1 Introduction

1.1 The Joy of Particulate Products

Particulate products represent a large proportion of *formulated products.* The performance of these products is a function not only of their composition, but also of their particulate structure, properties, and attributes. There are a remarkable array of such products, including crystals, granules, compacts, pastes, and emulsions. The products appear in industry sectors as diverse as agricultural and specialty chemicals, food, consumer goods, agricultural products, energetic materials, and pharmaceuticals. In fact, 70% of products from these industries are in particulate form. Particle products contribute more than one trillion dollars to the US economy, which is the world's largest manufacturer of these high-value particulate products. They impact positively on people's quality of life all over the world.

Why are particulate products so wildly popular? They have a number of advantages over simple liquid formulations.

1. They reduce transport and handling costs through not having to transport large amounts of solvent, typically water, over large distances.
2. They have improved physical and chemical stability over liquid products. This gives longer shelf life and improves safety for consumers for food and pharmaceutical products, for example.
3. They allow us to design-in complex product performance – e.g., a controlled-release profile for a drug. Sometimes, the performance attributes are apparently in direct competition – e.g., an agricultural chemical granule that is strong to resist attrition during handling, but "instantaneously" breaks down and dissolves when mixed with water.
4. The product can be designed to consist of many components – e.g., a detergent granule or tablet can include surfactant, bleach, enzymes, etc.
5. Consumers like them!

In many cases, the final delivery form for a particulate product is a structure containing smaller, primary particles that is built up over many length scales. Figure 1.1 illustrates this for a pharmaceutical solid oral dosage form – a tablet. The active pharmaceutical ingredient (API) is a molecule, often present as a crystalline particle. Single crystals interact with each other, and aggregate or agglomerate. This helps define how they behave as a bulk powder. The API powder is blended with

Table 1.1 Some examples of particulate products and their required attributes

Product	Form	Desired attributes
Table sugar	Crystals	• White, pleasant appearance • Non-sticky • Flows freely • Resists caking
Herbicides	Granules	• Flows freely • Resists attrition • Non-dusty • Disperses instantaneously in water
Pharmaceutical oral dosage form	Tablet	• Drug content uniformity • Resists attrition, breakage • Has good physical and chemical stability • Dissolves in the GI tract at the required rate
Paint	Suspension	• Opaque to light in visible wavelength region • Complex rheology – sticks on the brush, but easily spreads on the wall • Physically stable – is not a sludge with clear liquor on top when the tin is opened

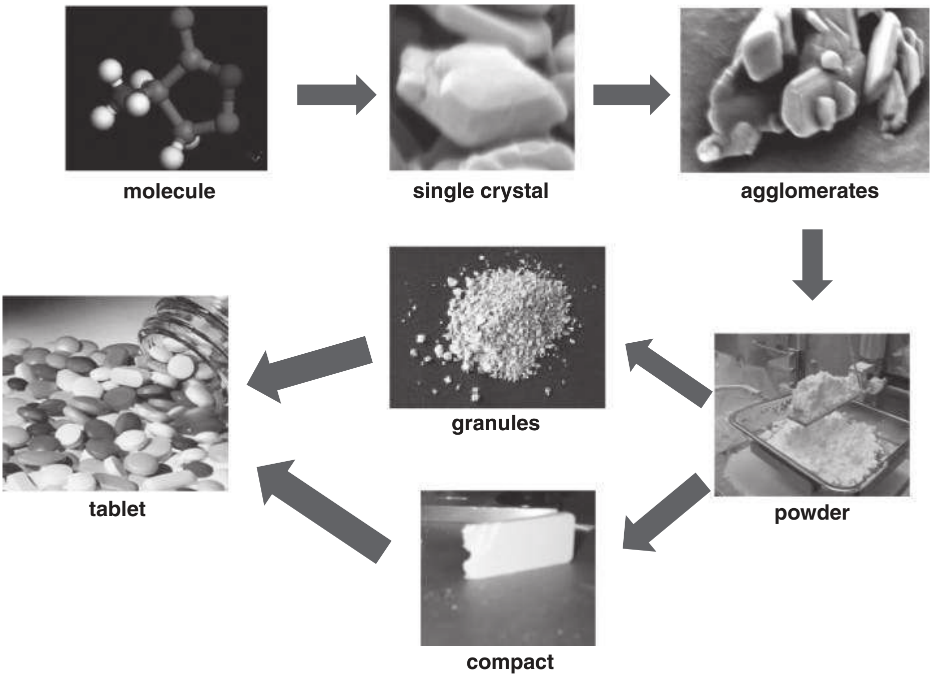

Figure 1.1 A pharmaceutical tablet is a particulate product built up over many length scales.

