

Chapter 2

Characterization of Inert Cores for Multiparticulate Dosage Forms

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Abstract For many multiparticulate products, the process begins with an inert core. As the starting material, the characteristics of an inert core influence each successive step including the end-product performance. Identifying the critical to quality attributes (CQA) of an inert core and how they influence a product is essential throughout the development, scale-up, and manufacturing stages. In this chapter, various characteristics such as surface area, particle size distribution, various density, shape, surface morphology, robustness and processability, hardness and tensile strength, and friability are discussed. These tests are beyond the pharmacopeial tests of standard and purity and usually do not appear on most of the inert core excipient manufacturers' certificate of analysis. Understanding these characteristics helps in developing a robust product and also understands any unforeseen variability between different and the same batch of final multiparticulate dosage form.

Keywords Inert cores • Sugar sphere • Pellets • Beads • Multiparticulates • Particle size • Friability

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2.1 Introduction

For many multiparticulate products, the process begins with an inert core. As the starting material, the characteristics of an inert core influence each successive step including the end-product performance. Identifying the critical to quality attributes (CQA) of an inert core and how they influence a product is essential throughout the development, scale-up, and manufacturing stages.

This chapter introduces characteristics of inert cores important to multiparticulate dosage forms. With the wide range of process technologies used for multiparticulate dosage forms, not all the characteristics listed are considered CQAs for every application. Each characteristic is discussed in isolation, but often multiple characteristics are changing simultaneously. The ability to quantify each characteristic and understand how they are interrelated will provide benefits in the long term.

2.2 Inert Cores (Pellets)

An inert core is defined as a material used as a carrier for layering a drug substance or active pharmaceutical ingredient (API). The substrate is composed of one or more ingredients like starch, sucrose, or microcrystalline cellulose [1, 2]. While many multiparticulate processes, like extrusion spheronization, incorporate the drug into the particle, a key difference of inert cores is that the starting core does not contain the API [3]. Many of the properties discussed can be used to characterize any multiparticulate substrate, but the focus here in this chapter is on inert cores. Inert cores are often referred by different names such as nonpareil seeds,

Table 2.1 List of commercially available inert cores

Core pellet material	Brand/Generic spheres (Manufacturer)
Sugar	Suglet [®] (Colorcon), Sugar spheres (Werner, Sanaq)
Microcrystalline cellulose	Cellets (Glatt), Celspheres (Asahi Kasei)
Isomalt	Galen IQ 980 (Beneo)
Xylitol	Xylinerts (IPS)
Mannitol	MCELL (Pharmatran), Mannitol spheres MAS (Umang)
Silica/glass	Spray spheres – AS (Umang)
Tartaric acid	TAP (Sanaq), Tartaric acid spheres – LS (Umang)
Carnauba wax	C-Wax pellets (Sanaq)

starter core, starter pellets, pellets, neutral pellets, starter spheres, and beads. From this point on in this chapter, they would be referred as pellets. There are a limited number of commercially available pellets developed for pharmaceutical multiparticulate applications, and Table 2.1 lists the most common materials. Sugar spheres and microcrystalline cellulose spheres are the only products currently listed in the US Pharmacopeia/National Formulary (USP/NF). A wide range of other materials have been evaluated as inert cores, but these require extra processing like granulation or extrusion/spheronization to achieve a substrate with desirable characteristics. The use of these materials is common when the substrate exhibits some minor functionality. An example is tartaric acid pellets used as a substrate to control the pH environment around the drug substance [4].

2.3 Product Quality for Pellets

The various compendia (USP/NF, Ph. Eur., and JP) provide a starting point for characterizing pellets. The objective of any compendia is to define the minimum standards of quality, and it is common for the specifications to focus on identity, safety, and purity. For pellets that are not listed in the compendia, the manufacturer's certificate of authenticity (COA) lends guidance to the quality of the material.

Table 2.2 shows the USP/NF and Ph. Eur. specifications for sugar spheres, focusing on the composition (assay and loss on drying), grade (particle size estimation), and purity (chemical and microbial impurities) of the product. Though the particle size of a substrate is a well-known critical quality attribute (CQA) [5], sieve analysis does not provide details about the particle size diameter. As discussed later, other test methods, such as image analysis, provide a more detailed particle size description.

Table 2.2 Sugar sphere monograph specification

Characteristic	Test method	USP38/NF32	Ph. Eur. 8.0
Assay	Optical rotation	62.5–91.5%	NMT 92%
Impurities	Residual on ignition	NMT 0.25%	–
	Sulfated ash	–	NMT 0.2%
	Heavy metals	5 µg/g	Max 5 PPM
Specific test	Loss on drying	NMT 4%	Max 5%
Microbial	Enumeration test	10 ² cfu/g	10 ² cfu/g
	Specified microorganisms	Tests for absence	Tests for absence
Particle size estimation by sieve analysis	Coarse sieve (%retained)	NMT 10%	NMT 10%
	Fine sieve (% retained)	NLT 90%	NLT 90%
	Fine sieve (% Max thru)	NMT 10%	NMT 10%
	Between coarse and fine sieve	–	90–100%

2.4 Materials and Manufacturing of Pellets

The process of choosing a pellet is similar to choosing other excipients. Technical and commercial constraints like compatibility, cost, supply, and functionality need to be balanced. For a pellet, the materials and method of manufacturing provide flexibility to balance these criteria.

As seen throughout this chapter, different classes of pellets like sugar spheres and microcrystalline cellulose (MCC) spheres provide distinct options when evaluating physical properties or excipient compatibility. Within the same class of pellets, the source of ingredients or composition could potentially affect the product attributes. A common example is the source of sucrose used in manufacturing sugar spheres. Manufacturers in Europe often source beet sugar, while in the United States, sugar spheres are typically manufactured with cane sugar. This difference in choice of raw material is strictly based on local availability of source and cost of sugar. For most applications, these materials are considered interchangeable [6]. Another example is the source of starch used as a secondary material in the manufacture of sugar spheres. Generally corn starch is used; however, there could be different grades of corn starch having different ratios of amylose and amylopectin. It is known that in rare cases, depending on the source of raw material and its supplier, small differences in impurity profiles may affect drug product stability [7].

In addition to the type and source of material, the ratio of ingredients could be different within different sugar sphere grades from different manufacturers. This may alter the pellets' characteristics. USP/NF defines sugar spheres to contain 62.5–91.5% sucrose on a dried basis, with the remainder consisting chiefly of starch. Sugar spheres may also contain color additives permitted by FDA. On the other hand, Ph. Eur. defines sugar spheres (*sacchari sphaerae*) to contain no more than (NMT) 92% sucrose on dried basis, with the remainder consisting of maize starch. They may also contain starch hydrolysates and color additives. Thus, there could be a wide range of possible combinations of sucrose and starch and the manufacturing process (dusting/ladling versus spraying in coating pan using water

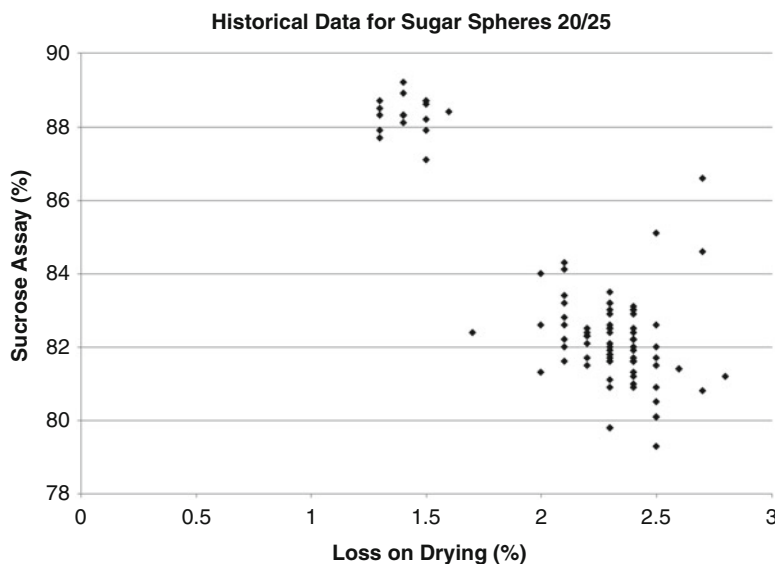


Fig. 2.1 Correlation of loss on drying (LOD) and sucrose for sugar spheres 20/25# (710–850 μm)

as solvent) based on current pharmacopeial requirements in both USP/NF and Ph. Eur. Such a vast range of possible composition often affects multiple attributes, and understanding their relationships is complex.

For example, water is a critical component in sugar spheres and is present in “bound” or “mobile” states. The presence of residual moisture, defined as “mobile” water remaining after the manufacturing process, can cause drug stability issues. To investigate the effect of residual moisture in a sugar spheres, it is common to relate the loss on drying (LOD) specification to product stability. With starches known to contain high levels of bound water, though, small changes in the sugar sphere composition may skew the LOD results. Figure 2.1 shows the correlation of LOD and sucrose assay from 95 batches of sugar spheres. A decrease in sucrose assay indicates higher levels of starch which contributes more moisture to the core, and therefore higher LOD values are reported. Other methods, like water activity, provide a more accurate measurement of residual moisture and are less susceptible to composition changes.

