International Journal of Advances in Pharmaceutics

Journal home page:http://ijap.ssjournals.com

Review Article

Optimizing Tabletting Processes with Quality by Design: An Overview

Nwoko Valentine E

[*]Production Pharmacist, Pharmatex Industries, Lagos, Nigeria

***Correspondence Info:**

Nwoko Valentine E
Production Pharmacist, Pharmatex Industries, Lagos, Nigeria
Email:valentinenwoko@yahoo.com

Keywords:

control strategy, critical material attributes, critical process parameters, design space, quality by design,

Abstract

The elements of quality by design are examined and a consistent nomenclature for quality by design, critical quality attribute, critical process parameter, critical material attribute, and control strategy is proposed.

A process is well understood when all critical sources of variability are identified and explained, variability is managed by the process, and product quality attributes can be accurately and reliably predicted over the design space. Quality by Design (QbD) is a systematic approach to development of products and processes that begins with predefined objectives and emphasizes product and process understanding and process control based on sound science, statistical methods and quality risk management. In an attempt to curb rising development costs and regulatory barriers to innovation and creativity, the FDA and ICH have recently started promoting QbD in the pharmaceutical industry. QbD is partially based on the application of multivariate statistical methods and a statistical Design of Experiments strategy to the development of both analytical methods and pharmaceutical formulations. The talk will review the basics of QbD with case studies from the pharmaceutical industry

1. Introduction

As the industry focuses on better manufacturing efficiency, there is greater interest in identifying powder properties that directly influence tabletting in-process performance and final product quality. Particle-size distribution is a critical primary particle characteristic of powders, but it is only one of many variables that impact bulk powder properties, which in turn dictate in-process behaviour and product quality[1]. Bulk property measurements can be an efficient way of accelerating and supporting process optimization studies because they quantify the net effect of all primary particle properties (e.g., size, shape, texture, surface energy and porosity), whether these can be measured directly or not. Furthermore, even if all primary particle properties that influence in-process behaviour could be measured, the mathematical relationship between bulk powder behaviour and particle characteristics remains elusive and highly complex. Hence, the most effective way forward is to measure process relevant characteristics of the bulk powder.

Tablet production can be divided into at least four discrete processes :

- Discharge from the hopper
- Flow into and through the feed frame
- Die filling
- Compression

Each of these processes subjects the powder to a specific set of environmental conditions (e.g., flow rates, stresses,

and equipment surface properties), making different bulk properties more relevant at different stages. I would highlight the following as especially valuable:

- Dynamic flow properties (including Basic Flowability Energy, Specific Energy, Aerated Energy, and Flow Rate Index): to optimise the flow regime in the feed frame and the efficiency of die filling, to investigate the effect of paddle geometry, to assess the likelihood of attrition, segregation and agglomeration.
- Shear properties: for optimising flow from the feed hopper, where shear properties of powder–powder and powder–wall are important.
- Permeability and compressibility: for assessing how easily the powder can transmit air and the impact of compression on the powder. Both characteristics are important during the filling and compression steps.

Success in tabletting does indeed depend on many factors. It is important, for example, to control the flowabilty and compressibility of the tabletting blend, as well as any tendency towards segregation, to ensure the production of uniform tablets at the required rate. Particle size and particle size distribution are recognised as critical material attributes because they are known to directly impact these properties, as well as others such as solubility and bioavailability, which may define clinical efficacy as highlighted in ICH Q6A.

As analytical techniques evolve, however, it is becoming easier to identify other parameters that also impact behavior in the tablet press. Highlighting particle shape, a parameter that, like particle size, is known to affect powder flowability and segregation. In the past, shape information was gathered by microscopy, but the advent of automated imaging has made it much faster and easier to access statistically relevant data. Such information forms a foundation for scientific investigation of the impact of shape and supports the development of more successful tabletting blends.

2. QbD approaches to tabletting and granulation processes

QbD calls for product quality to be 'designed in' rather than tested for in postproduction. It requires a detailed understanding of all the factors that can impact product quality and clinical efficacy, including those related to the materials employed and the process itself. Traditionally, it has been assumed that raw materials and intermediates can be suitably qualified and the process can be fixed, resulting in a consistent high-quality product[2]. However, this is only achieved by knowing what material properties need to be qualified. While particle size distribution is important, there are many other particle properties that rarely feature in the specification, but that can be as influential as particle size, such as particle shape and particle surface roughness[3]. Excluding these properties from the quality specification allows variation in raw materials to go undetected, resulting in variable in-process performance and product quality. Adopting a QbD approach requires an acceptance that raw materials are likely to vary batch to batch, while simultaneously demonstrating a good grasp of how to configure the process settings within the 'control space' to accommodate the unavoidable variation in material properties, and ultimately achieve consistent product with the desired attributes.