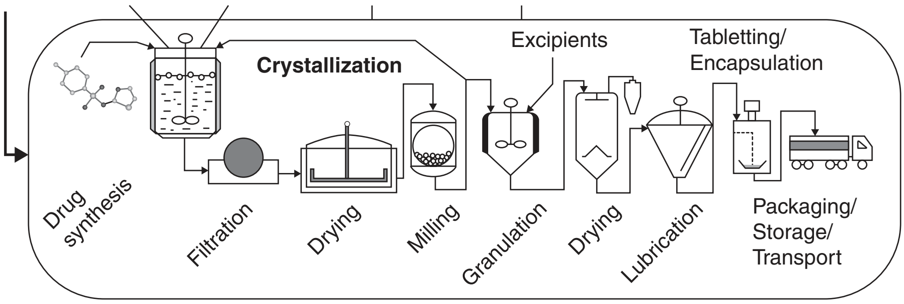

Figure 1.2 A simplified flowsheet for the manufacture of a pharmaceutical solid oral dosage form.

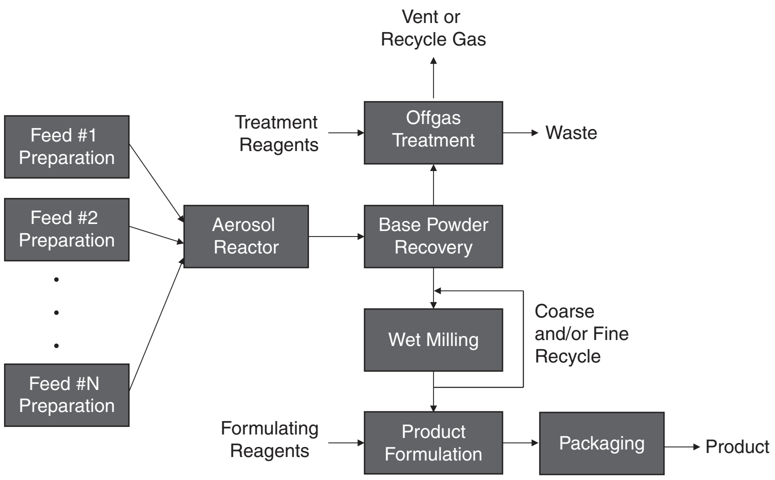

Figure 1.3 A simplified flowsheet for paint pigment manufacture via an aerosol reactor.

excipients and granulated (wet or dry) to give free-flowing granules suitable for compacting into a tablet. Building such complex products requires complex process flowsheets involving many unit operations (see Figure 1.2).

Figure 1.3 shows the flowsheet for producing a very different particulate product – paint pigments. Here, the submicron primary particles are produced in a flame reactor. They self-agglomerate, which is useful to help separate them from the flowing gas stream. Downstream, they may be granulated into some easy-to-handle particulate form. Ultimately, the agglomerates must be milled and dispersed as a stable, shear-thinning suspension – paint.

Note that many of the unit operations on the flowsheets are processes that create new particles, modify particle properties, or build new particulate delivery forms: crystallization, aerosol reactors, grinding, agglomeration, compaction, and so on. These are the processes of interest in this book. We need to be able to predict the particle properties (size and size distribution, morphology, porosity, and structure) that result from these processes. We are interested in *made-to-measure designer particles*. Other texts in particle technology deal primarily in *off-the-rack* particles, and how they are processed and handled. The engineer has no control over off-the-rack particles. He or she must simply deal with them. Designer particles offer the opportunity for creativity and synthesis, which we think is much more interesting.

Particulate products are complex, and the physics of particulate materials is not completely understood. For example, the full constituitive behavior of powder flow has not yet been defined in the way Stokes did for fluid mechanics 150 years ago. Furthermore, the discrete nature of particulate materials means that we also must track distributions of particle properties, not just point values. This means that it is rare we can design a product or process completely from first principles. Nevertheless, quantitative engineering tools based on fundamental physics do exist for most processes and they should be used! That is the rationale for this book.

