Integrating Particle Microstructure, Surface and Mechanical Characterization with Bulk Powder Processing

Rodolfo Pinal* and M. Teresa Carvajal

1 Department of Industrial and Physical Pharmacy, Purdue University, USA
2 Department of Agricultural and Biological Engineering, Purdue University, USA

Abstract

Multiple industrial applications, including pharmaceuticals, rely on the processing of powders. The current powder characterization framework is fragmented into two general areas. One deals with understanding powders from the standpoint of its constituting agents—particles. The other deals with understanding based on the bulk—the collective behavior of particles. While complementary, the two aspects provide distinct pieces of information. Whenever possible, experimental techniques should be used to predict powder behavior. However, it is equally important to recognize that because of the natural complexity of powders, existing predictive approaches will continue to be of limited success for predicting the collective behavior of particles. This article discusses the understanding of powder properties from two perspectives. One is the effect of surface energy at the bulk level (large collections of particles), which controls interactions between powders. This aspect is most useful if studied at the bulk-powder level, not at the single-particle level. Another perspective deals with the physico-mechanical properties of individual particles, responsible for the observed behavior of powders when subjected to mechanical stress from unit operations such as milling. This aspect, which controls the failure mechanism of powders subjected to milling, is most useful if assessed at the single-particle, not at the bulk level. Therefore, in order to fully understand, and eventually predict, or at least effectively model powder behavior, a good-judgement-based combination of microscopic and bulk-level analytical methods is necessary.

Keywords: powder, particle, surface energetics, surface composition, nanoindentation, flowability

1. Introduction

Imagine trying to obtain a wide-angle panoramic image of a particular view, using a regular photographic camera. The task requires multiple frames, where each frame provides detailed information about a small segment of the whole picture. The panoramic image can then be obtained by “stitching” together the multiple frames captured by the camera. One important consideration is that in order to successfully stitch the multiple frames into a faithful representation of the panoramic view, it is also necessary that each individual frame also exhibits some degree of overlap with the neighboring images. The panoramic image example just described, is analogous to that of the physical characterization of powders. Each analytical technique utilized provides a “snapshot” of a particular attribute of the powder, and a fundamental understanding about the properties and behavior of the material, or panoramic view, comes from integrating the information obtained from the multiple analytical techniques. The wide-angle photograph notion provides a useful general starting point. However, for every analogy, there is always a point at which it ceases to be applicable, and this is no exception. One critical difference between the panoramic image situation and the characterization of a powder material, is that constructing the panoramic view is a mono-dimensional task, whereas the physical characterization of a powder material is a multi-dimensional one. In other words, in making the panoramic image, every single shot carries the same type of (exclusively visual) information, whereas in powder characterization, each single shot counterpart (analytical technique) provides different type (dimension) of information.

Handling and processing powders is an integral aspect in various industries, including pharmaceuticals, food and nutraceuticals, cement and ceramics, among others. This report focuses on pharmaceutical and food applications. However, the principles covered in the discussion presented here are not necessarily limited to these industry segments, but should be valid for powders in general.
We often refer to the handling and processing of bulk powders. At first, the term “bulk powder” is self-explanatory. However, it will become clear through the presentation of this article, that a refinement of the term “bulk” is necessary, in order to give proper context to what is meant by powder characterization. Specifically, in terms of the properties of interest and the instrumental techniques utilized to make the corresponding measurements.

As stated in a recent publication (Hickey A., 2018), the complexity of pharmaceutical powders resides on their variety of physicochemical characteristics that impact bulk requirements such as powder flow, agglomeration and dispersion. The similarity in complexity has the same type of effect on food-relevant powders (Burgain J. et al., 2017; Kim E. et al., 2005; Thakur S. et al., 2013).

Powders consist of large collections of solid particles. In subjecting a powder to the various analytical tests utilized for physical characterization, it is important to keep track what aspect of the particles is being interrogated by the analytical method used (Crowder T. and Hickey A., 2000; Feeley J. et al., 1998; Hickey A. et al., 2003; Shi J. et al., 2015).

Consider for example powder X-ray diffraction (PXRD) and BET gas adsorption isotherm testing. These two methods can be typically conducted on the same “bulk” powder. However, each of these analytical methods probes into (allowing us to look into) distinctly different parts of the same powder sample. PXRD provides information regarding the arrangement of molecules making the inner core of the powder particles, but it provides no information regarding the surface properties of the same particles. The BET analysis on the other hand, provides information about the surface ability to interact with the gas adsorbate, but reveals nothing about the inner core of the particles. Needless to say, full physical characterization of powders requires understanding both surface- and core-particle properties (Feeley J. et al., 1998; Ho R. et al., 2009; Otte A. and Carvajal T., 2011; Shi J. et al., 2015; Willart J. et al., 2006). Accordingly, both sets of properties are equally important. However, the relative relevance of surface- vs. (inner) core-particle properties depends on the specific process under study or on the focus of the specific investigation being carried out on powders. In the discussion presented in this article, we make the distinction between “bulk-core” and “bulk-surface” properties. Bulk-core properties are exemplified, without limitation, by PXRD, while bulk-surface properties are exemplified (without limitation again) by BET gas adsorption analysis. The purpose of such differentiation is to be able to discuss the properties of “bulk powders” without the encumbrance of ambiguity. Table 1 shows a partial list of analytical techniques commonly used in the physical characterization of powders. The list includes the type of sample interrogation (core vs. surface) provided by each technique.

Despite a large body of published work on the subject (Begat P. et al., 2005; Khoo J. et al., 2011; Heng J. et al., 2006; Ho R. et al., 2011; Ho R. et al., 2009; Leturia M. et al., 2014; Roberts R and Rowe R., 1987; Shi J. et al.,

### Table 1

| Analytical Technique                                      | Core-bulk information | Surface-bulk information |
|-----------------------------------------------------------|-----------------------|--------------------------|
| X-ray Powder Diffraction (PXRD)                           | ✓                     |                          |
| BET Adsorption                                            |                       | ✓                        |
| Differential Scanning Calorimetry (DSC)                   | ✓                     |                          |
| Infrared Spectroscopy (IR)                                | ✓                     |                          |
| Inverse Gas Chromatography (IGC)                          |                       | ✓                        |
| Laser Diffraction                                         | ✓                     |                          |
| Water Uptake/Hygroscopicity (1)                           | ✓                     | ✓                        |
| SEM (2)                                                   |                       | ✓                        |
| X-ray Photoelectron Spectroscopy (XPS)                    |                       | ✓                        |
| AFM/Nanoindentation (3)                                   | ✓                     | ✓                        |
| Near Infrared Spectroscopy (NIR)                          |                       | ✓                        |

(1) Depending the mechanism of water uptake, adsorption or absorption, surface- or core- information is obtained.

(2) Qualitative information about surface topography.

