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Ali R. Rajabi-Siahboomi *Editor*

Multiparticulate Drug Delivery

Formulation, Processing and Manufacturing

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I dedicate this book to my parents who despite
their lack of formal education, inspired me
to learn and share my learning, even though
it meant that we did not see each other
for many years; to my lovely wife, Angela;
and sons, Jonathan and Anthony, for their
support and inspiration to always do my best.

Preface

Multiparticulate drug delivery systems are widely used in the pharmaceutical industry due to their formulation flexibility for the manufacturers and clinical benefits that they offer to the patients. Although the introduction and use of this platform technology dates back to 1950s (under the concept of Spansules by SmithKline and French), there is still a significant level of interest to leverage multiparticulates for achieving various release profiles and for special age groups like pediatric and elderly patients. Multiparticulate systems are developed in a wide range of sizes, i.e., as small as 150 μm or as large as 2–3 mm in diameter and offer superior clinical and technical advantages over many other specialized drug delivery technologies. Due to their multiplicity of units and small sizes, they exhibit reduced risk of dose dumping, spread along the gastro-intestinal tract (GIT), when taken orally, and therefore, offer specific biopharmaceutics advantages over the larger single units. Their transit time through different segments of the GIT is more predictable, reducing inter- and intra-subject variability. Multiparticulates possess large surface area for drug release and when dispersed along the gut, maximize drug absorption without possible local irritation in the GIT.

There is a widespread availability of machinery suitable for the development and manufacture of multiparticulates in the pharmaceutical industry, which is another driving factor for popularity of this drug delivery technology. Most pharmaceutical companies have small- to large-scale fluid bed technology with various setup options to handle multiparticulates and, therefore, enable development of desired formulations using various design approaches with polymers in aqueous or solvent-based systems. In addition, there is a wealth of knowledge and know-how around this technology in the literature, among suppliers of raw materials, polymers, and machine manufacturers serving formulation scientists achieve their desired formulation design and finish drug products. This book is an accumulation of experiences, thoughts, and best practices offered by leading experts from academia, users, and manufacturers. It is complementary to *Multiparticulate Oral Drug Delivery*, a book edited by Isaac Ghebre-Sellassie and published by Marcel Dekker, Inc. in 1994, with a view to update some of the content and add recent advances related to the technology. This book is intended for scientists who are new or already familiar with the multiparticulate technology, whether in the academia or in the industry. It is based on science and practice which provides the readers with knowledge of various choices available to formulate, scale-up, and test the quality and performance of multiparticulates.

The manufacture of inert starter seeds, mainly based on sugar spheres and their functionally related characteristics, has been discussed in Chap. 2. These starter seeds are then used for drug layering and further processing based on target release profiles. Alternative methods for the development and manufacture of multiparticulates such as extrusion-spheronization, mini-tabs, and microencapsulation where drug is included in the core of the multiparticulates are discussed in Chaps. 3, 5, and 6, respectively. Majority of processing of multiparticulates are carried out using a fluid bed machine, and the late David Jones, who was the undisputed subject matter expert in this area, described the fundamentals of fluid bed technology with special emphasis on process robustness and scale-up in Chap. 4. Polymers are generally used to coat the drug bearing multiparticulates in order to modulate the release of the drug. The most commonly used functional polymers for these purposes: poly(meth)acrylate copolymers and ethylcellulose have been described, with specific case studies for their unique applications, in Chaps. 10 and 11, respectively. In most cases, multiparticulates are filled into hard shell capsules as described in Chap. 13 or on occasions, they are compressed into tablets. In recent years, there has been a major interest in special applications of multiparticulates for fixed dose combinations and pediatric formulations, and Chaps. 7 and 9 cover these important topics. Chapters 8, 12, and 14 discuss at length the characterization of multiparticulates. While Chap. 12 describes various ways for in-line characterization of multiparticulates, Chap. 8 discusses the dissolution testing of the final formulation and how to relate these data to *in vivo* performance (Chap. 14).

I would like to express my special thanks to all contributors who allocated their time and effort to prepare their respective chapters, review the others, and help me bring this book to completion.

