Pharmaceutical Solids: Size, Shape, and Surface Area

“Pharmaceutical Solids” discusses scientific principles associated with pharmaceutical solids useful to practitioners in validation and compliance. We intend this column to help the understanding of principles associated with pharmaceutical solids and to be a useful resource for daily work applications. The key objective for this column: Useful information.

Reader comments, questions, and suggestions are needed to help us fulfill our objective for this column. Suggestions for future discussion topics or questions to be addressed are requested. Case studies illustrating principles associated with pharmaceutical solids submitted by readers are also most welcome. Please send your comments and suggestions to column coordinator John Bauer at consultjb@comcast.net or to journal coordinating editor Susan Haigney at shaigney@advanstar.com.

KEY POINTS DISCUSSED
The following key points are discussed:
• Physical properties of pharmaceutical solids such as particle size, particle shape, and particle surface characteristics
• Physical properties may have significant effects on pharmaceutical manufacturing
• Particle size is the primary parameter monitored in pharmaceutical manufacturing
• Particle shape and particle surface area including porosity are linked to particle size
• Particle surface area may influence flowability, compactability, hygroscopicy, and other solids properties
• Specific analytical methods are used to determine particle size, particle shape, and particle surface area
• Particle size is measured by several different methodologies. Comparison of data between lots should utilize the same instrumental method and be accompanied by microscopic examination
• Particle size data is often reported as “equivalent spheres” through mathematical calculation
• Certain pharmaceutical processes such as milling, wet granulation, and encapsulation may be significantly impacted by physical properties
• International Conference on Harmonisation (ICH)/Code of Federal Regulations (CFR) guidelines provide a decision tree to determine whether a particle size specification is recommended
• The difficulty of sampling pharmaceutical solids may contribute to data variation. Sampling using process analytical technology (PAT) methods is recommended.
• Practical implications of particle size may include active pharmaceutical ingredient (API) biopharmaceutics, API and product process effects, raw material supply, and change control
• The discussion and recommendations herein are consistent with the recent US Food and Drug Administration draft guidance on process validation.

INTRODUCTION
The large majority of APIs and excipients are solids at room temperature. Most manufacturing processes for both bulk drug and dosage forms involve isolation of solids, flowing of solids, mixing of solids, and wetting and drying of solids. How efficiently and reproducibly these operations can be performed is dependent on the characteristics of the solids involved.

The last issue of this column discussed extensively the phenomenon of solid form and, specifically, crystal form. The solid form is important because of the effect it has on the physical properties of the solid.

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**Figure 1:** Photomicrography of Ritonavir forms 1 and 2.

**Figure 2:** ICH classification of particle shapes.

These physical properties have a direct impact on the physical processes or unit operations involved in drug manufacturing. There are four intrinsic properties of each single solid used and each component in the formulation mixture. They are composition, particle size, particle shape, and particle surface characteristics. Composition is usually determined by chemical analysis in combination with dispensing records. In the author's multiple years working in the pharmaceutical industry, the large majority of the manufacturing problems encountered has been related to physical properties rather than composition.

This article discusses particle size, particle shape, and particle surface characteristics; how they are characterized; their impact on various stages of manufacturing; and whether a specification is needed. Particle size is the usual physical property monitored for bulk solids and granulations. However, before discussing particle size, we will discuss particle shape and surface area. Particle shape and particle surface area including porosity are inextricably connected to particle size. Analytical methods, data interpretation, regulatory guidelines, and practical implications of this information are also discussed.

**PARTICLE SHAPE (MORPHOLOGY, HABIT)**

The crystal packing or internal arrangement of a solid can impact and often determine the shape of growing crystals. This in turn may impact the shape of solid particles that are formed as the compound is precipitated or solidified. The reason for this is that crystals grow by attaching new molecules onto the surface of existing crystals. If all the attachable sites are on one end of the crystal, then that crystal can only grow in one direction. The extreme example of this is a thin elongated needle that gets longer very quickly but wider only slowly. Figure 1 shows the shapes for the two crystal forms of the protease inhibitor, Ritonavir. Since crystal forms can influence shape, sometimes a certain form is preferred because of the particles it produces. Figure 2 shows the ICH classification (1) for describing particle shapes. The general shape of the solid is its morphology and these external shapes are referred to as crystal habits.

