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Commentary

Functionality related tests for excipients[1]

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1. Introduction

An excipient has been defined (Pharmacopoeial Forum, 1995;21:863) as 'any component, other than the active substances, intentionally added to the formulation of a dosage form'. It is not defined as an 'inert' commodity nor as an 'inert' component of a dosage form. It has been known for many years that excipients are not necessarily pharmaceutically inert. For example, bioavailability of phenytoin was shown to be dependent on the diluent used in capsule fills (Tyrer et al., 1970), and the increase in hydrophobicity of tablets caused by the lubricant magnesium stearate is well known (Bolhuis and Lerk, 1977).

With active materials, there is initially usually only one source, and it is that one manufacturer who 'sets the standard'. This standard can later form part of a pharmacopoeial monograph, which will in turn become an international standard which subsequent manufacturers will adopt. This is also true of a few excipients. They may emanate from one manufacturer, but as patent protection runs out, they become available from other sources. Thus most excipients are likely to be available from a multitude of sources.

A further point to bear in mind is that excipients are usually produced by a batch process, with the possibility of batch-to-batch variation from the same manufacturer. The 18th edition of the National Formulary draws attention to this: 'Because of differing characteristics not standardised by this formulary, all sources and types of some excipients may not have identical properties with respect to use in a specific formulation. To assure interchangeability in such circumstances, users may wish to ascertain final performance equivalency or determine such characteristics before use'. Such tests are thus related to the function that the excipient is carrying out in a specific formulation.

2. Pharmacopoeial standards and functionality tests for excipients

Some years ago, it was appreciated that there was an urgent need for harmonisation in the

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excipient field (Halperin and Grady, 1995). A meeting took place in Williamsburg in 1989, which ultimately led to the formation of The International Pharmaceutical Excipients Council (IPEC) (Blecher, 1991). After the Williamsburg meeting, pharmaceutical manufacturers were asked the following questions:

- Which excipients have been the source of problems or delay?
- What are the candidates for the top ten excipients for harmonisation?
- Has it been necessary to repeat stability or bioavailability studies because of differences in standards for excipients?

From the response to these questions, a list of the 'top ten' excipients was compiled and is given below (Halperin and Grady, 1995). The list was later extended to twenty five excipients.

Magnesium stearate
Microcrystalline cellulose
Lactose
Starch
Cellulose derivatives
Sucrose
Povidone
Stearic acid
Dibasic calcium phosphate
Polyethylene glycol

The example which has been chosen to highlight the current situation is microcrystalline cellulose. It ranks second in the 'top ten' list cited by Halperin and Grady (1995), and is a widely used excipient in solid dosage forms. Originally introduced by FMC as Avicel in the 1960s, it is now available from a number of sources. There have been many reports of differences in the properties of microcrystalline cellulose, depending on the source. See, for example, Doelker, 1993; Landin et al., 1993a,b; Podczeck and Revesz, 1993).

2.1. Pharmacopoeias

Table 1 gives the list of tests in monographs for microcrystalline cellulose which were given in the original versions of the 1993 British Pharmacopoeia (official from December 1st, 1993) and the 18th edition of the National Formulary, which became official on January 1st, 1995. In the BP 1993, microcrystalline cellulose is described as a 'pharmaceutical aid'. Specific uses are not mentioned because the pharmacopoeias are primarily books of analytical standards which enable the identity and purity of the substance to be established. Note the different array of tests in the two publications. Even when the same test is apparently in both, subtle differences may be present, highlighting the urgent need for harmonisation.

2.2. Handbook of pharmaceutical excipients

Both the chemical and the physical properties of some 200 excipients are contained in the Handbook of Pharmaceutical Excipients (2nd edition, The Pharmaceutical Press, 1994). Table 2 lists data for microcrystalline cellulose.

In addition to providing data useful to the formulator, the Handbook also provides details of the methodology used to obtain some of that information. These are the 'described methods' as indicated in Table 2. No attempt was made by the editors of the Handbook to impose standardised methods. Indeed this would have been impossible since monographs in the Handbook were compiled by a group of knowledgeable volunteers who

Table 1
Compendial specifications for microcrystalline cellulose

	BP 1993	NF 18
Characteristics		
Colour	+	
Odour	+	
Particle size	+	
Acidity/alkalinity	+	
Solubility in ammoniacal solution of copper tetrammine	+	
Ether soluble substances	+	
Water soluble substances	+	+
Starch and dextrins	+	+
Heavy metals	+	+
Organic impurities	+	
Loss on drying	+	+
Sulphated ash	+	
Assay		+
Identification	+	+
pH		+
Residue on ignition		+
Organic volatile impurities		+

Table 2
Data in the Handbook of Pharmaceutical Excipients relating to microcrystalline cellulose

Description
Pharmacopoeial specifications
Angle of repose
Bulk density*
Tapped bulk density*
Density*
Flowability
Melting point
Moisture content*
Mean size
Solubility*
Specific surface area

* Signifies a 'described method'.

in turn collected information from published sources, or obtained it themselves using the techniques they had available to them. Thus, for example, there are ten methods described for the determination of particle size distribution (Table 3). None of these methods is necessarily 'wrong'. What is undoubtedly true is that if two or more of these methods had been used on the same material, it is possible that different results would be obtained (and which would have been the 'correct' result?). The Handbook quotes sieve data for several grades of microcrystalline cellulose, but no details are given of the method which was actually used to derive the data.

