Functionality and Performance of Excipients

By R. Christian Moreton

The objective of a medicinal formulation development project is to deliver drug to the patient in the required amount, at the required rate, consistently within a batch, from batch to batch, and over the product's shelf life.

The US Food and Drug Administration's Quality in the 21st Century initiative, which includes the quality by design (QbD) and process analytical technologies (PAT) initiatives, requires that the pharmaceutical industry better understand its product formulations and manufacturing unit processes. In addition, ICH Q8—Pharmaceutical Development (also issued by FDA as a Guidance for Industry), links in to the common technical document (CTD) and suggests the need for greater understanding in the design and development of pharmaceutical formulations and processes.

Consequently, industry is expected to demonstrate that it understands its formulations and processes and can define the appropriate design space that will allow the routine manufacture of pharmaceutical products that deliver the correct amount of drug to the patient, at the required rate, consistently from dose to dose and from lot to lot, over the shelf-life of the product (i.e., a "robust formulation").

A robust formulation may be defined as:

A formulation that is able to accommodate the typical variability seen in the API, excipients, and process without the manufacture, stability, or performance of the product being compromised.

The larger the design space, the more likely we will produce a robust formulation.

Product variability. Most formulations have three components: the active pharmaceutical ingredient drug (API), the excipient(s), and the manufacturing process(es) (see Figure 1). In some instances, there is a fourth component: the primary packaging.

To understand product variability, we must understand input variability. The variability of the API, excipients, and process parameters are obvious components of the overall variability. Nonetheless, other factors could affect the manufacture, stability, or performance of the product. For example, how materials are fed into the unit process,
materials interact together during processing, and how an operator carries out the operations can all affect the final product attributes.

Thus, for a given formulation and process, we must understand variability in the raw materials and their interactions to define the process and then demonstrate sufficient understanding of the process to define the design space for the product. We can represent this process schematically using variance as a measure of variability (see Figure 2).

**Achieving consistency.** Two main approaches can be used to achieve consistent products. The traditional approach is to specify the input parameters more tightly, particularly the excipients and process (but also the API), and to limit the product variability by limiting the input variability. This approach does not address the variability in interactions. This interaction factor, the sum of all the interactions, also can cause problems (see equation in Figure 2).

A second, more modern approach is to accept that there will be input variability and work to gain a sufficient understanding of the process to define an appropriate process end-point. A particular unit process is thus continued until the end-point is achieved. This second approach seems better matched to the intent of the QbD initiative, and also is likely to give a larger design space, and, thus, a more flexible formulation and process.

**Functionality, functionality-related characteristics, and excipients performance**

Functionality applies equally to APIs and excipients. Functionality has been defined as:

> A desirable property of a [material] that aids manufacturing and improves the manufacture, quality or performance of the drug product (1).

In the context of pharmaceutical formulations and products, each formulation will have its own peculiar requirements for functionality. Thus, functionality can only be properly tested by the manufacture and subsequent testing of a batch of product. This process is less than desirable.

An approach currently in vogue is to identify a surrogate test, usually a physical test, that bears some relation to the required functionality. The *European Pharmacopoeia* defines such properties as "functionality-related characteristics"; the *USP–NF* uses the term "performance tests." The *European Pharmacopoeia* proposes to define functionality-related characteristics as they relate to pharmacopeia materials as follows:
Physical and/or physicochemical characteristics that are critical to the typical uses of an excipient (2).

In the context of a pharmacopoeia monograph, the term "typical" raises the question: what can be done for atypical uses? Will there eventually be further regulatory "creep" in Europe requiring formulators to stick to "typical" uses in the design and development of new medicines? To many pharmaceutical scientists, this would be an anathema because it suggests that we should stifle innovation in the use of excipients, without which the drug delivery sector of our industry would never have emerged.

This leads to a further point: most excipients are included in many different products and may impart several different types of functionality depending on a particular type of application. Is it better, in the context of the pharmacopeias, to try to define the functionality-related characteristics for a particular material? Or, to define the types of functionality for a particular application and then to suggest tests that may be appropriate as a performance test?