Formulators often rely on excipient manufacturers to supply pellets for formulation development. Once they select the pellet (based on their type/chemistry and size), they use these inert spheres for drug layering (by either liquid or powder layering process) and subsequently coat the drug-layered beads by one or multiple layers of functional coatings to modulate the drug release profile. For the drug release to be robust and free of any variability, the physical attributes (critical quality attributes) of the pellets can have a profound impact. Let us look at different physical attributes of pellets. The emphasis of discussion henceforth will be on sugar spheres, which are the most commonly used pellets for multiparticulate modified-release dosage forms.

2.5 Surface Area of Pellets

During the development of a multiparticulate dosage form, the key goal is to determine the functional film coating thickness that achieves a desired product performance. This is done by evaluating the amount of coating applied to drug-loaded beads calculated on a weight basis. Higher weight gain creates a thicker coating layer. A good correlation was shown between theoretical and actual weight gain by applying Surelease[®], an aqueous ethyl cellulose dispersion on drug-layered beads [8]. Once the target performance has been determined, the percent weight gain is held constant with the intent of achieving a consistent film thickness in future trials and batches.

Applying a constant amount of coating is a common practice, but a variety of other variables, like coating parameters, coating formulation, and the pellets, can influence the actual coating thickness achieved. To illustrate this, let's take an example of spheres with different diameters. Using Eqs. 2.1, 2.2, 2.3, and 2.4, the surface area, volume of each sphere, total number of spheres in a 1 g sample, as well as total surface area for spheres in a 1 g sample are calculated (Table 2.3).

Equation 2.1 Surface Area of Sphere

$$\text{Surface area of a sphere} = 4\pi(\text{radius})^2$$

Equation 2.2 Volume of Sphere

$$\text{Volume of a sphere} = \frac{4}{3}\pi(\text{radius})^3$$

Equation 2.3 Total number of Spheres in 1 g sample

$$\text{Total number of spheres in one gram} = \frac{6 \times 10^{12}}{\pi \times \text{density} \times (\text{diameter})^3}$$

Table 2.3 Total surface area calculations for various sphere diameters

Particle size diameter (micron)	Surface area of one sphere (microns ²)	Volume of one sphere (microns ³)	Number of spheres in 1 gram sample ^a	Total surface area
1200	4.52E + 06	9.04E + 08	1106	5.00E + 09
1000	3.14E + 06	5.23E + 08	1911	6.00E + 09
800	2.01E + 06	2.68E + 08	3732	7.50E + 09
600	1.13E + 06	1.13E + 08	8846	1.00E + 10
400	5.02E + 05	3.35E + 07	29,857	1.50E + 10
200	1.26E + 05	4.19E + 06	238,854	3.00E + 10

^aDensity considered as 1 g/cc for calculations

Equation 2.4

Total surface area of spheres in 1gram sample
 $= (\text{surface area of a sphere}) \times (\text{total number of spheres in 1gram sample})$

As sphere diameter decreases, the surface area and volume of each sphere decrease; however, the total number of particles per gram of sample actually increases. This means, to coat the same quantity of spheres, the total surface area of spheres in a unit quantity of sample will increase with decreasing sphere diameter and vice versa. The total surface area is sometimes referred to as specific surface area and may be calculated in a different manner (Eq. 2.5).

Equation 2.5 Specific Surface Area

$$\text{SSA} = \frac{\text{Area of Sphere}}{\text{Volume of Sphere} \times \text{True Density}} = \frac{3}{\text{Radius} \times \text{True Density}}$$

There are different analytical techniques to determine specific surface area that take into account the surface characteristics of particles including porosity. These relationships between particle surface area, volume, and number are important as the following section discusses how particle size, shape, density, and surface morphology are related to specific surface area.

2.6 Particle Size Diameter of Pellets

Different grades of pellets are defined by their particle size. Typical grades available in the market for modified-release drug delivery applications are given in Table 2.4. Some suppliers also provide customized particle size grades for specific applications by using different combinations of sieve sizes for different size fractions.

Sieve analysis, such as the procedure described in the USP/NF general chapter <786> [10], has been adopted as a standard method for classifying the particle size

Table 2.4 Typical particle size of sugar spheres [9]

Mesh size (ASTM)	Size (microns)
12/14	1400–1700
14/18	1000–1400
16/18	1000–1180
16/20	850–1180
18/20	850–1000
20/25	710–850
25/30	600–710
30/35	500–600
45/60	250–355
60/80	180–250

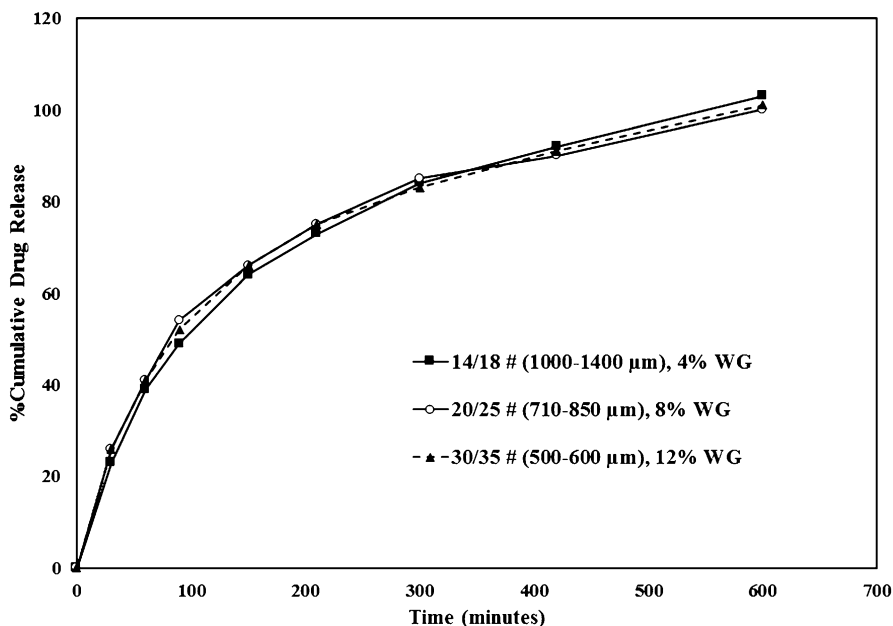


Fig. 2.2 Effect of sugar sphere starting particle size and weight gain of Surelease barrier membrane coating on release of chlorpheniramine maleate

distribution. The grade of sugar spheres is identified by the pair of mesh screens, for example, 20/25, or their equivalent μm range of the sieves, for example, 710–850 μm . The availability of different grades provides flexibility during the development of a new product, for example, Fig. 2.2 shows how combining different pellet particle sizes and functional coating weight gains can produce equivalent dissolution profiles [8].

Drug release from drug-layered inert spheres coated with functional membrane typically follows diffusion mechanism, and coating film thickness is a critical parameter in altering drug dissolution [11]. Since coating functionality is related to the film thickness, understanding how much coating is required for different particle sizes is important. Equation 2.6, which was derived from basic geometry and density equations, can be used to calculate the theoretical amount of coating required to maintain a specific film thickness irrespective of sphere diameter.

Equation 2.6 Theoretical Coated Particle Diameter Calculation

$$D = 2 \times \left[\left(\frac{m}{m_0 \times \rho} \right) \times \left(\frac{D_0}{2} \right)^2 \right]^{1/3}$$

D = final sphere diameter

D_0 = starting sphere diameter

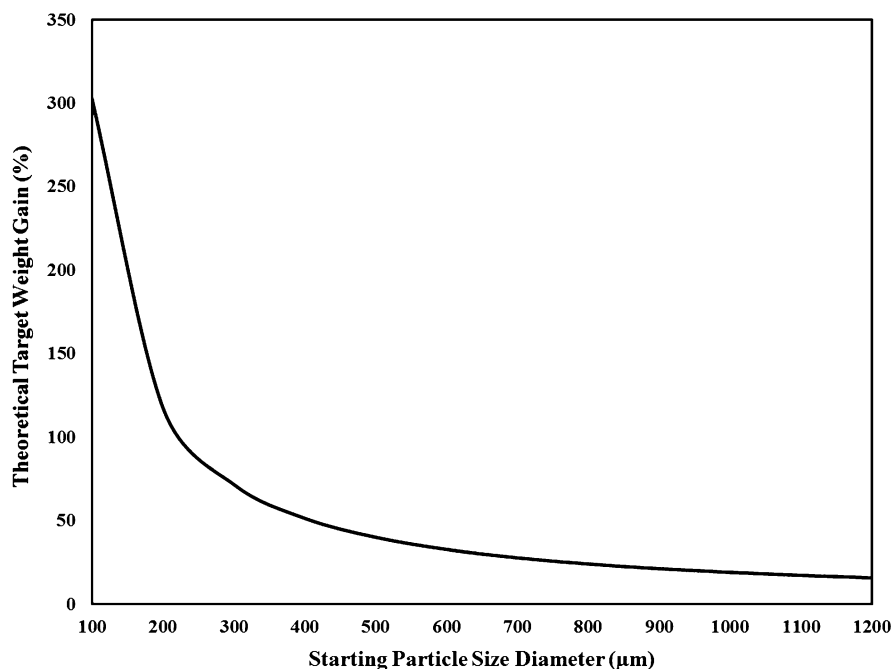


Fig. 2.3 Theoretical coating weight gain required to achieve constant film thickness of 30 μm for different starting particle diameters

m = final dose/batch weight

m_0 = starting sugar sphere weight

ρ = density

As an example, Fig. 2.3 gives a graphical representation of the theoretical amount of coating required to maintain a 30 μm film thickness for particle diameters in the range of 100–1200 μm . As you move to smaller particles (for instance <500 μm), small changes in diameter lead to larger and larger relative changes in surface area and thus require significantly higher amounts of coating to maintain consistent coating thickness. This suggests products developed with smaller pellets may be more susceptible to incremental changes in particle size. These small changes in particle size are investigated in more detail later.