(3) Surface topography (physical and interactive). Nanoindentation provides mechanical information pertaining to the core of the particle.
It is unfortunate that among industrial scientists involved in powder processing applications, the role and hence the importance of the surface properties of powders does not occupy the prominent position it actually warrants. To put the situation in perspective, let us take the case of nanoparticle systems for example. Even introductory-level knowledge on this subject makes it clear that at the nanoscale level, surface properties become dominant over core-particle properties. In fact, one of the tenets of the nanoparticle filed, is that when the majority of the molecules in a solid sample are located at the surface instead of in the core of the particles, material properties begin to operate in a different domain, i.e., in the nanoscale domain. It is generally considered, that outside the nanoparticle domain, i.e., in the micro-scale or even macro-particle range, since the proportion of molecules occupying the surface is negligibly small compared to the proportion occupying the core of the particles, the effect of surface molecules is not of major consequence. This general notion is as incorrect as it is widespread. Actually, independently of what percent of the total number of molecules of a powder sample is located at the surface, interaction among the particles in a powder are predominantly controlled by surface properties. That is, when two particles encounter each other (Stewart P., 1986), their interaction is blind, so to speak, to the nature of their cores, but entirely determined by the nature of their surfaces. Consider for example two sets of glass beads of equal diameter, with the difference that one set of beads is all solid glass, while the other consists of hollow beads filled with a different material, water for example. Even if water is the main component of the hollow beads, it will play no role on the interaction (beyond that of density) among beads of the same or different type. The interaction between solid and water-filled beads will be entirely a manifestation of glass-with-glass surface encounters. If the surfaces of the two types of beads are equal, so will be their respective surface properties, and the result will be what is referred to as ideal mixing, as further discussed below.

2. Surface characterization—Surface energetics

The effects of milling on material properties has been addressed in terms of disruption of the crystalline structure, assessed by PXRD, and by studying thermal properties (Feng T. et al., 2008; Wildfong P. et al., 2006; Willart J. and Descamps M., 2008; Willart J. et al., 2006). However, it is recognized that further research is needed on this area. Consider the hypothetical situation where the milling of a crystalline powder results in particle size reduction but without any disruption of the crystal lattice. Each crystalline structure is characterized by a series of diffraction planes. Depending on the strength of the intermolecular interactions between parallel layers of a specific plane, some planes are mechanically favored toward providing openings for cleavage, leading in turn to crystal fracture. Milling crystalline materials results in particle size reduction by means of particle fracture. The fracture pattern tends to follow the favorable cleavage openings that are characteristic of the particular crystal structure. For this reason, milling crystals results in more than just a general increase in exposed surface area. The mere increase in surface area produced by milling, bears an inherent change in the specific surface energy of the milled powder. The fracture of crystal particles at cleavage planes results in an increase in the abundance of exposed cleavage-plane surfaces, and the surface energy of such surfaces is a function of cross-sectional exposure of functional groups located on the particular cleavage plane. Studies on the surface energy of the crystal faces exposed upon milling have been reported, giving a wealth of useful information (Chamarthy S. and Pinal R., 2008a,b; Feeley J. et al., 1998; Ho R. et al., 2012; Otte A. et al., 2012; Planinsek O. et al., 2010). However, under the conditions of industrial applications of milling, particle size reduction is almost invariably accompanied by disruption of the crystal structure of the particles. Such crystal disruption is an unintended but inevitable “side effect” of milling. Moreover, in industrial applications of milling, particle fracture patterns rarely, if ever, “abide” by exclusively breaking at the most favorable cleavage openings. Independently of the particle fracture pattern during milling, particle size reduction is invariably accompanied by an increase in surface area.

One important consideration is that the milling-induced surface area increase is inherently heterogeneous in terms of its energetic content. Thus, the following section discusses the usefulness of conducting surface properties analysis using inverse gas chromatography (IGC) for powder systems. This approach is more relevant to industrial applications, since it is not possible in practice to control the fracture patterns of the particles, nor to prevent the disruption of the crystal structure during the process. Detailed reviews on the principles of IGC covering pharmaceutical systems are available in the literature (Heng J. et al., 2006; Ho R. and Heng J., 2013).

As stated, particle-particle interactions in powders are mediated by the surfaces involved. The surface energy of the particles in powders is a major factor on the attributes of powder blends. Consider the blending of two powder materials, 1 and 2. Let us assume that particles of the two powders have different physicochemical properties but similar particle size distribution. In this report, we follow the common convention of using the term cohesion to refer to attractive interaction among particles of the same material and the term adhesion to refer to attraction between
particles of different materials. The work (energy) of cohesion, for each of the two components of the powder mixture is given by the geometric mean rule:

$$W_{c}^{1} = 2 \sqrt{\gamma_{d}^{1} \times \gamma_{d}^{1}}$$

(1)

$$W_{c}^{2} = 2 \sqrt{\gamma_{d}^{2} \times \gamma_{d}^{2}}$$

(2)

where $W_{c}$ is the work of cohesion, $\gamma_{d}$ is the dispersive component of the surface energy, and the subscripts denote powder component 1 and 2, respectively. Analogously, the work of adhesion is given by:

$$W_{a}^{1} = 2 \sqrt{\gamma_{a}^{1} \times \gamma_{a}^{1}}$$

(3)

where the subscripts 1 and 2 denote the interaction between the two different powders, 1 and 2.

It is noteworthy that among dispersive, dipole and hydrogen bonding interactions, dispersive interactions are the weakest, yet they often dominate over the other types of (stronger) intermolecular interactions when it comes to powder mixing. The reason is that dispersive interactions are non-directional; the only parameter at play for their operation is distance. The non-directionality of dispersive interactions is in fact the basis for the applicability of the geometric mean rule. Dipolar interactions, and to a considerably greater extent hydrogen bonding interactions, are highly directional, i.e., they require a precise molecular orientation in order to take effect. In liquid mixtures, molecules are free to rotate and orient themselves, thus readily satisfying the geometric requirements imposed by inter-dipole as well as donor-acceptor hydrogen bonding interactions. For this reason, hydrogen bonding and dipolar interactions are dominant in liquid mixtures, rendering dispersive interactions comparatively inconsequential. The situation is quite different in the solid state, where the inability of the molecules to freely orient themselves renders the orientation-dependent, specific interactions practically inconsequential, or at least non-dominant. The result is that the non-specific (non-directional) dispersive type of intermolecular interactions control inter-particle interactions, and with that, they control powder mixing to a large extent.

The type of mixing and resulting blend between powders 1 and 2 depends on the overall energetic balance between cohesive and adhesive interactions. Ideal powder mixing is observed when

$$W_{c}^{1} \approx W_{a}^{1} = W_{c}^{2}$$

(4)

That is, when the dispersive surface free energy of each powder, 1 and 2 alone (cohesion), as well as the particle-particle interaction work resulting from the blend (adhesion), are all of similar magnitude. From a conceptual point of view, an ideal powder blend can be said to be symmetric, in the sense that swapping the positions of any two particles of equal (or similar) surface area and size in the blend can be done at (nearly) zero energy cost. From a practical point of view, the symmetry of an ideal blend manifests itself as a highly homogeneous mixture. Fig. 1 shows an example of a nearly-ideal powder blend, consisting of 50:50 (w/w) lactose and tolmetin, an anti-arthritis drug (Ely D. et al., 2006). Blend uniformity was monitored during blending using near infrared (NIR) spectroscopy. Fig. 1 shows that the 50% composition is reached very shortly after the start of mixing. Furthermore, the magnitude of the standard deviation also falls very sharply right at the onset of mixing. The result is a highly uniform powder blend, generated very quickly and, most significant, stable to prolonged mixing. In relation to Equation 4, the $W_{c}$ values determined using IGC for lactose, tolmetin and the lactose-tolmetin mix are 100.1, 102.7 and 101.4 mJ·m⁻², respectively (Ely D. et al., 2006). The closeness among these values indicates that lactose-lactose, tolmetin-tolmetin and lactose-tolmetin interactions are all energetically nearly equivalent. Consequently, none of them is favored over another, leading to symmetric mixing. The result is a random, highly uniform mixture.

