

# **HANDBOOK OF PHARMACEUTICAL WET GRANULATION**

# HANDBOOK OF PHARMACEUTICAL WET GRANULATION

Theory and Practice in a  
Quality by Design Paradigm

Edited by

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## DEDICATION

*To the path of innovation amidst our busy daily lives ...*

I dedicate this work to the sacrifices of my parents, Mr. Tirath Singh and Mrs. Gurdip Kaur, and my wife, Swayamjot; to the love of my brother, Supreet, and sons, Manvir and Arjun; and to the confidence and critique bestowed upon me by my teachers and mentors.

**Ajit S. Narang**

To my beloved family; my wife Irene and sons, Ramy and Daniel in gratitude for their continued support. To the memory of my father who instilled in me the love for science. To my mother in gratitude for her love and sacrifice.

**Sherif I.F. Badawy**

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He holds over 15 years of pharmaceutical industry experience in the development and commercialization of oral and parenteral dosage forms and drug delivery platforms across preclinical through commercialization stages for both small and large molecule drugs. In addition to Genentech, he has worked for Bristol-Myers Squibb, Co., in New Brunswick, NJ, Ranbaxy Research Labs (currently a subsidiary of Daiichi Sankyo, Japan) in Gurgaon, India, and Morton Grove Pharmaceuticals (currently, Wockhardt USA) in Gurnee, IL. He holds an undergraduate pharmacy degree from the University of Delhi, India, and graduate degrees in pharmaceutics from the Banaras Hindu University, India, and the University of Tennessee Health Science Center (UTHSC) in Memphis, TN.

He has contributed to several preclinical, clinical, and commercialized drug products including NDAs, ANDAs, and 505B2s. He is credited with 54 peer-reviewed articles, 22 editorial contributions, 5 books, 10 patent applications, 47 invited talks, and 85 presentations at various scientific meetings. His current research interests are translation from preclinical to clinical and commercial drug product design, incorporation of QbD elements in drug product development, and mechanistic understanding of the role of material properties on product performance.



**Sherif I.F. Badawy** is a research fellow in the Drug Product Science and Technology division of the Bristol-Myers Squibb Company. He received his B.S. in pharmacy and M.S. in pharmaceuticals from Cairo University, and his Ph.D. in pharmaceuticals from Duquesne University. He has more than 22 years of industrial experience in drug product development. His current responsibilities at Bristol-Myers Squibb include formulation and process development and scale-up of commercial oral solid and liquid dosage forms. His areas of research interest include high-shear wet granulation, tablet compaction, stability of solid dosage forms, and bioavailability enhancement of poorly water-soluble compounds. He has authored more than 44 manuscripts and numerous abstracts and presentations in those areas.

## FOREWORD BY COURTNEY V. FLETCHER

Education and practice of the pharmaceutical sciences is rapidly evolving in these modern times. The pace of such advancements creates an increasing need for updated and contemporary resources for students and faculty, and for practitioners in the fields of pharmaceuticals. I am pleased to see this book, which covers that gap by highlighting modern practices and recent advancements in the well-established field of pharmaceutical processing by wet granulation.

This text features outstanding contributions from leading scientists across the globe from all practices of the profession—industry, regulatory, and academic. The topics cover the depth and breadth of the various facets of technology and practice.

I am confident this book will enable a deeper understanding of the fundamental principles and provide a wider perspective of their practice to our next generations of students and scientists—while also fueling innovation in the evolving areas.

Happy reading!

**Courtney V. Fletcher, Pharm.D.**

Dean and Professor, College of Pharmacy  
University of Nebraska Medical Center  
Omaha, NE, United States

## FOREWORD BY XIAOLING LI

It is my pleasure to write this foreword for this book co-edited by Dr. Ajit Narang and Dr. Sherif Badawy. Topics in this book encompass fundamental principles of the industrial practice of wet granulation. As a crucial step in pharmaceutical product development, the granulation process has evolved over the years of my teaching, consulting, and pharmaceutical product development career. While the fundamental scientific principles remain unchanged, application of technology and cross-disciplinary knowledge have definitely accelerated progress in this specific field. As emerging technologies fuse into pharmaceutical product-development, the process design for development of new drug products has shifted to a new paradigm. Quality by design (QbD) is just one of important shifts that impact and enhance pharmaceutical product development. This book provides ample insights into these aspects through both the depth and breadth of coverage of content in the field of high-shear wet granulation. The sections on process analytical technologies, process modeling, and emerging trends in pharmaceutical sciences highlight the technological advancements and the multidisciplinary nature of these advancements. The sections on control strategy, material attributes, and process design highlight the evolution of the field itself in the context of QbD.