Beyond classifying the grade of material, sieve analysis is used as a specification for controlling the distribution of particles. As shown in Table 2.2, the specification reports the percent mass retained on a pair of mesh sieves. Most sieve analysis data requires additional calculation to produce an estimated mean particle diameter [12], but for pellets, the calculations do not provide an accurate prediction because the specification requires 90% of the particles to be between two adjacent screens. This low measurement resolution results in the bulk of material not being characterized in detail, and the calculations are a poor estimation of particle size and its distribution. In general, sieve analysis has three major limitations, the resolution or its

Table 2.5 Possible scenarios for sieve analysis results for sugar spheres size 18/20# (850–1000 µm) all passing USP/NF and Ph. Eur. specification for particle size

Scenarios	% Retained on coarse sieve – 18# (1000 µm)	% Retained on fine sieve – 20# (850 µm)	% Max through fine sieve – 20 # (850 µm)	% Retained between coarse and fine sieve	Median particle size ± std. dev (µm) ^a
1. 10% retained on coarse sieve and 90% retained between coarse and fine sieve	10	90	0	90	965.34 ± 27.04
2. 0% retained on coarse sieve and 100% retained between coarse and fine sieve	0	100	0	100	925.00 ± 17.59
3. 5% retained on coarse sieve and 90% retained between coarse and fine sieve	5	90	5	90	925.00 ± 45.60
4. 0% retained on coarse sieve and 90% retained between coarse and fine sieve	0	90	10	90	884.66 ± 27.04

^aMedian particle size and standard deviation calculated by using Eq. 2.7

ability to distinguish small changes in particle size distribution, the degree of sensitivity or ability to distinguish between different shapes, and its ability to provide a meaningful particle diameter.

Table 2.5 shows four possible scenarios for sieve analysis results for sugar spheres size 18/20# (850–1000 µm) all passing USP/NF and Ph. Eur. specification for particle size. A normal distribution curve can be fitted to these four scenarios using Eq. 2.7 [13] to calculate median particle size and standard deviation. As shown in Table 2.5, it is possible to have large variation in median particle size of spheres from 886 to 956 µm and yet pass the particle size specification mentioned in USP/NF and Ph. Eur. Though this transformation is only an estimate, it does provide practical limits for designing quality-by-design (QbD) studies. This window is smaller than the often misleading 850–1000 µm range used to describe this grade of sugar spheres.

Equation 2.7 Normal Distribution

$$f(x, \mu, \sigma) = \frac{1}{\sigma\sqrt{2\pi}} e^{-\frac{(x-\mu)^2}{2\sigma^2}}$$




μ = mean or median or mode

σ = standard deviation (σ^2 = variance)

To eliminate confusion and quantify the particle size distribution into meaningful terms, we should use better test methods. Techniques such as image analysis provide a more detailed particle size distribution and report summary statistics like the median particle diameter and standard deviation. These statistics provide convenient values to analyze for the comparison of different materials [14].

Image analysis techniques work by taking pictures of individual particles which are converted into two-dimensional shadows. Specialized software is used to measure the images and extrapolate the information to a three-dimensional sphere. As discussed later, the shape of pellets is not always spherical, and defining the diameter of irregular-shaped particles is complex. Table 2.6 shows common definitions used to describe and measure a non-spherical particle’s size. Depending on the particle shape, each definition can provide different distributions as seen in Fig. 2.4. The pharmaceutical industry has commonly relied on the minimum chord length as it is closely related to sieve analysis measurements for particles that have irregular or non-spherical shape [15]. When measuring round particles like sugar spheres and MCC spheres, the differences in measured particle sizes are minimal.

Table 2.6 Description of measurements used to characterize particle diameters

Diameter measurement	Description	
Minimum chord	Sphere of equivalent width	
Maximum ferets	Length of particle	
Area	Sphere based on projected surface area	

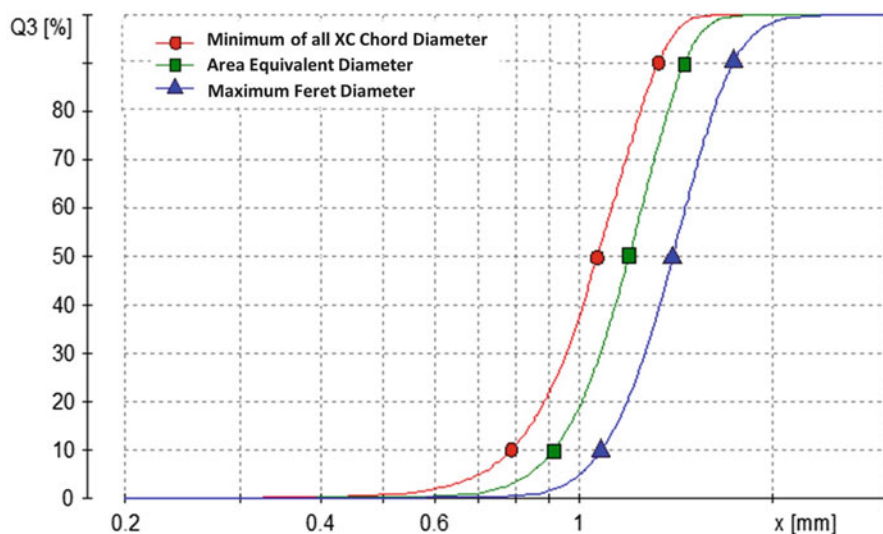


Fig. 2.4 Particle size distribution using different particle size definitions (Courtesy: HORIBA Instruments Inc., USA)

Static image analysis is one method which uses a digital microscope equipped with a high-resolution camera to characterize the particles. The sample prep method creates a bias for irregular-shaped particles because they have a preferred orientation when laying on the flat horizontal slide. The preparation of samples is also time-consuming considering the need to measure a statistically significant amount of particles (i.e., 500–10,000 particles) [16]. The result of the slower testing does provide opportunity to capture higher-resolution images compared to the more preferred method of dynamic image analysis.

Dynamic image analysis (e.g., using a Camsizer) is able to measure more than 10,000 particles in as little as 2 min. Unlike static image analysis, the orientation of the particle is randomized due to the sample feed mechanism. The combination of measuring the orientation randomly and a large number of particles analyzed creates a very reproducible and accurate description of distribution. Particle size analysis using laser diffraction does not yield information about shape or morphology of particles and is usually less suitable for typical pellet sizes in the range of 200–1000 μm .

2.6.1 Case Study: Effect of a Small Shift in Median Particle Size of Pellets on Drug Release

Multiparticulate dosage forms are known to be sensitive to small shifts in particle size. By using Eq. 2.6, the impact of a shift in median particle size of the starter

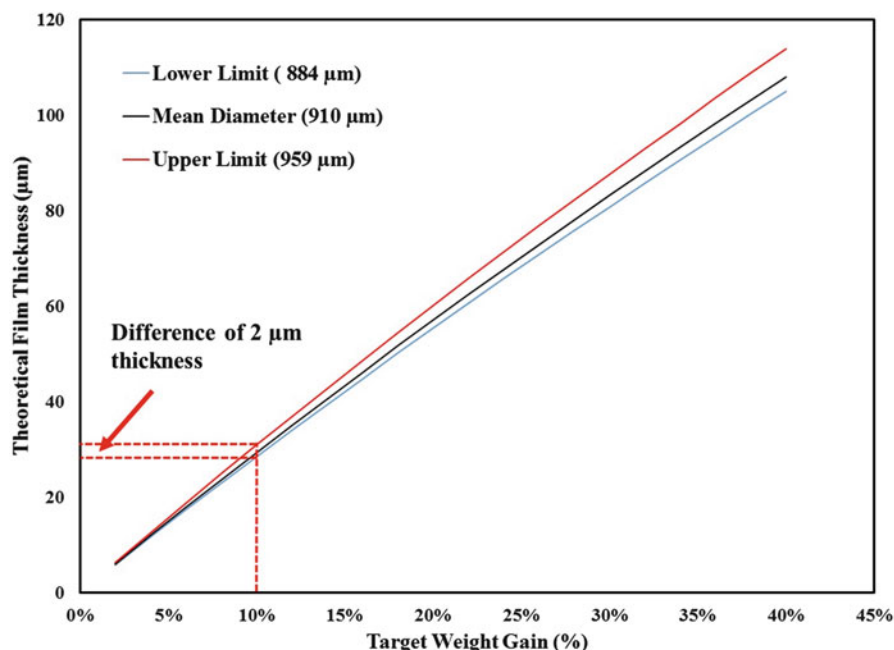


Fig. 2.5 A shift in median particle size from 884 to 959 μm (75 μm) of sugar spheres 18/20# (850–1000 μm) results in a theoretical difference in 2 μm film thickness

pellet on final film thickness variation may be predicted. Figure 2.5 shows that if 10% weight gain is applied on a pellet having a median particle size of 884–959 μm , which is a difference of 75 μm in diameter, it would give 2 μm variation in film thickness of coating layer applied on the core.

