Excipient data for the modern era of drug product formulation.

R. Christian Moreton*
FinnBrit Consulting

Editorial

KEY WORDS: Excipients, excipient variability, excipient characterization, future needs, quality by design

The range of pharmaceutical drugs continues to increase, as does the range of types of formulation. The past 50 years have seen advances in the treatment of many types of disease and the range of drug molecules has expanded from small molecules, and some peptides (e.g., insulin) to include higher molecular weight small molecules, oligopeptides, proteins and monoclonal antibodies. Many of the vaccines have been around for a long time, but even these are changing as it has been possible to improve their effectiveness, reduce side-effects and target new diseases.

The majority of the excipients that are in use today are those that were around 50 years ago. There have been some new excipients in the past 40 years, but precious few. For the most part the industry is still using what might be termed 'traditional' excipients. These traditional excipients have served patients well, and will continue to be used by formulation scientists. However, in this modern era of Quality by Design (QbD), continuous pharmaceutical product manufacture, and advanced therapeutic products and delivery systems, there is a need to better understand all excipients, new and old, in order to be able to formulate robust medicinal products.

A generally accepted definition of a robust medicinal product is a medicinal product which will meet the requirements of the Clinical/Quality Target Product Profile and be able to accommodate the typical variability seen in the drug substance, excipients and drug product manufacturing processes.

It is this author's long held belief that not enough is known about any of the excipients used today. For example, it is still not known precisely why microcrystalline cellulose (MCC) works or how its variability arises. It is, for instance, not known if it is possible to adjust the MCC manufacturing process for even better performance, without resorting to co-processing. New information is still being discovered about very commonly used excipients. For example, in a recent paper, Delaney *et al.*, (1) were able to show differences in commercial samples of magnesium stearate using ^{13}C solid state nuclear magnetic resonance (^{13}C-SS-NMR). These differences were related to the differences in the content of various hydrates and other forms of magnesium stearate. It is well known that magnesium stearate is an awkward excipient. Should the content of the different forms of magnesium stearate be something that should be checked when looking for an alternate source, or even on a routine basis in order to obtain information on the variability of the existing source material?

*Corresponding address: 29, Shawmut Road, Waltham, MA 02452, USA, E-mail: TheMoretons@usa.net, Tel: (+1) 781 894 2572

There is a need to understand a lot more about excipient variability (common cause variation). It is known that variability in an excipient Critical Material Attribute (CMA) has the potential to impact the finished product Critical Quality Attributes. However, the pharmaceutical industry is still woefully ignorant of the origins or causes of excipient variability.

From the above discussion, it should be clear that there is still a lot to be learned about excipients, both new and old. In the past, excipient research has tended to focus on parameters directly linked to performance, e.g., compaction profiles. Going forward, while performance must always be considered, consideration should also be given to investigating excipients using more fundamental methods such as, the different forms of spectroscopy available and thermal methods on a routine basis. This would be a proactive data gathering exercise which would naturally incur some cost, but without such data, we will continue to be surprised when things go wrong. If there was such a set of data, it would make it easier to investigate certain out-of-trend and out-of-specification issues. In addition, it would likely also provide further understanding of the excipients and highlight differences between excipient sources, and even different batches. It may be possible, for certain formulations, to correlate differences in the excipient characterization results with differences in product performance during development, and possibly during commercial manufacture.

There is still a need to physically characterize excipients better. Additionally, there is also a need to think about how the excipient is being used in order to determine the appropriate method to be used. Particle size is a good example; there are many methods each giving slightly different results. For example, is sieve analysis really the best method to use for a lactose intended for inhalation? Surface area is another example; is nitrogen absorption always the best method to use? If you are looking at adsorption of drugs onto activated charcoal, possibly nitrogen absorption is appropriate, but not if you are looking at ordered mixing of solids where envelope surface area of the carrier material may be more appropriate.

Even with a well designed and executed Design of Experiments, taking into account all imaginable excipient performance variabilities, there is still the potential for unexpected product failure due to special cause variation. The application of these non-traditional excipient characterization method could provide pointers to the origin(s) of the special cause variation and would thus assist in the root cause investigation.

When continuous manufacture of finished pharmaceutical products is under consideration, being able to predict the consequences of variability in a particular excipient characteristic may be the difference between success and failure of continuous manufacturing for the product. Besides being able to avoid certain batches or sources of an excipient, it may also be possible to compensate for the variability by some other means. For example, if there were a means to continuously assess blend particle size distribution, it may be possible to adjust the amount of magnesium stearate added at the lubrication step of the process.

Generating relevant data on all excipients is beyond the scope of any one organization, industrial or academic, but all have the need for it. So how can the data be made available so that everyone benefits? Obviously, the data would need to be published, and this journal would be an excellent place for such information to be distributed. In some instances, the information could be in the form of a full scientific paper, in other instances, it may be more appropriate to consider a technical note. This latter approach may be beneficial for industrial organizations where intellectual property concerns regarding the drug product may prevent the publication of a full paper.

REFERENCES

1 Sean P. Delaney, Matthew J. Nethercott, Christopher J. Mays, Nickolas T. Winquist, Donia Arthur, Julie L. Calahan, Manish Sethi, Daniel S. Pardue, Junghyun Kim, Gregory Amidon, and Eric J. Munson, (2017), Characterization of Synthesized and Commercial Forms of Magnesium Stearate Using Differential Scanning Calorimetry, Thermogravimetric Analysis, Powder X-Ray Diffraction, and Solid-State NMR Spectroscopy, J. Pharm. Sci., 106(1), 338-347.