It must be pointed out that these are not standards. Indeed in its introduction, the editors of the Handbook emphasise this point, and stress that the Handbook has no official status. It must also be noted that these are not tests for functionality either. There is no test for the function for which microcrystalline cellulose is being added to the formulation.

Table 3
Methods for the determination of particle size distribution (PSD) described in the Handbook of Pharmaceutical Excipients

PSD	Method
1	Shaking sieves
2	Shaking sieves
3	Shaking sieves
4	Shaking sieves
5A	Air-jet sieving
5B	Wet sieving
6	Shaking sieves
7	Air permeability
8	Sedimentation
9	Microscopy

2.3. USP advisory panel on physical test methods

The Handbook of Pharmaceutical Excipients describes a range of test methods with no attempt at standardisation. The USP has taken the process a stage further, in that it has proposed a series of standardised physical test methods.

These are:

- Particle characterisation by microscopy (Amidon, 1992)
- Particle size distribution by analytical sieving (Marshall, 1993)
- Reporting particle size distributions (Brittain, 1993b)
- Specific surface area determination by dynamic gas adsorption (Grant, 1993)
- Density of solids (Augsburger and Amidon, 1994)
- Bulk density and tapped density (Bergren, 1994)

It must be stressed that these are still not 'functionality' tests. It is not the function of a solid to have a particle size distribution—it is a property of the solid. There is a danger of confusion here. It is of interest to note the title of the body set up by the USP. It was originally called 'the USP advisory panel on physical test methods—functionality' and this title was used in its first report on particle characterisation by microscopy (Amidon, 1992). In subsequent reports, the word 'functionality' is omitted from the title.

Brittain (1993a), who is a member of the USP advisory panel, has described the tests and the thinking behind them. However the title of his article is 'Functionality testing of excipient materials', which adds to the confusion.

One of the prerequisites of standardised tests is that both apparatus and technique must be fully defined. Thus one technique is selected to the exclusion of other methods which might be equally valid. Presumably the chosen method

reflects the preferences of the compiler of the report, or is the apparatus to which he has access. Compare this to the range of methods used in the Handbook of Pharmaceutical Excipients. A good example would be the choice of dynamic gas adsorption for the measurement of surface area. There are several other methods for measuring surface area—static gas adsorption, porosimetry, permeametry—which could have been selected. They will all probably give different results to dynamic gas adsorption because they are measuring different things.

It would be more accurate to call such tests functionality-related tests. A measurement is being made of a property of an excipient which it is reasonable to believe has an influence on that excipients function. A good example occurs in the recently published fifth supplement of the 18th edition of the National Formulary. The monograph for microcrystalline cellulose stipulates that the label of this substance should give information regarding bulk density and degree of polymerisation. The same monograph then specifies methods for determining these properties, though interestingly, the method used for the measurement of bulk density differs from that described by Augsburger and Amidon (1994).

2.4. Functionality tests

If true functionality tests are to be introduced, then there must be two prerequisites.

2.4.1. The real function of the excipient must be known

When microcrystalline cellulose was first introduced, it was as a direct compression tablet diluent. However other uses for this material have subsequently been found, for example as an extrusion aid in the spheronisation process (Fielden and Newton, 1992). It would therefore be pointless specifying tests for microcrystalline cellulose which were appropriate to its diluent function but irrelevant to extrusion. In other cases, the true role might not be so obvious. Consider lactose as further example. In a hard shell capsule, it is present as a diluent. In a tablet, its function may solely be that of diluent, but it may also be an aid to tablet manufacture. On the other hand, what is the function of lactose in a dry powder inhaler—purely a diluent, or does it have a more active role and contribute to the therapeutic efficacy of the product? If the latter, what properties of the lactose contribute to this function?

2.4.2. There must be a specified and standardised method for carrying out the test

The difficulties involved in devising such a test could be immense.

Let us assume that microcrystalline cellulose is to be used as a direct compression diluent. How would a true functionality test be devised for that material if it had to be of universal applicability as opposed to an 'in-house' test for a particular company?

Probably a relationship between compression pressure and tablet breaking strength would be constructed.

All the following would need to be defined:

- Rotary or eccentric tablet press
- Speed of operation of the press—microcrystalline cellulose is known to be sensitive to changes in punch speed (Armstrong, 1989).
- Tablet dimensions
- Range of compression pressures
- Method of measuring tablet breaking strength, including full details of the apparatus to be used
- Lubrication—microcrystalline cellulose, being a plastically deforming material, is sensitive to changes in lubricant concentration and method of incorporation.
- Dilution potential—measurement of the 'capacity' of microcrystalline cellulose by incorporation of a 'standard' drug—the identity properties of which would need to be established
- Disintegrant activity

3. Conclusions

There is undoubtedly a need to characterise excipients as fully as possible. However devising true functionality tests of excipients as opposed to tests which may be related to function, must be

approached with caution. The actual function of the excipient must be known, a relevant property identified, and a truly unambiguous and clearly defined test devised. Only then can such functionality tests appear in compendia which, at least in some parts of the world, have a statutory function.

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