Excipient Functionality

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"Excipient functionality" is one of the latest buzz phrases, but it is frequently used by those who have little understanding of the particular nature of excipients. Excipients are not active pharmaceutical ingredients (APIs) and they do not treat medical conditions. But without them, the therapeutic revolution of the past 50–60 years could not have occurred. The watchwords for APIs and finished products are—and rightly so—safety and efficacy. Although the emphasis on APIs and analytical chemistry has resulted in many very good methods for assay development and the determination of purity (including impurities), it is clear that we still lack the understanding and the means to determine why some materials behave in certain ways when included in a formulation (i.e., their functionality).

Functionality can only be properly assessed in the context of a particular formulation and manufacturing process. Because functionality is linked inextricably to the formulation and process, and all formulations are different, functionality per se is a matter for the excipient user and supplier. It would be impossible to establish a widely accepted standard for a particular excipient's functionality in a pharmacopeia monograph. One formulation's functionality can be another formulation's dysfunctionality.

However, certain excipient properties may relate to functionality in a more general sense and can be controlled. In effect, these functionally related characteristics (FRCs) are surrogates for functionality because they can be measured and limits can be set.

In some instances, special requirements exist relating to the route of administration of the drug product in which an excipient is used. For example, the approaches and considerations needed for the excipients used in parenteral products are very different from those for excipients used in conventional oral administration. However, in the context of functionality, those differences may be less important and will not be discussed in detail here. This discussion will focus on oral and other heterogeneous formulations in which functionality is more obvious than with parenterals and the size of the market has more potential for a greater economic impact.

With the advent of FDA's process analytical technologies (PAT) initiative, a basic paradigm is proposed that better-controlled products will result from improving control over the process. This improved control, in turn, will rely on a better characterization and understanding of excipients and the characteristics that affect their performance in the formulation and the process. However, process functionality and a finished product's performance may not be the same thing. For example, the amount of magnesium stearate required for lubrication and the amount that will cause changes in the dissolution of the finished product are different. PAT relates to process performances, not finished product performance. But in many instances, it will be necessary to balance opposing requirements. From the previous example, we require a thoroughly mixed blend of the drug and the carrier materials, but would we want to thoroughly mix (over mix) the magnesium stearate?

Sometimes excipients are available in different qualities that are colloquially referred to as grades such as technical or industrial grades. Outside the United States, the terms denote lower-quality materials that are not intended for pharmaceutical use. In this discussion, the term different grade means a different physical grade, not a different quality.

Many excipients for pharmaceutical use are available in different grades. Pharmaceutical grades frequently are differentiated by means of physical characteristics (e.g., the different grades of lactose and microcrystalline cellulose). They may also be chemically different (e.g., sodium starch glycolate and polysorbate esters). Particularly for excipients for which grade differentiation is determined by means of one or more physical characteristics, the reason for the grades is to change the performance characteristics of the excipient. Because we have separate grades with various...
In this article, the author discusses the concept of functional requirements criteria (FRCs) and how they can be included in pharmaceutical monographs. FRCs can be physical requirements or functional tests that are necessary to differentiate between pharmaceutical grades. The inclusion of FRCs is often difficult because they are not always included in the pharmacopeia monographs.

The author notes that the variability of excipients can be significant, and this variability can affect the functionality of a product. For example, the size of the particle can affect the flow properties of a product. The author suggests that the inclusion of FRCs can help to control the variability of excipients, but this does not always happen.

The author also discusses the importance of controlling the variability of excipients, particularly as it relates to the functionality of a product. The author notes that the variability of excipients can affect the performance of a product, and this can lead to problems for both the manufacturer and the consumer.

The article concludes with a discussion of the importance of controlling the variability of excipients, and the author notes that this is an important issue to consider when developing new products.
The key to a successful formulation is to understand the API, the excipients and the process, and in particular, their limitations. This is an important consideration when developing robust formulations. However, many companies have lost their experience formulation scientists for a variety of reasons, including early retirement plans, and many companies have had to rebuild their experience bases slowly. It is likely that the immediate effect of the loss of the formulators' knowledge was the development of less robust formulations.

Although the means of controlling an excipient's physical grade exists, it must also be noted that it is not known precisely what causes most excipients to perform the way they do. For example, at least ten different grades of microcrystalline cellulose exist (see Table 1). For most grades, there are also several suppliers. Several trends are evident:

- an increase in particle size reduces compaction properties
- an increase in particle size provides better powder flow
- an increase in bulk density reduces compaction properties
- an increase in bulk density increases powder flow
- a decrease in moisture content < ~3% reduces compaction properties.

However, it is also known that microcrystalline cellulose is not 100% pure cellulose; other materials such as hemicelluloses and sugar residues from hydrolysis are present. Findings from both academic and pharmaceutical studies indicate that these materials play an important role in the overall performance of microcrystalline cellulose. However, its performance may change as the source of the wood pulp, the pulping process, and other factors are altered.

The industry does not understand the interactions among these different factors and what is necessary for performance. It is clear that these "functional components" are not impurities or process residues; rather, they are an integral part of the excipient. Unfortunately, the determination of functional components is not always easy. For example, the determination of hemicelluloses in microcrystalline cellulose possibly could be achieved with the use of a solid-state quantitative FTIR; not a straightforward task. This type of scenario could be repeated for many excipients.

The question is how far can or should we go in our attempts to define excipients by means of monographs. If we go too far, manufacturers may find it uneconomical to continue supplying to the pharmaceutical markets, and innovation may be stifled. If we are too lax, we run the risk of causing problems for the excipient users in standardizing processes. To achieve the economies, a manufacturer typically will use the same plant to produce a material for all its needs and markets. Sometimes, this sharing means that food and pharmaceutical grades produced in the same facility are really the same material with a different set of tests (USP-NF or Food Chemicals Codex). For other materials, the plant in-process operating conditions may be tightened to enable pharmaceutical-grade materials to be manufactured (e.g., immediately after the deionized water resin have been recharged).

In summary, functionality testing cannot; in the author's opinion, be included in a pharmacopeia monograph. Certain tests, usually physical, can be used to differentiate among different pharmaceutical grades, and these might be included in a labeling or a non-specification section of a monograph. However, it is important to allow both the user and the manufacturer a sufficient amount of flexibility so as not to inhibit innovation. The inclusion of tests that are used to differentiate between different pharmaceutical grades seems reasonable. Going beyond this, unless safety concerns exist, it is likely to be counter-productive because there will be less incentive for suppliers to continue to produce materials that comply with the pharmacopeia specifications. The old adage, "Be careful what you ask for; you may get it!" comes to mind.