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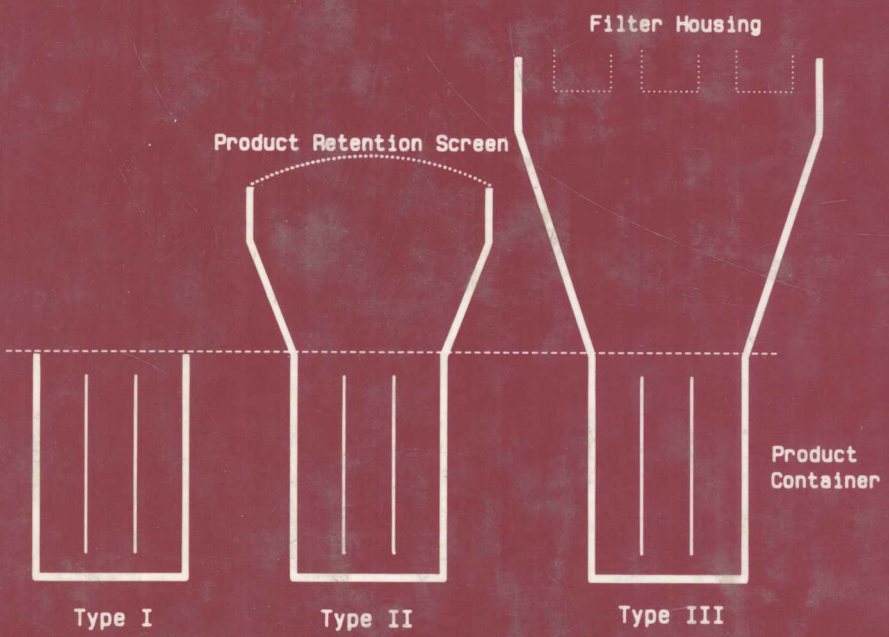
Pharmaceutical Pelletization Technology



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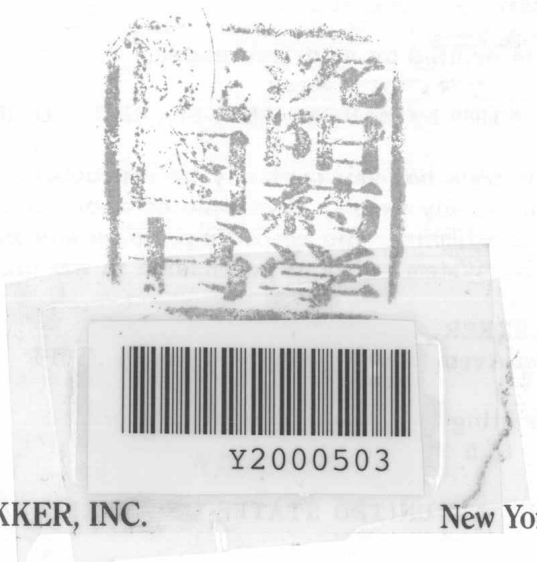

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Preface

Spherical oral dosage forms such as pills have been used in the pharmaceutical industry for a long time, but the full impact of systematically agglomerated spherical units or pellets on oral dosage form design and performance was not realized until the early 1950s, when attempts were made to develop extended release products. Since then, the manufacture of pellets has been the subject of intensive research, in terms of both innovative formulations and processing equipment. Consequently, the number of pelletized products available to health professionals and the public at large has been increasing steadily. The trend is expected to continue well into the twenty-first century.

In spite of the current popularity of pellets in dosage form design and development, a systematic and organized description of the various formulation routes and pelletization processes pertinent to the pharmaceutical industry is practically nonexistent. Except for a few articles, the available literature on the subject deals with the food, confectionary, veterinary, agricultural, and chemical industries. The objective of this book is, therefore, not only to serve as a formulation and processing guide during the development of pelletized dosage forms, but also to provide the pharmaceutical technologist with basic information about the design aspects of the relevant processing equipment.