Fig. 2 shows an example where the mismatch in surface energy between the components of a powder blend leads to non-uniform mixing. That is, in a segregating powder mixture. The experiment of Fig. 2 involves a 50:50 (w/w) mixture of two pharmaceutical excipients, dextrose and Di-Tab (dicalcium phosphate). The experiment was carried out in the same way as that of Fig. 1 (Ely D. et al., 2006). However, the results are quite different in each case. Fig. 2 shows that the dextrose-Di-Tab mixture is highly segregated. Throughout the blending time, the Di-Tab concentration recorded is lower than its actual content in the mixture. This result indicates that the distribution of the components is highly non-uniform, with dextrose physically masking Di-Tab, hence interfering
The concept of pharmaceutical quality, along with the driving principles for safety and efficacy, are inextricably connected to the ability to reproduce, i.e., to always produce a consistent product in all its properties and attributes. Regulatory authorities recognize that raw materials used in pharmaceutical manufacturing, many of which are supplied as powders, bear some degree of inherent variability (Yu L. et al., 2014). Such that in order to obtain a consistent product, it is necessary to adjust the manufacturing process as needed, that is, to account for, and accommodate the observed variability among different lots or batches of what is nominally considered the same raw material. In this regard, the concept of sameness among different lots a raw material used in pharmaceutical manufacturing plays a central role.

Sameness has two different connotations, one at the raw material level, and one at the product level, although each leads to the same overall result. Sameness refers to the actual match in properties and attributes among different lots of the same raw material, such that every lot will function in precisely the same way when used in pharmaceutical processing.

Conversely, when different lots of the same raw material do not quite match each other, sameness is achieved by adjusting the process parameters accordingly, such the same end-product is obtained with different lots of the raw material. It is important to point out that in either case, it is necessary to have a thorough understanding of those specific functional attributes of the raw material that are critical to the process outcome. A pernicious problem often faced in pharmaceutical development, is that despite being deemed as meeting the criteria for sameness (on the basis of physical characterization testing), different lots of the same raw material are found not to function in the same way during processing.

An illustration of the importance of properly differentiating between core-bulk and surface-bulk properties in the context of assessing lot-to-lot sameness (or variability) is provided in a study involving soluble starch, a material used as compressing aid (Chamarthy S. et al., 2009). A starting sample of soluble starch was divided into two portions. One portion was subjected only to sieving, in preparation to using it to make compressed compacts. The other portion was subjected to a washing process, drying and subsequent sieving in order to de-agglomerate and match the particle size distribution of the unwashed portion. The two samples were subjected to a series of analytical tests involving the instrumental methods routinely used for the physical characterization of powders. Results from different tests, each probing the core-bulk properties (PXRD under different humidity conditions, FTIR, true density and hygroscopicity) gave the same results for the two powder samples. Even the BET-determined surface areas where the same within 2% for nitrogen gas and

Fig. 2 Non-ideal (segregating) powder mixture. Near IR monitoring of the composition of a 50:50 dextrose-Di-Tab mixture as a function of blending time. Reprinted with permission from Ref. (Ely D. et al., 2006). Copyright: (2006) Elsevier B.V.
within 10% for water vapor for the two samples. Based on the analytical results, the two portions (or “lots”) of soluble starch would typically be deemed as equivalent, *i.e.*, as meeting the sameness criteria, thus making them suitable substitutes for each other when used in pharmaceutical manufacturing. However, when actually used to make compacts, the two samples did not produce equivalent compacts, under any of the processing conditions investigated. The washed portion of the starch produced mechanically stronger compacts under all conditions of applied compression force, as well as under all equilibrium relative humidity conditions tested. It should be pointed out that the difference in mechanical strength between the two samples held even under the limiting conditions of zero porosity, based on Ryshkewitch analysis (Newton J. et al., 1993; Ryshkewitch E., 1953). This means that the difference in mechanical properties was in fact the result of different energy of interaction between conjoined particles forming the compact and not the result of differences in spatial distribution of the particles within the compacted solid. Surface energy analysis revealed that the washed portion of the starch powder was more energetic than the unwashed portion, in terms of both the polar and dispersive components. However, the greatest difference was observed in the dispersive surface energy component, which as discussed above, is the dominant part when it comes to solid inter-particle interactions. The soluble starch study is a clear example of a situation commonly faced in pharmaceutical processing. Namely, one where from an analytical point of view, two “lots” of a raw material are the same, but they are never the same when it comes to the functional/processing point of view. The fact that the core-bulk testing methods gave essentially the same results for the two samples of soluble starch is not surprising. After all, the chemical and physical composition of the material is minimally affected, if at all, by a simple washing process. Furthermore, the fact that the BET surface area, a classic surface-bulk analysis technique, gave very similar results for the two samples, offers a lesson worth bearing in mind: differences in surface energy of powders may be missed if based on the interaction with a single gas (or vapor) probe molecule, as it is the case with BET analysis. Dispersive surface energy measured using IGC relies on a series of vapor probe molecules, not just one. In other words, surface energy analysis base on IGC carries a greater information content.

Milling powders is one of the most commonly used unit operations in pharmaceutical processing. Even though the single objective of milling is the reduction of particle size, the input of mechanical energy into the system invariably leads to unintended, hence uncontrolled physical changes of the sample. Fig. 3 depicts the physical changes undergone by crystalline particles when the powder is subjected to milling. A portion of the mechanical energy supplied during milling results in the fracture of the particles, thus leading to the sought after particle size reduction. Naturally, a significant portion of the energy supplied is dissipated as heat. However, some of the energy supply in milling is neither consumed toward particle fracture nor dissipated as heat. There is a portion of the mechanical energy that results in dislocations made to the orderly arrangement of the molecules in the crystal. Such dislocations constitute crystal defects, depicted in the bottom left corner of Fig. 3. Continued supply of mechanical energy results in an increase in the concentration of dislocations within the crystal lattice. As the concentration of crystal defects increases, it is possible to reach a threshold defect-concentration value, such that the orderly molecular arrangement of the crystal becomes completely obliterated. This situation, often referred to as amorphization, gives place to place to the amorphous form of the material, as depicted on the bottom right corner of Fig. 3. The disruption of the crystalline structure of powders induced by milling is termed powder activation. The particles in activated powders are more energetic than the particles in the original ( unmilled) material. Powder activation is thus a mechanism by which milled powders, through a change in the arrangement of the molecules, are capable of storing a portion of the mechanical energy supplied during the milling process. The mechanical activation of powders is both a core-bulk and a surface-bulk property, observable both in terms of surface interactions and inner particle properties. It is important to point out that the depiction of mechanical activation in Fig. 3 is a rather simplistic one, but it correctly captures the general processes at work.

There is a widespread misconception that prolonged milling of powders will eventually lead, in general, to the amorphous form. That is not so. Whether or not continued
milling (mechanical energy supplied) leads to the formation of the amorphous form depends on the properties of the crystalline material itself. For example, the milling of ketoconazole (an antifungal drug) first results in crystal defects, while prolonged milling eventually leads to complete amorphization. Conversely, the milling of griseofulvin (another antifungal drug) invariably results in mechanical activation in the form of crystal defects, and no matter how long the milling time is extended, complete amorphization of griseofulvin is not achieved. On the contrary, synchrotron source PXRD studies reveal that milling amorphous griseofulvin results in the formation of defect-bearing crystals (Chamarthy S. and Pinal R., 2008a; Feng T. et al., 2008; Otte A. et al., 2012).