Considering a granulation process as an example, this might conventionally be defined in the following terms: process for A minutes at an impeller speed of B rpm, whilst adding C% of water at a consistent addition rate. Processing conditions are essentially fixed and applied to each new batch of feed. This means that there is little flexibility to respond to variability arising from any source, such as a new batch of excipient or inadequate control of an upstream operation, for example. Furthermore, problems are usually detected only when granulation is complete.

QbD places emphasis on controlling process output, rather than the fixed definition of operating conditions. For granulation, the process definition might change to: manipulate impeller speed, amount of water, and/or processing time, to produce granules with these specific properties. Adopting this approach, however, relies on being able to identify those specific properties—the criteria for success—and also learning how to control them.

In the same way, in tabletting, a QbD approach would focus on the defining characteristics of the finished product, such as content uniformity and dissolution or disintegration properties. Process development then works back from that point, identifying all the factors that influence these properties.

Successful implementation of QbD relies on understanding both the process and product in detail[2]. The focus is on fully evaluating the impact of all variables that influence product quality, and learning how to control them effectively, rather than just identifying a manufacturing route that works. QbD extends through to control of the commercial process so it serves to highlight areas where real-time monitoring can be beneficially applied to meet processing targets.

One important feature of particle size analysis is that, unlike many analytical techniques, it is already a proven technology for real-time plant monitoring. In granulation processes, for example, both in-line probes based on spatial particle velocimetry and on-line laser diffraction particle size analysers are regularly used for real-time measurement. Both

enable the continuous tracking of particle size growth during the granulation process towards an established endpoint.

Endpoint detection is a notoriously difficult aspect of granulation so this ability to continuously monitor particle size is extremely useful when manufacturing to meet a defined output, as advocated by QbD. In addition, however, real-time measurement is extremely valuable during design space scoping studies because it enables rapid and reliable assessment of the impact of a change in operating conditions. Continuous particle-size measurement can therefore accelerate and improve the process development studies associated with QbD[1].

3. Key challenges in understanding particle attributes in a tabletting and granulation process

The bulk properties that define process ability depend on a wide array of particle attributes, such as particle size and shape, roughness, surface charge, density and porosity. Learning how to control tabletting and granulation processes relies, in part, on understanding the relationships between particle attributes and bulk powder properties[4,5].

This is an area of specific interest and involved in a number of experimental studies, with industrial partners, to investigate, for example, the influence of particle size and shape, and of surface charge, on powder flowability, shear properties and bulk parameters, such as compressibility and permeability[6,7].

Because QbD places emphasis on thoroughly understanding the impact of all processing variables, it may call for information that is not easily accessed using conventional testing methods. As a result, the implementation of QbD is encouraging the pharmaceutical industry to adopt new analytical technologies as they become available(8). One such technology is morphologically directed imaging, which can combine imaging technology with spectroscopy, such as Raman, to provide chemical identification alongside size and shape measurement. It allows different particles in a dispersed sample, often initially screened on the basis of size or shape, to be reliably identified as specific chemical entities.

A conventional way to assay a tablet is to dissolve it and carry out high-performance liquid chromatography analysis. This gives an averaged measure of the concentration of the active that can be used to assess dose consistency, but it provides no information about the size of discrete active particles that are delivered to the body as the tablet disintegrates[9]. In contrast, applying morphologically directed imaging to a disintegrated tablet sample allows differently sized elements of the resulting powder to be precisely identified as active or excipient. This not only generates useful information for engineering sophisticated drug delivery profiles, but also provides evidence to support claims of bioequivalence for a generic product

4. Challenges in bulk powder attributes

Pharmaceutical industry's ability to understand how bulk powder properties impact process behavior has been constrained by a lack of reliable bulk powder property data. The reproducible measurement of defining powder characteristics, such as flowabilty, has long been a goal, but the results have been mixed. Traditional techniques, such as flow through an orifice and tapped density methods, are not ideal for the extended, detailed experimental work required to support QbD[11]. Shear-cell measurements are ideal for understanding flow in hoppers, but are less useful for understanding lower stress processes, such as mixing, filling and aerosolization. Here, different measurement techniques are required.

Powder testing has developed considerably in the past decade, including the introduction of dynamic testing[12]. Dynamic characterization reproducibly and directly measures powder flowabilty, for conditioned powders and for those that are consolidated or aerated, thereby generating reliable and valuable information for process development. Used in combination with bulk and shear property measurement, dynamic testing enables the kind of multifaceted powder characterization required to fully rationalise in-process behavior.

