Powder Technology 258 (2014) 222–233

Contents lists available at ScienceDirect

Powder Technology

journal homepage: www.elsevier.com/locate/powtec

A control strategy for bioavailability enhancement by size reduction: Effect of micronization conditions on the bulk, surface and blending characteristics of an active pharmaceutical ingredient

Dolapo Olusanmi [a,*], Dimuthu Jayawickrama [a], Dongsheng Bu [a], Gary McGeorge [a], Helen Sailes [c], Joanne Kelleher [c], John F. Gamble [b], Umang V. Shah [d], Mike Tobyn [b]

[a] Bristol-Myers Squibb Pharmaceuticals, 1 Squibb Drive, New Brunswick, NJ 08903, USA
[b] Bristol-Myers Squibb Pharmaceuticals, Reeds Lane, Moreton, Wirral CH46 1QW, UK
[c] Bristol-Myers Squibb Pharmaceuticals, Watery Lane, Swords, Dublin, Ireland
[d] Imperial College London, South Kensington, London SW7 2AZ, UK

ARTICLE INFO

Article history:
Received 13 September 2013
Received in revised form 7 March 2014
Accepted 8 March 2014
Available online 14 March 2014

Keywords:
Micronization
Milling
QbD
Blending
Surface energy
Surface area
Cohesion

ABSTRACT

In a Quality by Design (QbD) development environment the effect of early process parameters on downstream manufacturing parameters, and the ultimate effect on drug product quality, need to be understood. For poorly soluble drugs, size reduction is frequently employed to obtain consistent in-vivo exposures. As a result, micronization is a key early stage processing step for many active pharmaceutical ingredients (APIs).

This paper demonstrates the effect of varying micronization conditions on an API for which micronization is deemed necessary to ensure consistent drug delivery after human administration. Material micronized to different extents are confirmed as different by surface area, surface energy, particle size analysis, bulk density and surface adhesion measurements.

These material characteristics can be correlated with the outcomes from a key processing step, blending. The evolution of the blending process is followed using PAT techniques, so that an overall understanding of the relationship between particle properties and blend uniformity can be demonstrated.

Execution of such a study during drug development can enable selection of the appropriate control strategy to ensure production of API in the desired range where consistent optimal bioavailability and downstream processability are achieved.

1. Introduction

In the pharmaceutical industry a significant percentage of marketed drugs [1] and new chemical entities [2] are classified as BCS Class II, where bioavailability is controlled by the drug release from the product matrix due to the inherent low solubility of the drug substance. In order to improve the absorption of such drug substances which may be first in line in terms of their therapeutic benefits pharmaceutical scientists often employ alternative approaches to designing the active pharmaceutical ingredient (API) and also the finished product. These include but are not limited to amorphous forms, salt formation of the API, co-crystal formation, spray dried intermediates, deposition on inorganic mesoporous materials and particle size control. The formation of salts of ionisable drug entities, often weak salts [3], while increasing solubility will also alter properties such as hygroscopicity, electrostatics, melting point, polymorphism and mechanical properties; all of which can impact chemical stability [4]. Additionally, not all drug entities are ionisable and in fact developing salt forms of APIs is not beneficial in every case [5]. In some cases crystal size modification can be employed. This can be achieved either through bottom-up (crystallization) or top-down (size reduction) approaches to obtain the desired dissolution rate enhancement.

Furthermore, for low dose formulations particle size control is needed to ensure content uniformity (CU), a regulated quality standard of oral solid dosage forms. A key aspect of the drug development process is crystallization, and a primary challenge of crystallization is associated with difficulties in controlling the size and shape distribution of crystals, especially when complex crystallization processes are involved [6,7], and with increasing complexity of molecules [8]. In cases where bioavailability of drug entities can be improved by size and shape modification the ideal scenario would be to "*dial a particle size and shape distribution*" using robust bottom-up approaches from crystallization that can be scaled up to commercial scale, while maintaining required polymorphic form, crystallinity and stability. The use of supercritical fluid technology to produce crystalline API of narrow size distribution in the sub-micron range has been developed and discussed [9,10], however, instances where the process has been scaled up for commercial

* Corresponding author. Tel.: +1 732 227 6131.
E-mail address: dolapo.olusanmi@bms.com (D. Olusanmi).

http://dx.doi.org/10.1016/j.powtec.2014.03.032
0032-5910/

scale manufacture have not been found, therefore as yet it is not a commercially viable option.

Rohrs et al. [11] developed a method to estimate the particle size limits needed to ensure that content uniformity criteria for a solid dosage form are met based on median particle size, particle size distribution spread and dose. The method assumes uniform mixing of the blend, and a log-normal particle size distribution for the API, with key input factors such as d[0.5], ratio of the d[0.9]/d[0.5], dose and API particle density. For a given dose the maximum value of d[0.5] that can be accommodated without the risk of failing blend content uniformity is affected by the ratio of the d[0.9]/d[0.5]. As the latter increases, the d[0.5] value has to be reduced in order to pass content uniformity. This is particularly applicable to low dose formulations where the presence of large particles would be expected to have a greater impact on CU. Further reduction of the dose at a specified tablet weight would increase the risk of CU failure.

As a consequence of the aforementioned factors when particle size reduction is required to enhance bioavailability and/or ensure content uniformity milling, particularly micronization, is often widely employed. The mechanical activation during milling may inadvertently cause varying and uncontrolled degrees of disruption to the particle surfaces [9], as well as exposure of non-habit surfaces due to plastic deformation and fracture. Therefore the principles of Quality by Design (QbD) should be applied to this process.