Figure 2.6 shows the dissolution profile of a model formulation (CPM drug-layered pellets coated with Surelease), using sugar spheres 18/20 (850–1000 μm) with median particle diameter of 910 μm (determined by Camsizer). Based on the possible scenarios outlined in Table 2.5, the outer limits of the sieve analysis specification were engineered by blending sugar spheres (18/20) with lower and higher particle size grades to shift the median particle size of blended spheres to 884 and 959 μm . These blended sugar spheres were then drug layered and coated with Surelease to investigate the impact of a 2 μm change in theoretically calculated film thickness on ultimate drug release [17].

The dissolution profiles were variable due to the differences in the mean particle size of different lots above samples tested. The similarity factor (f_2) [18] calculation was applied to the release profiles. For two profiles to be similar, the f_2 value should be in the range of 50–100. Figure 2.6 shows that the dissolution profiles obtained for product manufactured with sugar spheres at the outer limits of allowable mean particle size are significantly different. These results demonstrated that the drug release performance may be significantly affected by the variation in particle size of

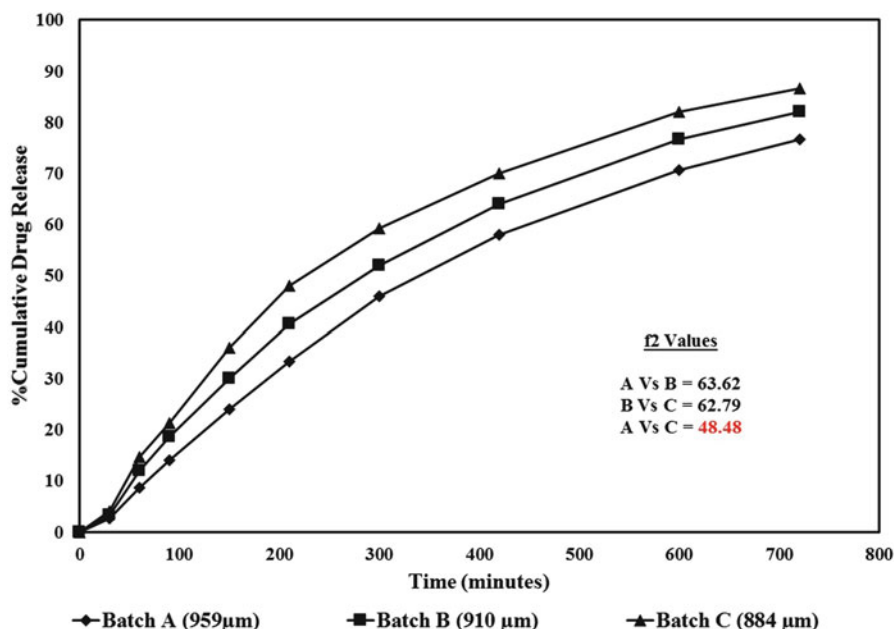


Fig. 2.6 Effect of median particle size (884, 910, and 959 µm) of sugar spheres on dissolution of chlorpheniramine maleate-layered beads coated with 10% weight gain of Surelease

spheres, within the USP/NF specification. Therefore, after establishing the grade of pellets and coating weight gain (film thickness), investigating the sensitivity of the formulation to natural variation in the particle size is the next step in developing a robust product. Through QbD principles, the variation of particle size that is expected should be evaluated experimentally. Historical trend lines on manufacturing records and image analysis like that shown in Fig. 2.7 are indispensable in quantifying the range of variation that may occur in pellets. Such historical data also provides insight on the pellet suppliers' manufacturing capability. When this level of detail is unavailable, returning to the sieve analysis specification is helpful.

2.7 Particle Size Distribution of Pellets

Median particle size is often the focus when characterizing pellets because it provides a single value that summarizes a pellet, but the distribution spread affects the product as well. Pellets with a narrow distribution behave more predictably, and many of the assumptions made earlier hold true. As the distribution widens, the complexity increases. For example, different size particles have been reported to fluidize differently during a Würster coating process [19]. The development of an in-house substrate through granulation or extrusion-spheronization techniques

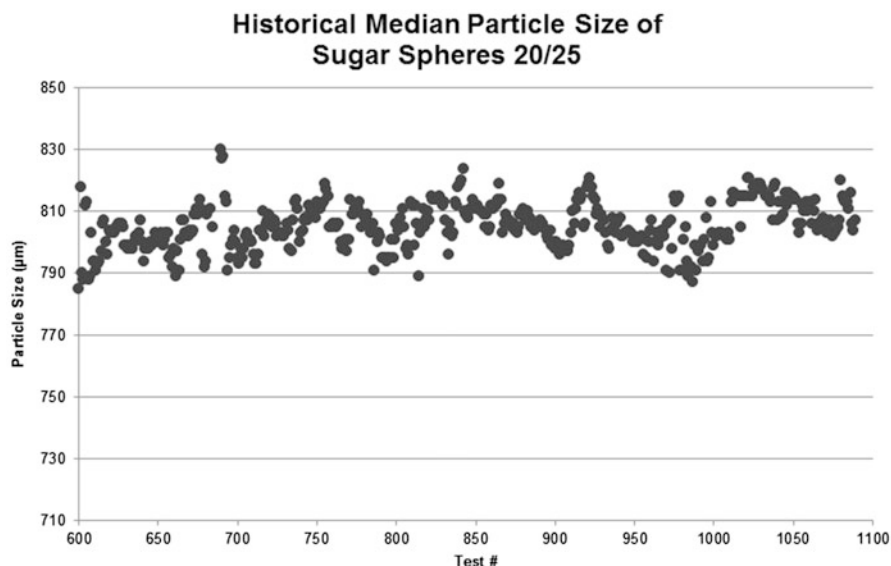


Fig. 2.7 Historical median particle size of sugar spheres 20/25# (710–850 μm) (*Suglets[®] technical bulletin, www.colorcon.com/*)

often yields a very wide particle size distribution. Though screening will narrow the distribution, this comes at a higher cost and increased waste. When working with pellets that are not purposefully designed for multiparticulate applications, additional screening should be considered.

2.7.1 Case Study: Effect of Particle Size Distribution of Pellets from Different Suppliers on Drug Release

The particle size distributions of two enteric-coated formulations using sugar spheres from two different suppliers are shown in Fig. 2.8a, b. Sugar spheres from Supplier 1 had a narrow particle size distribution (Fig. 2.8a) and mean starting particle size of 859 μm , while sugar spheres from Supplier 2 had a wide particle size distribution (Fig. 2.8b) and mean starting particle size of 1048 μm . These beads were drug layered and enteric coated to achieve approximately 62 μm film thickness. The theoretical weight gain was calculated using Eq. 2.6 for both formulations to achieve 62 μm . Upon final enteric coating, it was observed that narrow particle size sugar spheres from Supplier 1 gave narrow distribution of final enteric-coated beads having 62 μm film thickness, whereas wide particle size sugar spheres from Supplier 2 gave wide distribution of enteric-coated beads having 65 μm film thickness. Figure 2.9 shows that formulation based on Supplier 2 failed enteric dissolution even though the particles had the same estimated film thickness,