As mentioned in the previous column (2), solids can exist as crystalline material (i.e., with an established repeating unit of organization or unit cell), or as an amorphous solid with various degrees of disorder. A pharmaceutical compound, however, can exist in a particular crystal form yet be isolated in different habits depending on such factors as supersaturation of the crystallizing solution, pH, agitation rate and time, cooling rate, impurities, drying technique, and other factors. In other words, constancy of these conditions is very important to the manufacture of reproducible particles.

The shape of particles can affect their mechanical properties, for example flowability. A particle’s tendency to flow is related to sphericity—the greater the sphericity, the better the flow properties—needles and plates do not flow very well. Additionally, particle orientation can occur during compression, weakening the final tablet. The degree of agglomeration is also dependent on crystal shape (habit).

Crystal habit can also influence interfacial properties that directly affect bioavailability. Most significant of these are wettability and dissolution rate.
These properties depend on the nature of the functional groups exposed at dominant faces. More polar groups on the faces promote wetting by aqueous fluids and faster dissolution; non-polar groups hinder these important physical properties and may affect the biopharmaceutics of a drug.

**PARTICLE SURFACE AREA**

The relative amount of active groups exposed for an individual lot of solid is expressed in terms of surface area. There is no generally accepted definition of surface area for an irregular or porous solid. Rather, the specific surface area of a solid is defined in terms of an indirect measurement. This is determined by physical adsorption of a gas, usually helium or nitrogen, on the surface of the solid.

The surface area may be correlated to dissolution rate and other physical parameters. For example, the maintenance of a consistent surface area for the lubricant magnesium stearate may be needed to ensure that lubrication occurs without overcoating the drug particles and impeding dissolution.

Processes that may be affected by surface area include the following:

- Aggregation/deaggregation of particles during blending
- Flowability of drug, excipients and mixed powder
- Amount of granulating liquid required to avoid either overmassing or undermassing
- Compactability of powder or granulation
- Hygroscopicity of powder or powder mix.

By nature of the solid form, amorphous solids have greater surface area and are consequently more prone to problems.

**PARTICLE SIZE**

A third physical property of solids which can in some ways be considered as incorporating the impact of both particle shape and surface area is particle size. In some cases, the undesirable properties resulting from particle shape can be minimized if the size of the particle is controlled. The same can be true of the surface area and, as a result, particle size is the parameter most often specified in control documents.

As one might expect, however, particle size and surface area are not interchangeable. The correlation between surface area and particle size is dependent on the shape of the particle. For example, a sphere with a 10-micron diameter will have a surface area of 310 meters squared/gram while a cube with a 10-micron edge will have almost twice the surface area at 600 meters squared/gram. Most particle size detectors will see both of these as 10 micron particles. Therefore the choice between applying surface area specification or particle size specifications must be made on the basis of the specific application. Surface area is more appropriate for applications involving hygroscopicity or oxidation concerns. Particle size is more appropriate for applications involving bulk density and mixing concerns. If surface area is found to be the significant parameter, the porosity of the solid must be kept in mind and a validated quantitation method distinguishing the two must be developed.

In most cases, particle size is the parameter that is chosen to be monitored. However, as mentioned previously, the shape of the particle will influence the interpretation of data such as “particles between 10 microns and 100 microns.” These could be particles that are flat plates 100 microns by 100 microns or needles 100 microns long. It is critical that particles should always be observed microscopically as a sanity check on particle size data.

Particle size is often manipulated during the solid (i.e., API or excipient) manufacturing process by controlling precipitation rates, cooling rates, and times. These techniques naturally control the size by controlling crystal growth. Particle size is also often controlled by mechanically reducing the size through either screening (i.e., forcing through a given mesh size screen) or by milling. The milling operation can produce uniform particle size but can also produce high energy areas or areas of disorder in the particles that may increase hygroscopicity and decrease stability. Therefore, milling should be carefully characterized and validated and any changes in milling techniques should require a new validation.