The implementation of QbD, a systematic approach to drug development, in the pharmaceutical industry is advocated by the regulatory agencies, and the principles are given in the ICH Q8 guideline [12]. This practice involves determining the functional relationships that link material attributes and processing parameters to product 'critical quality attributes' (CQAs). The use of Process Analytical Technology (PAT) during development enhances process understanding thus leading to improved control of the manufacturing process [13]. In addition to drug product CQAs that impact the desired quality, safety and efficacy, CQAs can additionally include those properties that affect downstream processability [12]. A substantial effort is made to ensure the former part because without it a product cannot make it onto the market, however, the latter is also important. The design space, i.e. the linkage between the process inputs and CQAs, should be determined for each unit operation that forms part of the manufacturing process. For micronization the optimal design space is achieving the powder properties required for the biopharmaceutics requirements, while ensuring the best possible downstream processability. Downstream processability can be defined in terms of ease of bulk powder handling, processing time to ensure quality etc.; essentially all these can be summed up into processing efficiency. Without establishing an optimal design space for the micronization operation a wide range of materials can be produced which meet the specifications for particle size, e.g. d[0.9] < 40 μm, but which may differ widely in terms of processability. As discussed by Olusanmi et al. [14] the 3-dimensional long-range order associated with crystalline organic materials can result in asymmetrical properties of the various crystal facets which can consequently impact their mechanical properties. The surface chemistry on each crystal facet may vary as the various crystallographic planes dissect the unit cell (the fundamental building block of crystals repeated in space to form the crystal structure) at different planar orientations and angles. Thus milling may result in the exposure of differing chemical groups, and differing surface concentration of those groups [15]. As a consequence, the surface energetics of a micronized sample may be significantly different to the original un-milled material.

The surface energetics of pharmaceutical powders are often characterized in terms of their dispersive surface energy, with a higher dispersive surface energy often suggested to represent a more "reactive" surface [16]. The total surface free energy of a solid can be split into dispersive (non polar) and specific (polar) components. The former are non-specific interactions which are due to long-range London dispersive forces, while the latter are specific short-range directional chemical interactions which involve charge redistribution and sharing [17].

Techniques used to characterize the surface energetics of pharmaceutical powders include IGC (Inverse Gas Chromatography) [9,18–22], sessile drop contact angle methods on compacted powders, and contact angle methods on macroscopic single crystals [15,23,24]. There are several drawbacks associated with the sessile drop contact angle methods and these have been discussed extensively by a number of authors [25–27]. Furthermore dispersive surface energy measurements by liquid wetting angle techniques are difficult to implement reproducibly on free-flowing powders [28]. For sessile drop contact angle measurements on individual crystal faces large specially grown crystals are required, but these give better indications of dispersive surface energy anisotropy resulting from surface chemistry differences, rather than an averaged value obtained from powder samples [15,24]. Surface energy values determined by measurements at infinite dilution, as described by Thielmann [13], are mostly biased towards the highest energy sites of the powder sample [29] because the amount of probe injected only covers a small percentage, <0.1%, of the powder sample [17]. This has the benefit of distinguishing subtle differences in the surface properties, even in the case of nominally similar batches of the same material [9].

In some cases the distribution of active sites may be more relevant to the practical properties of a material than the high energy sites [16]. This is particularly pertinent in cases where the effect of milling on dispersive surface energy is of interest. In the case of materials with cleavage planes, following exposure of such faces during processes such as milling or agitated drying, the properties of the cleavage plane may dominate the surface energetics of the resulting product. Heng et al. [18] observed an increase in the dispersive surface energy, measured by IGC, of paracetamol form I powder with milling, and this was attributed to an increase in the proportion of the (010) facet, the cleavage plane, which exhibited the highest dispersive surface energy compared to the other facets as determined by sessile drop contact angle measurements on individual crystal faces of macroscopic crystals. Exposure of non-habit surfaces due to fracture may subsequently introduce further complexities in the interaction of organic particulates with different chemical entities compared to unmilled material. Overall, processes which involve size reduction may further compound the dispersive surface energy heterogeneity of the product due to exposure of new surfaces coupled with the possible disordering of crystalline surfaces caused by mechanical stress. Therefore when micronization is required it is essential that during development, the effect of micronization extent within the acceptable range for the biopharmaceutical requirements on powder properties (both surface and bulk) and downstream processability is understood.

Work has been reported in literature on the effect of milling on the surface properties of APIs and particulate materials in general. While some authors have reported decreases in surface energy with milling [19,21,30], others have observed milling to increase the surface energy of powders [18,31]. Where surface energy increases with milling extent has been reported it has often been attributed to the exposure of higher energy crystal facets and/or the creation of higher energetic surfaces on the particles. Typically a number of these publications report changes to the degree of crystallinity of the milled material either due to localized lattice disorder and/or reduced crystallinity [20,30,32], changes to the surface chemistry of milled material [18,31]. An important question, which has not been addressed, is what is the effect of micronization and associated change in surface energetics on the bulk handling and processing behavior of pharmaceutical API during development and manufacture? Publications where the effect of these milling-induced changes are demonstrated are limited e.g. Vippagunta et al. [33]. To enable better implementation of quality by design and more efficient drug development it is important to understand the impact of such changes to other downstream processing operations, and this subject would be the focus of this present work.

The objective of this milling study is to establish a control strategy for producing micronized API with consistent powder properties in the desired target product profile for dissolution enhancement.