Harleysville, PA, USA Ali R. Rajabi-Siahboomi

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Chapter 1
Overview of Multiparticulate Systems for Oral Drug Delivery

Ali R. Rajabi-Siahboomi

Oral route remains the gold standard for drug delivery despite the new trends in the development of complex biotech therapeutic agents under specialty or biologic categories. This is mainly due to the patient preference for solid dosage forms, convenience of administration, accuracy of dosing, and therefore safety of the patients. In addition, the technologies involved in development and manufacture of tablets and capsules are well established and understood by scientists and regulators. Moreover there is a huge capacity, and capability already exists in most corners of the world, which means no new significant investments are required in order to develop and manufacture tablets and capsules. The development time of solid dosage forms is generally short, and manufacturing is fast, with high yields. The finished solid dose products exhibit very good stability when formulated and packaged appropriately. Therefore, the most common dosage types for oral drug delivery are tablets and capsules, and they will remain popular by the producers and users. According to the IMS Health data [1], total pharmaceutical market in 2015 was more than $950 billion (USD) with a compound annual growth of around 5% over the last 3–5 years. Over $475 billion were oral solid dosage forms consisting a staggering 1675 billion counting units of solid dosages in 2015. Multiparticulate sales were in the order of $34 billion and around 91 billion counting units and a growth of around 6% in 2015. There are many drug products in the market place that use multiparticulate drug delivery technology and an increasing number of pipeline products which are under development.

Oral multiparticulate systems are dosage forms consisting of many small discrete drug delivery units. They are known under many terminologies such as multiple units, pellets, beads, granules, micro-granules, spheroids, or mini- or micro-tablets. Their reported size ranges vary and may be as small as 150 μm

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(in the case of taste-masked multiparticulates) and as large as 2–3 mm (in the case of mini-tabs) in diameter. Multiparticulate formulations may contain single drug or multiple drug combinations ranging from orally dissolving particles, immediate release to various modified-release formulations. Many of the marketed multiparticulate products consist of coated spheres with either immediate-release coatings for protection or taste masking of the drug or insoluble coatings to modulate the release of the contained drug(s). Multiparticulate systems are reliably administered as a single dose of the drug(s) using hard shell capsules, sachets or, after mixing with additional excipients and compression, in the form of tablets [2].

Multiparticulate drug delivery systems offer unique advantages to formulators, care providers, and patients. Some of the key benefits may be listed as:

(a) Flexibility for the choice of finished dosage form such as capsules, sachets, or compressed to tablets
(b) Flexibility in modulation of drug release by mixing beads with different coatings for different drug release profiles
(c) Easier dose-weight proportionality as compared to single-unit dosage forms
(d) Flexibility for fixed-dose combination formulations
(e) Reduction in intra- or inter-subject variability due to reduced variation in gastric emptying rate and overall gastrointestinal transit time
(f) Flexibility in dose titration without compromising drug release, which is often an issue for extended-release monolithic tablets
(g) Flexibility in mixing them with food for easy swallowability in case of pediatric and geriatric population.

Multiparticulate drug delivery systems offer the classic advantages of solid dosage forms over liquid preparations such as improved stability, reduced weight, and bulkiness resulting in easier transportation, better taste masking, and accurate dosing. They are used for patients that have difficulty swallowing, making multiparticulate systems as an attractive dosage form for pediatric and geriatric patients.

An important and convenient application of multiparticulate technology is the development of fixed-dose combination (FDC) that is used to deliver two or more drug substances in a single dosage form. The primary objective of an FDC formulation is that the contained drugs individually or synergistically contribute to the overall therapeutic effect(s) for specific patient population who benefits from treatment with the intended combination of actives in a fixed ratio of doses. FDCs are commonly used to improve not only efficacy but also adherence and compliance of the patient by reducing the pill burden while ensuring that the required doses are delivered to the patient. Some FDC formulations are developed to reduce costs and simplify handling of medicines for developing markets. These advantages have resulted in the development of a number of FDC formulations for the treatment of HIV/AIDS, tuberculosis, malaria, and cardiovascular conditions.

On ingestion and dissolution of the hard shell capsules (or disintegration, in the case of compressed tablets), multiparticulates disperse in the GI tract due to their small sizes, which results in several advantages over single-unit dosage forms.

For example, they exhibit a reduced intra- and inter-subject variability arising from a more predictable and faster gastric emptying rates, less susceptibility to dose dumping due to a better spread in the GI tract and less likelihood of all units releasing payloads in a burst manner, and avoidance of high local drug concentrations in the GI tract that may irritate the GI mucosa [3]. In addition, compared to large single-unit dosage forms, multiparticulates offer flexibility for the dose to be divided and administered per body weight without changing the formulation or the manufacturing process.

