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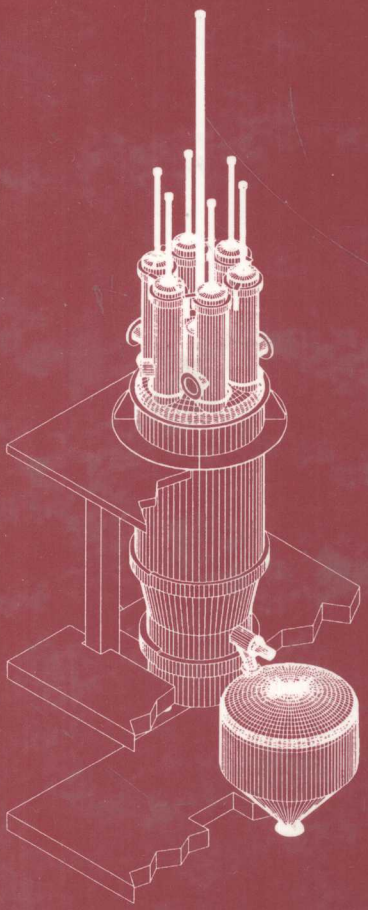

edited by
Dilip M. Parikh

Handbook of Pharmaceutical Granulation Technology

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Atlantic Pharmaceutical Services Inc.
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What lies behind us and what lies before us are tiny matters compared to what lies within us.

—*Oliver Wendell Holmes*

To my lovely wife
Leena

and my talented son
Neehar

Thanks for your patience and support during this project.

Preface

Granulation of powders to produce a pharmaceutical solid-dosage form is an essential unit operation. The process of enlarging particles is carried out elsewhere, such as in the food, agrochemical, dyestuff, and chemical industries, to produce from fine powders free-flowing, dust-free granules for further processing. Granulation in the pharmaceutical industry poses unique challenges, as it has the additional requirements of content uniformity and consistent physical properties, such as particle size, moisture, bulk density, porosity, hardness, and compressibility. Production of pellets for controlled-release application, which employs similar technology, requires pellets to be of consistent density, size, porosity, and surface morphology.

Regulatory requirements in the pharmaceutical industry have created the need for an understanding of this unit operation at an early stage of product formulation, method selection, and process development. Because the processes and specifications for the pivotal test batches and full-scale production ''must be equivalent,'' the need for reliable control of the manufacturing process used to produce the test and clinical batches cannot be overemphasized. Drug substance characterization, granulation analysis, dose uniformity, and dissolution profile are the key controls that should be in place at an early stage.

In the past 20 years, the pharmaceutical industry has been introduced to a number of different methods for producing pharmaceutical granulation. These methods have offered a number of advantages, such as process efficiency, while addressing product quality and regulatory compliance.

The current climate in the pharmaceutical marketplace has created economic challenges for the industry, which must constantly comply with current FDA regulations and policy. Because pharmaceutical granulation is

a critical unit operation in the manufacture of solid-dosage forms, cost-effective methods have been sought by the industry. Besides the FDA, other regulatory authorities, such as OSHA and EPA in the United States, are concerned about the safety of employees who handle and granulate ''potent'' compounds. These concerns have resulted in the development of ''contained'' systems. Potent compounds can now be granulated in so-called one-pot systems, which offer a greater measure of safety to the operator by providing a single ''pot,'' or bowl, to granulate and dry the product. Another approach to containment is the use of an integrated granulating plant comprising various process equipment that requires minimal or no handling by the operator as the product goes through the granulation steps.

Another trend in the pharmaceutical industry is the move toward continuous granulation of pharmaceuticals. Roller compactor units have long provided a method to produce dry granulation for some products, but availability of compact units for wet granulations is now a reality. These units provide economic advantages, while providing easy scalability from pilot-size batches to production-size lots.

Pharmaceutical granulation technology continues to change. Economic and regulatory forces make it mandatory to select cost-effective, safe methods for production of pharmaceutical granulation. The method selected must meet stringent regulatory requirements to produce a product with the desired characteristics and consistency.

This book is designed to give readers comprehensive knowledge of the subject. An appropriate level of theory has been incorporated to provide fundamentals of powder characterization, granulation, and state-of-the-art technology. However, the emphasis is on the application of these basic principles to the industrial practice of producing pharmaceutical granulation. The new technologies employed in the industry and contemporary approaches to producing pharmaceutical granulation are important areas covered in this book.

Pharmaceutical professionals, such as research and development scientists, process engineers, validation specialists, process specialists, and quality control scientists, will find the level of theory appropriate and the wealth of practical information invaluable for selecting and using each method, while keeping in mind regulatory requirements and cost effectiveness.

I sincerely acknowledge the support of the contributing authors of this book and thank them. Their timely submission of manuscripts greatly expedited publication. My heartfelt gratitude goes to my colleagues at Niro Inc. (parent company of Atlantic Pharmaceutical Services Inc.) for their help, and special thanks go to Mr. Steven M. Kaplan, President, and Mr. Steven A. Lancos, Executive Vice President of Niro Inc., for their support and encouragement during the preparation of this book.

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Introduction

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The granulation process of size enlargement used within the pharmaceutical industry has its roots in ancient times. Perry's Chemical Engineer's Handbook [1] defines the granulation process as ''any process whereby small particles are gathered into larger, permanent masses in which the original particles can still be identified.'' This definition is of course particularly appropriate to a pharmaceutical granulation where the rapid breakdown of agglomerates is important to maximize the available surface area and aid in solution of the active drug.

The practice of delivering medicinal powder by hand rolling into a pill by using honey or sugar has been used since ancient times. It is still a practice to deliver the botanical and herbal extract in Ayurvedic and homeopathic branches of medicine. The term ''granulated'' material is derived from the Latin word ''granulatum,'' meaning grained. The granulation material can be obtained by direct size enlargement of primary particles, or size reduction from dry compacted material. In modern times, granulation