Chapter 1 gives a general overview of pellet technology and discusses the historical development of pellets and pelletization processes, the factors that impact upon the fabrication of pelletized dosage forms, and the classification of pharmaceutical pelletization processes. General descriptions of the design features

of the most widely used processing equipment—coating pans, fluid-bed machines, extruders/spheronizers, and centrifugal equipment—are covered in Chapters 2 through 5, and each of these four chapters provides a list of the suppliers of the various pieces of equipment. Chapter 6 describes the physical and mechanical forces that govern the mechanism of pellet formation and growth during a given pelletization process. Chapters 7 through 9 are devoted to a thorough discussion of the most popular pelletization processes available to the pharmaceutical industry. Included are descriptions of the critical processing variables during solution/suspension layering, powder layering, and extrusion/spheronization.

Formulation variables are discussed in Chapter 10. Although a few excipients are mentioned in relation to some specific processes in order to highlight certain functions, the main thrust of the chapter is description of the functions of excipients in general terms. Practical examples of pellet formulations and processing conditions are given to underscore the role of formulation components during the manufacture of drug-loaded pellets. Chapter 11 describes the techniques that are utilized to evaluate and characterize pellets prior to the start of other unit operations in the dosage form development sequence.

The material discussed in the book covers the various areas that are pertinent to the successful development of pelletized pharmaceutical products and is expected to lay the groundwork for further refinement and optimization of modern pelletization processes. It must be emphasized, however, that the book is limited to the processes and equipment relevant to the manufacture of core pellets, and does not address in detail the coating, encapsulation, or compression of pellets.

I would like to thank all those who helped in different ways during the preparation of the book, in particular, the authors of the various chapters, who graciously volunteered their leisure time to make the publication of this book a reality. Thanks also to Dr. Mahdi B. Fawzi and Dr. Russell U. Nesbitt, respectively, Vice President and Director, Product Development, Parke-Davis Pharmaceutical Research Division, Warner-Lambert Company, for their support and encouragement. Moreover, I am very grateful to my colleagues at Parke-Davis for their constructive suggestions and to Mrs. Ruth G. Cohnstein, who did a superb job of typing the manuscript.

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Pharmaceutical Pelletization Technology

Contents

1

Pellets: A General Overview

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I. DEFINITION

Traditionally, the word "pellet" has been used to describe a variety of systematically produced, geometrically defined agglomerates obtained from diverse starting materials utilizing different processing conditions. These products may be fertilizers, animal feeds, iron ores, or pharmaceutical dosage forms, to mention but a few. It is appropriate, therefore, at the outset to define the words "pellet" and "pelletization" in the context in which they are used in the book in order to avoid confusion. Pelletization is an agglomeration process that converts fine powders or granules of bulk drugs and excipients into small, free-flowing, spherical or semi-spherical units, referred to as pellets. Pellets range in size, typically, between 0.5–1.5 mm, though other sizes could be prepared, depending on the processing technologies employed. The most widely used pelletization processes in the pharmaceutical industry are extrusion/spheronization, solution/suspension layering, and powder layering. Each of these processes is discussed in detail later in the book and need not be defined here. Other processes with limited application in the development of pharmaceutical pelletized products include globulation, balling, and compression (Figure 1) and are briefly described below.

Globulation or droplet formation describes the two related processes of spray drying and spray congealing [1]. During spray drying, drug entities in solution or in suspension form are sprayed, with or without excipients, into a hot-air stream