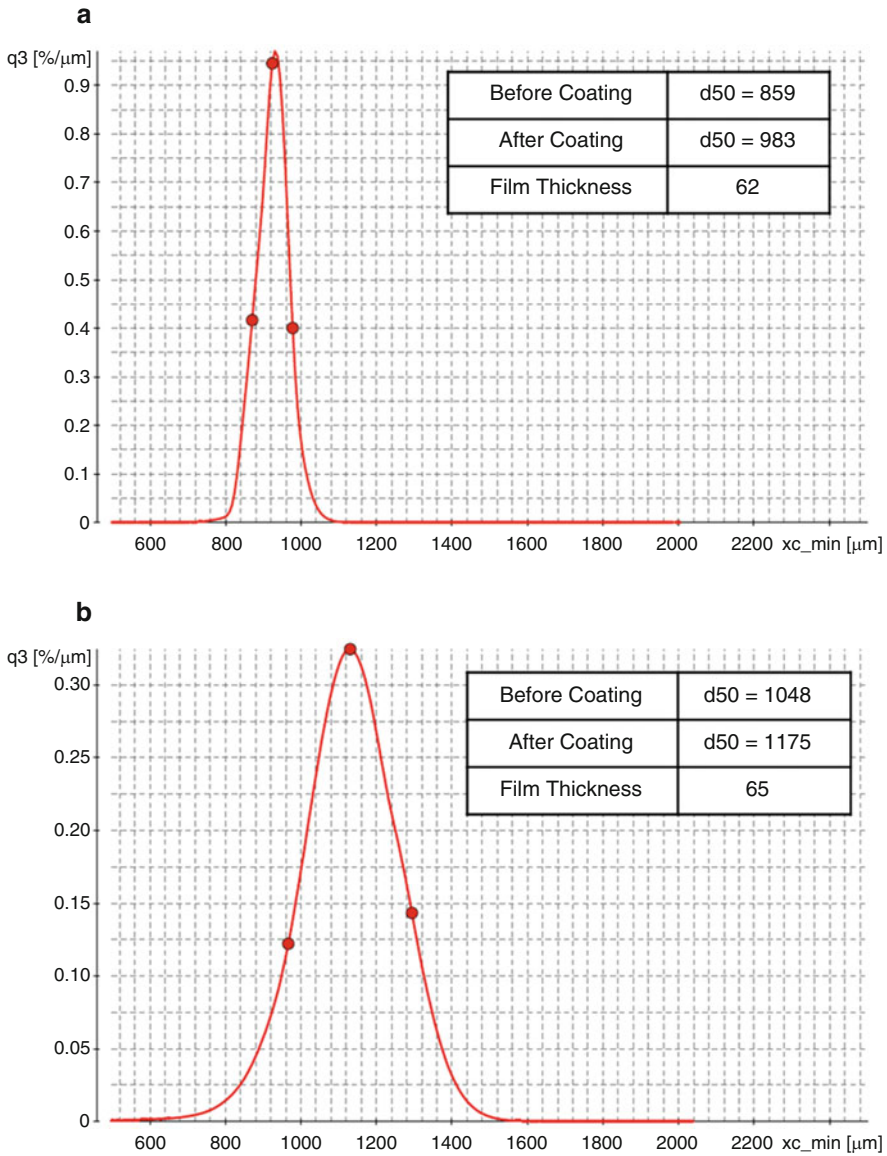


Fig. 2.8 Particle size distribution of two enteric-coated formulations using inert cores from Supplier 1 **(a)** having narrow distribution or Supplier 2 **(b)** having wide distribution

whereas the formulation based on Supplier 1 passed the enteric dissolution test. Further inspection showed the wider distribution of particles from Supplier 2 resulted in a small tail of particles that were smaller than those from Supplier 1. Although there were only a small portion of the pellets with smaller size, these were thought to be the cause of enteric failure due to a thinner film thickness. The

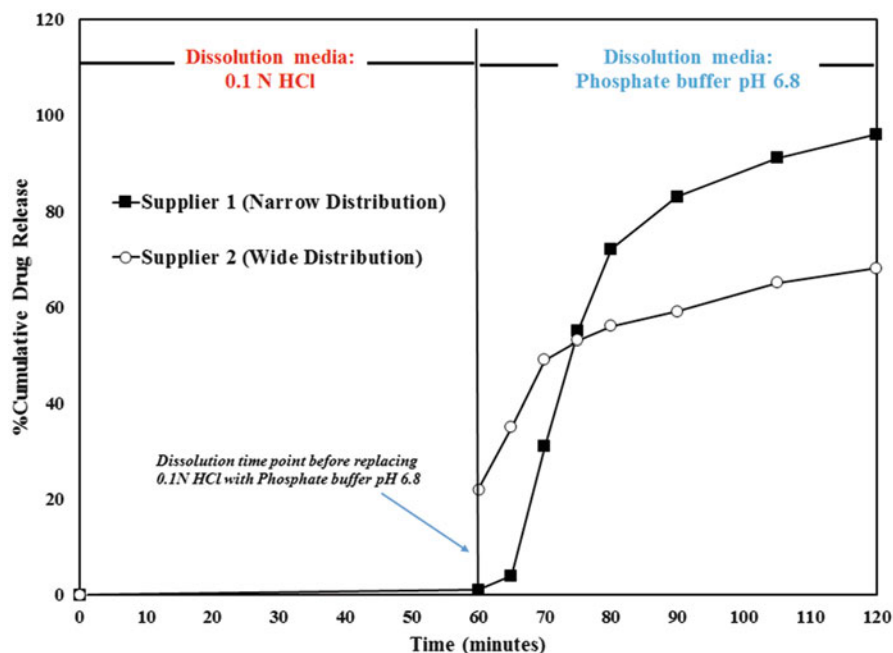


Fig. 2.9 Enteric dissolution profile of a proton pump inhibitor layered on sugar spheres with different particle size distributions obtained from different suppliers

median particle size and width of the distribution are often changing together, and therefore, characterizing both parameters will help in predicting product performance.

2.8 Volume Versus Number Distribution of Pellets

Particle size distribution may be characterized using volume or number distribution. A volume distribution is calculated by determining the percent volume a particle contributes to the total volume of the pellets. Number distribution is calculated by the percent number of particles in the total population of particles analyzed. Typical sieve analysis is used to determine volume distribution. Volume distribution has a limitation, that it does not give information on the number of particles that are smaller than the smallest sieve size or the number of particles that are bigger than the largest sieve used. These outliers are often referred as fines and agglomerates, respectively. In general, agglomerates are particles that are at least 2–3 times the size of the median particle diameter. A better understanding of the presence and quantity of fines or agglomerates is indicated by number distribution. Number distribution cannot be obtained by simple sieve analysis; however image

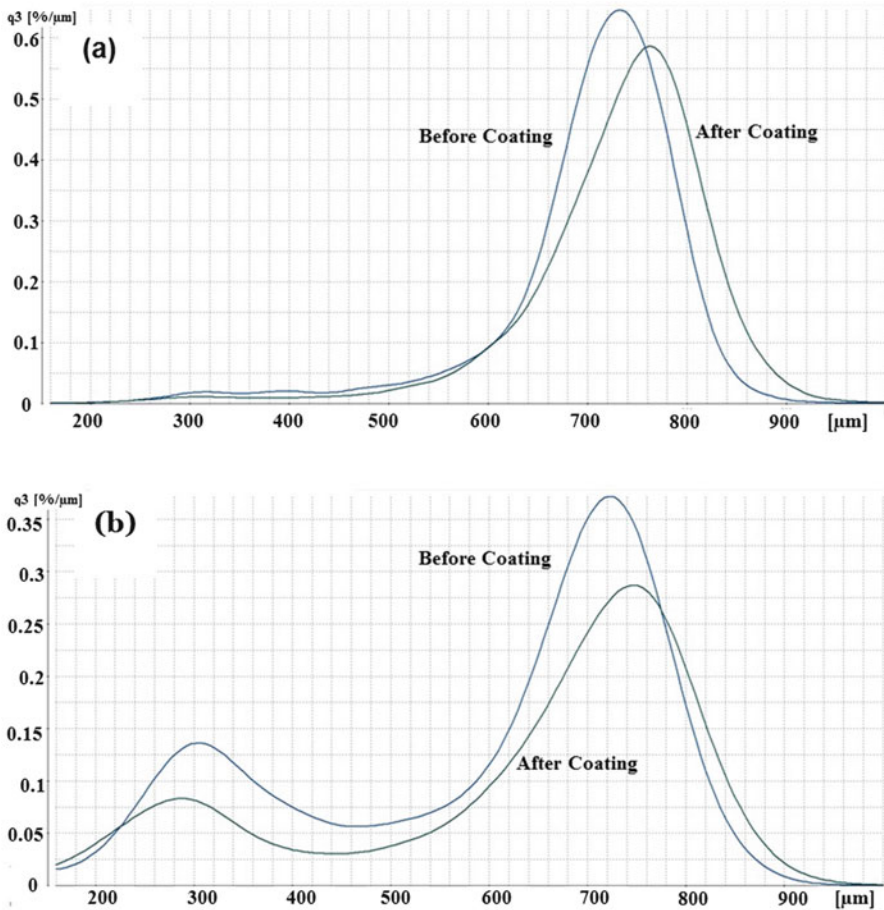


Fig. 2.10 Comparison of particle size distribution of beads before and after coating containing fines, (a) volume distribution, and (b) number distribution

analyzers have the capability to give both volume and number distribution since they can analyze a huge number of individual particles.

As shown earlier in Table 2.3, the smaller the particle size of the sphere is, the smaller the volume of the individual sphere. However, the number of such small spheres in 1 g of sample is much higher compared to the number of bigger spheres. When such small particles or fines are characterized for volume and number distribution, they are easily seen in a number distribution but not in a volume distribution. This effect is shown in Fig. 2.10a, b with a pellet containing a large population of fines. Even with detailed results from dynamic image analysis, the volume distribution does not indicate the presence of any fines (Fig. 2.10a). When using the number distribution, a second peak appears around 300 μm due to the fines (Fig. 2.10b).