As stated above, mechanical activation of powders directly affects both core-bulk and surface-bulk properties. The importance of differentiation between core- and surface-aspects is clearly illustrated by comparing the properties of milled crystals with their corresponding amorphous form. Fig. 4 shows the dispersive surface energy of griseofulvin and felodipine (a blood pressure lowering drug). Each graph shows the surface energy values for the native (original, unmilled) crystal used as reference, as well as those of the milled crystals and of the amorphous form. From the core-bulk point of view, the energy rank order for both drugs is necessarily amorphous > milled crystal > reference, and there cannot be any dispute about that, since this is precisely the rank order of energy requirements to achieve full and partial disruption of the crystal structure, with the unmilled crystal as baseline reference, in each case. However, it is noteworthy that from the point of view of the surface alone, the energetic rank order is milled crystal > reference > amorphous. This may seem an anomalous result. However, it would be anomalous if only core-bulk properties counted and surface properties were irrelevant, which is never the case. Here we have a situation where the material with the highest core-bulk energy content is also the one with the lowest surface-bulk energy. The reason for the most energetic core-bulk form, i.e., the amorphous, exhibiting the lowest surface energy is attributable to the higher degree of molecular mobility that is characteristic of the amorphous form, relative to its crystalline (either native or milled) counterpart. Molecules at interfaces bear an excess in free energy, relative to the molecules inside the core. Any system will have a tendency to spontaneously minimize its surface energy. The question is whether the driving potential is strong enough to overcome the kinetic threshold of the process. Molecules in the amorphous state bear an excess amount of energy equivalent to the heat of melting (save a heat capacity correction for liquefaction taking place below the melting temperature), relative to the native crystal. In contrast, dislocated molecules in a milled crystal bear only a fraction of the equivalent of the heat of melting. One important consideration is that molecules in the amorphous state also have a high degree of mobility. Specifically, a degree of mobility lacking in molecules confined in a crystalline arrangement, including dislocated molecules, relative to their reference position/orientation in the orderly crystal. Consequently, molecules at the surface of the amorphous form are more readily capable or rearranging themselves in order to spontaneously minimize the overall surface energy of the particle. Conversely, molecules occupying surface dislocations in the crystal, remain wedged in place without nearly the same ability to reorient themselves in order to reduce (minimize) energy of the particle surface.

Putting aside the reasons for the higher surface energy observed in milled crystals, it is important to consider the potential impact in terms the practical aspects of powder properties and performance. For example, the data in Fig. 4 suggest that the powder of milled crystals may be, initially, more easily wetted than the amorphous powder. Once wetted however, the amorphous powder will necessarily dissolve considerably faster. Further studies are needed in order to compare the cohesive properties of the milled crystals with those of the amorphous powder.

![Fig. 4](image-url) Dispersive surface energy of three powders from a common source: Original crystal, milled crystal and amorphous powders of griseofulvin and felodipine.
Especially considering that the high molecular mobility in the amorphous form, responsible for its lowest relative surface energy, will also tend to promote inter-particle fusion. After all, inter-particle fusion provides a simple mechanism for surface energy minimization, which is the ultimate driving force. Conversely, in the absence of any annealing (which typically requires elevated temperatures or long inter-particle contact times), cohesion of particles in the milled powder will be mostly controlled by dispersive surface interactions, with a comparatively minimal effect from molecular mobility.

It is pertinent to consider the impact of the interrogation scale of the analysis performed, on the type of information obtainable regarding powder properties. The advancement of nanotechnology along with its associated analytical tools, on multiple application fronts, has resulted in the ability to study particle (including surface) properties at ever higher levels of resolution. In parallel to these advances, the notion that the higher the level of resolution on the analysis of particle surfaces provides the path toward complete understanding of the surface properties and behavior of powders, has been gaining popularity.

Consider the hypothetical situation where the physical and energetic properties of every constituent particle of a powder sample are perfectly uniform. Under such a scenario, the obtainable information would be essentially the same, whether the analysis method used probed one square meter or one square micron of surface. Accordingly, under this idealized situation, differences in bulk powder properties between different lots of the same material will be primarily the result of differences in their particle size distributions. In real systems however, surface heterogeneity is an inherent characteristic of powders, and the lack of surface homogeneity is precisely one of the most important factors responsible for the observed behavior of bulk powders.

Let us now consider two surface analysis methods on opposite ends of the resolution spectrum. Before proceeding with this comparison, it is important to clearly differentiate between sensitivity and resolution. Atomic force microscopy (AFM) and IGC are both highly sensitive methods, in the sense that each gives distinctly different readings based on differences among samples that may be undetected by other methods. However, AFM and IGC have very different levels of resolution. AFM interrogates very small, localized sections of the surface, whereas IGC interrogates very large, unconfined sections of the same surface. As received, typical pharmaceutical powders of organic materials have specific surface area in the order of 1–3 m²·g⁻¹. Accordingly, a typical IGC surface energy analysis test provides information on powder surface area in the order of 1 m². That is, IGC reports on a sample of actual “bulk powder,” not simply on a collection of particles (the significance of this point is further discussed below). AFM analysis generates images typically of the order of 5 × 5 to 20 × 20 μm². Consider a hypothetical powder sample with a specific surface area of 2 m²·g⁻¹ subjected to analysis using both IGC and AFM. Since IGC is a non-destructive method, the analysis by both methods could conceivably be performed using the exact same set of particles. AFM provides highly detailed information, including unambiguous quantification of the magnitude and distribution of energetic heterogeneity present in the test specimen. This type of information has a level of resolution that is inaccessible by other analytical methods. Precisely because the high resolution however, full assessment of the powder surface using AFM would require collecting substantially more than 10⁹ images. Alternatively, in order to reduce the number of collected AFM images to a practicable number that is nonetheless statistically representative, it would be necessary to know, a priori, the energy distribution of the surface from two points of view: the range of the magnitude of the surface energy, as well as the energy distribution across the powder surface, in order to select the appropriate physical locations that give a representative sample. But these two pieces of information are, precisely, what the surface analysis is meant to provide in the first place. The limitations of using IGC for surface analysis go in the opposite direction. IGC provides surface energy values based on probing the entirety of the sample, i.e., in the example discussed here, the entirety of 2 m² of surface in 1 g of powder. The contrast between the capabilities of AFM and IGC embodies their complementarity. AFM provides exquisitely detailed information, capable of clearly differentiating between very small regions of surface in the same powder, but it would make it a formidable task to unambiguously differentiate between different lots of the same powder material. Conversely, IGC is exquisitely suited to differentiate between lots of the same powder material, but such a capability comes at the expense of not being able to provide any information about the energetic properties of specific regions in the sample. IGC provides a characteristic surface energy value but it provides no information about surface energy in any particular region of the sample.

2.1 Powder complexity

Particle engineering applications deal with controlling the conditions of particle generation such that the attributes of the particles obtained can be made to meet specific (desirable) parameters. We should take into account that the end-product of the majority of particle engineering methods is a powder. One important question has to do with the connection between particle properties and bulk powder properties, as discussed below.

There is wide agreement that powders exhibit complex
behavior, so it is necessary to discuss the complexity of powders, specifically, in connection to powder characterization by analytical methods. We must point out that the term complexity has multiple connotations, spanning from lay usage to its informal and formal scientific use. In this report, the term complexity (or Complexity) is used in the context of emergent properties (or Emergent Properties) from the point of view of classical systems theory.

