Application of Image-Based Particle Size and Shape Characterization Systems in the Development of Small Molecule Pharmaceuticals

JOHN F. GAMBLE,[1] MIKE TOBYN,[1] RHYE HAMEY[2]

[1]Drug Product Science and Technology, Bristol-Myers Squibb, Reeds Lane, Moreton, Wirral CH46 1QW, UK
[2]Drug Product Science and Technology, Bristol-Myers Squibb, New Brunswick, New Jersey, USA

Received 21 November 2014; revised 15 January 2015; accepted 20 January 2015

Published online in Wiley Online Library (wileyonlinelibrary.com). DOI 10.1002/jps.24382

ABSTRACT: With the introduction of Quality by Design (QbD) to the pharmaceutical industry, there has been an increased focus on understanding the nature of particles and composites, with the aim of understanding and modeling how they interact in complex systems, leading to robust dosage forms. Particle characterization tools have evolved and now enable a greater level of understanding of powder systems and blends. Tools that can elucidate the size and shape of particulate systems can provide significantly more information about the nature of the particles being analyzed, than a conventional particle size measurement. Although accurate size and shape analysis has always been regarded as the "gold standard" in understanding the nature of particulate systems, neither imaging systems nor IT infrastructure was sufficiently developed to allow this to be performed with sufficient accuracy in a timely manner. The aim of this review is to provide an insight into developments in the field of size and shape analysis of pharmaceutical systems, and how these can now realistically be used as robust development tools. Examples of current uses of such technologies will be explored as well as investigating future applications such as combined image/spectroscopic analyses to track single components within blended systems. © 2015 Wiley Periodicals, Inc. and the American Pharmacists Association J Pharm Sci

Keywords: image analysis; physical characterization; pharmaceuticals; particle sizing; particle shape; materials science; microscopy; imaging methods; crystal shape

INTRODUCTION

The measurement of particle size within the pharmaceutical industry is a well-established foundation of the particle characterization tool box, with a vast array of techniques available for the measurement of this parameter.[1] Particle size can be measured for many reasons, be that to understand the dissolution and bioavailability behaviour of an active pharmaceutical ingredient (API), the risk of issues such as segregation and content uniformity, or in order to better understand the impact of the powder properties on processing conditions, to mention but a few.

Increasingly, more emphasis has been placed on greater understanding of our materials, whether they are APIs, excipients and/or intermediates, and their impact upon processes, and vice versa; particle characterization tools have evolved to support this greater level of understanding.

The rationale behind any size measurement, and to what end it is being used, is therefore paramount, a concept that is by no means new. In the closing remarks at the first major particle size congress in 1966, Heywood[2] was quoted as remarking that "particle size analysis is not an objective in itself but is a means to an end, the end being the correlation of powder properties with some manufacture, usage or preparation". However, particle size may not always be the most appropriate measurement; indeed, there may be situations where particle shape could be the most relevant material attribute.

Although the impact of particle size on processibility is widely accepted, the impact of particle shape is being considered with increasing frequency. The idea that particle shape, and not just size, is important is again not a new development, indeed a method for the classification of sand into five groups based on shape and surface characteristics was described in 1880 by Sorby,[3] whereas the variability in the shapes of windblown sand grains was discussed by Free[4] in 1911.

Image-based particle characterization tools have evolved such that they now enable a greater level of knowledge and understanding. Such tools, which can elucidate the size and shape of particulate systems, can provide significantly more information about the nature of the particles being analyzed than simply a median particle size value. Although accurate size and shape analysis has always been regarded as the "gold standard" in understanding the nature of particulate systems, neither imaging systems or IT infrastructure were sufficiently developed to enable this to be performed in a timely manner with sufficient accuracy and precision for particles in the sub 100 μm region, the typical particle size range for the bulk of powdered pharmaceutical systems.

There are numerous other beneficial attributes of image-based characterization systems with respect to the early pharmaceutical development arena. At early stages of pharmaceutical development, the API synthesis and recrystallization routes are often in ongoing development in order to increase yield, purity, and efficacy, but also with the aim to obtain API with

Abbreviations used: API, active pharmaceutical ingredient; DEM, discrete element modeling; FBRM, focused beam reflectance measurement; ISO, International Organization for Standardization; LLS, laser light scattering; LOD, limit of detection; PLS, partial least squares; QbD, Quality by Design; SEM, scanning electron microscopy.