Developing multiple strengths of modified-release formulations is often a challenge for the formulators. Therefore, the concept of dose-weight proportionality is an important topic for modified-release dosage forms. Dose-weight proportional formulation design means developing only one formulation that can be weighed proportional to the dose strength per unit dosage form and provide similar release profile irrespective of dose strength. Such formulations would save time for the formulators from preformulation to formulation, quality by design (QbD), stability, validation, and potentially *in vivo* bioequivalent studies. There is excellent dose-weight proportionality with extended-release multiparticulate formulations [4].

Each unit of the multiparticulate system exhibits inherent functional characteristics that are different to and are independent of other units, which allows the formulation scientist to control the release pattern of the active pharmaceutical ingredient (API). Multiparticulates may be presented as immediate- or modified-release dosage forms, orally disintegrating tablets (ODT), or chewable tablets. Irrespective of the method of presentation, the underlying principle is that the dosage form releases the discrete units that make up the multiparticulate system on administration and entry into the gastrointestinal tract.

Most of the oral multiparticulate dosages available today belong to the group of oral modified-release (MR) formulations. However, there is a recent interest to improve the availability and quality of pediatric and geriatric dosage forms, and therefore, the development of orally disintegrating granules or immediate-release multiparticulates is also becoming important.

From a regulatory perspective, drug development process using multiparticulate systems is similar to other dosage forms. If a new chemical entity is used in multiparticulates, the general safety evaluation, clinical efficacy, dose finding, risk management plans, plus pharmaceutical quality, stability, and manufacturing aspects at different phases of development have to be conducted. If the active ingredient is already on the market and excipients used are well known and monographed, no additional preclinical studies are required. Pharmacokinetic (PK) studies may be sufficient if clinical efficacy and safety of the drug is already established.

The objective of this book is to provide information on recent advances that have been made in the pharmaceutical machinery, raw materials, formulation, and manufacturing in the area of oral multiparticulate systems with a deeper, more scientific understanding of the technology. There is no substitute for good and current science. The book starts with methods of manufacture and characterization of inert spherical cores for fabricating multiparticulates through drug layering

(Chap. 2). For various reasons, including high drug loading (for high-dose strength), extrusion-spheronization may be used to manufacture multiparticulates. The science and everyday practice of the extrusion spheronization is thoroughly covered in Chap. 3. No matter which method is used to produce the multiparticulates, majority are surface coated with a functional coating system using a fluid bed technology. The fluid bed process and scale-up guidelines are discussed in Chap. 4. Alternative ways of producing multiparticulates are in the form of minitabs (Chap. 5) or microencapsulation (Chap. 6), and both of these technologies are currently utilized in the market place, and new developments are in the pipeline. Special uses of multiparticulates are covered in Chaps. 7 and 9, where fixed-dose combinations and pediatric and geriatric formulations are described, respectively. Various polymers are used for modifying drug release from multiparticulates mainly to achieve delayed- or extended-release profiles. The most commonly used polymers are poly(meth)acrylates (Chap. 10) and ethyl cellulose (Chap. 11) with long history, excellent safety, and great familiarity of scientists and regulators alike. The quality and stability attributes of multiparticulates are critical to their safety and efficacy, and therefore, development of dissolution methods to mimic *in vivo* behavior during product development and later as a tool for quality control after manufacturing is described in Chap. 8. With current emphasis on process analytical technologies, quality by design, and continuous manufacturing, Chap. 12 describes the possibilities for in-line characterization of particle size for multiparticulates. Chapter 13 discusses the filling of multiparticulates into hard shell capsules, covering recent advances made in encapsulation as well as critical process parameters to consider. And finally Chap. 14 describes approaches to study and characterize the passage of multiparticulates through the gastrointestinal tract in relation to their biopharmaceutical considerations. It is hoped that this book would introduce the multiparticulate dosage forms to those who are not familiar with the technology and further enhance the knowledge of those who are familiar with them and provide best practice guidelines for those who develop and manufacture multiparticulate products.