Physically speaking, we can say without ambiguity that powders are solid materials. However, their dynamic properties, especially those involved in energy dissipation, do not conform to the behavior of classical solids, liquids or gases. Even when viewed as collections of multiple particles, powders stand apart from other multi-particle systems such as suspensions or dense gases (Jaeger H. et al., 2000). The same is true when trying to treat the dynamic properties of solids in the same way as those of continuous systems. Compare for example the case of mixing two liquids, with that of mixing two powders. In the liquid, molecular thermal motions suffice to spontaneously reduce to zero, hence eliminating, all concentration gradients thus giving a homogeneous mixture. In a powder mixture on the other hand, thermal motions are essentially irrelevant, since external forces such as gravity dominate the behavior of the material. Furthermore, for particles at or below a critical, material-dependent size, electrostatic (coulombic) forces begin to compete with, and at sufficiently small size, eventually dominate over gravity. Consequently, the reduction of composition gradients necessary to obtain a homogeneous powder blend, requires the application of external energy, such as that provided by tumbling or by the action of a propeller. However, even when the energy supply requirement for gradient elimination is fully satisfied in each (liquid and solid) mixture case, powder mixtures exhibit distinctly different behavior. For example, thermal motions suffice to prevent segregation of components in liquid mixtures. In other words, thermal motions overcome any tendency toward segregation resulting from differences in molecular dimensions or from differences in density (more appropriately, partial molar volume) between the components in a liquid mixture. Conversely, in the case of powder mixtures, density differences not only can have an effect, but depending on the magnitude of the difference, the same effect can actually operate in opposite directions (Oshitani J. et al., 2016). For this reason, the widely used V-blender type, so frequently used to blend pharmaceutical powders, often actually functions an effective particle separator (Jaeger H. et al., 2000).

Let us consider the powder mixtures presented in Figs. 1 and 2 above. We can say that a tumble mixer is analogous to a kaleidoscope toy. Namely, each rotation of the tumbler gives place to one among an infinite number of possible different physical combinatorial arrangements of the particles. As stated above, the mixture represented in Fig. 1 can be considered (energetically) symmetric. As a result, once the blend reaches the pre-established 50% content for each component, each subsequent tumbling rotation will give place to a different physical arrangement of the particles. However, because of its symmetric nature, all different physical arrangements created will be energetically equivalent to each other, i.e., a different configuration of the same uniform blend.

The situation is different for the powder mixture represented in Fig. 2. The lower-than-nominal (50%) composition detected indicates a non-uniform mixture throughout the mixing process. Even more telling is the unstable standard deviation value accompanying the fluctuating composition. These unstable values are rather superficial signs of the blend’s inability to reach equilibrium, either as a homogeneous or as a non-homogeneous but ordered mix, despite the continuous influx of mechanical energy. Therefore, the underlying issue here is one of energy dissipation. Energy dissipation is in fact the conduit responsible for bringing systems toward, or away from, equilibrium (Jaeger H. et al., 2000). These considerations point to a fundamental difference between the behavior of powder and liquid mixtures. In liquid mixtures, mechanical energy leads either to a uniform single-phase mixture (miscible components), or to two-phase system (partially miscible components). In either case, the end result is a dissipative system, i.e., at some point, any additional energy influx does not alter the composition of the mixture. In contrast, some powder mixtures, like the one illustrated in Fig. 2, do not reach equilibrium or even a steady state, despite continued energy influx.

Based on the above considerations, it is worth looking into the cause and effect of uniform vs. non-uniform mixtures. We can say that the mixture of Fig. 1 is uniform because it is energetically stable, while the opposite is true for the mixture of Fig. 2. In a uniform powder mixture, continued influx of mechanical energy leads only to multiple configurations of the same zero gradient blend. The rest of the mechanical energy is very effectively dissipated as heat. In an unstable, hence non-uniform mixture, such as that of Fig. 2, the continued influx of mechanical energy does not have the same clean-cut partitioning. Energy dissipation is particularly different. In each reconfiguration of the collection of particles, a portion of the energy supplied is chaotically absorbed and released, in the form of segregation and desegregation of the powder components, such that the mixture is never able to achieve full desegregation (uniform mix), nor full segregation into “two phases” (clean separation of the two powders). The unstable mixing of Fig. 2 should not be confused with the term “overmixing” often used in connection with lubrication using magnesium stearate (MgSt), for example. Optimal lubrication of powders with MgSt usually relies on
Generally speaking, powders are complex systems in terms of their properties and behavior. However, the type of complexity, or lack thereof, resides on the specific property in question and on the type of behavior it elicits on the powder. According to classical systems theory, systems can be Simple, Complicated or Complex (Cotsaftis M., 2009)—the uppercase notation on this first instance is meant to reflect that, as used here, these terms carry specific meanings. Accordingly, a simple system is one where each agent (particle in the case of powders) is weakly coupled with other agents. That is, each particle operates as an almost independent one-component subsystem. For example, consider a powder for which the microscopic characterization has been fully achieved down to the single-particle level. Taking the mass of the powder as a property of interest, it is simply the summation of the mass of every constituting particle. That is, the effect of one particle is completely unperturbed by the action of other particles.

A complicated system is one where the action of the constituting agents (particles) are somewhat, although weakly, coupled to the actions of other agents, but the system can still be decoupled for the most part. For example, for the hypothetical powder system described above, for which every single particle has been catalogued, it would be possible to predict the tapped density, with a reasonable level of confidence. That is, the action of one particle is somewhat perturbed by the action of other particles, but not to the extent of obliterating its effect on the property of interest.

A complex system is one where the action of one agent (particle) is strongly coupled to other agents. That is, the dynamics of the system are determined by the inter-agent interactions, effectively placing a shield to the tracking of other constituting agents. Consider once more the case of a fully characterized powder at the microscopic level. No extent of single-particle characterization, no matter how exhaustive, would be able to lead to a prediction of the avalanching behavior of the powder. The avalanching behavior of a powder is neither the total nor partial combination of the avalanching properties of its constituting particles. The avalanching phenomenon is a cooperative (powder) property, not a particle property. We can therefore say that avalanching is an example of an Emerging Property in powders (Corning P., 2002). Emergent properties (or emergent phenomena) is one of the manifestations of systems complexity. Emergence refers to properties or behavior observable in arrangements of multi-agent systems but not present in the individual agents making up the system (Corning P., 2002; Sitte R., 2009). The complex behavior of bulk powders is also observable in other properties. For example, the angle of repose (AOR) parameter, which has been widely used for decades, is an example of a deceptively simple, complex property. It is a very simple matter to experimentally measure the AOR. However, the usefulness of the AOR is severely limited as a design, control or operating tool, because its value depends on a multitude of parameters (Wouters I. and Geldart D., 1996). The AOR is another manifestation of complexity in powders; it is also an emergent property, and as such, it is the result of many variables operating all at once (Sitte R., 2009), some of which are not even traceable to the individual particles.

It is not surprising that efforts to predict powder properties have not been very successful for the most part. In predicting fluidized bed behavior for example, it is often assumed that particles behave independently from each other in the bed. More specifically, the equations and correlations carry the assumption that interactions among particles are exclusively collisional, and discrete elements models (DEM) rarely capture particle clustering for example. The reason is that no mechanistic model exists yet (McMillan J. et al., 2013). Paradoxically, it seems that the very strength of simulation models like DEM for example, i.e., their foundation on first-principles, is also at the root of their limitations in predicting the complex behavior of powders.

