

Excipient Functionality

R. Christian Moreton



An excipient's functionality can only be assessed in the context of a particular formulation and manufacturing process.

"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 het-

erogeneous 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

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Table I: The principal grades of microcrystalline cellulose and their defining characteristics.

Grade	Nominal particle size (μ)	Bulk density	Moisture content (%)
pH 101	~55	medium	4–5%
pH 102	~110	medium	4–5%
pH 103	~55	medium	<3%
pH 105	<20	medium/low	4–5%
pH 112	~110	medium	<1.5%
pH 113	~55	medium	<1.5%
pH 200	~180	medium	4–5%
pH 301	~55	high	4–5%
pH 302	~100	high	4–5%
coelus	—	low	—

FRCs, we obviously have the means to control the grades, and thereby, the excipient. But sometimes, those physical tests are not included in the pharmacopeia. A key question for the inclusion of such tests in the pharmacopeia monograph is whether the tests that enable the differentiation of the available pharmaceutical grades—to the extent that it is wise for the pharmacopeias to use tests for functionality-related characteristics—are already included in either a General Chapter or in a labeling section of the pharmacopeia monograph.

For materials in which grades are differentiated chemically, the reasons for the grades can be either to cause a change in the excipient's performance in the formulation (e.g., polysorbate esters), or to avoid a chemical interaction that would compromise the product (e.g., sodium starch glycolate Type B). Sometimes, it is both reasons.

We have the means to control certain excipients in some ways, but there are different opinions about how to do so. Some experts believe that functionality should be a mandatory test in the monograph. Others feel that the tests that can differentiate between pharmaceutical grades are not appropriate for inclusion in a pharmacopeia. This author believes that the pharmacopeia monographs should include the tests that establish the safety of the excipient and include the tests that are necessary to differentiate between available pharmaceutical grades, but in a labeling section or an alternate section, which will allow the necessary flexibility, to include all different pharmaceutical grades in the monograph.

It is probably unwise for the pharma-

ceuticals to go beyond this measure because they do not have the expertise, understanding, or resources to do so. Including functional tests is straightforward for materials with grades differentiated by means of physical tests, but it is more difficult when the grades are chemically different.

For materials available in only one pharmaceutical grade, the inclusion of appropriate tests for FRCs is inherently less straightforward. In such circumstances, there will be considerable debate about which parameters should be tested and what the limits should be. Another trend is for excipient users to demand tighter specifications from their suppliers and lower prices. But concerns exist about whether we are getting to the stage at which users' demands are exceeding manufacturers' capabilities to deliver a product routinely that meets the tighter specifications. Another supplementary question that bears consideration is how far the excipient manufacturers can or should go to overcome the problems associated with poorly formulated products.

Excipients frequently are manufactured in dedicated plants on a continuous basis. In part because of the size of the plants, variability is an inherent part of any production process. For example, a temperature difference exists between the fluid coming into a pipe and the environment outside the pipe. Therefore, there will be a temperature variation across and along the pipe. For a 1-in. diameter pipe, the variation across the diameter of the pipe could be quite small (ignoring, for the purposes of this discussion, the differences between laminar and turbulent flow). However, for a 12-in. diameter pipe, the potential exists for a much greater variation in the temperature across the diameter of the pipe.

Some plants produce tens of thousands of tons of excipients each year for various industries. There will be some inevitable differences between batches, but it is vital

that this variability is kept within acceptable limits. Because the pharmaceutical market may only represent a small percentage of a manufacturer's total production volume, it can be difficult to persuade a company to work with unnecessary tight controls for a small part of its output. If these demands become unreasonable, the manufacturer may simply decide to withdraw from the pharmaceutical market, or to drop its pharmacopeia designation. This scenario recently occurred in the United States with a supplier of Liquid Glucose NF, although for reasons other than tighter specifications. Whenever this situation occurs and for whatever reason, the excipient user is put in a difficult position, particularly if no alternative source of pharmaceutical-grade material is available.

Other important concerns that bear directly on FDA's PAT initiative are the extent to which an excipient's quality can be improved without overburdening its price and whether customers' demands for tighter specifications are now exceeding the capability of the process. This scenario will vary for each excipient, but it is an important point. If a manufacturer selects batches for a particular customer because of a tighter agreed specification, the other batches should be suitable for other customers. But if the specification generally becomes tighter, the supplier may find that it only can use every second batch, for example. The remaining unusable batches must be either reprocessed or reworked, if permitted, thereby increasing costs.

In a large, dedicated plant, the size of the equipment implies a certain capacity, which also should not be ignored. Several years ago, the author was working for an excipient supplier and the company was approached by a customer for a tighter size-specification for a product. The customer was asked about its potential for commercialization because the quantity used in development would be small. The reply was that it could be quite a big product and the customer might buy 500 kg/year when the market was established. The client was very surprised to learn that the smallest batch the facility could produce was ~10 tons because of the size of the dedicated plant. The customer realized that this was an uneconomic proposition

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and decided to consider an alternative formulation.

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 experienced 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 I). 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 $< \sim 3\%$ reduces compaction properties.

However, it is also known that microcrystalline cellulose is not 100% pure α -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

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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 resins 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. **PT**

Calendar

May 2004

10-13: Facility Qualification, Elizabeth, NJ.
Contact: Institute of Validation Technology, tel. 561.790.2025, fax 561.790.2065, registration@ivthome.com, www.ivthome.com/conferences

11-12: Measuring and Predicting pKa and log P; Pharmaceutical Excipients; Philadelphia, PA.
Contact: Barnett Educational Services, tel. 800.856.2556, ext. 2200, fax 610.565.4584, customer.service@parexel.com, www.barnettinternational.com

12-13: VelQuest Event: International Meeting on Automated Compliance Systems, New Brunswick, NJ.

Contact: VelQuest Corp., 35 South St., Hopkinton, MA 01748, tel. 508.497.9911, fax 508.497.2396, info@velquest.com, www.velquest.com

13-14: Aseptic Processing; CAPA/Root Cause Analysis; Philadelphia, PA.

Contact: Barnett Educational Services, tel. 800.856.2556, ext. 2200, fax 610.565.4584, customer.service@parexel.com, www.barnettinternational.com

16-19: 2004 AAPS National Biotechnology Conference, Boston, MA.

Contact: American Association of Pharmaceutical Scientists, 2107 Wilson Blvd., Suite 700, Arlington, VA 22201, tel. 703.243.2800, fax 703.243.9650, pr@aaps.org, www.aapspharmaceutica.com

17-18: Pharmaceutical Microtechnology World Summit, San Diego, CA.

Contact: Strategic Research Institute, L.P., 333 Seventh Ave., Ninth Fl., New York, NY 10001-5004, tel. 212.967.0095, fax 212.967.7973, info@srinstitute.com, www.srinstitute.com

17-21: 2004 PDA International Congress, Courses, and Tabletop Exhibits, Singapore.

Contact: Parenteral Drug Association, 3 Bethesda Metro Center, Suite 1500, Bethesda, MD 20814, tel. 301.986.0293, fax 301.986.0296, info@pda.org, www.pda.org

19-21: Interphex Japan/Pharma IT Solutions Expo, Tokyo, Japan.

Contact: Reed Exhibitions Japan Ltd., 18F Shinjuku-Nomura Bldg., 1-26-2 Nishishinjuku, Shinjuku-ku, Tokyo 163-0570, Japan, tel. +81 3 3349 8509, fax +81 3 3349 4900, interphex@reedexpo.co.jp, www.interphex.jp/english/it

24-25: Lyophilization; Blend Uniformity; Philadelphia, PA.

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