GRANULATION TECHNOLOGY *for* BIOPRODUCTS

Kiran L. Kadam

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Editor

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PREFACE

Granulation is an important unit operation in a variety of industries, and a body of knowledge exists for its successful application in the chemical industry. Two good books on the topic of granulation in general are *Granulation* by P. J. Sherrington and R. Oliver (Heyden & Son, London, 1981) and *Particle Size Enlargement* by C. E. Capes (Elsevier, Amsterdam, 1980). The specific application of granulation technology to biological products is the thrust of this book. Bioactive products such as pharmaceutical (of synthetic as well as biological origin) and biologically derived products such as industrial enzymes both need to be often marketed in granular forms. Granulation of bioproducts has thus become an operation of considerable import. While working on granulation processes for industrial enzymes such as alkaline proteases and for microbial cells such as lactic acid bacteria, I was struck by the lack of coherent information in the field. The paucity of organized literature on granulating biological products seemed to be in inverse proportion to their economic importance. These products, being high value entities, represent a much larger monetary activity than their relatively low volume would indicate. For example, granular detergent enzymes represent a world market of about $175 to $200 million, at a price of $6 to $8/lb (formulated product). The perception of this lacuna led to this undertaking.

The book contains chapters from experts in the field and the slant is towards the practical aspects of producing granular bioproducts. Hence, if the reader finds theoretical treatments to be brief, it is so by design. Traditional methods such as extrusion, fluid bed agglomeration, and high intensity mixing are covered as well as newer techniques such as liquid phase agglomeration and microencapsulation. The discussion of suitable granulation processes along with individual chapters on post-granulation operations such as drying and coating provides a well-rounded account of the subject. These features in conjunction with chapters on industrial practice in the enzyme industry and on selection of suitable granulation processes should make this a justifiable endeavor. Such justification is hardly needed, however, considering the dearth of a cogent discourse on the topic both in the primary and the secondary literature. It is hoped that this collective treatise fills the lacuna in some measure.

I wish to sincerely thank all the contributors for their efforts and cooperation; without them this project would not have come to fruition. I am also grateful to CRC Press, Inc. for making this book a reality. I enjoyed my part as an author and the editor of the book; the former was relatively easy, but the latter was frustrating at times! The preventable and inevitable delays notwithstanding, the final product is timely and something all those involved can feel proud of. I hope that the readers — practitioners and novices alike — share this sentiment.

Kiran L. Kadam
Greenville, South Carolina
March, 1990

To
my lovely wife
Anjali
for her patience and inspiration during this project

and
my adorable daughters
Priyanka and Samira
for sacrificing time that was rightfully theirs

THE EDITOR

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INTRODUCTION

Kiran L. Kadam

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I. INTRODUCTION

Agglomeration techniques have been known to mankind for centuries. The roots of this know-how can be traced to such ancient practices as the formation of clay bricks and other building materials, the manufacture of various items from precious metal powders, and the formulation of medicinal agents into solid dosages.[1] In modern times, granulation technology plays an important role in many other areas such as fertilizer production, minerals and ore processing, recovery and dedusting of obnoxious waste powders, etc.

Though *granulation* is an important unit operation in many industrial processes, until recently, the practice was limited to inorganic or organic materials. The development of fermentation technology has resulted in many biological products which need to be packaged in a dry state. Hence, granulation of biological products is assuming increasing importance. Pharmaceuticals of both synthetic and fermentative origin have been traditionally granulated as a prelude to the tabletting operation. There is considerable literature on this particular topic. However, there is a dearth of literature on granulating other bioproducts such as enzymes, microbial cells, etc. The objective of this treatise is to illuminate various aspects of granulation technology as it relates to bioproducts. The term "bioproducts" is broadly defined to include the following: bioactive substances such as pharmaceuticals produced via fermentation or synthesis, and other biological products such as enzymes, proteins, viable cells, etc. Granulation of bioproducts is as much an art as a science. Given the importance of these products and the fact that the available information is sparse and scattered over various disciplines, it is a worthwhile exercise to collate the collective wisdom on this topic into a single volume.