1.2 Process and Product Engineering

Typically, chemical engineers are very good at process engineering – designing and optimizing individual unit operations and integrated flowsheets to produce the right production rate of material while minimizing cost and waste. This is a good approach for commodity chemicals produced in large tonnages over a long period of time. However, process engineers have little knowledge of formulation or new product development and the engineering tools are usually designed for processes involving simple fluids rather than particulate materials or complex fluids such as emulsions.

Traditionally, formulators in industries making particulate products have taken a product engineering view. New products are formulated to give the desired product attributes. Manufacture is recipe driven using available off-the-shelf equipment with heuristics used to choose and scale the equipment. This can lead to time-consuming experiments at many scales to get the product to manufacture and often non-optimal processes. This dichotomy between formulators and process engineers is often reinforced in the company structure.

A better way is needed. Optimal engineering development and scale up of a particulate product requires a combination of *both* process and product engineering. This approach is illustrated in Figure 1.4. First, the properties of the formulation must be carefully characterized (product engineering). This characterization step is always essential because the properties of particles and powders are not only a function of their *thermodynamic* state, but also their *particulate* state, which depends on their particle property distributions (especially size) and their processing history. Second, the key operating conditions in the process equipment (velocity, concentration, and stress fields) must be characterized in terms of process parameters that can be controlled: impeller speed, temperature, etc. (process engineering).

For each operation, we need a *process model* that tracks the evolution of the particle properties distributions in the process equipment. Where possible, we use a

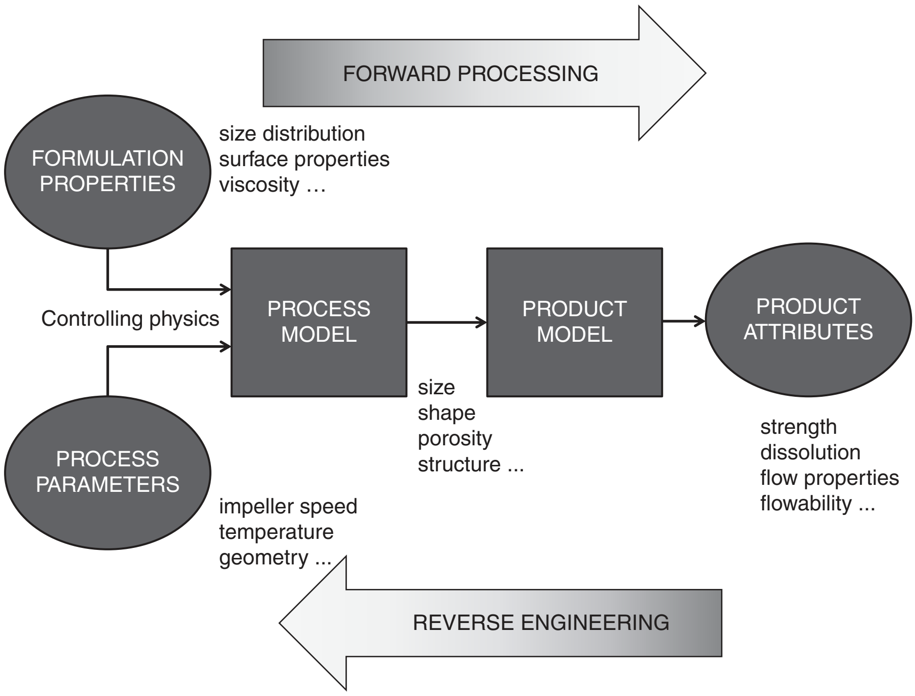

Figure 1.4 Combining product and process engineering for particulate product design and manufacture.

mathematical tool, the population balance, as the framework for the process model in combination with mass and energy balances. The structure of the model, and the value of the rate constants, are linked to the process parameters and formulation properties through an understanding of the controlling physics and/or chemistry.

We are not finished yet. Typically, our end goal is to know the product attributes such as those described in Table 1.1. For this we need a *product model* which predicts product performance – e.g., dissolution rate – given the particulate product structure and property distribution.

To this point, we have described a combination of product and process engineering for forward development. This approach is generally used to scale up and optimize a new formulation with an existing process or choice of processes. Ideally, in the design phase we should be *reverse engineering* our product. By this I mean that we first define our required product attributes, then work backwards using our product and process models to choose a process and formulation that meets our needs. Reverse engineering is more challenging because there is no single correct solution, but rather a family of possible solutions that can be used.