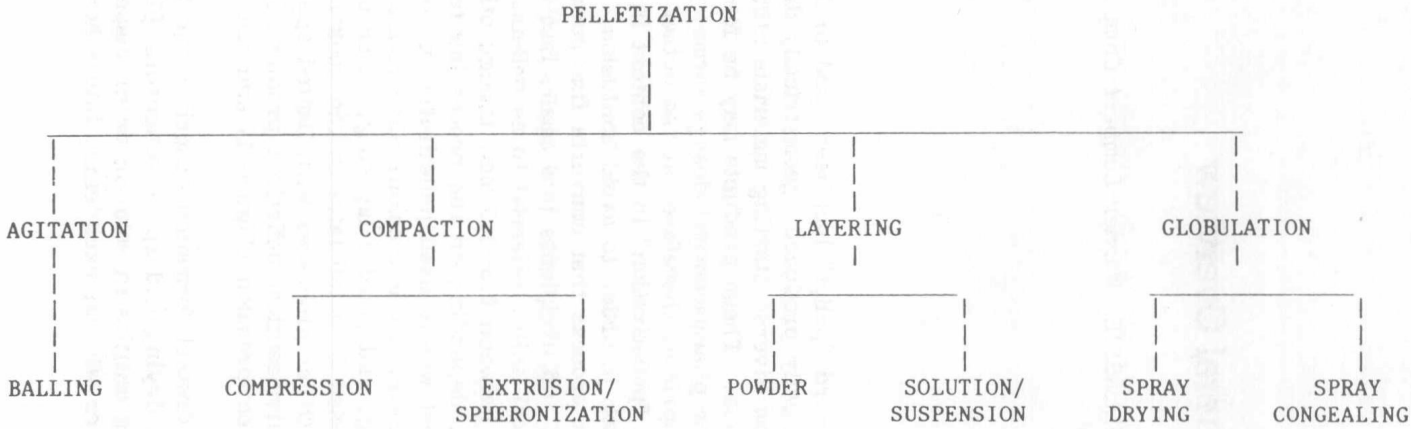

FIGURE 1 Classification of pellitization processes. (From Ref. 1.)

to generate dry and highly spherical particles. Though the technique is suitable for the development of controlled-release pellets, it is generally employed to improve the dissolution rates and, hence, bioavailability of poorly soluble drugs. Spray drying has been used for years for a variety of reasons. Consequently, the literature is replete with descriptions of both process and equipment.

Spray congealing is a process in which a drug is allowed to melt, disperse, or dissolve in hot melts of gums, waxes, fatty acids, etc., and is sprayed into an air chamber where the temperature is below the melting points of the formulation components, to provide, under appropriate processing conditions, spherical congealed pellets. Depending on the physicochemical properties of the ingredients and other formulation variables, pellets with immediate- or controlled-release behavior can be produced.

Compression is a pelletization process in which mixtures or blends of active ingredients and excipients are compacted under pressure to generate pellets of defined shape and size. The pellets are small enough to be filled into capsules. The formulation and processing variables that govern the production of pellets during compression are similar to those that are routinely employed in tablet manufacturing. In fact, pellets produced by compression are nothing but small tablets that are approximately spheroidal in shape.

Balling describes a pelletization process in which finely divided particles are converted, upon the addition of appropriate quantities of liquid, to spherical particles by a continuous rolling or tumbling motion. The liquid may be added prior to or during the agitation stage. Pans, discs, drums, or mixers may be used to produce pellets by the balling process.

II. HISTORICAL DEVELOPMENT

Although various industries have routinely utilized pelletization processes since the turn of the century to manufacture particles with defined sizes and shapes, it was only in the early 1950s, in response to a desire to sustain the release of drugs over extended periods of time, that the pharmaceutical industry developed a keen interest in the technology. Pellet-based extended-release products initially employed conventional pills [2]. Pills of different release profiles were combined in predetermined proportions and encapsulated in hard gelatin capsules to produce

sustained-release oral dosage forms. However, the number of pills that could be filled into a single capsule was limited, and the duration of release could not be extended beyond a few hours [2]. In addition, the manufacturing process of the pills was cumbersome and labor-intensive. It also required experienced artisans to do the job, thereby making the process an art rather than a science. As the processing equipment got more sophisticated, tablet machines that were capable of producing thousands of tablets in a matter of minutes became available. However, in spite of the tremendous strides made in reducing processing times and perfecting the technology that led to the production of minitablets suitable for encapsulation, the approach did not alleviate the size limitation that was encountered during the development of pills-based sustained-release products. That is, the volume that could be made and the number of pellets that could be filled into a capsule were prohibitively small. Consequently, extensive research was conducted to develop alternative techniques to provide pelletized dosage forms that exhibit extended-release properties.

