into or distributed through the patient’s systemic circulation;
- Delivering the API to the site of absorption (in the case of oral medicines) or distribution (in the case of intravenous medicines) in the body;
- Releasing the API at a rate that provides optimal therapy for the patient;
- Allowing the medicinal product to be manufactured at commercially acceptable speeds and quantities; and
- Providing for a sufficiently long shelf-life to allow the medicinal product to pass through the supply chain from the manufacturing site to the patient.

Excipients must perform consistently in each formulation to ensure the efficacy and quality of the final drug product. It follows that excipient quality must include an evaluation of aspects of performance. However, excipient performance is beyond the scope of the pharmacopeias, as it would be impossible to provide performance tests in a pharmacopeia monograph that would be relevant to all uses of that excipient.

So how do we address the quality of our excipients, and how do we assess that quality? Before we attempt to answer these questions, we need to define some key terms.

**What is quality?**

Chapter I of Title 21 of the Code of Federal Regulations (21 CFR) applies to the US Food and Drug Administration (FDA) good manufacturing practice, and Parts 210 and 211 detail the current Good Manufacturing Practices for pharmaceuticals. Surprisingly, 21 CFR Parts 210 and 211 do not contain a definition of quality. However, 21 CFR 820 Quality System Regulations, which applies to medical devices, defines quality as “the totality of features and characteristics that bear on the ability of a device to satisfy fitness-for-use, including safety and performance” [1]. While clearly related to medical devices rather than pharmaceutical products, this definition does show the FDA’s thinking on quality. If we substitute the term “excipient” for “device,” we have an applicable definition.

**What is an excipient?**

The nearest to an official definition of an excipient can be found in the pharmacopeias. The General Notices of the European Pharmacopoeia defines an excipient as “Any constituent of a medicinal product that is not an active substance. Adjuvants, stabilisers, antimicrobial preservatives, diluents, antioxidants, for example, are excipients” [2].

General Chapter <1078> Good manufacturing practices for bulk pharmaceutical excipients of the US Pharmacopoeia states: “Pharmaceutical excipients are substances other than the active pharmaceutical ingredient (API) that have been appropriately evaluated for safety and are intentionally included in a drug delivery system. For example, excipients can do the following:

- aid in the processing of the drug delivery system during its manufacture;
- protect, support, or enhance stability, bioavailability, or patient acceptability;
- assist in product identification, and
- enhance any other attribute of the overall safety, effectiveness, or delivery of the drug during storage or use” [3].

These two definitions are very similar. The important point in both definitions is that excipients are not APIs. They are intended to bring performance attributes (functionality) to the formulation to overcome some of the APIs deficiencies.

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**Why we use excipients and what we need from them**

We use excipients in combination with the API and the product manufacturing process to make the finished dosage form, as shown in Figure 1. Remove any one of these components and we will not have a pharmaceutical product. We also must consider the packaging, since many formulations would not be acceptable to the patient without the packaging (liquids, for example).

In general terms, we need our excipients to be:

- Safe at the level used and via the route of administration;
- Made to an acceptable standard of good manufacturing practice;
- Compatible with and able to maintain the chemical and physical stability of the drug product under the specified conditions of storage and use; and
- Consistent in performance in the application (formulation and product manufacturing process).

Above all else, we need to ensure that we can routinely manufacture the drug product at commercial scale. Whatever the cause, drug product shortages can compromise patient health and well-being.
Drug product variability

Now let’s consider variability of the final drug product and how excipient variability may impact it. Variability is inherent in everything, our tolerance of it depends on the level of scrutiny we need to apply. Pharmaceutical products are no exception. Pharmaceutical product variability can arise in several ways, as shown in Figure 2. However, this is not the complete picture. There is a further term relating to how API variability, excipient variability, and processing variability interact. We must also take this interaction term into account if we are to develop robust drug products.

Taking into account this interaction term, product variability then becomes:

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\sigma^2_{\text{Product}} = \sigma^2_{\text{Active}} + \sigma^2_{\text{Excipients}} + \sigma^2_{\text{Process}} + \sigma^2_{\text{Interactions}}
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Note that the variance (\(\sigma^2\)) has been used because variances are additive. The “interactions” term is deliberately plural and may contain many different components relating to factors such as how the operator loads the blender, material cohesiveness, material adhesive-ness, and others. To have the best chance of developing a robust product, we need to reduce all the variability contributions to below an acceptable maximum, including the excipient variability.

Excipient composition

For bulk APIs, the purity of the material is linked to efficacy and possibly the reduction of side-effects. The mantra “safety, purity, and efficacy” applies. Excipients, by contrast, are very often mixtures of materials with major and minor components, and the minor components may contribute to the overall performance of the excipient in a particular application. For example, the compactibility of coarse-grade dibasic calcium phosphate dihydrate is influenced by the presence of foreign ions in the crystal lattice, which cause dislocations and weakness, allowing brittle fracture to take place. Very pure coarse-grade dibasic calcium phosphate dihydrate does not compact as well.

However, in general, the exact relationship between excipient composition and excipient performance is not well understood and will vary with each application. Excipient monographs are evolving, and there is an effort to develop more specific tests that can better determine the excipient’s composition. However, there is still a lot of work to be done, and we do not have methods to determine the composition of all excipients.

Excipient standards

This leads to the next question of how we should control excipient quality. What standards and specifications should we apply on a routine basis for our application? When we think about excipient standards, the pharma-
Conclusions

Excipient performance is very different from API performance. For APIs, we can use assay and related substances to assess chemical purity, which is related to quality. Excipients often contain other (concomitant) minor components that may influence performance in a given application. The pharmacopeia monograph or supplier’s specification typically only addresses the excipient’s identity and possibly the means to differentiate between grades of the same material. QbD DoE can help users control their excipients. However, excipient users must agree upon test methods and limits for such extra specifications with their excipient suppliers.

References

1. 21CFR820.3(s): (Revised as of April 1, 2019). Available at: www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfr/cfrSearch.cfm?fr=820.3.

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