Correspondence to: John F. Gamble (Telephone: +44-151-552-1646; Fax: +44-151-552-1650; E-mail: john.gamble@bms.com)

Journal of Pharmaceutical Sciences

improved morphological, and thereby handling and processing characteristics. A consequence of this is that the particle characteristics can change from batch to batch and therefore dispersion methods may also require constant redevelopment, a process that can be time-consuming and expensive in terms of material utilization at a stage when API availability is constrained and so at a premium. Method development for image-based tools can be a lot less time-consuming and thus more easily adaptable in line with the ever-shifting API characteristics, whereas question marks about the suitability of dispersion methods can be quickly tested through direct optical assessment of the particles, predispersion and postdispersion, thus validating the dispersion *in situ*. The aim of this review is to provide an insight into recent developments in the field of size and shape analysis of pharmaceutical systems, and how these can now realistically be used as robust development tools in the early stages of pharmaceutical development of small molecule APIs. The review will also discuss the range of such image-based characterization techniques currently available, as well as the relative benefits versus more standard techniques such as laser light scattering (LLS). Examples of the current uses of such technologies will be explored as well as investigating the future applications such as combined image/spectroscopic analyses to track the size of single components within blended systems.

HISTORICAL DEVELOPMENT OF IMAGE-BASED PARTICLE CHARACTERIZATION

Although LLS methods overwhelmingly dominate the pharmaceutical industry when it comes to validated size analysis, in early pharmaceutical development the application of image-based particle characterisation tools is rapidly expanding. The rise in popularity of these complementary technologies could be suggested as simply a consequence of the increase in ability and computational power of newer systems enabling the measurement of statistically viable data with no subjective bias, but one could equally suggest that the ability of such techniques to provide more than just size information, information such as numerical population distributions and particle shape characteristics, for example, is an increasingly important factor.

Historically, the limitations of early image analysis, computing systems (e.g. low memory), combined with the need for manual particle measurement and filtering made particle characterization extremely time-consuming[5,6] and meant that measurements using such approaches could only be carried out on very small particle populations, meaning that data were prone to high variability, because of nonrepresentative sampling and thereby low precision (reproducibility).

In 1953, Rose[7] wrote "It is probably a not unfair summing-up to state that the microscope as a means of powder size analysis should be looked upon as a last resource and is not suitable for routine analysis". He went on to suggest that data from such tools were highly prone to human influence "such as fatigue, boredom and ill-health".

Although this standpoint may be applicable to sizing using manual microscopy, for example, optical microscopy or scanning electron microscopy (SEM), image-based particle characterization systems have come a long way since then. Current imaging technologies are now fully automated, thus removing the human influence, whereas modern computer systems are better equipped to deal with the high volume of data required for such measurements.

Consequently, the previously suggested limitations of image-based particle characterisation are becoming less of an issue. This has led to an increased interest in these technologies in the pharmaceutical industry as a means of getting more than just particle size. However, although there is indeed a great deal of additional data that can be extracted from such systems, there are also many practical considerations that should be considered, not to mention a number of potential pitfalls for unsuspecting analysts.

CONSIDERATIONS FOR IMAGE-BASED CHARACTERIZATION

Sample Population Size

For image-based tools, the number of particles required to ensure statistical confidence that the final result will be indicative of the original sample has long been a topic of intense scrutiny. In the hypothetical scenario that a sample is made up of only identically sized (monodisperse) particles, then a single measurement of any particle within the sample population would be sufficient. As the width of the distribution increases, the number of particles required to ensure that the sample population will be indicative of the original sample will also increase, particularly when dealing with skewed distributions containing small populations of high-volume coarse particles. Numerous approaches to determining the appropriate number of particles have been proposed[8–11]; however, achieving such statistically acceptable particle numbers has not always been feasible using optical methods. Taking a sample of references across a 30-year period (Fig. 1), it can be seen that there has been an exponential increase in the number of particles analyzed as part of reported measurements in manuscripts.[5,12–24] This increase can be suggested to be linked to the rapid advancements in the associated computer technologies, coupled with the introduction of automated particle analysis. This means that image-based systems are now capable of analyzing greater numbers of particles and thereby reducing the apparent lack of precision while also reducing the sensitivity to human interference as suggested by Rose.[7]

The introduction of different approaches to image-based particle characterization during that time frame should also be noted. Although much of the early work was based upon static measurements using optical microscopes, the use of dynamic

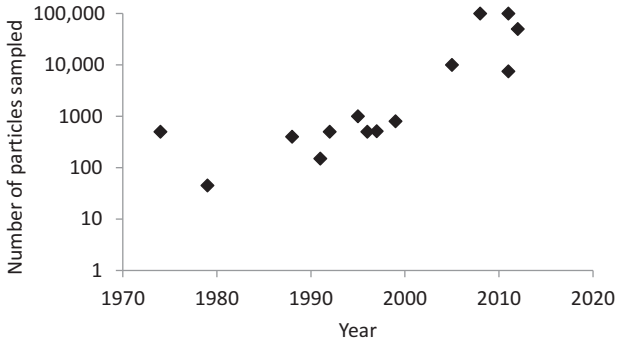

Figure 1. Plot of number of particles measured for image-based publications.[5,12–24]