**ANALYTICAL METHODOLOGY**

Particle shape or morphology, particle surface area, and particle size can be investigated and quantitated by the following methods:

- Morphology is evaluated by direct microscopic observation. Image analyzers are used to examine a sample of solid and produce images, measure dimensions, and determine aspect ratios (i.e., width divided by height).
- Surface area as mentioned previously is quantitated indirectly by measuring the amount of an inert gas that is adsorbed as a monolayer on the surface of the solid.
Particle size measurements can be done directly by gravimetrically determining the percent of a solid sample that passes through a given pore size sieve. Using a series of sieves, a size distribution can be determined. This method requires a large sample and is labor intensive. Most often an indirect technique is used by measuring particles as they pass detectors of various kinds: X-ray diffraction, light scattering, X-ray absorption, or passing through a calibrated orifice. A very common technique is light obscuration which measures individual particles by passing each through a laser and measuring the area of the shadow. These methods can be used to generate particle size distributions for various lots. The distribution will indicate whether the batch of solid has a narrow range of particle size, a bimodal distribution, or a bell shaped (normal) distribution as shown in Figure 3.

The normal or Gaussian distribution would indicate that the solid very likely came from a single batch through a natural crystallization or precipitation process. The narrow distribution can be the result of screening the solid through select screens then selecting an individual cut. Bimodal distributions can come from combining two such individual cuts or from inadvertently combining two populations. All these distributions can have benefits and drawbacks. Looking at the sizes and particle numbers in the three distributions shown in Figure 3, one would calculate approximately 80 microns as the average particle size in all cases; however, these lots will behave differently in formulation processing. The normal distribution is preferred for uniform mixing and blending in such operations as pre-granulation or dry mixing processes.

It is, therefore, necessary to fully understand the type of data being generated and its relevance to the particular manufacturing process involved. This author suggests that size distributions be the preferred data output.

UNDERSTANDING PARTICLE SIZE RESULTS
In order for the various analytical instruments to compensate for the variety of solid particle shapes, instruments use an algorithm or mathematical conversion to determine the equivalent spherical diameter (i.e., the equivalent size of any shaped particle when it is rolled into a sphere) (see Figure 4).

The further away from spherical the actual particle shape is, the greater the difference between instrument results and the actual dimension. For this reason and...
because different techniques and instrument manufacturers use different algorithms, particle size values should not be compared between techniques or instruments. Data should be treated as relative values—in other words, to compare particle sizes between lots and not to determine actual size. The size distributions, on the other hand, should be comparable across techniques as long as one allows for differences in size values and for individual technique limitations (1). In order to relate particle size measurements to actual behavior of the solid in a particular manufacturing process, one must keep sample preparation in mind and what data are important: Smallest particle size, particle as processed, particle as used, or size distribution. Results must be interpreted in conjunction with direct microscopic observation. Although there are some theoretical correlations between particle size and manufacturing performance as the examples in Table I show, any meaningful correlation between particle size and performance must be experimentally determined (i.e., through a series of process runs using different particle size material). Only in this manner can one determine if particle size is critical and must be controlled for their particular manufacturing process.

REGULATORY GUIDELINES

Figure 5 shows the CFR decision tree (3) on particle size specification requirements. The first question concerning solubility can in some cases be addressed by the Biopharmaceutics Classification System (BCS) category (see Table II) of the drug substance. But in general, the four basic questions can only be accurately answered through process justification experiments. Answering the following questions determines whether or not a particle size specification is recommended:

- Is the particle size critical to dissolution, solubility, or bioavailability?
- Is the particle size critical to drug product processability?
- Is particle size critical to drug product stability?
- Is particle size critical to content uniformity?

If the answer to any of the questions is “yes,” a particle size specification is needed. If the answer to all of the questions is “no,” a particle size specification is not needed.