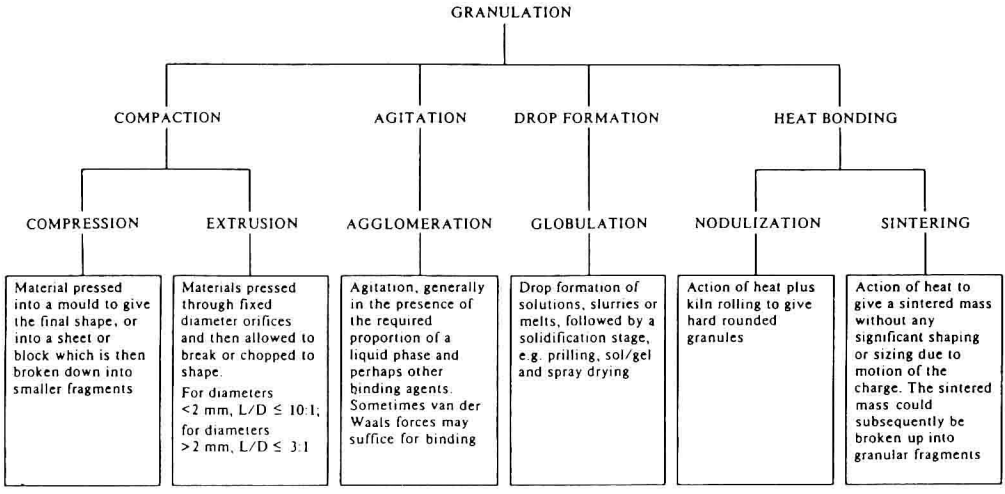
II. DEFINITION AND OBJECTIVES OF GRANULATION

Granulation and agglomeration are the terms generally used to describe the process of particle formation or size enlargement. Granulation can be defined as a process of producing an optimum-sized, nearly spherical product from fines, melts, or slurries.[2] The agglomeration of moist particulate solids into nearly spherical pellets by tumbling, rolling, or some other systematic agitation of the mass is called "granulation" in the fertilizer industry and "balling" or "wet/green pelletization" in the iron ore industry.[3] Dry pelletization refers to the agglomeration of finely divided moisture-free powder into dense free-flowing spheroids. The formation of granules from finely divided solids in liquid suspension in the presence of a small amount of second immiscible liquid, which preferentially wets the solid, is known as spherical agglomeration. Since the "industrial art" of granulation was developed in several relatively independent industries, the overlaps in language and use of imprecise terms can confuse the uninitiated. In general, granulation, balling, pelletization, and agglomeration are used interchangeably, and the spheroidal ensemble of particles is called a granule, ball, pellet, or agglomerate. Granulation will be the preferred term for this work.

Granulation covers a wide range of processes such as tabletting (compaction), briquetting, pelletizing, extrusion, pelleting, spray drying, prilling, induration, nodulizing, etc. Sherrington and Oliver[4] provide a comprehensive overview of the field of granulation (Table 1). If we are to use the classification denoted in Table 1, only the processes using extrusion, agglomeration (pelletizing), and globulation are applicable to the particle formation of enzyme and cells. Compression is usually used for making tablets and briquettes, and is not suitable if very small (0.5 to 2 mm) particles are desired. Nodulization and sintering are not suitable for biological products since they employ heat bonding.

Pietsch[5] classifies agglomeration as a unit operation characterized by combination of materials with a change in particle size (Table 2). He looks upon agglomeration as sticking and balling of — often very fine — powder particles due to short-range physical forces.

TABLE 1
Classification of Granulation Processes



From Sherrington, P. J. and Oliver, R., *Granulation*, Heyden & Son, London, 1981, chap. 1. With permission.

TABLE 2
Agglomeration as a Unit Operation

	Combination of materials	Separation of materials
Without change in particle size	Mixing	Mechanical separation, screening, filtration
With change in particle size	Agglomeration	Crushing, grinding

Reproduced from Pietsch, W., *Aufbereit. Tech.*, 23(4), 193, 1982. With permission.

Therefore, these forces become active only if the individual particles are brought together by external forces. This view limits the application of the term agglomeration/size enlargement such that, for example, the grain growth during crystallization is not covered by this unit operation.