A major breakthrough occurred in 1949 when a pharmaceutical scientist at Smith Kline & French (SKF) realized the potential application of candy seeds in sustained-release preparations and embarked on the development of tiny drug pellets that could be loaded into capsules [2]. The candy seeds were nothing but small sugar particles that were used for topping decorations on pastries and related foodstuffs, and were prepared by a process, at the time, unknown to the pharmaceutical industry. However, in 1951 a landmark paper, which described in detail the manufacturing process of the seeds, appeared in the *Confectioners Journal* and revolutionized the production of pelletized products [3]. The process utilized standard coating pans and involved successive layering of powder and binder on sugar granules until spherical seeds of the desired size were obtained. The process was lengthy and required days to be completed. It, nevertheless, spearheaded a new era and provided the basis for the development of future pelletization processes. Not only was the process directly applicable to drug candidates, but also the candy seeds or nonpareils, which are inert and innocuous, functioned as starter seeds upon which drugs were layered, with or without sustaining materials. During the early days, the technology was refined and perfected by SKF and was applied to a number of its prescription drugs, for which the company received a series of patents [4–6]. It was, however, the major success of the long-acting cold remedy, Contac, that partially

fueled a renewed interest in the development of extended-release pelletized products [2]. While substantial effort was made to further improve and refine the existing pelletization techniques, major resources were also allocated toward exploring alternative methods that were faster, cheaper, and more efficeint, both in terms of formulations and processing equipment.

In 1964, a new pelletization technique that provided sustained-release pellets ranging in size between 0.25–2.0 mm was patented by SKF [7]. It comprised a spray congealing process in which the drugs were dissolved or dispersed in a lipid material in the molten state to form a slurry, followed by atomization of the slurry into a low-temperature gas chamber until spherical congealed pellets were produced. The sizes of the pellets obtained from a given formulation and a set of processing conditions were determined by the nozzle orifice. The pellets were manufactured in a spray dryer, a piece of equipment that already had a wide application in the industry.

At about the same time, the Marumerizer was commercially introduced. This new machine was developed in Japan and could produce large quantities of spherical pellets in a relatively short time. The Marumerizer and variations of it were subsequently patented in the United States [8–10]. Basically, the process involves extrusion of a wetted mass of a mixture of active ingredients and excipients to provide cylindrical segments or extrudates followed by spheronization of the extrudates in the Marumerizer or Spheronizer. Extruders and spheronizers, which are the main pieces of equipment employed for this process, are described at length in Chapter 4. Suffice it to say that the emergence of the process as a practical pelletization technique enhanced the status of pellets in pharmaceutical drug dosage form development. The process is capable of producing pellets containing more than 90% active, provided that the physicochemical properties of the drug and other formulation constituents are optimum. Direct pharmaceutical applications of the process for the development of pellets were first published in the literature in the early 1970s [11–14] and the process has been the subject of intensive research ever since.

As drug delivery systems became more sophisticated, the role of pellets in drug dosage form design and development increased substantially, and both manufacturers of processing equipment and private investigators have intensified their search for highly efficient processing equipment in order to accommodate the increased demand. Not only are already existing pieces of equipment being continuously improved upon, but also new de-

signs are reaching the market at an increasing rate. The trend is expected to continue in the foreseeable future.

III. RATIONALE FOR PELLETIZATION

Pellets are of great interest to the pharmaceutical industry for a variety of reasons. Pelletized products not only offer flexibility in dosage form design and development, but are also utilized to improve the safety and efficacy of bioactive agents. However, the single most important factor responsible for the proliferation of pelletized products is the popularity of controlled-release technology in the delivery of drugs.

When pellets containing the active ingredient are administered in vivo in the form of suspensions, capsules, or disintegrating tablets, they offer significant therapeutic advantages over single-unit dosage forms [15]. Because pellets disperse freely in the gastrointestinal tract, they invariably maximize drug absorption, reduce peak plasma fluctuations, and minimize potential side effects without appreciably lowering drug bioavailability. Pellets also reduce variations in gastric emptying rates and overall transit times. Thus, intra- and inter-subject variability of plasma profiles, which are common with single-unit regimens, are minimized. Another advantage of pellets over single-unit dosage forms is that high local concentrations of bioactive agents, which may inherently be irritative or anesthetic, can be avoided. When formulated as modified-release dosage forms, pellets are less susceptible to dose dumping than the reservoir-type, single-unit formulations.