Simulation models inherently (perhaps unavoidably) bear the reductionist notion that a fundamental understanding of the properties and behavior of the different parts of the system inevitably leads toward a thorough understanding of the whole. This view is not necessarily naive, but perhaps somewhat anachronistic. That is, a legacy from the reductionist hubris from the early 20th Century and subsequent decades. Specifically, from the period when physics could arguably be considered as the king of science. In the early 21st Century, it is biology the science that arguably occupies the pinnacle placement. It is impossible to describe the attributes of living entities without deliberately counting on Complexity and Emergent Properties, since it involves a wealth of properties of the system that cannot be induced (predicted) from an understanding, even if thorough, of the constituting parts (Corning P., 2002). Accordingly, the last few decades have produced a resurgence in the study of complex systems and emergent properties, extending beyond living systems, including physics (Cornacchio J., 1977; Corning P., 2002).

Computer simulations of powder properties are firmly based on first-principles. However, to the extent that the existing set of first-principles remains incapable of predicting emergent properties, simulation-based description of powder behavior will continue to be limited. For instance, an elegant example of a first-principles based sequential simulation of powder materials, starting with quantum mechanical modeling, followed by molecular
mechanics simulation and subsequently DEM modeling, was very successful in predicting density, but not nearly as successful in predicting surface energy (Loh J. et al., 2013). We should point out that, like mass, density is the property of a simple or a complicated system (see definitions above). On the other hand, the surface energy of a powder is the property of a complex system. It is worth noting that the complexity of a system is not a single all-encompassing quality; a complex system is likely to have different types of complexity, depending on the property under consideration (e.g., density vs. surface energy) (Sitte R., 2009). Moreover, it is unlikely that all emergent effects play a role in every case (i.e., property under consideration), or that one emergent force has the controlling effect in all cases (McMillan J. et al., 2013). It appears that the notion of being able to predict bulk powder properties through computer simulations firmly based on first-principles is by no means incorrect, it is rather incomplete.

Predicting emergent properties is, by definition, beyond the reach of the current modeling paradigm. In addition to the first-principles already in place, the successful simulation and prediction of emergent properties and behavior of powders will require a set of second-principles. More appropriately put, there is a need for a second set of first-principles for emergent properties, which as of today, are not yet established. One can venture to say that no amount of computing power or degree of refinement on existing first-principle-based equations, will suffice to fully describe the complex properties of bulk powders. Today, the first-principles conundrum posed by Complexity is amply recognized across different segments of the scientific community, and significant advances toward elucidating those novel first-principles that govern emergent properties are being made (Chen C. et al., 2009; Galla T. and Guhne O., 2012).

2.2 Powder processing and surface properties modification

Full prediction of powder properties is still in the future at this time, but correlations involving bulk powder properties relevant to processing such as flowability, blending and compactability have been reported using bulk-surface energy measurements based on IGC. This approach has been useful in explaining certain phenomena and behavior that typical analysis methods cannot elucidate. The graphical insets in Table 2 show examples where IGC-based surface energy analysis of various systems help understand performance and associated responses during processing. However, in order to ascertain the presence of process-induced structural alterations, microscopic-level information, such as that provided by AFM or SPM (scanning probe microscopy) are indeed invaluable. The results show that a systematic characterization of milled molecular crystals provides fundamental insight essential to potentially predict and control bulk powder behavior.

A study on the surface of mannitol (Ho R. et al., 2010) found agreement between surface energy values obtained from contact angle measurements and those obtained from IGC analysis. Furthermore, the study found that the heterogeneity of surface energy resides mainly on the polar groups populating the surface, such that surfaces become more homogeneous when the polar groups are capped with non-polar functional groups using silanization. It is important for the significance of this finding to be clear. The heterogeneity of surface energy resides mainly on the polar groups populating the surface. However, the effect of such heterogeneity is mainly manifested through the dispersive (non-polar) component of the surface energy.

Table 3 lists powder materials that have been recently studied in our laboratory. The list includes two basic materials, waxy corn starch and a food powder (not identified for confidentiality reasons). Subjecting the basic materials to different processes results in different powders, each identified on the first column of Table 3. The different powder samples identified in the table have been subjected to surface-property evaluation using different techniques, including IGC, scanning electron microscopy (SEM), and X-ray photoelectron spectroscopy (XPS). Subjecting the basic materials to different processes gives place to different surface-modified powders in each case. The result of surface modification is a change in powder properties, as discussed below.

Fig. 5 shows the effect of exposing starch to enzymatic reactions on the surface energy of the powder. One of the effects of the enzymatic treatment of starch is the development of fine pores on the surface of the particles. There is also an increase in the surface energy of the treated powders, relative to the native (untreated) material. The dispersive component surface energy values span from 36.71 (native) to 43.34 mJ·m⁻², with AMG < CGT < AML. It is noteworthy that this magnitude of variation of the dispersive surface energy among the different starch powders, is of similar magnitude as the range found to result in completely different compaction properties for soluble starch (Chamarthy S. et al., 2009).

It is expected for powders in general, that the chemical composition of the surface has a direct effect on surface energy. It is further expected that the surface energy of the powder will have a strong effect on bulk properties such as powder flow. The food powder material in Table 3 provides a clear example this type of chained relationship.

The chemical bond composition of the surface of the five food powders produced by different processes was determined using XPS. The XPS results are listed in
Table 4. It is noteworthy that even though the starting material for making all five food powders is the same, the surface abundance of different chemical bonds, including the carbon/oxygen ratio, vary substantially among them. These results indicate that besides being an inherent characteristic of bulk powders, surface variability in terms of chemical composition can be substantial, depending on the processing conditions chosen. Therefore, it is important not to confuse surface heterogeneity assessed from a single particle (as done with microscopically-based methods), with surface heterogeneity assessed with bulk powder-based methods. The former provides a highly detailed, but a very small frame, of a truly large, multi-frame “panoramic” picture.

The results of surface energy analysis using IGC for the five food powders are listed in Table 5. The choice of process employed to produce different powders from the same starting material, results surface energy values that span from 31.2 to 43.3 mJ·m⁻². Notice once again that the magnitude of this difference in surface energy is of the order of that resulting in non-uniform mixing (see Fig. 2), as well as that conducive to distinctly different compaction properties (Chamarthy S. et al., 2009). Based on the spread of surface energy values among the different food powders, it is clear that surface energy is a critical factor in determining the performance of these materials in various applications.

Table 5. Examples of behavior tendencies of various powder systems in relation to their surface energy.

| Powder System                   | Surface Energy Tendencies |
|---------------------------------|---------------------------|
| Surface energy of milled griseofulvin associated with defects (dislocations) showing dislocations have the highest surface energy | Chamartihy S. and Pinal R., 2008a. |
| Surface energy of milled dl-propranolol increases with decreasing particle size. | (Adapted from York P. et al., 1998). |
| Decrease in surface energy of wood-polyethylene composite results in lower tensile strength | (Adapted with permission from Dominkovics Z. et al., 2007. Copyright: (2007) Elsevier B.V.). |
| Milling-induced amorphization of indomethacin monitored by IGC | (Reprinted with permission from Ref. Planinsek O. et al., 2010. Copyright (2010) Elsevier B.V.). |
powder lots, as initial estimate, it would be reasonable to expect different bulk powder properties among the differently processed food powders.