One final point is that excipients are a very diverse group of materials with a diverse range of properties and functionalities. We still do not know in detail why many excipients work as they do. Can we define what we do not understand? Can we specify what we cannot define?

In some instances, product manufacturers have established a correlation between a product and/or manufacturing performance and some physicochemical property of a key ingredient. In such circumstances, the product manufacturer may request an additional test to be included in its specification for that ingredient.

**The perils of excipient lot selection**

As a short-term fix for existing formulations or, in some cases, as a longer-term strategy, excipient companies are frequently approached by customers to supply material to a tighter specification than the regular material. How valid is such an approach?

It is important to remember that many excipients are not produced using simple batch processing. Most of the large-use excipients are produced using some form of continuous processing (24–7 operation). For such manufacture, the lot number refers to a defined time in the plant, and the lot size is governed by the risk to the manufacturer of a recall. The capacity of such manufacturing plants is rated in thousands of tons per annum. The plants are operated to produce material that passes specification, but there is an inherent variability in the output that cannot be avoided. In addition, the pharmaceutical usage of many excipients is small in comparison with the overall output.
If the excipient manufacturer is approached to undertake extra testing to select the lot(s) to be delivered to a customer, what are the implications? This is represented schematically in Figure 3. We have assumed that upper and lower limits exist for the “functionality” parameter (performance parameter or functionality-related characteristic). In cases for which there is only an upper or a lower limit, the following discussion may be amended appropriately.

The three batches are represented in Figure 3a. The key issue is to understand how the inherent variability affects the “functionality.”

In Figure 3b, the effect of the variability is small in relation to the required specification. In this situation, there a negligible effect for either the excipient manufacturer or the user beyond the cost of the extra testing (of which more later). Nonetheless, this is frequently not the case.

The alternative scenario whereby only a proportion of batches meet the criteria is shown in Figure 3c. In this example, approximately 50% of batches meet the criteria. The schematics are idealized and show a very regular cyclical variation. Reality is not as regular, and the issue of how many lots must be tested to identify one lot that meets the criteria is economically important. In this example, three or four lots may need to be tested for each order.

Figures 3d and 3e are examples in which the required specification is at one or other extreme of the observed variability. In these examples, about 10% of excipient lots would meet specification, and 10 or more lots may need to be tested for each order.

In addition, the continuity of supply is an issue when lot selection is used. The excipient manufacturer may be forced to set aside particular lots for the particular customer to maintain supply continuity, which adds to the costs associated with the order. It is questionable in the circumstances depicted in Figures 3d and 3e whether lot selection is a viable strategy for supply and, thus, product manufacturing continuity.

Who pays for the extra testing?

Excipients, for the most part, are commodity items and are priced accordingly. Though some of the smaller-volume excipients are priced above $100/kg, most of the larger-volume excipients (e.g., microcrystalline cellulose and lactose) are less than $10/kg.
It is also important to understand how much of that amount is profit. Net profit for many excipients is about 5%. The market is competitive, with little room for slack. When the excipient user requests extra testing from its supplier, the economic effect can be considerable. It can mean the difference between profit and loss at these margins (see Table I).

The examples shown in Table I assume the following: the manufacturer does not routinely use the tests for the product and the equipment is not currently available (i.e., either the equipment must be purchased or the work contracted out by the supplier). Given the profit structures in Table I, any account taking less than about 50 tons per annum will scarcely break even that year, whatever the price of the testing. Under such circumstances, can we expect the excipient manufacturer to undertake the extra testing and stay in the pharmaceutical business? An alternative might be for the excipient purchaser to undertake the necessary testing.

**What happens if we lose suppliers of pharmacopeia-grade materials?**

If we make testing requirements too onerous for manufacturers, they may cease to supply material that is designated as pharmacopeia grade. If suppliers stop distributing USP or NF material, the consequences can be considerable for the excipient user, particularly in terms of regulatory updates, revalidation, and further stability.

