



Pharmaceutical excipients – the continuing paradox(es) of formulation science.

R. Christian Moreton*

FinnBrit Consulting

Editorial

KEY WORDS: Quality by Design, QbD, excipients, excipient variability, new excipients

One of the paradoxes of pharmaceutical formulation science is that, although excipients do not treat the disease, the disease cannot be treated without them. Not only that, but we add to the paradox (compound the felony?) by asserting that they are only inert carriers, and consequently classify them as commodities, with all that such a classification implies.

Unformulated, most bulk active drugs (APIs) are not particularly useful to the patient. It is only when they are converted into medicinal products that they become useful. Excipients are used to help convert APIs into medicinal products that can conveniently be taken by, or administered to, patients. Unless a drug can be delivered to the patient in the correct amount, at the correct rate, consistently within a batch and from different batches, and over the shelf-life of the product (i.e., a robust product) the patients' best needs will not be served (for therapeutic efficacy, safety and/or cost).

So how can the chances of developing robust products be boosted? The answer lies in improved (enhanced?) knowledge and

understanding of excipients, APIs and unit operations involved in the manufacture of the medicinal product, how they interact to produce robust formulations and products, and the variability within all this. This gets to the essence of Quality by Design (QbD) in the pharmaceutical industry.

Excipients are an important part of nearly all medicinal products. They have the potential to impact the release of the API from the formulation, both *in vitro* and *in vivo*. Isn't this the whole idea behind modified release? They also have the potential to impact the stability of the API, the drug product manufacturing process, and its consistency. Since these characteristics are the essence of a robust formulation, it makes sense to treat excipients as more than inert carriers, because they have the potential to make or break a formulation development project.

In order to develop robust pharmaceutical products we have to be able to produce product that consistently meets specification and provides the requisite efficacy. Thus, it will be necessary to address variability of the product, which will, in turn, be comprised of the variability of the API, excipients and processing, and in how they interact together.

* Corresponding author: R.C. Moreton, FinnBrit Consulting, 29 Shawmut Road, Waltham, MA 02452, Tel: +1 - 781 894 2572, E-mail: info@finnbrit.com

Focusing on excipient variability for the moment, the question is how can it be incorporated into the Design of Experiments in QbD formulation projects?

Before everyone starts contacting their suppliers and demanding batches at the limits of specification for whatever key parameters they consider important, please be aware that the manufacturer is unlikely to have samples that will cover the excipient users' every need. Many excipients are manufactured using some form of continuous processing, and the excipient manufacturing plants are designed to produce the material at the center of specification.

Continuous processing plants tend to run at a 'steady state', in effect they operate in a state of dynamic equilibrium. If a change is made at one stage in the process, then likely a compensatory adjustment has to be made elsewhere. This means that, even if the process is adjusted for one parameter in the specification, the other specification parameters could not be kept constant (within the limits of normal variation) resulting in a change in another. This also applies to batch manufacturing where changing set parameters will require, for example, QA involvement and approval, etc.

Each excipient application (formulation or pharmaceutical product) is different. There will be subtle differences in the performance required of the excipient, and the excipient's critical material attributes will be different, or require different limits. The excipient manufacturer is not going to be able to provide samples that cover every possible extreme of specification for all customers. In addition, the excipient manufacturer may not know precisely how their excipient is being used. It may not be possible to manufacture material to cover the desired variability in some instances due to the limitations of the manufacturing equipment and process (whether for batch or continuous processing).

Even before asking for samples, it is a good idea to identify exactly what you want to achieve, how you can achieve it, select potential excipients, and then to assess what characteristics of those excipients have the potential to impact product manufacturability, stability and *in vivo* performance, i.e., what are the critical material attributes for the excipient in the particular application. Then you can begin to plan your Design of Experiments (DoE), etc.

However, you still need to incorporate excipient variability into your DoE. If the excipient manufacturer cannot help, what other options do you have? Under QbD there may be several. They may not be perfect, but they may get you to where you need to be (but perhaps not necessarily where you 'want' to be!). The difficulty may be in persuading the excipient users to forgo their dreams of the perfect DoE, and accept a workable compromise because, with the best will in the world, the excipient manufacturer will not be able to provide all the samples the user wants.