The practical applications of the type of information provided in Tables 4 and 5 is reflected in the bulk properties, such as powder flow. The cohesiveness of the differently processed food powder lots was investigated by its effect on the flow properties of the bulk powder. The avalanching energy was measured using a Revolution Powder Analyzer, RPA (Mercury Scientific Inc.) apparatus. Briefly, RPA uses a low stress and dynamic avalanching technique to determine the flow of the powder. The parameters determined on the RPA include the avalanche angle, the avalanche time, and the avalanche energy. The more cohesive, less flowing the powder, the greater the avalanche energy.

The results are graphically shown in Fig. 6. The figure shows that there is a correlation between the C-C signal from the surface of the powder obtained by XPS and the dispersive component of the surface energy. The figure also shows a correlation between the dispersive free energy of the powder, which is attributable in part to the
abundance of non-polar C-C bonds at the surface, and the tendency toward cohesiveness, or difficulty to flow of the powder.

The example in Fig. 6 is of great practical significance. It shows that subjecting the same starting material to the same unit operation (e.g., spray-drying), makes it is possible to obtain a powder exhibiting easy flow, or one exhibiting difficult flow, or even one with borderline flow behavior, all depending on the choice of process parameters.

The examples of Figs. 5 and 6, as well as the data for dispersive and composition on Tables 4 and 5, show the importance of the surface chemistry of excipients and food powders. Several reports on the effect of surface composition on the flowability and the nature of cohesiveness of powders upon handling can be found in the literature (Begat P. et al., 2005; Burgain J. et al., 2017; Chamarthy S. et al., 2007; Heng J. et al., 2006; Kim E. et al., 2005; Leturia M. et al., 2014; Thakur S. et al., 2013).

3. Complementarity of bulk- and microscopic (mechanical)-based analysis methods

Microscopic-level techniques such as AFM or SPM and bulk-level techniques such as IGC are all high sensitivity methods, although with very different scales of analysis (resolution). The two types of techniques are complementary toward the ability to fully understand powder properties and behavior. Each of the two types of analysis methods provides different pieces of information, which together make a fuller picture. AFM and SPM inform about the individual agents (particles), while IGC informs about the cooperative (emerging) properties from such agents. It is important to point out that even though microscopic, single-particle analysis methods make it a practically impossible task to ascertain surface heterogeneity at the bulk (m²) scale, it does not mean that such methods are unsuitable for assessing bulk properties of powders in general. On the contrary, based on single-particle analysis, microscopic techniques are uniquely suited for informing about bulk behavior in processes such as milling.

Powder materials are prevalent in various industrial segments, and milling is equally almost ever-present as the unit operation of choice for particle size reduction. An important disadvantage is that as a rule, the milling process is difficult to control, making it almost impossible to tell much in advance about the response of the powder as its constituting particles undergo size reduction.

This section discusses a viable approach for probing the mechanical response, such as plastic-elastic properties and fracture phenomena of APIs (active pharmaceutical ingredients) molecular crystals, obtainable in advance to subjecting powders to unit operations that involve mechanical stress. The approach consists in using SPM-based nano- and micro-scale measurements, in order to establish the likely macroscopic-scale behavior. This type of single-particle approach provides the possibility of predicting particle size outcome with minimal crystal disruption, giving a level of confidence about the physical changes induced by milling without the need to conduct run-and-stop milling tests in order to ascertain the desired milling endpoint. The underlying concept is based on taking advantage of the ability to microscopically measure the inherent mechanical properties of the crystal. This information is then used to predict particle fracture behavior during milling. The parameters obtained from this type of testing provide a new perspective toward the fundamental understanding of the complex bulk process of milling.

As mentioned earlier in this report, of the mechanical energy supplied during milling, a portion is consumed in particle fracture, a portion is dissipated as heat, and another portion gets incorporated into the activated powder. Activation, in turn, occurs both at the core-particle level, as disruptions to the crystal lattice, and at the surface level, as changes in the surface energy of the powder. The preceding sections of this article focused primarily on the surface activation effect. In this section, we focus on the energy portion first named above. Specifically, on the way microscopic analysis methods can provide specific information about particle fracture, and how this information can help in predicting some bulk properties of the resulting powder.

The plastic-elastic properties of materials play a determining role on their behavior during milling. Plasticity in crystals results from activating multiple slip systems to accommodate strains in multiple directions. In pharmaceutically relevant crystals, the chance of activating a rather limited number of slip planes simultaneously, is significantly greater than in the case of cubic unit cell systems, common in easily deformed metals, for example. Studies on succinic acid (Jing Y. et al., 2011) using nanoindentation show the presence of a limited numbers of slip planes. A similar situation has been observed with other organic crystals, such as acetaminophen (Ho R. and Heng J., 2013). The abundance, or lack thereof, of slip planes in the crystal is critical in determining whether materials will deform plastically via slip, or if fracture will occur. Creation of dislocations or defect-induced amorphization (Ho R. and Heng J., 2013; Jing Y. et al., 2011) are possible with plastic deformation. Lower tendency toward amorphization is usually conducive to particle fracture. Particle fracture, in turn, may be either a desirable (micronizing) or undesirable (tabletting) response of a solid.

The mechanical properties profile curves for pharmaceuticals is similar to that obtained with ceramic and...
energetic materials (explosives), measured using nanoindentation (Taw M. et al., 2017). Plastic deformation in these systems can be imparted during processing (milling and compaction), and the defect density subsequently influences properties such as hardness and elastic modulus, as well as performance attributes (Nibur K. and Bahr D., 2003). A study on the deformation of a brittle molecular crystal such as sucrose using nanoindentation, allowed the identification of the onset of dislocation motion prior to fracture (Ramos K. and Bahr D. 2007). This type of experiments showed promising results on the applicability of nanoindentation to quantify plasticity of pharmaceutical and food materials.

The crystal lattice of a solid is one of the dominant factors for controlling the response of the material to an applied stress. Nanoindentation allows mechanical testing of submillimeter crystals, in order to determine the stress-strain-fracture behavior of solids. This allows to quantify elastic, plastic, and fracture behavior tendencies. Nanoindentation is a technique that has been used to experimentally identify slip planes in inorganic materials like metals and semiconductors (Bradby J. et al., 2001; Nibur K. and Bahr D., 2003; Ramos K. et al., 2009; Stelmashenko N. et al., 1993).

Fig. 7 shows an example of force-displacement curves involving caffeine (Ghosh S. et al., 2013). The shift behavior can be related directly to both slip and fracture events, and provides insight into the way the competition between these two phenomena, determine how brittle a molecular crystal is.

The crack initiation threshold, subject to elastic/plastic indentation has been reported from indentation studies in ceramic materials (Lankford J. and Davidson D., 1979). The strength of particles was calculated based on the interaction between crystal flaws, where flaws play a dominant role in particle fracture, and the local stresses are significantly greater than the loading stress (Inglis C., 1913). During particle fractionation in a mill, particles are first stressed, then cracks may propagate from preexisting flaws, leading to maximum the tensile stress (Wong R. et al., 2001). Following these reports, and recognizing that in the pharmaceutical industry crystalline APIs are rarely used without milling, de Vegt O. et al. (2009) studied the influence of flaws and crystal properties on particle fracture in a jet mill, using sodium chloride as model compound. It was concluded that impurities and pre-existing flaws in the crystals influence the fracture behavior of particles in a jet mill. Prediction of fracture behavior of molecular crystals has been proposed using the hardness to stress ratio as criterion (Burch A. et al., 2017a). Organic molecular crystals are more challenging; they exhibit much less symmetry, are anisotropic and with very complex structures compared to those of many metallic or ceramic inorganic materials.