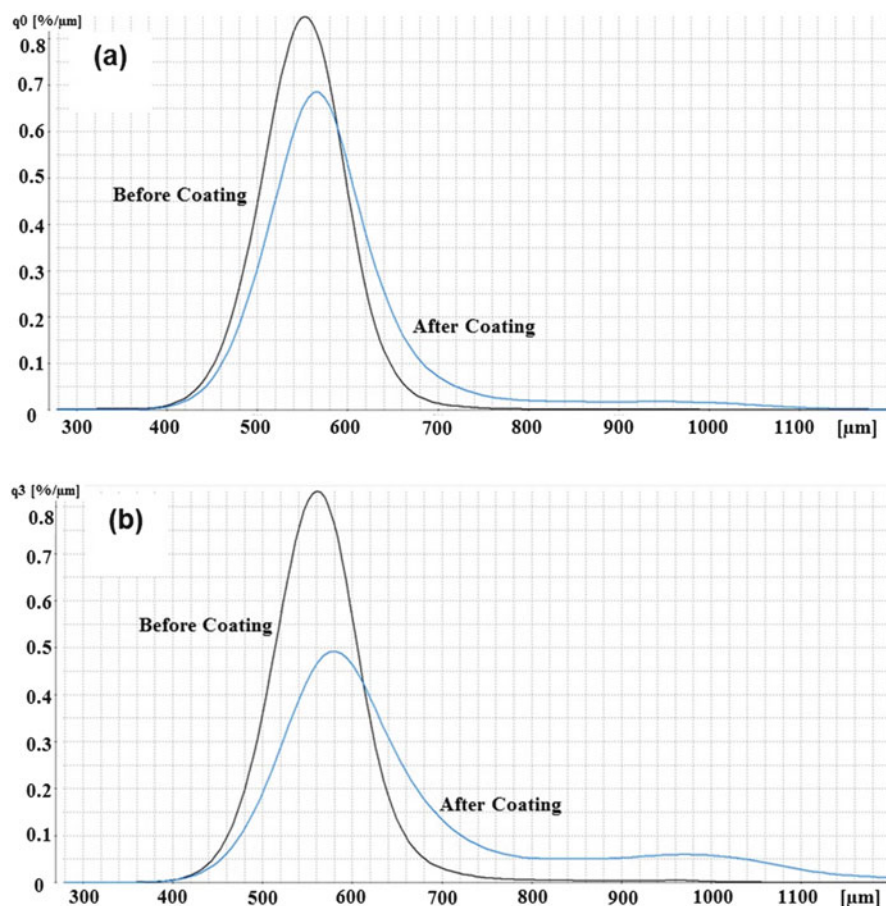


Fig. 2.11 Comparison of particle size distribution of beads before and after coating containing agglomerates, (a) volume distribution, and (b) number distribution

When looking for agglomerates, the number distribution becomes less sensitive. Figure 2.11a, b compares the particle size distribution of samples with and without agglomeration. By only analyzing the number distribution, it may be concluded that the particle size grew more for the batch containing agglomerates. Actually the distribution is being skewed by the very large agglomerated particles. This can be confirmed by looking at the volume distribution (Fig. 2.11a).

Depending on the size and quantity of the fines and agglomerates, issues like product yield, coating uniformity, and film thickness can all be affected. The degree of variation is related to the processing techniques. For example, powder layering uses a dusting process to apply a high weight gain in a short amount of time. After the first few minutes of processing, the amount of fine powder intentionally introduced makes any fines from the pellets insignificant. However, for a solution coating process with a thin coating thickness, fines are more detrimental as they will

be incorporated into the coating creating inclusions. These inclusions create failure points resulting in variation in the product performance.

Early understanding of the formulation sensitivity to changes in particle size provides opportunities to adjust the coating formulation, manufacturing methods, and grade of pellets to create a robust product. Although the median particle diameter and width of the distribution are often the biggest contributors, there are other attributes that would also cause variation in performance of the multiparticulate products.

2.9 Density of Pellets

The density of powders and multiparticulates may be characterized differently in order to provide an insight into their performance-related attributes [20].

2.9.1 True Density of Pellets

True density is defined as the density of the materials excluding the volume of any open or closed pores. Table 2.7 lists typical densities for pellets of different materials. Since true density is dependent only on the composition of the pellets, the cellulosic material in MCC spheres creates a lower density as compared to the crystalline nature of sucrose or isomalt in sugar spheres. With variation in sugar sphere composition, the true density may vary, with larger sugar spheres decreasing in true density. This change in true density due to composition is related to the sucrose-starch dispersion used in the manufacturing of sugar spheres. Manufacturing methods also cause density changes, but these are better measured by envelope density.

2.9.2 Envelope Density of Pellets

Envelope density is defined as the density of the materials including the volume of any open and closed pores but excludes void spaces created between particles. The

Table 2.7 Typical densities of inert cores of different materials

Material	True density (g/ml)	Bulk density (g/ml)
Sugar sphere	1.49–1.57 ^a	0.68–0.73
Isomalt	1.53	0.42–0.85
Microcrystalline cellulose	1.38	0.75–0.85

Adapted from Ref. [21]

^aDensity will vary based on sucrose to starch ratio

difference between true and envelope densities is referred to as porosity and is considered the amount of pores or void space found in the pellet. The porosity or void spaces are created during the manufacturing process of the pellets. Sugar spheres that are manufactured through a liquid layering process produce pellets with low porosities. Some sugar sphere manufacturers apply powdered sucrose and starch using a dusting process. This dusting technique reduces the manufacturing time and cost but is more prone to generating porous pellets. Envelope density can be determined using displacement measurement technique such as GeoPyc from Micromeritics Instrument Corporation.

2.9.3 Bulk Density of Pellets

Bulk density is defined as the envelope density plus the void spaces created between particles. Focusing on this type of density is referred to as the packing density or packing orientation and is the measurement of how the inert particles align to fill and minimize the void space. This is influenced by the particle size distribution and shape of the pellets. Understanding bulk density is important as it can affect the final fill weight of the pellet-based formulation in capsule shells during capsule filling process. Table 2.8 provides the effect of changing bulk densities on maximum fill weight of common capsule sizes.

Small changes in the density of pellets lead to changes in the specific surface area and therefore resulting in a different coating film thickness for a given weight gain. Figure 2.12 shows the impact of different substrates such as sugar spheres and MCC spheres having true density of 1.54 g/cc and 1.38 g/cc, respectively, on the coating film thickness. The values shown in Fig. 2.12 have been calculated based on Eq. 2.6 and using the density values of both spheres, while keeping the film density equal to 1 g/cc (assuming that the same coating is used on both spheres). It clearly shows that, to obtain a coating film thickness of 30 μm , there is a difference of about 2% weight gain.

Table 2.8 Theoretical capsule fill weights based on bulk density

Bulk density (g/ml)	Capsule size 0 (volume 0.68 ml) fill weight (mg)	Capsule size 1 (volume 0.5 ml) fill weight (mg)	Capsule size 2 (volume 0.37 ml) fill weight (mg)
0.60	408	300	222
0.80	544	400	296
1.00	680	500	370

Adapted from Ref. [22]

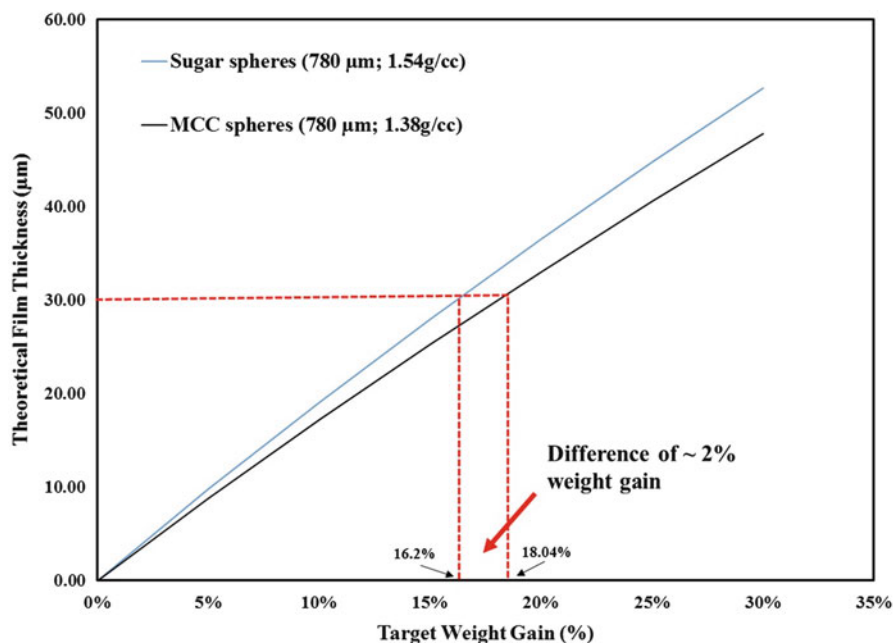


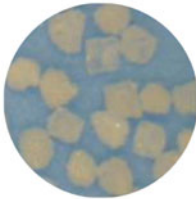
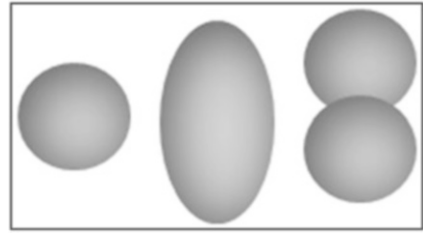
Fig. 2.12 Impact of starting substrate density on the coating film thickness

2.10 Shape of Pellets

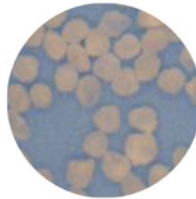
As noted earlier, the shape of the particles influences how the particle diameters are measured. Sieve analysis is often influenced by changes in particle shape. Figure 2.13 shows three particle shapes with an equivalent minimum chord length, but all would not be considered spheres. Because sieve analysis is dependent on particle shape, the estimated particle size distribution can obscure the results significantly. As shown earlier, a detailed understanding of the particle diameter is important in developing a robust multiparticulate formulation. Again, characterizing the shape through image analysis provides a more detailed understanding of a pellet and its variation.

The shape of the particles can be defined by different measurements such as sphericity and aspect ratio. Sphericity is defined in Eq. 2.8 and is the relationship of a particle's perimeter to its area. This shape parameter also characterizes the roughness of the particles. Figure 2.14 provides images of particles with different sphericity. Please note that the lower sphericity values have sharp edges and are cube-like.