The objectives of granulation can be summarized as follows:[1,6-8]

1. To produce useful structural forms and shapes
2. To provide a definite quantitative unit for metering, dispensing, and administering
3. To make a dust-free product that reduces handling hazards and losses
4. To achieve uniform composition of mixtures of solids and to prevent segregation
5. To improve flow properties
6. To densify the material for shipment or storage
7. To reduce the tendency of materials, generally hygroscopic, to form lumps or cakes
8. To improve dispersibility/solubility of product in water
9. To control porosity and surface-to-volume ratio
10. To improve product appearance

TABLE 3
Constraints for Bioproducts

Type of constraint	Examples of products affected	Effect on processing
Heat lability	Enzymes, viable cells, some drugs	Process throughput is limited since higher temperatures are not allowed; for example, in fluid bed granulation $\Delta T = T_i - T_o$ is relatively small due to a limit on T_i, thereby restricting throughput
Sensitivity to oxygen	Facultative anaerobes such as lactic acid bacteria	Use of inert atmosphere may be necessary, or cells may have to be stabilized via additives; a low residence time in the granulator is desired
Compliance with food and drug regulations	Enzymes, viable cells, drugs, and all other products falling under the jurisdiction of the regulatory agency such as the FDA in the U.S.	GMP conditions are mandatory

III. CONSTRAINTS FOR BIOPRODUCTS

Examples of products where granulation is used are fertilizers, iron ore and other metalliferous ores, nuclear fuels, pulverized fuel ash, ceramics, carbon black, catalysts, pesticides, some plastics, pharmaceutical products, food products, particularly instant products, metallurgical fluxes, cement kiln feeds, and detergents.[4] To update this list enzymes and cells must be added to the above examples. Most of these products are nonbiological, and their ruggedness offers a latitude in process selection and operating conditions. Conversely, the bioproducts, being more delicate in nature, provide a more challenging task in designing granulation processes.

As mentioned earlier, granulation of pharmaceuticals is a well-established area, whereas only recently has the technology been applied to enzymes, viable cells, and other fermentation-derived nondrug products. Since bioproducts come in contact with humans either during procesing or end-use, granulation of such entities entails certain restrictions imposed by regulating agencies. GMP (good manufacturing practice) conditions are a must for granulation processes designed for most biological products. Besides regulatory constraints, bioproducts pose operational limitations due to their susceptibility to extreme processing conditions or, in some cases, even to ambient conditions (Table 3). Heat lability of proteins, enzymes, and viable cells becomes a limiting factor since heat input, either intentional or incidental, has to be restricted to avoid heat denaturation of the active material. Heat lability is not as severe a constraint when processing pharmaceuticals. In the case of facultative anaerobes such as lactic acid bacteria, normal exposure to even the atmospheric oxygen during granulation can be detrimental. In such instances, then, the bacteria would have to be stabilized via additives to facilitate granulation in ambient environment.

Another difference between biological and nonbiological products such as fertilizers is that the bioproducts are, relatively speaking, low-volume entities. This affects the selection of granulation processes appropriate for biological products.

IV. GRANULATION PROCESSES

As explained earlier, granulation is an operation in which small particles are built into larger masses. The techniques of granulation can be broadly classified into two main cat-

egories. Forming-type processes fall in the first category in which the properties of *individual agglomerate* such as shape, size, composition, density, etc. are carefully controlled. In the second category, coarser material is created from fine powders. The properties of *bulk material* are controlled in this type of process, and the characteristics of the individual granules are important only inasmuch as they influence properties of the whole or bulk product.[9] Examples of forming-type processes are pelleting using a pellet mill, roll compaction, and tabletting. Examples of the bulk material-type processes are high shear granulation, fluid bed granulation, and prilling. The processes suitable for bioproducts fall mostly into the latter category. Four cardinal mechanisms are utilized in size enlargment: agglomeration by tumbling and other agitation methods; pressure compaction and extrusion methods; heat reaction, fusion, and drying methods; and agglomeration from liquid suspensions.[9]

As mentioned earlier, some of the granulating techniques do not apply to biological products such as enzymes or cells. In briquetting, tabletting, and pelleting, the granule size is large (5 to 25 mm), and in sintering, nodulizing, and induration, heat is used. It is obvious that heat bonding would destroy most biological activity. Detergent enzymes like alkaline proteases, α-amylases, and lipases are used in a soluble form and need to dissolve and disperse fast (within a minute or two of addition), hence a smaller particle size is desired (0.25 to 0.85 mm). For immobilized or "insoluble" forms of enzymes such as glucose isomerase, the particle size again has to be small enough (0.4 to 1.2 mm) to minimize diffusion limitation in column reactors. Particle size requirement is also a major consideration during granulation of pharmaceuticals, for example, over-the-counter medications like acetaminophen and prescription drugs like tetracycline. The granules of the active drug are incorporated into solid dosages which are required to rapidly disintegrate in the gastric and intestinal fluids; this again calls for a smaller particle size ($\leq$1 mm). This is true whether the granulated medicament is eventually made into a tablet or a capsule.