A study on the characterization of the mechanical properties of five pharmaceutical materials was conducted using a similar fracture mechanics approach to that applied to ceramics and semi-brittle materials. The study was performed using large size crystals, providing differentiating information between brittle and semi-brittle materials (Taylor L. et al., 2004). This type of information can be used for cataloguing solids to be subjected to milling.

The study of mechanical deformation of molecular crystals is often challenging because of their brittle or ductile nature. Conventional methods of testing, including microindentation of compacts or microindentation of single crystals, leads more often than not to fracture (Bradby et al., 2001; Maughan et al., 2015). A further complication is that growing large size (millimeter) crystals of many pharmaceutical materials is difficult if not impossible.

More recently, a nanoindenter was used to test very small, submillimeter crystals, in the range of 50 to 200 μm. With this approach, a wide variety of crystalline solids can be examined, including those that are difficult to grow into larger single crystals. Studies on the mechanical properties of griseofulvin (Maughan M. et al., 2015), idoxuridine and pentfluorobenzamimide (Burch A. et al., 2017b) demonstrated that brittleness of pharmaceutical crystals can be determined by nanoindentation. The technique allows testing with a variety of tip geometries and very high local stresses at ultra-low loads, making it possible to identify the nucleation of dislocations and orientation dependent strength prior to fracture (Burch A. et al., 2017b; Maughan M. et al., 2015). Thus, the nanoindentation technique has excellent potential as a means for predicting the degree of size reduction upon milling.

Force-displacement curves provide information on the plastic-elastic deformation of materials. Assessing fracture behavior, elastic and plastic properties of molecular crystalline structures including pharmaceuticals, food...
and some explosives are of interest due to the need of understanding and controlling the range of behavior of materials under mechanical stress. Clearly, the materials from these industries have very different specific uses and practical applications. However, all these crystalline materials share similarities in their molecular arrangements and in their physical and mechanical responses. Actually, studies on energetic materials (explosives), often rely on APIs used as “mocks” due to safety, handling and cost considerations.

Table 6 and Fig. 8a show the force displacement similarities, and lack thereof, between two APIs and one explosive using a Berkovich indenter (Burch A. et al., 2017b). The crystalline explosive cyclotetramethyl- enetetranitramine (HMX), and two crystalline APIs serving as inert “mock” materials, idoxuridine (IDX), and 2,3,4,5,6-pentafluorobenzamide (PFBA), were used for comparison. It was found that IDX served as a suitable inert “mock” material to study and simulate the properties of the explosive HMX, whereas PFBA was not a suitable “mock” material.

Fig. 8b shows the unloading traces of IDX. At maximum load, the traces are superimposable, an indication that the sample did not crack (Burch A. et al., 2017b). Notice that if cracking occurred, the degree of cracking, as well as the distribution of cracks would need to be identical between the two samples for their profiles to overlap (Morris, 2007).

An important aspect is that in the field of propellants, explosive and pyrotechnic materials, pharmaceutical organic compounds are used as surrogates to understand their properties. Thus, the pharmaceutical field will clearly benefit from the analysis methods developed in the high energy materials field. It is now possible with these methods to study plastic-elastic deformation and to apply this knowledge during formulation and process development.

Nanoindentation studies are promising for determining the mechanical properties of materials that can in turn predict particle size output after milling or compaction behavior. Recent studies establish nanoindentation as a useful technique to measure mechanical properties (elastic-plastic properties and fracture behavior) of submillimeter samples where traditional mechanical testing techniques fail to meet the size or geometric requirements (Burch A. et al., 2017a). The physical parameters at the single-particle level, or more precisely, at the single-plane of the particle surface level, obtained using nanoindentation are informative about the bulk powder level response of crystalline materials subjected to milling. An example of a bulk property of powders that is better assessed using microscopic (non-bulk) analysis methods is the pulverization factor, P, obtained from nanoindentation measurements (Zbib M., 2015). This parameter provides information on the primary failure mechanism of the particles, i.e., comminution vs. cracking.

4. Conclusions

Structural differences in the arrangement of powders and the state of agglomeration within a formulated powder do not depend directly on the properties of the constituting particles. The behavior of large collections of particles involve emergent properties, i.e., attributes that cannot be

Table 6  Mechanical properties for HMX (explosive) and two “mock” APIs (*20 indentations × 10 crystals per material).

| Material | *H (GPa) | *E_r (GPa) |
|----------|----------|------------|
| HMX      | 1.00 ± 0.11 | 25.2 ± 2.1 |
| IDX      | 1.00 ± 0.15 | 23.3 ± 2.2 |
| PFBA     | 0.25 ± 0.04 | 4.69 ± 1.43 |

* Reprinted with permission from Ref. Burch A. et al., 2017a

![Fig. 8a](image-url)  Force-displacement curves and Fig. 8b. Unloading profiles Reprinted with permission from Ref. Burch A. et al., 2017a. Copyright 2017.
directly traced back to the particles themselves, but originate as cooperative properties. Therefore, many critical bulk properties of powders depend, to a very significant degree, on the combined surface properties of collections of particles, which operate as a whole and for the most part, cannot be traced down to partial contributions from individual particles. In addition, environmental factors and processing history, including manufacturing processes and storage conditions become encoded primarily, although not exclusively, on the surface of the materials, thus playing a dominant part in powder properties and performance.

Processing conditions involved in milling, spray drying and freeze drying invariably alter the surface of powder materials. The changes in surface involve variations on the type of functional groups exposed at the surface. The direct result of such variations is variations on surface energy and consequently variations on cooperative interactions that manifest themselves in bulk properties such as powder flow, compaction, wetting and blending properties.

Some but not all bulk properties of powders depend on material characteristics and the size of the primary particles. Particle size reduction effects can be reliably related to the properties of the constituting particles, especially using nanoindentation techniques.

We have shown that the characterization of powders needs to go beyond traditional physicochemical assessment. A combined assessment of bulk-surface and nano-mechanical properties will be necessary in order to achieve a through characterization mapping of the particle properties along with a robust understanding of their collective behavior.

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Authors’ Short Biographies

Rodolfo Pinal

Dr. Pinal is Associate Professor of Industrial and Physical Pharmacy and director of the Dane O. Kildsig Center for Pharmaceutical Processing Research (CPPR) at Purdue University. He obtained his PhD in Physical Pharmacy from the University of Arizona. Before joining Purdue, Rodolfo worked for thirteen years in the pharmaceutical industry. He was Research Leader at Hoffmann-La Roche, heading the Solid State Pharmaceutics/characterization group. His research focuses on solubility and solubilization of drugs from both the solid-state properties and solution chemistry perspectives. His research includes studies on excipient functionality and he is currently working on formulation technologies for patient-centered medicine.

M. Teresa Carvajal

Dr. Carvajal is a Faculty Member at the Agricultural and Biological Engineering department at Purdue University. Prior to joining Purdue University, Dr. Carvajal worked in the pharmaceutical industry for 13 years, Hoffmann-LaRoche (NJ) and Bayer (CT). She obtained her Ph.D. in Powder Technology from the University of Bath, UK, M.S. in Physical Pharmacy, a minor in Physical chemistry from the University of Arizona, USA and B.S. in Chemical Pharmaceutical Biologist from the UNAM, México. Carvajal’s research approach is on surface-mechanical-processing relationships for understanding bulk properties and impact on formulation development, processing and performance of Food and Pharmaceutical powders.