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Chapter 2
Characterization of Inert Cores for Multiparticulate Dosage Forms

Richard Sidwell, Jason Hansell, Manish Rane, and Ali R. Rajabi-Siahboomi

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

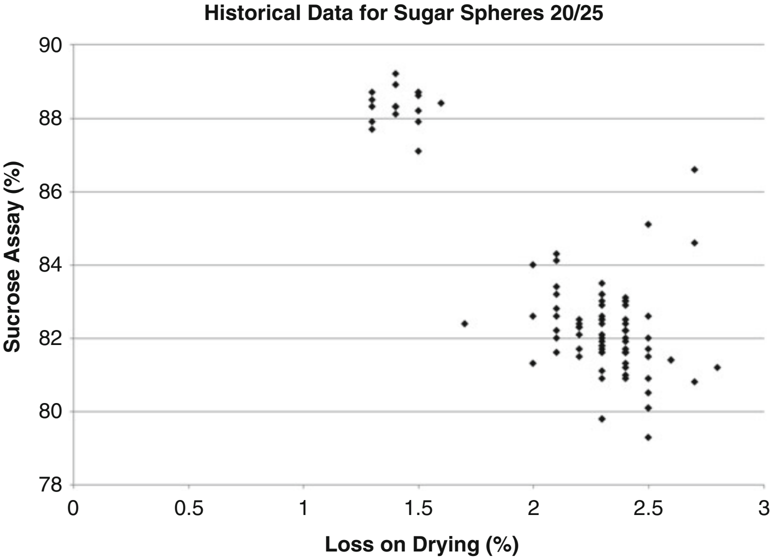

Fig. 2.1 Correlation of loss on drying (LOD) and sucrose for sugar spheres 20/25# (710–850 μm)

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

[a] Density considered as 1 g/cc for calculations

Equation 2.4

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

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

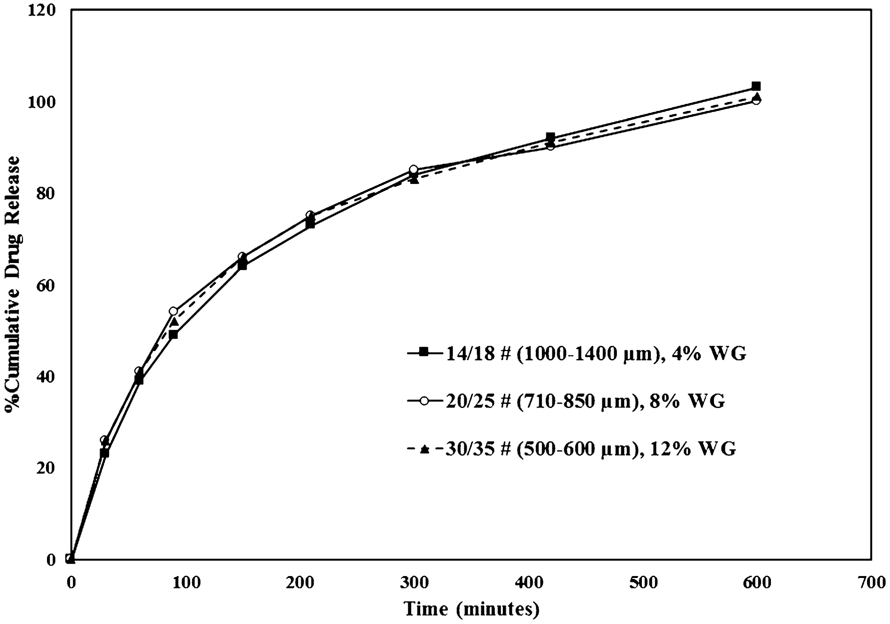

Fig. 2.2 Effect of sugar sphere starting particle size and weight gain of Surelease barrier membrane coating on release of chlorpheniramine maleate