With diminishing contents of this book in current undergraduate and graduate curriculum in the United States, this book provides a much-needed contents on fundamentals, practice, and evolution of an important step in pharmaceutical product development with the contemporary QbD embedded in the contents. This book is a very valuable reference and tool for those entering the field from different disciplines, as well as those seeking systemic and advanced knowledge in wet granulation. The advance of science and practice for wet granulation will be driven by needs in pharmaceutical product development, regulatory requirements, and emerging technologies. Therefore, this book will also serve as a launching pad to inspire scientists in this field to continue to innovate in the future.

**Xiaoling Li, Ph.D.**

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## FOREWORD BY CLIVE WILSON

The pharmaceutical industry is in a constant flux, with high market growth, new medical entities and the challenge of different regulations across the world pressuring the manufacturing sector. In addition, and importantly, as the industry focuses on taking risks in the discovery and development of the new molecular entities, the risks involved in every other part of the development pathway and commercialization of new drugs must be minimized and addressed in the contemporary quality by design (QbD) paradigm. The fundamental scientific principles and technologies have stood the test of time, but additionally, in-line instrumentation of process operations allows critical attributes to be determined. The QbD method of drug development empowers developers thorough understanding and practical utilization of tools and technologies that translate the product and process understanding to build robust drug products that will be consistent and of high quality over time.

While QbD has been constantly making its mark in the field of pharmaceutical development, a book that outlines and delves in-depth into the QbD application to one of the core processes of pharmaceutical manufacturing—wet granulation—has long been needed. The authors have tackled the task admirably, aided by excellent editorship from two scientists at the top of this field. The content on very practical applications in wet granulation written by industry leaders is complemented by academia–industry applications in Process Analytical Technology (PAT) and modeling in the final sections. This book fulfills this important role of highlighting how QbD is understood and applied by the pharmaceuticals professionals in new drug product development.

I am confident that all members of the pharmaceutical community will find the contents of this book relevant and meaningful to their study and work.

**Clive Wilson, Ph.D.**

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## PREFACE

This handbook is designed for pharmaceutical students, researchers, regulators, and practitioners alike. It brings forth a mix of basic principles, current practices, and advancements in the evolving science and technology of wet granulation—making for *an integrated approach* to benefit busy professionals.

Granulation process transforms the shape, size, surface, and density of powders or powder mixtures to improve their physicochemical properties and handling to enable rapid and robust manufacture on high-speed commercial equipment. The success of a granulation operation depends on optimal achievement of several quality attributes including size enlargement with uniformity of drug and excipient distribution, improved flow, and densification without compromising compactibility, compressibility, tabletability, and drug release. Focusing primarily on pharmaceutical wet granulation, this book provides extensive and in-depth understanding of *current* paradigms and practices.

The industrial practice of pharmaceutical wet granulation was dominated in the last few decades by high-shear wet granulation (HSWG). Fluid bed granulation is not uncommon in the pharmaceutical industry, but its application has been limited by a number of factors—not the least of which is the ability to uniformly fluidize the cohesive initial blend characteristic of many pharmaceutical formulations. The focus of this book, therefore, is the more widely practiced HSWG.

Despite its wide utilization, the practice and evolution of HSWG have been loaded with challenges, which are inherent to the fundamental concepts of HSWG. In its fundamental form, HSWG entails the use of a high-shear blender to mix liquid and powder components creating time dependent trajectory of the wet mass attributes until the desired attributes are achieved at the process end point. Early practice of HSWG emphasized end point determination as the main goal of process development and paid little attention to fundamental process understanding. Wet granulation processes have been traditionally developed using a trial and error approach, with the main objective of identifying a “magical” tool to detect granulation end point. A major limitation of the end point concept was the use of methods with only empirical and indirect correlations to the wet mass quality attributes critical to downstream process and product performance. In fact, the favorite approach for end point determination in the early days was the “fist test,” in which the operator squeezes a sample of the wet mass and subjectively decides, based on the wet mass consistency, if the end point has been reached. The evolving scientific development and understanding of end point determination methods are discussed in [Chapters 14, 15, 16, and 18](#).