Controlled-release pellets are manufactured either to deliver the bioactive agent at a specific site within the gastrointestinal tract or to sustain the action of drugs over an extended period of time. While these results have been traditionally achieved through the application of a functional coating material, at times the core pellets themselves have been modified to provide the desired effect. In vivo experiments involving ileostomy patients showed that the average transit time of pellets in the intestine increased with an increase in the specific weight or density of the pellets [16]. Although the findings have yet to be substantiated using healthy subjects, and there has been a report to the contrary [17], the studies were able to stimulate considerable interest and further enhanced the role of pellets in oral dosage form development. As a result, a number of studies aimed at prolonging the gastrointestinal transit time of pellets, and, hence,

the duration of action of a bioactive agent through the modification of the surface property or core of pellets have been conducted [18, 19].

Pellets also provide the pharmaceutical scientist with tremendous flexibility during the development of oral dosage forms. For instance, pellets composed of different drug entities can be blended and formulated in a single dosage form. Such an approach has numerous advantages. It allows the combined delivery of two or more bioactive agents, that may or may not be chemically compatible, at the same site or at different sites within the gastrointestinal tract. It also permits the combination of pellets of different release rates of the same drug in a single dosage form. In addition, pellets have a low surface area-to-volume ratio and provide an ideal shape for the application of film coatings. Because pellets flow and pack freely, it is not difficult to obtain uniform and reproducible fill weights in capsules, provided that the size and densities of the pellets are favorable. Pellets can also be made attractive due to the various shades of color that can easily be imparted to them during the manufacturing process.

IV. MANUFACTURING CONSIDERATIONS

Whenever pellets are considered as vehicles for the delivery of drugs, there are certain manufacturing constraints that must be examined before a decision for production is made. Production of pellets generally involves expensive processes or highly specialized equipment. Equipment, which is readily available in a given setting due to its suitability for other applications such as coating, tends to obviate the need for the purchase of a new and specialized machine. Pellets could be prepared in the same equipment, with or without modification. Unfortunately, except in special cases, the pelletization processes are usually lengthy and expensive. Processing of a single batch may sometimes require hours or even days to be completed. As a result, the processing cost incurred offsets the savings made due to the availability of equipment, and boosts the overall manufacturing cost. Conversely, if a short processing time is desired, it becomes mandatory to utilize highly efficient and, at times, unique pieces of equipment that require the allocation of substantial capital investment. Extruders, spheronizers, and rotor granulators fall under this category. Formulation variables should, therefore, be manipulated to accommodate the availability of the equipment and the cost-effectiveness of the process.

Another processing step that heavily impacts on the successful development of pelletized products is coating of the newly formed drug pellets. Although pellets could conceivably be coated in any tablet coating equipment, they generally require specialized coating machinery for optimum processability, whether the intent of the coating is for aesthetic, identification, or controlled release purposes. Therefore, accessability of the relevant coating equipment should be assessed before a decision is made to develop pelletized products. Since the performance of the coated product is dictated by the surface morphology, shape, and composition of the core pellets, drug pellets that possess surface properties optimum for the application of coherent films must be selected.

Finally, pellets must be encapsulated in the appropriate sizes of hard-gelatin capsules or compressed into tablets before they are packaged for distribution. Irrespective of the pelletization process, pellets are not uniform in size and generally represent a narrow mesh fraction. These pellets may be coated with functional membranes to provide the target release profiles. They may also be blended with other pellets to generate a unique release profile or to produce combination products. Placebo pellets may also be added to active pellets to adjust for potency. It is obvious, therefore, that attaining content-uniformity and reproducibility could be a serious problem, especially if segregation occurs. Segregation occurs whenever a homogeneous blend of pellets is subjected to any kind of vibration. It is primarily induced by differences in size or density. Lighter or larger pellets tend to float at or near the top of the pellet mass, thereby severely altering the uniformity of the pellet blend and causing variability in the drug content or potency of the dosage form.

Segregation resulting from differences in size and density is overcome if a narrow mesh cut of pellets that have similar densities is employed. While it is relatively easy to manufacture active pellets of the same densities, it may be difficult to prepare active and placebo pellets that have identical densities. In that instance, differences in densities may be compensated for by blending the active pellets with slightly larger or smaller placebo pellets, as the case may be [20].

Other factors that lead to segregation are static electricity and surface morphology. Static electricity may be generated during the blending process as a result of interparticle friction and may cause the particles to segregate. Similarly, if the surface of the pellets is rough and uneven, it is almost impossible