This book is the first text to provide a comprehensive assessment of the application of fundamental principles of dissolution and drug release testing to poorly soluble compounds and formulations. Such drug products are, vis-à-vis their physical and chemical properties, inherently incompatible with aqueous dissolution. However, dissolution methods are required for product development and selection, as well as for the fulfillment of regulatory obligations with respect to biopharmaceutical assessment and product quality understanding. The percentage of poorly soluble drugs, defined in classes 2 and 4 of the Biopharmaceutics Classification System (BCS), has significantly increased in the modern pharmaceutical development pipeline. This book provides a thorough exposition of general method development strategies for such drugs, including instrumentation and media selection, the use of compendial and non-compendial techniques in product development, and phase-appropriate approaches to dissolution development.

Emerging topics in the field of dissolution are also discussed, including biorelevant and biphasic dissolution, the use on enzymes in dissolution testing, dissolution of suspensions, and drug release of non-oral products. Of particular interest to the industrial pharmaceutical professional, a brief overview of the formulation and solubilization techniques employed in the development of BCS class 2 and 4 drugs to overcome solubility challenges is provided and is complemented by a collection of chapters that survey the approaches and considerations in developing dissolution methodologies for enabling drug delivery technologies, including nanosuspensions, lipid-based formulations, and stabilized amorphous drug formulations.

Gregory K. Webster is a senior principal research scientist with AbbVie Inc.'s Global Analytical Research and Development. He obtained his BS in chemistry from St. Xavier College, USA, MS in analytical chemistry from Governors State University, USA, and PhD in analytical chemistry from Northern Illinois University. Dr. Webster’s industrial career spans an employment history with several major pharmaceutical companies. His first book with Pan Stanford Publishing, Supercritical Fluid Chromatography: Advances and Applications in Pharmaceutical Analysis, was published in 2014.

J. Derek Jackson is director of Analytical Development at Flexion Therapeutics Inc, USA. He earned his BS and MA in chemistry from the College of William and Mary in Virginia. Derek has been engaged in all stages of pharmaceutical discovery, research, and development for 20 years, in both large pharma and small-to-midcap biotech companies.

Robert G. Bell is president of Drug and Biotechnology Development LLC, USA, a consultancy to the pharmaceutical industry and academia for biological, drug, and device development. He received his education from the University of Florida and has worked with the pharmaceutical industry for over 30 years. Dr. Bell is adjunct faculty at Virginia Commonwealth University and the University of Florida College of Pharmacy and a member of the Council of Experts, General Chapters—Biological Analysis for United States Pharmacopeia.
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Foreword

Roughly twenty years ago, it became clear that drug product development had entered a new era of difficulty with the increased throughput of therapeutically effective but poorly soluble drug candidates. Gone are the days when all drug candidates were rapidly dissolving and absorbing drugs that were relatively easy to formulate and even easier to test. Now the development of an in vitro method for poorly soluble drugs is not boring. Rather, it’s a stimulating endeavor.

High-throughput screening has contributed to the invention and discovery of many new poorly soluble molecules. This book, *Poorly Soluble Drugs: Dissolution and Drug Release*, is most timely as the authors are up to the challenge of sharing the knowledge and tools to tackle the in vitro testing and manufacturing of these products. This work is unique in that it has provided the linkage between testing and formulating the products with equal importance given to each aspect.

In vitro testing of poorly soluble drug products is especially challenging and important since dissolution is the rate-limiting step to drug absorption and exposure. The path forward is clear: methods must be able to take advantage of this characteristic by providing meaningful elucidation of the release rate or, in some cases, the actual release mechanism, and hence giving critical clinically relevant information.

Poorly soluble drugs require special attention during formulation and manufacturing to enhance the effectiveness of the drug through methods as simple as reducing particle size to the much more complex areas of formulation manipulation and engineering technology to increase in vivo concentrations and adsorption.

The practical matter is that the demands from regulators, the globalization of pharmaceuticals, and the competitive arena of
market share drive the need to quickly educate and strengthen the knowledge of scientists working on these products. This book is quite essential to this effort.

The development of clinically relevant dissolution methods for drug products with limited water solubility has been a challenge for scientists in the drug industry as well as the regulatory agencies. The trend has started with the powerful tools available through quality by design (QbD) to create a clinically relevant dissolution test. Designing robust dosage forms of poorly soluble actives employs a thorough understanding of the components, matrix, and variability, thus following QbD concepts. This book gives a thorough investigation of the role of QbD with poorly soluble dosage forms, including design of experiments (DOE).

Development scientists are tasked with making these compounds soluble in a medium that is foreign to the poorly soluble drug but is necessary for oral drug formulation absorption. Aqueous solubility is the primary gauge of the success or failure of a drug and drug product. Solubility and dissolution performance in the gastrointestinal tract are critical for the bioavailability, and hence efficacy, of the product.

There are some emerging topics that are starting to acquire additional in-depth understanding—in particular, topics such as sink versus non-sink conditions in the dissolution method, contribution of solid-state properties, the chemistry of surfactants, in silico modeling, dose dumping, and capsule properties. The chapters in this book give these and other new topics well-referenced and refreshingly up-to-date attention. The work in this book bridges with established art and then builds links to, in some cases, entirely new directions.

The authors are from industry and academia, giving a well-rounded approach to this unique topic that has not been treated in book form to date. The subject is treated well beyond current guidances and USP chapters, a step much further than the status quo. I know the authors personally or by reputation, and they are experts in their areas. Many have a long history of direct involvement with the in vitro release test from the simpler testing equipment and methods to more complex and in some cases closer to the in vivo condition.
In vitro testing shows that the product is dissolved and therefore available for absorption and therapeutic effect thus linking what occurs in the patient's body to the efficacy of the product. The FDA and USP have emphasized the dissolution test for this reason as a proof that a commercial product on the market for many years will still be efficacious if it passes that test developed with the biobatch formulation. Hence the push to improve and make more robust the dissolution methods to link to in vivo performance. A way to forecast the in vivo performance is by making the dissolution test conditions as close to in vivo conditions as is possible. Approaches to assist the analyst in developing a sensitive method to characterize the release rate are explored thoroughly in this book along with the topics of in vitro and in vivo correlations and relationships.

Historically, a defining moment for poorly soluble drugs is the Biopharmaceutics Classification System, where the poorly soluble drug was described and characterized with some clarity. At that time, it became apparent that biowaivers for poorly soluble dosage forms were in most part unobtainable. With the exception of in vitro and in vivo correlations, clinical studies seemed to always be necessary, and little has changed over the years in this regard. The book offers insight into the development of predictive dissolution methods. Furthermore, knowing that poorly soluble drugs are uniquely sensitive to the testing environment (e.g. equipment design, vibration and de-aeration) is helpful when interpreting dissolution results.

Formal education of the industry analyst may not be provided for this topic. Because developing methodology for poorly soluble drugs demands more resources and research, this work will be helpful to the analyst to work more efficiently and solve problems more rapidly with this new knowledge in hand.

I commend the authors for their very considerable effort in bringing out this valuable publication.

Vivian Gray
Managing Director
Dissolution Technologies, Inc.
Hockessin, DE, USA
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