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

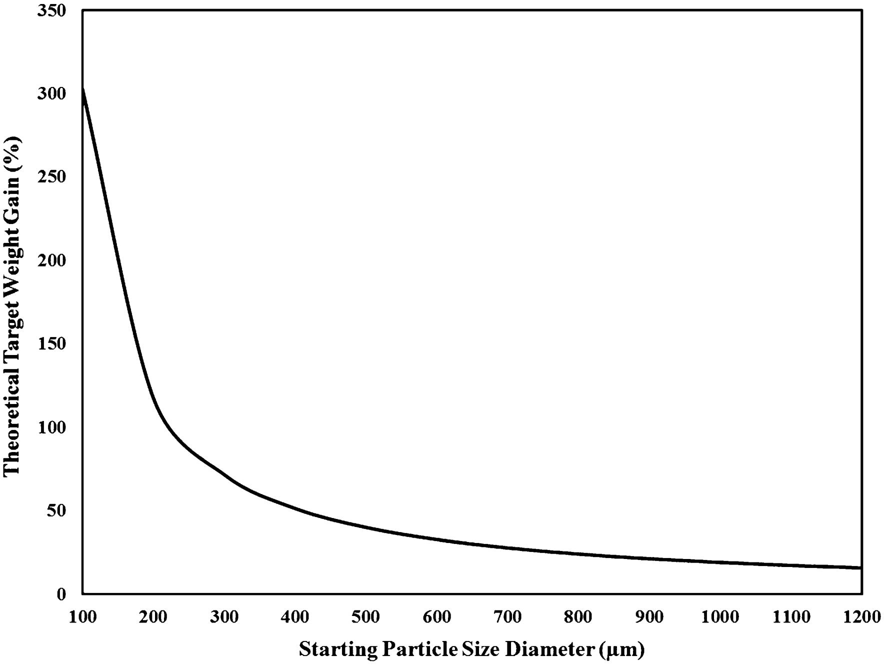

Fig. 2.3 Theoretical coating weight gain required to achieve constant film thickness of 30 μm for different starting particle diameters

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

[a] Median 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

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

$\mu = mean\ or\ median\ or\ mode$
$\sigma = standard\ deviation\ (\sigma^2 = variance)$

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	

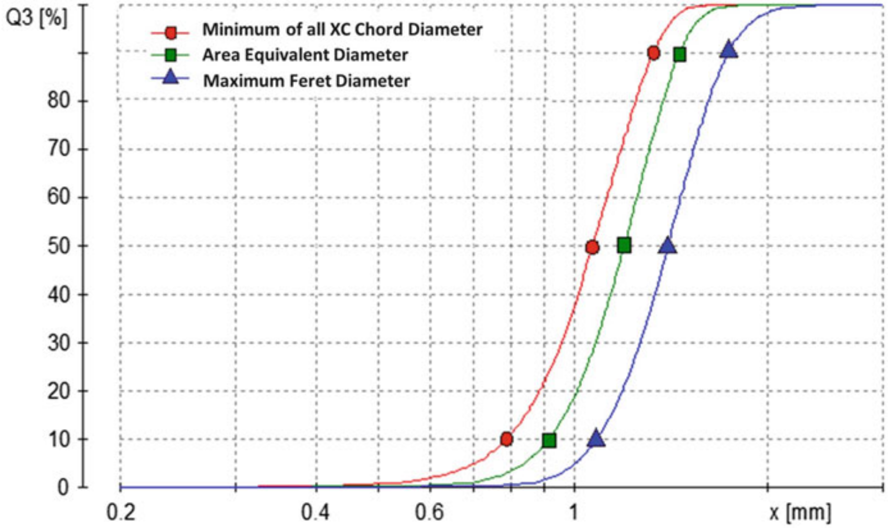

Fig. 2.4 Particle size distribution using different particle size definitions (Courtesy: HORIBA Instruments Inc., USA)

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

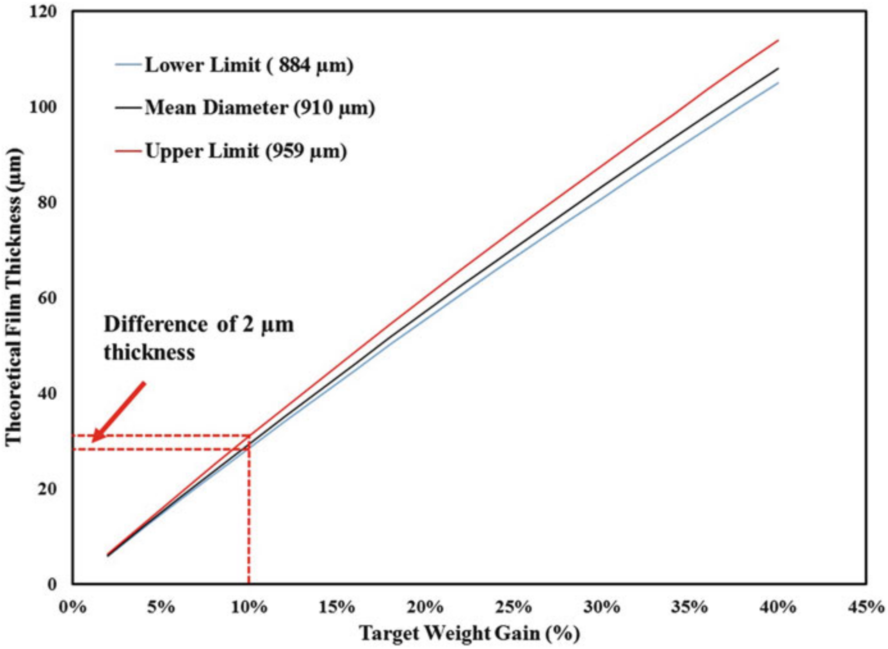

Fig. 2.5 A shift in median particle size from 884 to 959 µm (75 µm) of sugar spheres 18/20# (850–1000 µm) results in a theoretical difference in 2 µm film thickness