As mentioned previously, particle size can have an influence on wettability and dissolution. If one is trying to formulate an active ingredient that falls into BCS class II or IV (i.e., it has low solubility), it is sometimes possible to overcome this obstacle by reducing the particle size of the drug greatly using a micronizing mill. This technique has made it possible for several important drugs to be formulated effectively in spite of unfavorable intrinsic properties.

The decision tree in Figure 5 addresses drug substance. However, the same particle size concerns are applicable to excipients and granulations.

Snorek, Bauer et al (4), sponsored by the Product Quality Research Institute (PQRI) (5), presented a comprehensive discussion of particle size techniques.

| Table I: Examples of impact of physical properties on individual unit operations. |
|-------------------------------------|-----------------|---------------------------------------------------------------|
| Unit operation         | Physical property | Potential impact                                                                                             |
| Sizing/milling         | Morphology       | A change in morphology can affect the fracture properties of the solid thereby altering the final particle size obtained |
| Encapsulation          | Morphology       | Higher aspect ratio solids (needle-like) flow poorly                                                        |
| Encapsulation          | Particle size    | Generally a decrease in particle size decreases flowability                                                  |
| Wet granulation        | Surface area     | Increase in surface area may cause increase in massing time or granulation fluid                           |
| Wet granulation        | Particle size    | Decrease in particle size may cause decrease in massing time or granulation fluid                           |
| Compaction             | Particle size    | Smaller particles are more brittle than larger particles but have higher bonding index                       |
| Suspension             | Particle size    | Increase in particle size will increase settling rate and decrease suspension stability                     |
| Suspension             | Morphology       | Spherical particles settle faster than non-spherical particles                                              |
method validation, and decision trees for particle monitoring throughout the development process.

**SAMPLING AND PROCESS ANALYTICAL TECHNOLOGY**

In any of the particle characterization techniques, an analyst could be examining less than a gram of solid to determine the particle properties of several kilos of powder. Unlike purity, impurity profile and other characteristics, particle size, shape, and surface area are not necessarily uniform throughout a batch of solid. Sampling is critical when determining these properties. This includes sampling from the batch, sub-sampling for the analytical assessment and further sub-sampling for the individual technique. According to the “Golden Rule of Sampling” (6), a powder should be sampled when in motion, and the whole sample stream should be taken over multiple short time increments, rather than part of the stream being taken for a longer time. Because it is not always possible to sample batches in this manner, in-line particle size monitoring offers many advantages. In this technique, methodology such as Raman spectroscopy or a Lasentech instrument is used to continuously monitor particle size during processing.

Sub-sampling for analytical testing is also critical. Allen (7) presents a good comparison of the common methods. He concludes that a spinning riffler is the best approach. A riffler uses a vibratory feeder trough to provide a constant flow of material from a hopper; then, a dividing head sharply separates the flowing material into as many as 16 sample vessels. Sampling problems with solids have been recently discussed by Smith (8).
PRACTICAL IMPLICATIONS OF PARTICLE SIZE

The following key topics associated with particle size are important considerations for pharmaceutical solids:

- Formulation and process understanding including risk analysis
- API biopharmaceutics
- API process effects
- Pharmaceutical product process effects
- Change control and validation
- Manual processes
- Raw material supply
- Analytical data
- Contract manufacturing and testing.

Formulation And Process Understanding Including Risk Analysis

Fundamental to appropriate control of particle size in API and product manufacturing is understanding of formulation and process considerations. Evaluation using risk analysis methods will help focus attention on potential problem situations. Identification of high-risk materials will enable appropriate focus on control strategies and problem prevention. For example, processing of a high-potency, low-dosage API will likely require greater in-process control than a low-potency, high-dosage API for bioavailability or manufacturing-process reasons. FDA is aware of the importance of physical properties and requires that their impact be studied as part of any new submission. These studies, however, are directed towards active ingredients even though that is by no means the only solid involved in dosage form manufacture. The same comments made here about the properties of a drug also apply to excipients. As shown by the examples (see Table I) in this article, each of these properties can have significant effect on the different unit operations involved in the process—or could have no impact at all. For any new process or any change in solid supply, evaluation is necessary to determine whether physical property specifications are required.