The processes suitable for granulating biological products are listed below.

Dispersion methods
  Fluid bed granulation
  Spray drying
  Prilling
Compression methods
  Extrusion
Agitation methods
  High intensity granulation
Thermal methods
  Freeze drying
Miscellaneous methods
  Microencapsulation
  Spherical agglomeration

These processes can be employed for producing granular bioproducts since they can yield small enough particles without inflicting excessive damage to the active material. Table 4 compares these methods in terms of their major features and current use.

Figure 1 depicts operational envelopes for various granulation techniques. Since operating temperatures and granule size are two major constraints for biological products, an envelope is generated for each method, the boundaries of the envelope indicating temperature and size ranges. These domains then tell us at a glance the limits and capabilities of each method. The higher limits of temperature ranges indicated for spray drying and fluid bed granulation are those of the inlet air temperature; the product does not necessarily encounter these high temperatures. Outlet air temperatures can be 60°C for spray drying and 40°C for fluid bed granulation. In the case of prilling, the higher temperature limit indicated is that of the hot melt; the droplets encounter an air stream at about 10°C. Microencapsulation

TABLE 4
Granulation Techniques Suitable for Bioproducts

Granulation technique	Products currently made using the technique	Comments
Fluid bed granulation	Pharmaceuticals, enzymes	Versatile equipment; can be used for granulating, drying, and coating
Spray drying	Pharmaceuticals, enzymes	Produces finer particles than most methods
Prilling	Enzymes	Produces teardrop-shaped particles with a smooth surface
Extrusion	Pharmaceuticals, enzymes	Produces spheroidal particles if used in conjunction with spheronization
High intensity granulation	Pharmaceuticals, enzymes	Well established for pharmaceuticals; also used on industrial scale for granulating detergent enzymes
Freeze drying	Viable microbial cells	Excellent for drying and granulating viable cells; industrial examples: lactic acid bacteria, ice nucleating bacteria
Microencapsulation	Pharmaceuticals	Relatively new technique; can produce spherical particles
Liquid phase granulation	Dry agglomerates of activated sludge	Combines solids separation and agglomeration in one operation; produces spherical pellets

covers several subtechniques: the high temperature limit refers to the use of melted gelatin, and the lower limit is derived from the cooling steps that some techniques require. Both extrusion and high intensity granulation operate at about ambient temperature; however, there is some heat generated due to friction. The biggest temperature range is encountered during freeze drying, since droplets of active material are dropped into liquid nitrogen. Each of the techniques is discussed in depth in the ensuing chapters.

V. GRANULE CHARACTERISTICS

Regardless of the type of product, certain characteristics are desired of the granule. To ensure the desired embodiments, certain physical properties need to be determined and controlled. These properties are listed below; not all characteristics or properties may be important in a given situation.

Characteristics of Granules
- Size distribution
- Shape
- Texture or surface roughness
- Color and general appearance
- Porosity
- Surface-to-volume ratio
- Flowability
- Physical strength
- Density
- Moisture
- Hygroscopicity
- Dispersibility or solubility
- Dustiness, total dust, and dust as active material
- Odor
- Stability and shelf life