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

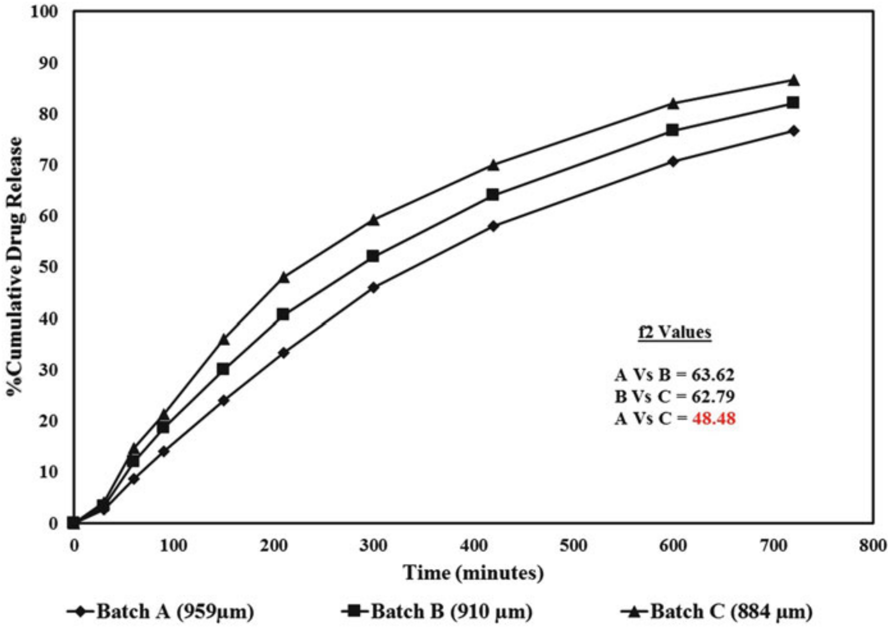

Fig. 2.6 Effect of median particle size (884, 910, and 959 µm) of sugar spheres on dissolution of chlorpheniramine maleate-layered beads coated with 10% weight gain of Surelease

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

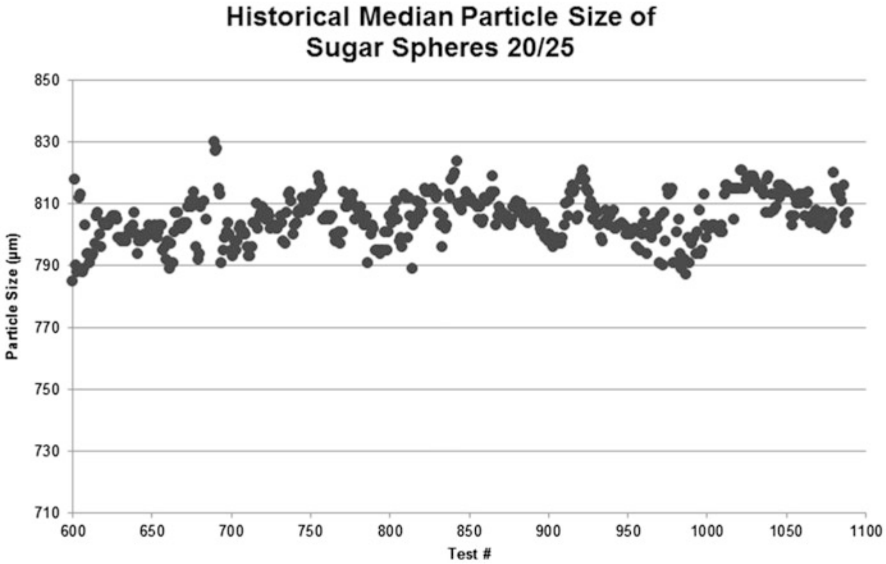

Fig. 2.7 Historical median particle size of sugar spheres 20/25# (710–850 µm) (*Suglets® technical bulletin,www.colorcon.com/*)

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,