API Biopharmaceutics

The biopharmaceutics properties of an API may be affected by changes in solid physical properties. This is especially important for BCS category II and IV compounds which have low solubility. The efficacy of low solubility drugs that have low bioavailability may be adversely affected by the inadvertent increasing of particle size because of lack of good in-process control.

<table>
<thead>
<tr>
<th>Class</th>
<th>Permeability</th>
<th>Solubility</th>
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<tr>
<td>I</td>
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API Process Effects

The internal structure or solid form in conjunction with manufacturing conditions such as degree of supersaturation, agitation, rate of cooling, and milling contribute to the external properties of size, shape, and surface area for the bulk solid. Consistency of these properties is necessary for the future reliable and reproducible dosage form manufacturing process.

Pharmaceutical Product Process Effects

There are several manufacturing processes that may potentially change the physical properties of pharmaceutical solids, and may subsequently affect bioavailability or manufacturing processes. For example, wet granulation and milling, if not well controlled, can significantly affect solid properties in the formulation.

Change Control And Validation

A comprehensive change control program that will enable evaluation for possible future validation is key to minimizing problem situations. Personnel must be trained to be mindful of change. For example, when milling of a specific pharmaceutical solid is known to affect further processing, manufacturing operators must be aware of this risk and control their performance appropriately.

Manual Processes

Manufacturing processes with performance or control by people are more likely to exhibit variation in physical properties. For example, the particle size of an API crystal may be affected by the rate of addition of solvent to a mixing tank. The particle size of milled solids may be affected by the rate of addition of solids to the impact mill. If these processes are completely controlled by manufacturing operators, high levels of variation may occur.
Raw Material Supply
High risk API or excipients obtained from outside sources should be carefully monitored. For example, significant changes in the particle size of material to be wet granulated may have a significant affect on the granulation process, resulting in poor subsequent processing and product dissolution problems. Changing suppliers of high-risk materials for cost savings reasons is a common practice with high potential for problems. High-risk materials from new suppliers should be carefully evaluated.

Analytical Data
Particle size may be measured by various analytical methods. Different methods use different operating principles and/or mathematical data treatment to determine particle size. Quantitation of any of these properties is unique to the technique used, and values should not be compared across methods. For example, particle size determined by a Malvern instrument will likely be different than particle size determined by an Accusizer instrument because of differences in measurement method. When comparing data from the same instrument, values should be used to compare the relative consistency of lots and not considered as absolute measurements.

Contract Manufacturing And Testing
Whenever any of the above processes or testing is conducted by an outside organization, the risk of changes or subtle differences and subsequent problems is increased. Data obtained from contract laboratories should always specify instrument make and model, sampling protocol, and data treatment method.

CONCLUSIONS
This discussion has attempted to briefly introduce important practical concepts associated with particle size and associated pharmaceutical solids physical properties. Although a drug’s chemical composition is the major consideration in the pharmacological activity of a pharmaceutical dosage form, the external physical properties of the drug solid and excipients are often more important to the manufacturing process. These physical properties are frequently overlooked as a cause of manufacturing problems. After a stable polymorphic form of API is selected for development and can be reproducibly manufactured, there are still many potential problems during API and pharmaceutical product manufacturing because of physical properties. Practitioners in pharmaceutical validation, manufacturing, quality, technical support, and associated functional groups must be aware of this potential. Fundamental to this awareness is basic understanding of the materials and processes, identification of potential input variation, and strategies for appropriate control throughout the entire product lifecycle. These points are consistent with the recent FDA draft guidance on process validation (9).

REFERENCES
5. www.pqri.org/index.asp

ARTICLE ACRONYM LISTING
API Active Pharmaceutical Ingredient
BCS Biopharmaceutics Classification System
CFR Code of Federal Regulations
FDA US Food and Drug Administration
ICH International Conference on Harmonisation
PQRI Product Quality Research Institute