IPEC-Americas' QbD Committee has been working to find a solution to this dilemma, and they are close to issuing a Guide to the Appropriate Selection of Quality by Design Samples of Excipients for use in Pharmaceutical Formulation Projects. As with all IPEC Americas Guides, this is a consensus document meaning that there were both users and excipient manufacturers involved in the preparation of this Guide. While it may not be perfect, it will at least provide some suggestions as to how to obtain the necessary samples that better meet the formulation scientist's requirements. The IPEC-Americas' Guide is expected to be available in the first half of 2014.

The advent of QbD for pharmaceutical formulation development has obviously raised the general awareness of excipients, and for that we must be grateful. There has also been an increasing awareness of the need for new

excipients, particularly for formulating newer drugs where the existing excipients are not able to allow sufficiently robust formulations to be produced. The term new can have many meanings but for the purposes of this discussion, new means an entirely new chemical entity.

There is, however, a major dilemma with the introduction of new excipients since in the US there is currently no process whereby an excipient can be approved by the FDA ahead of first use in a pharmaceutical formulation or product. Currently, excipients are 'approved' in that they have been included in an approved New Drug Application (NDA) or Abbreviated New Drug Application (ANDA), and the acceptable levels of maximum incorporation are given in the FDA's Inactive Ingredient Database (IID). For a new excipient, there is no precedence of use, and thus no established acceptable levels of maximum incorporation. For the purposes of a safety assessment, excipients are no different from APIs, and the FDA has a Guidance document (1) which details the studies that will be required before the FDA would consider approving a formulation containing a new excipient. The dilemma is that without some form of formal approval by the FDA of the safety data package for the new excipient, would any company want to risk their new drug approval by using a new excipient?

There have been very few new chemical excipients launched in the last 20 years. There have been several new co-processed excipients, and several new grades of existing excipients, but by the definition used in this discussion document these are not new chemical excipients. So, as the essence of the dilemma, everyone claims to be interested in the potential for new excipients, but no one wants to be first, to pave the way. This has not really changed in the last 20 years. In addition, without being able to 'piggy back' the excipient safety studies onto the drug safety studies, the development time lines are such that the patent would likely have expired before the drug product can be

launched, and there is no exclusivity period for a new excipient as there is for new drugs (2).

The focus then becomes on how the introduction of new excipients can be justified commercially? It is interesting to note that from a regulatory perspective, nothing much has changed since this question was asked in 1996 (2). IPEC-Americas has introduced a New Excipient Evaluation Procedure in an attempt to alleviate the problem. Under this procedure, the excipient safety data package would be evaluated by a panel of independent expert toxicologists who would assess if the safety data package was of a standard that would likely be accepted by the FDA. The New Excipient Evaluation Panel is administered separately from IPEC-Americas to maintain its impartiality. The FDA has been aware of this initiative from the beginning. They looked at the first excipient that was reviewed and were in agreement with the report of the expert panel. Several companies have used this procedure, both for new excipients, and to assess the suitability of the safety data packages to support the use of increased levels of existing excipients (beyond those listed in the IID). However, this is not approval by the FDA, only an assessment that the FDA is likely to accept (or reject) the safety data package.

There is now a project to look at the possibilities for prior FDA approval of new chemical excipients. Preliminary suggestions include the development of a user fee system analogous to that applicable to ANDA applications under the Generic Drug User Fee Act (GDUFA). It is early days, but the initiative is to be encouraged. If successful, this would represent a significant step forward in easing the development and commercialization of new excipients.

REFERENCES

- 1 Guidance for Industry: Nonclinical Studies for the, Safety Evaluation of Pharmaceutical Excipients, U.S. Department of Health and

Human Services, Food and Drug Administration, Center for Drug Evaluation and Research (CDER), Center for Biologics Evaluation and Research (CBER), May 2005. <http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/>

- 2 Moreton, R.C., Tablet excipients to the year 2001: A look into the crystal ball, Drug Dev. Ind. Pharm., (1996), 22, (1), 11 - 23.