Note that Figure 1.4 seems to imply our particulate product is made in a single step. As we saw from Figures 1.2 and 1.3, manufacturing a particulate product is a multistep process, so many process models are needed. The more complex the product, the more steps that are required. Broadly speaking, we can divide particulate

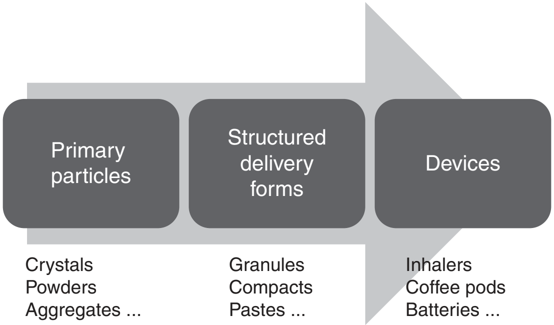

Figure 1.5 Increasing complexity of particulate products.

products into three categories (Figure 1.5). *Single particles and powders* are the simplest particulate products. Granular sugar is a good example. *Structured products and delivery forms* are often built from single particles and may have several components. For example, a pesticide water-dispersible granule to be reconstituted as a solution or slurry to spray onto crops will consist of the active ingredient combined with a binder, surfactant, and disintegrant into a porous, free-flowing granule. The most complex products are those where the particulate product is combined with a *delivery device*. For example, a dry powder inhalation system to deliver insulin to the lungs consists of (1) agglomerates of the active ingredient attached to lactose carrier particles, and (2) an inhalation device which is designed so the agglomerates break down by impact or shear and are inhaled as primary particles.

In the following chapters, we consider the manufacture of single particles, powders, and structured products in some details, but delivery device design in beyond the scope of the book.

1.3 How to Use this Book

The book is organized along the lines of process and product engineering described above (Table 1.2). Chapters 2 and 3 give essential tools for studying any particulate systems: (1) definitions of key properties and tools and for both formulation and product characterization, and (2) the mathematical basis for defining property distributions and tracking how they change during processing. Chapters 4–6 cover processes which generate single particles, while Chapters 7 and 8 cover processes that build particulate delivery forms. Chapters 9 and 10 give important product performance models that predict important behavior of the product in use. For each chapter:

1. the key rate processes are defined;
2. the relevant physics of the processes is presented leading to identification of the formulation properties and process parameters that control them; and

Table 1.2 Structure of the book

Essential tools	2. Particle Characterization 3. The Population Balance
Particle formation processes	4. Crystallization 5. Particle Size Reduction 6. Aerosol Processes
Particulate delivery forms	7. Spray drying and spray cooling 8. Wet Granulation
Product Models	9. Strength and attrition of agglomerates 10. Dispersion, disintegration and dissolution

3. the population balance is used as a framework to quantity these processes for synthesis and analysis.

Each chapter begins with a messy case study based on a real industrial example. The case study helps you to empathize with the engineer or technologists who face such challenges on a regular basis, and puts the chapter in context.

This book is primarily for use as a textbook for students studying courses in particulate processing and particle technology more broadly. Hopefully, it is also a resource for practitioners wanting to bring a more rigorous approach to product or process development. Chapters 2 and 3 give the students the tools necessary for the analysis in the following chapters. Students, lecturers or practitioners can cherry-pick from the unit operations covered in Chapters 4–8. We recommend that at least one of the product modeling chapters is included. I hope your course of study convinces you that quantitative engineering with a sound scientific basis can and should be applied to these complex products and processes. Enjoy!

1.4 Discussion Questions and Problems

1.1. Visit your supermarket and make a list of the particulate products you see on the shelf. Remember to visit the cleaning and laundry aisles as well as the food aisles. Group the products by their physical type: crystal, powder, granule, table, paste, and so on. For each product, list the product attributes important to its performance – e.g., fast dissolving, good shelf life. Look at the ingredient list. Is the product a single component (sugar) or a complex formulation (laundry detergent)? Based on your observations of the product, how do you think it is manufactured? Is the same product available in several different physical forms?

1.2. Repeat problem 1.1 at the pharmacy (drug store). Don't forget to look in the cosmetics and personal care aisles as well as the pharmaceuticals.