The excipient user has two options: to change to a new supplier of the NF material or continue to purchase the material from the original supplier and do the necessary testing in-house and undertake the necessary auditing of the excipient manufacturing site on a regular basis.

Can it happen? It already has in the past few years. A major supplier of corn syrup NF ceased supplying material with the NF designation although it continued to manufacture to the same specification, in the same plant, and under the same quality management system. NF-quality propylene glycol stearate is no longer available. Propylene glycol stearate may not be a large volume excipient, but it was a major headache for companies using it in either investigational medicinal products or commercial products. The corn syrup issue had wider ramifications because many oral solution and suspension products are formulated using corn syrup.

**Ways forward**

We must improve the way we specify and test excipients. In part, this improvement will be the result of revisions to the monograph (e.g., to include more modern analytical techniques). But, we must consider the roles of the regulatory agencies and the pharmacopeias.
In the United States, FDA’s remit is to safeguard the public health. The USP–NF supports this effort through the development of official standards for pharmaceutical materials and products. The Pharmacopeia is concerned with the purity, safety, and efficacy of drugs and medicines. For excipients, the issues are really safety and adulteration. Is chemical purity, in the absence of pharmacodynamic effect, something with which we should be concerned?

Excipients are seldom “pure” materials. Most excipients, with the exception of those intended for parenteral or other similar products, are mixtures of materials. Their functionality arises from the presence of other components that are crucial to the performance of the excipient. These other components have been variously termed “essential minor components” or “functional components.” In the USP–NF, they are referred to as “concomitant components.”

The problem is testing and controlling these concomitant components. At the same time, we must keep any potentially toxic components to an appropriately low level. Unfortunately, we are probably not there yet. We do not always know which concomitant component (there may be several) is critical for a particular application, and we do not necessarily have methods suitable for routine measurement. Thus, we must continue to use performance tests for the foreseeable future.

So, what can be done? Obviously we must continue to develop our understanding of both materials and unit processes, and how they interact. Some recent initiatives such as the National Institute of Pharmaceutical Technology and Education may help. The pharmacopeias can also help by providing the necessary standardized methods for performance tests.

There appears to be broad agreement that such tests should not be mandatory and should not have limits imposed by the pharmacopeias. Nonetheless, there seems to be disagreement on how to incorporate such tests into the pharmacopeias. The European Pharmacopoeia appears to favor designating the appropriate tests in the individual monographs, but including the list in a “nonmandatory” section of the monograph. The USP favors a nonmandatory General Information Chapter approach based on what types of tests might be applicable for specific applications rather than a specific excipient. TriPEC’s (an umbrella international organization comprising the three regional Excipient Councils; the International Pharmaceutical Excipients Council of the Americas, the International Pharmaceutical Excipients Council of Europe, and the Japanese Pharmaceutical Excipients Council) position is straightforward. A harmonized approach is needed. Whether all these different views can be resolved easily remains to be seen.

Conclusion

This article is intended as an overview. Though many details could be discussed further, some broad conclusions can be drawn.
Performance tests (functionality-related characteristics) will be an issue for the foreseeable future. We must establish a harmonized approach to how they are incorporated into the pharmacopeias and what tests are appropriate for which applications.

There probably will not be any broad "fixes," and we must continue to develop our knowledge and understanding of materials and processes and how they interact to produce medicines that consistently meet the public’s expectations.

Economic issues must also be addressed. There is no advantage in having the best monograph possible if we cannot get material that conforms to it.

Robust formulations and processes will also be a critical issue moving forward, particularly in the context of QbD and the trend toward less-soluble drugs for which formulation robustness is more critical.

Although it is outside the scope of this article, the issue of how we will train our future formulation and development scientists also must be addressed.

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This article was developed from a presentation given at the Pharm Tech Annual Event in June 2006.

References


2. European Pharmacopoeia, draft proposal for a chapter on "Functionality-related Characteristics," (European Directorate for the Quality of Medicines).
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