With these techniques in place, it is now possible to develop a detailed understanding of the way bulk properties influence tabletting, granulation and many other frequently employed unit operations. This type of knowledge development remains a work in progress, but the goalposts shift too[13]. Faster tabletting speeds are one example, but the long-term objectives of continuous production in integrated manufacturing suites adds another layer of complexity, requiring testing strategies that provide the deepest and most comprehensive information.

5. Best practices in application of QbD to tableting and granulation

QbD relies heavily on engineering an optimized, well-understood process. It is therefore important, from the outset, to work out how to gather analytical data that will accurately reflect process performance. Effective powder handling is central to the success of tableting, granulation and a wide range of other pharmaceutical unit operations. Appropriate powder characterization techniques are, therefore, an essential prerequisite[14].

The number of powder testing techniques available reflects both the importance of such testing and its difficulties.

When choosing which techniques to apply for QbD studies, I would suggest assessing against a number of criteria including:

- reproducibility and sensitivity
- process relevance
- ease of use.

One of the biggest challenges for those applying QbD is how to access and gather the necessary information. The full implementation of QbD demands a comprehensive understanding of process and product, and the identification of an effective control strategy for the manufacturing process[15]. Choice of analytical instrumentation is therefore crucial.

With well-established techniques such as laser diffraction particle-size measurement, customers can rightly expect the highest levels of automation and analytical productivity. Some systems can extend the efficiencies of dry measurement to more samples and combine rapid measurement times with assured data quality, to push analytical productivity to high levels for all users.

Of equal importance, however, are continuous laser diffraction particle size analyzers that offer real-time measurement for pilot-scale studies and commercial plant monitoring and control. These systems can significantly accelerate QbD studies. Running a pilot plant with real-time monitoring in place enables consistent control at the experimental conditions of interest and makes the impact of changes in operating variables instantly obvious.

For some types of analysis, the technology is newer, but it is vital to recognize what can now be achieved. Returning to the example of morphologically directed imaging, these systems involve considerable investment but can deliver significant value over the long term. Being able to measure not just size and shape but also the distribution of different chemical species within a dispersed sample, such as a disintegrated tablet, can be invaluable when trying to really understand how the process works and how to optimize it[16].

5. Conclusion

A combination of analytical and statistical methods could be used to improve a tablet tabletting process guided by quality by design (QbD) principles. A solid dosage form product was found to intermittently exhibit bad taste. A suspected cause was the variability in tabletting thickness which could lead to the subject tasting the active ingredient in some tablets .

References

1. ICH Q8 (R2), Revision from August 2009. Page 1
2. FDA Guidance Quality Systems Approach to CGMP Regulations, September 2006
3. Current USP (35), General Chapter <1216> “Tablet Friability”
4. Current USP (35), General Chapter <905> “Uniformity of Dosage Units.
5. Porter SC, Verseput RP, Cunningham CR. Process optimization using design of experiments. Pharmaceutical Technology Europe. 1997:44–52.
6. X. Fu et al., *Particuology* 10 (2), 203–208 (2012).
7. J. Khoo et al., "Use of Surface Energy Heterogeneity to Relate the Effect of Surface Modification to Powder Properties" (Freeman Technology website, 2012), http://www.freemantech.co.uk/goto.php?link=ART_POSTER_02/, accessed Apr. 16, 2012.
8. US Food and Drug Administration. *Guidance for Industry. PAT—A*
9. Framework for Innovative Pharmaceutical Manufacturing and Quality *Assurance. Pharmaceutical cGMPs.* Rockville, MD, 2004 Sept., 1–21.
10. Watts, C., Clark, J. E., *J Pro Ana Tech* 2006, *3*, 6-9.
11. Delasko, J.M., Cocchetto, D.M., Burke. L.B., *Target Product Profile: Beginning Drug Development with the End in Mind. Update.* January/February, Issue 1, 2005, http://www.fdli.org
12. Food and Drug Administration CDER. Draft Guidance for Industry and Review Staff: Target Product Profile- A Strategic Development Tool (March 2007).
13. Yu, L.X., Amidon, G.L., Polli, J.E., Zhao, H., Mehta, M., Conner, D.P. *et al*., *Pharm Res* 2002, *19*, 921-925.
14. Jain, J., Parmar, H., Patel, A., & Patel, V. Fast dissolving tablet: The new era. *International Journal of Biomedical Research*, 2010: 1(1), 06-10.
15. Gibson, M., Product Optimization: Pharmaceutical Preformulation and Formulation. Taylor & Francis, New York 2001.
16. Baluguri, P., Nama, S., Chandu, B., & Sakala, B. LC/MS:An essential tool in drug development. *International Journal of Advances In Pharmaceutical Analysis,* 2012 *1*(2), 24-37