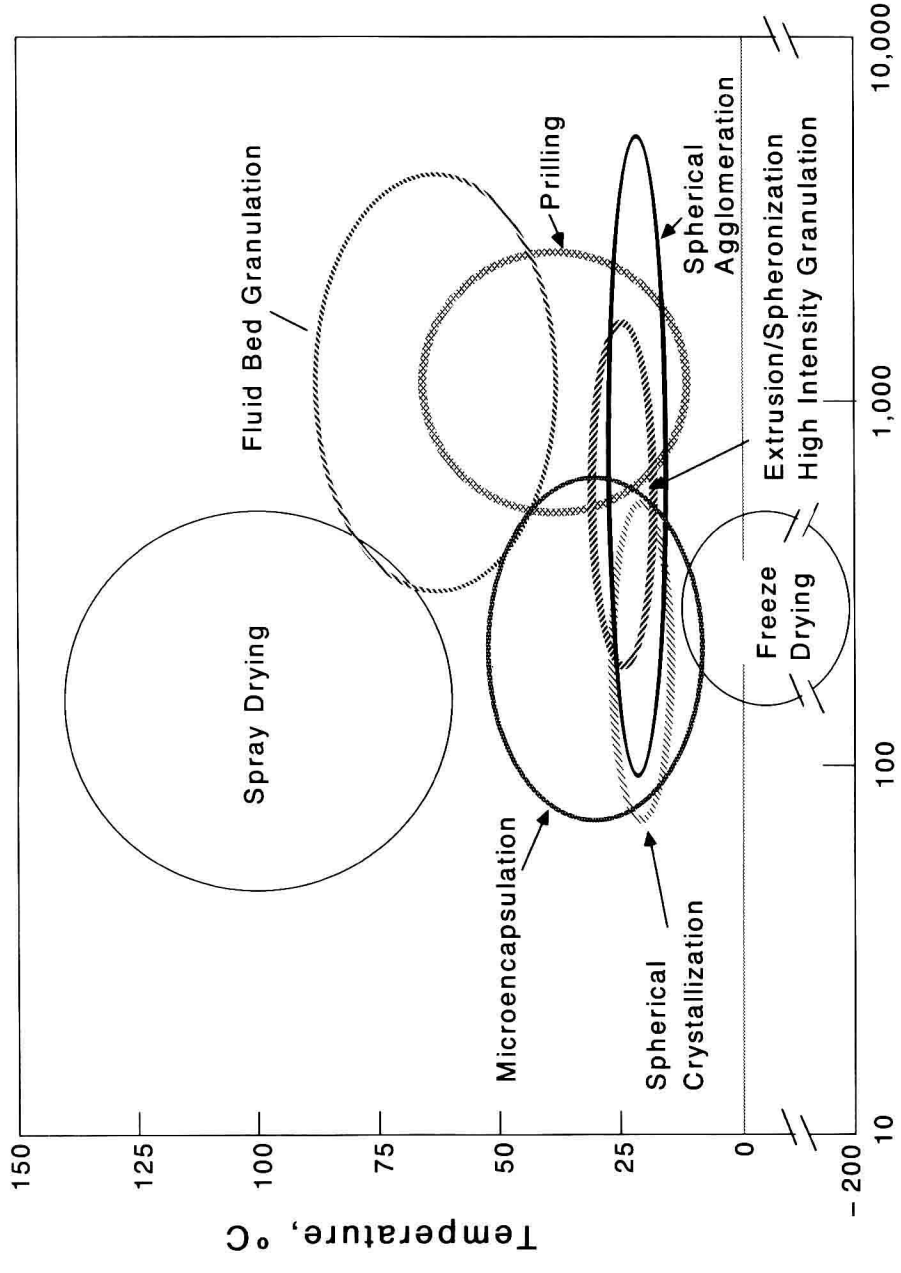


FIGURE 1. Domains bounded by temperature and particle size ranges for different granulation techniques.

The choice of a preferred granulation process is affected by the desired characteristics of the granules. The selection of suitable granulation processes is discussed in a later chapter.

VI. POSTGRANULATION OPERATIONS

Though the major thrust of this book is on granulation, two important postgranulation operations are also discussed, namely, drying and coating of granular bioproducts. Methods such as fluid bed granulation, spray drying, prilling, and freeze drying produce a dry granular product thereby obviating a separate drying step. Conversely, a drying step is needed for methods such as extrusion, high shear granulation, microencapsulation, etc. which produce a wet product. There are several methods available for drying wet granular bioproducts such as fluid bed drying, vacuum tray drying, vacuum tumble drying, etc. Since fluid bed drying is the most prevalent method of drying for bioproducts, it is the only one discussed. Coating of granular bioproducts is an important operation, since most often a protective coating is desired either to improve the product's appearance and shelf life or to further minimize dust inhalation by workers and consumers in the case of allergenic products.

Other postgranulation operations of interest are classification and packaging. These operations are not discussed in this work since they are very general in nature, and no specific constraints are imposed on these operations by granular bioproducts except GMP conditions. The reader can consult the various handbooks on powder and bulk solids handling to garner relevant information.

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