1.3. Repeat problem 1.1 at the hardware store.

1.4. Using an encyclopedia of chemical technology or web-based resources, look up typical manufacturing flowsheets for the following products (or any other you can think of):
   a. carbon black
   b. table sugar
   c. paracetamol (acetominaphen) tablets
   d. laundry detergent
   e. ammonium nitrate for (a) fertilizer; or (b) explosive production
   f. pyrotechnic fireworks
   g. toothpaste
   h. catalyst for using in catalytic cracking of petroleum fractions
   i. cement

In each case, identify the unit processes that form new particles, change the particle properties, or form them into structured particulate products.

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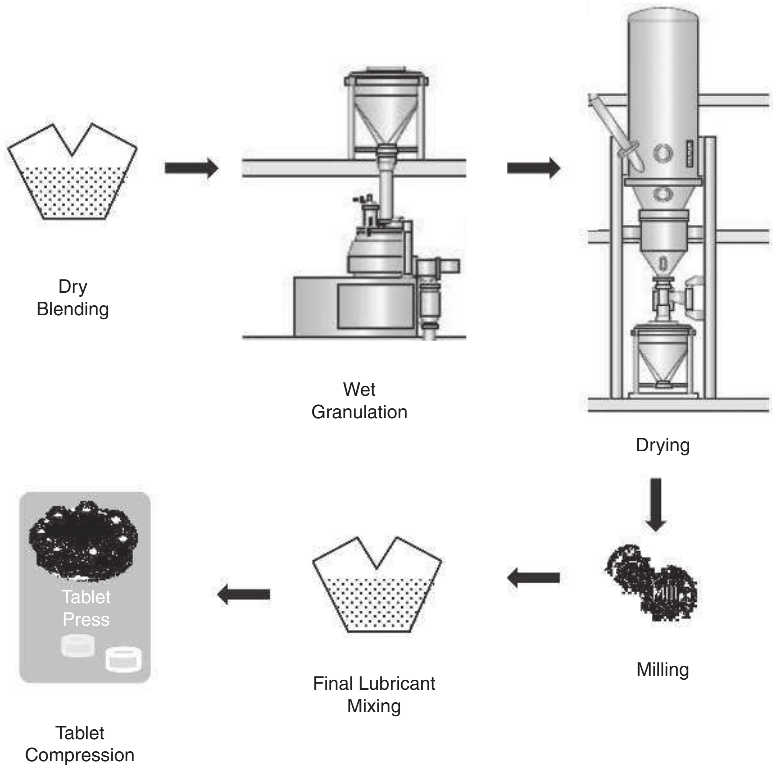
Jim Litster
Excerpt
More Information

2 Particle Characterization and Particle Property Distributions

2.1 Consider a Case Study …

Acme Modern Drugs
Memo to: Physical Characterization Lab.
From: Jim Litster, Placebo xx Development Team
Date: January 6, 2011

We have had serious problems in transferring our new antidepressant Placebo xx® from production in our Puerto Rican plant to the Rocklea facility in Brisbane, Australia. In the development batch, granulation was very poor. Tablets formed had low crush strength and high friability. This formulation has previously given no problems in Puerto Rico and none were anticipated in Australia, so production schedules have been pushed back. This is a serious issue as demand for Placebo xx® in Australia is booming. We suspect that the change in behavior of the formulation is due to sourcing of lactose powder which comprises 94.2% w/w of Placebo xx®. The lactose used at Rocklea is from the Delicious Dairy Co. in Hamilton, New Zealand, while Puerto Rico uses lactose from the US supplier. We have already established there is no difference in chemical properties between the two sources of lactose. Can you please: (1) identify any differences in physical properties of the two types of lactose that could explain their different granulation and tabletting behavior; (2) recommend a standard set of characterization tests to be performed on all newly sourced formulation ingredients in the future. We are receiving a visit from the Australian Food and Drug Agency next month so it is imperative we receive your memo by February 11 at the latest.



Background Information on Placebo xx ®Manufacture
Manufacture of Placebo xx ® consists of the following steps.

- Dry powder blending
- Wet granulation
- Fluid bed drying
- Milling (to crush lumps formed during granulation)
- Conveying to tablet press feed hoppers
- Tabletting

All processes are batch except for the final tabletting press. The batch size at full production scale is set by the size of the granulator (500-liter capacity). This combination of processes is typical for pharmaceutical tablet manufacture.

You may be surprised to know that problems like the one described above are very common and create continuous headaches for engineers and technologists.

- A new batch of material for processing behaves differently in processing to previous batches even though it meets the same specifications.