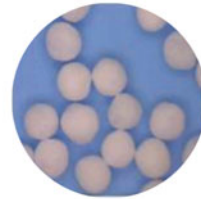
Fig. 2.13 Different particle shapes that have equivalent minimum cord length that can pass through same sieve when their orientation corresponds to sieve opening size



Sphericity = 0.87



Sphericity = 0.91



Sphericity = 0.97

Fig. 2.14 Images of sugar spheres with different sphericity values

Equation 2.8 Sphericity

$$\psi = \frac{\pi^{\frac{1}{3}}(6V_p)^{\frac{2}{3}}}{A_p}$$

A_p = area of a particle

V_p = volume of a particle

Aspect ratio, as shown in Eq. 2.9, is defined by the ratio of the particles' width (typically minimum chord length) and length (typically feret maximum) and provides a measure of particle elongation. Both of these measurements relate the particle shape to an ideal sphere. To some extent, they capture similar changes in particle shape, but often both parameters are needed to evaluate the shape of a particle.

Equation 2.9 Aspect Ratio

$$A_R = \frac{d_{\min}}{d_{\max}}$$

d_{\min} = minimum diameter of a particle

d_{\max} = maximum diameter of a particle

Changes in the shape of particles influence the surface area, and if changes are toward non-spherical shapes, then specific surface area increases. This results in

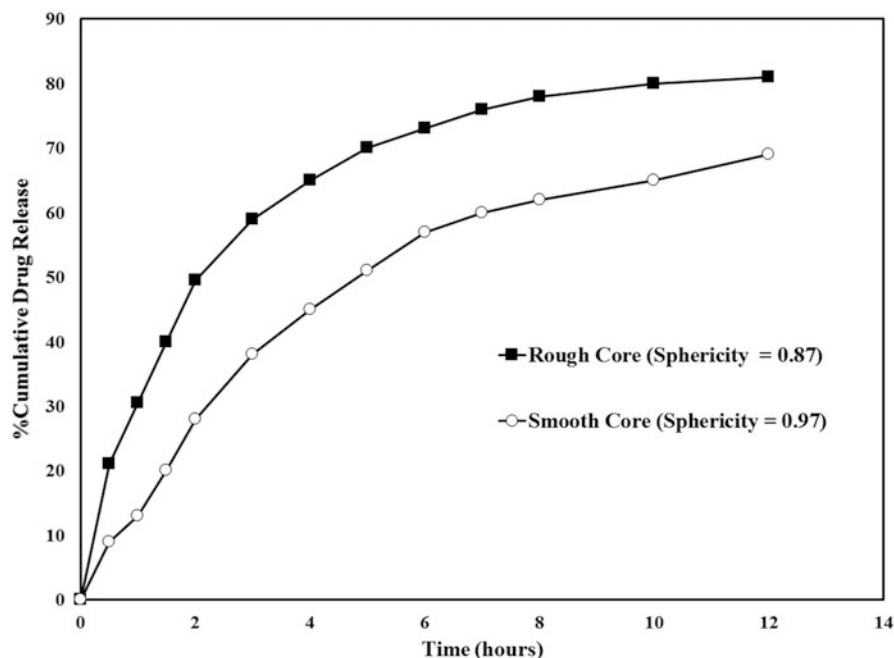


Fig. 2.15 Effect of particle shape as measured by sphericity of starting sugar spheres on release profile of chlorpheniramine maleate drug loaded on sugar spheres and then coated with Surelease barrier membrane coating at 10% weight gain

variation in coating thickness as shown in other examples. In addition, the uniformity of the coating across a pellet becomes uneven. When applying a thin coating layer, sharp edges like those shown in Fig. 2.14 are difficult to cover with an even film coating. In addition, these edges are prone to chipping during fluid bed coating, thereby creating defects in the coating process. The effects of additional surface area and coating uniformity are shown in Fig. 2.15 where an extended release coating was applied to pellets having different sphericity values.

When thicker film coatings are applied, any sharp edges of the pellet become smoothed, and the particle becomes more and more round with increasing weight gain. As a result, the starting shape may not be considered a CQA for applications with very high weight gains or when using rotor processing which facilitates the rounding of particles [23].

2.11 Surface Morphology of Pellets

Similar to how higher coating weight gains round a particle shape, the initial coating layer fills and covers over the small pores or crevasses found on the surface of a pellet. Most pellets have minimal porosity, and the pores found on the surface

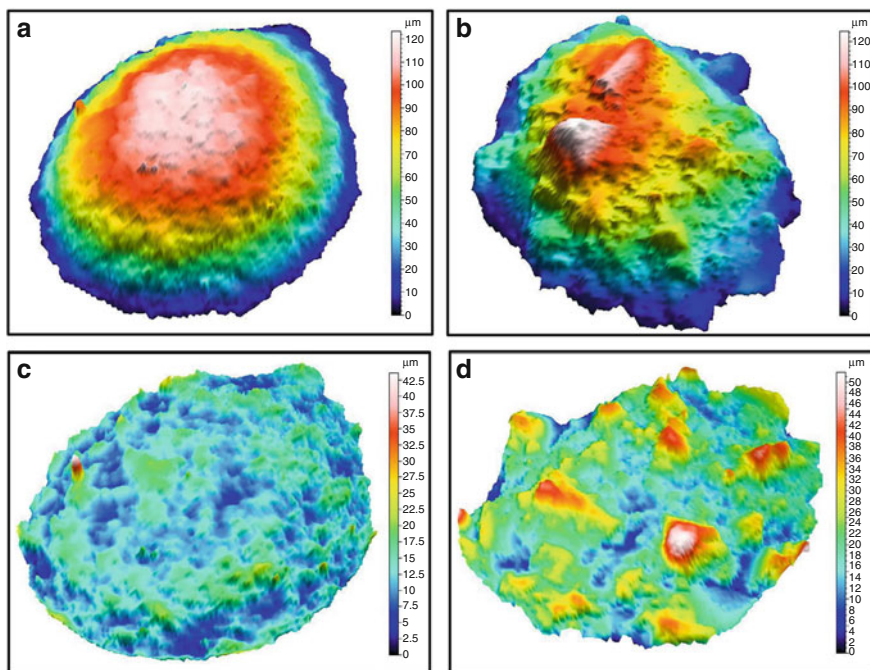


Fig. 2.16 Surface roughness measurements performed using a Nanovea 3D profilometer. Figures (a, b) show the curvature and surface morphology, respectively. In (c, d), the surface roughness profiles are shown following removal of the curvature of the cores

are often insignificant. In rare cases, characterizing the surface morphology is important.

To quantitatively measure surface roughness, instrumentation like the Nanovea 3D profilometer can provide detailed analysis. Figure 2.16a, b shows the output of measuring the surface morphology of sugar spheres from two different suppliers: Supplier 1 having smooth surface morphology (Fig. 2.16a) and Supplier 2 having rough surface morphology (Fig. 2.16b). These images include the curvature found from the spherical particles with Fig. 2.16c, d showing how the quantitative analysis is done after removing the curvature and measuring the height difference of the peaks and valleys.

2.11.1 Specific Surface Area of Pellets

So far, individual attributes have been described indicating how they influence the specific surface area. Since these attributes are always changing simultaneously, it becomes difficult to predict the final outcome on surface area. For this reason, measuring the specific surface area directly would provide a more meaningful indicator to product performance.

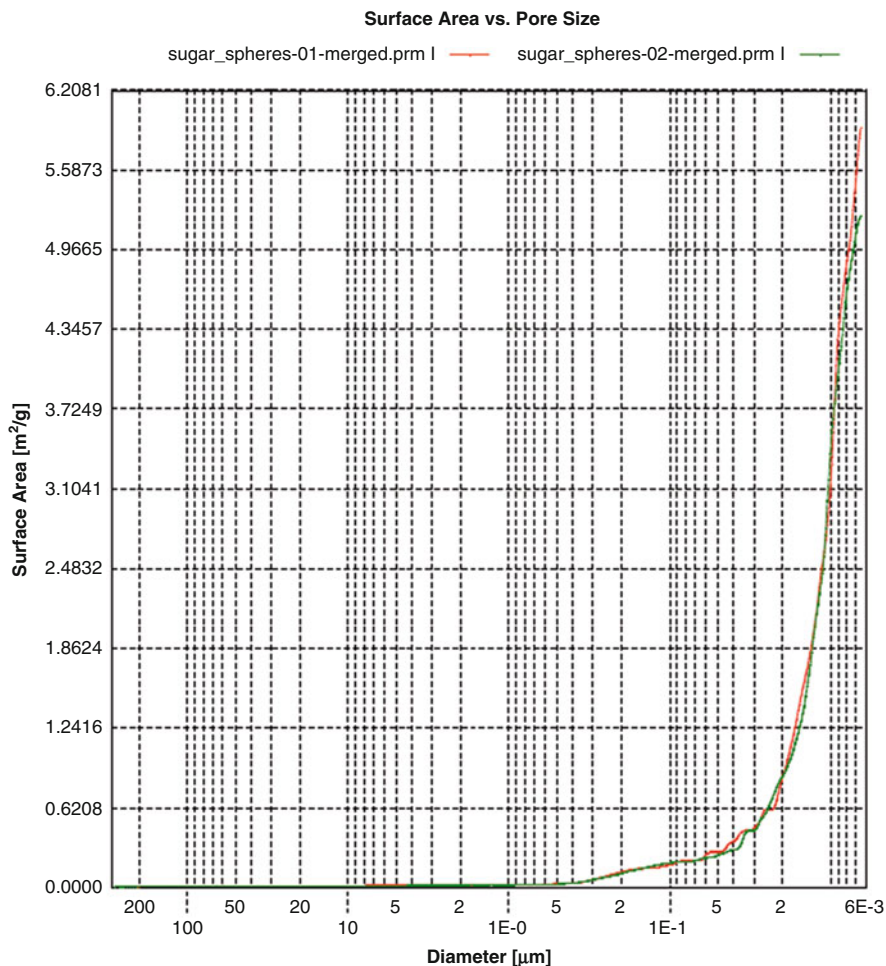


Fig. 2.17 Surface area versus pore size as determined by nitrogen adsorption

A common approach to measuring specific surface area is gas adsorption. This method is based on Brunauer-Emmett-Teller (BET) mathematical model that translates the adsorption of a gas into specific surface area. Gas adsorption also measures the surface area contributed from pores in the substrate. Depending on the parameters (such as gas pressure), the results can include surface area from very small pore openings. Figure 2.17 shows how the measured surface area grows rapidly when including pores of less than 1 μm . Similar to surface roughness, calculating the specific surface area with these smaller pores results in an overestimation for practical use, as the initial coating will quickly fill these smaller pores.

Through the right software and calculations, image analysis provides another option for measuring specific surface area. The calculations used are dependent on the extrapolation of the images of individual particles into three-dimensional

spheres. This extrapolation can result in a poor estimation for irregular-shaped particles. Though measuring the specific surface area quantifies this characteristic directly, it does not explain the cause of the fluctuation. Understanding how each attribute changes is important because each attribute can adversely affect other factors of a multiparticulate dosage form.

2.12 Robustness and Processability of Pellets

Consistent particle size and shape for pellets are critical to maintaining coating film thickness. In addition, the cores must be physically strong to withstand the coating process. Pellets are processed in different types of equipment and are exposed to mechanical shear, high air velocities, solvent, and heat. These conditions, among others, can cause the pellet to break, shear, dissolve, or swell. The following characteristics of pellets are used to predict how they can handle these stresses, especially during scale-up or actual manufacturing operation.

2.12.1 Hardness and Tensile Strength of Pellets

Similar to measuring the hardness of tablets, a texture analyzer may be used to measure the force required to break a pellet. A single pellet is placed under a probe which applies force to the particle. The texture analyzer records the initial diameter of the particle and the amount of force needed to break it. The texture analyzer data is best reported as tensile strength using Eq. 2.10.

Equation 2.10 Tensile Strength

$$\sigma = \frac{1.6 \times F}{\pi \times d^2}$$

F = force

d = diameter

Since the test is labor intensive, only a small sample of particles is tested. If smaller and larger particles are separated and their tensile strength measured (Fig. 2.18), the smaller particles show significantly lower tensile strength. These are often the particles that result in friability issues, breaking into many pieces under the physical stresses of the fluid bed coating processes.

2.12.2 Friability of Pellets

The various processing methods used for manufacturing multiparticulate dosage forms expose pellets to different forms and degrees of stress. The types of forces are dependent on scale, processing conditions, and equipment design [24].

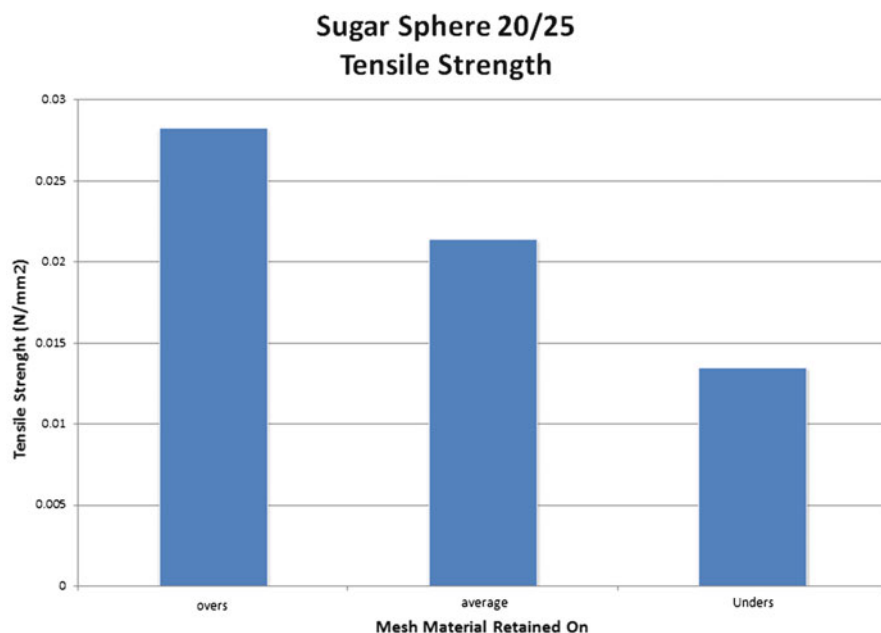


Fig. 2.18 Tensile strength of sugar spheres 20/25 (710–850 μm)

For Würster coating applications, the cores are most vulnerable during the initial phases of processing (i.e., prior to the start of spray). This is often seen in commercial scale equipment while the material is heated before coating. Once spraying has started, the coating layer begins to protect the core from breakage and attrition. The fluidization of the pellets can cause attrition, but often, the atomization air used for the spray nozzles contributes the most to the shear forces. Therefore, it is important to use an appropriate atomization air volume that allows for good spray atomization without causing damage to the pellets.

The European Pharmacopoeia has introduced a method, friability of granules and spheroids [25], which can be used to quantify the friability of inert pellets. The friability results do not always correlate to product performance, and therefore, it may be helpful to modify the method to provide more discriminatory values. Developing a method that predicts if a pellet breaks or erodes during the process provides the opportunity to adjust the processing conditions or identify a more robust pellet. Friability values of $<1.7\%$ w/w have been reported as acceptable to withstand stresses associated with fluid bed coating, handling, and for other processes [24]. Various methods have been earlier described to study the friability of granules and pellets [26, 27]. During a fluid bed coating operation, the atomization air pressure has the most significant impact on the friability of pellets. Vass et al. [26] showed that friability of the pellets increased when atomization pressure was increased from 1 bar to 4 bar, when pre-coating fluidization time was increased from 10 to 30 min, and when batch size was increased from 2 to 50 kg (Fig. 2.19).

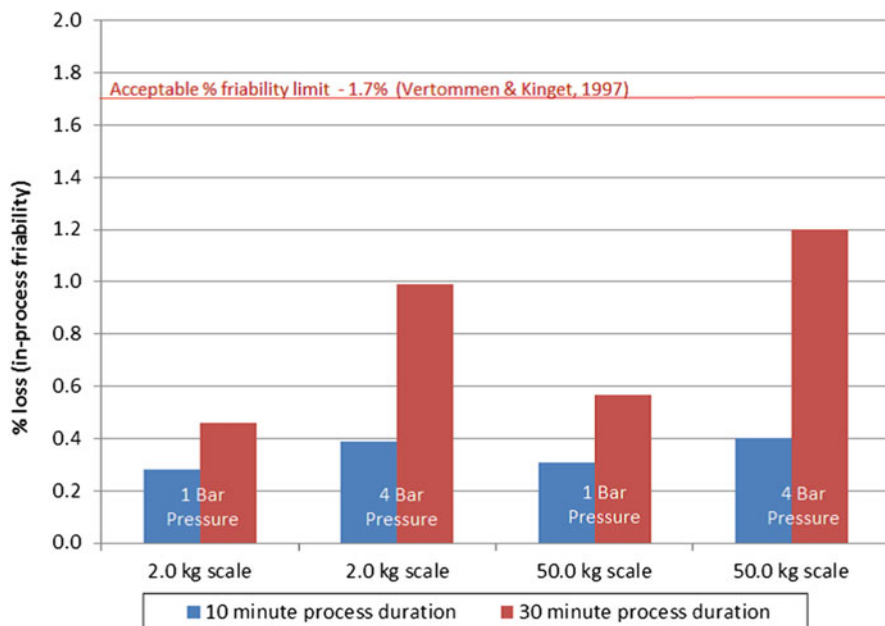


Fig. 2.19 Friability values for process fluidization trials of sugar spheres

The effect of friability is similar to particle size distribution, shape, fines, and density. These attributes are so similar and interconnected in their effects on product performance that the use of friable pellets or stressful coating process parameters makes it difficult to isolate the causes of product variability.

2.13 Conclusions

Like any pharmaceutical sciences topic, characterizing pellets for drug layering is not simple or straightforward. The attributes of the compendia and some suppliers are focused on identity, purity, and safety of the product. When considering product performance, these may not be sufficient. It is the job of the formulator to determine which attributes ultimately affect product performance. This chapter has described a number of common relationships between the performances of common multiparticulate products with the attributes of pellets. Depending on the specific application, many attributes will not be significant. Through careful experimentation, the critical to quality attributes of pellets and their relationship to product performance can be quantified.

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