Advances in Delivery Science and Technology

Navnit Shah
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Amorphous Solid Dispersions

Theory and Practice

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Advances in Delivery Science and Technology

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ISSN 2192-6204 ISSN 2192-6212 (electronic)
ISBN 978-1-4939-1597-2 ISBN 978-1-4939-1598-9 (eBook)
DOI 10.1007/978-1-4939-1598-9
Springer New York Heidelberg Dordrecht London

Library of Congress Control Number: 2014947686

Printed on acid-free paper

Springer is part of Springer Science+Business Media (www.springer.com)

To extraordinary scientists at Hoffmann-La Roche who advanced the field of amorphous science to transform poorly soluble "sand-like" compounds into important medicines

Preface

The idea of writing this book was triggered by the development of ASD utilizing microprecipitated bulk powder (MBP) technology at Hoffmann-La Roche and the successful application of this technology to poorly soluble molecules, such as vemurafenib. This technology was instrumental in transforming this novel molecule into a medicine (Zelboraf®) for malignant melanoma patients. It was a gratifying and fulfilling experience for all of us when Zelboraf® became a key drug for this deadly disease and made a difference in the lives of many patients. We believe that many pharmaceutical scientists face such a challenge, and a book covering the theory and practice of amorphous solid dispersion technologies would be very useful to industrial and academic scientists as well as students in understanding and handling the challenges associated with developing such molecules.

Poorly water soluble drug molecules emerging from contemporary discovery programs often have inadequate and/or variable in vivo exposure, presenting pharmaceutical scientists with considerable challenges during development. Drugs with poor and variable oral absorption often have suboptimal therapeutic performance and significant food effect, thereby raising safety concerns, particularly for narrow therapeutic window drugs. As a result, promising molecules can be terminated prematurely if these issues are not adequately addressed. A number of formulation strategies have been developed to enhance the bio-performance of such molecules. Among these technologies, particle size reduction by micronization or nano milling improves the rate of dissolution; however, this strategy has resulted in limited success for poorly water soluble molecules having a solubility of less than 10 mcg/mL. Solubilization in lipid vehicles and self-emulsifying delivery systems have certainly added value, but their utility has been limited by drug loading, which remains a major issue. Similarly, salts of weak acids and bases have met with limited success due to precipitation of these salts in physiological fluids resulting in significant variability. Co-crystallization has been recently explored, but its utility has yet to be realized for poorly soluble molecules.

The amorphous form of a drug offers high free energy and therefore higher kinetic solubility, which provides an opportunity for overcoming solubility-related absorption and bioavailability challenges. The amorphous form, however, is thermodynamically unstable, and stabilization of molecules in this physical state still

remains a formidable task. A greater understanding of the scientific principles governing these systems and the development of amorphous solid dispersion (ASD) formulations for stabilizing amorphous molecules have created tremendous opportunities for the pharmaceutical scientist to address issues relating to the bioavailability of poorly soluble molecules. ASD technology has become one of the most powerful and versatile technology platforms in recent years. The design and development of successful ASD formulations requires the integration of scientific, technological and biopharmaceutical aspects to arrive at a robust drug product. Amorphous formulation technologies and our understanding of amorphous systems have advanced significantly in the last decade. A greater appreciation of the underlying physical science and thermodynamics, the emergence of newer technologies for the preparation of amorphous formulations, and the availability of newer excipients and polymers for stabilizing ASD have vastly expanded the opportunities for pharmaceutical scientists to establish stabilization strategies for these systems. The interest in developing amorphous formulations has increased more than ever due to the successful market introduction of such products over the last decade.

Written by experts from industry, academia and government, this book provides an excellent reference for pharmaceutical research scientists in the understanding, preparation and stabilization of ASD. In this book, we present the three primary factors for the stabilization and successful development of ASD, namely (a) the physical and chemical properties of the drug substance, (b) polymers and their impact on the stability of the final product, and (c) processing technologies to put ASD into practice. These aspects are extensively covered by the inclusion of case studies.

The first few chapters of the book cover the fundamentals and theoretical aspects of amorphous systems, an overview of ASD technologies, and details on excipients and polymers used in ASD, along with their safety aspects. “Fundamentals of Amorphous Systems” discusses the theoretical aspects of thermodynamics and kinetics with respect to the energy barrier. Also addressed are the active pharmaceutical ingredient (API) properties and polymer characteristics necessary for preparing stable ASD, involving solubility and miscibility, interaction parameters and drug loading impact. “Overview of Amorphous Solid Dispersion Technologies” provides a detailed presentation of each technology and its limitations. The chapter on excipients presents different classes of excipients, their physico-chemical properties and their interrelationship with different processes; the safety and stability of excipients are also described at length.

Later chapters present details of ASD manufacturing technologies, including spray drying, hot melt extrusion, and a breakthrough novel solvent-controlled micro-precipitation technology (MBP). Each technology is illustrated with processing fundamentals and scale up factors along with specific case studies, which provide the scientist with approaches for handling challenges presented by different types of molecules as well as building process flexibility. In addition, a dedicated section covers the miniaturization of technologies for screening polymers and processes with small amounts of API, particularly during the discovery and early development phases addressing preclinical needs. Since all of the technologies used in preparing ASD systems require downstream processing for developing viable drug

products, the chapter on downstream processing covers the physical and mechanical factors impacting product performance. The analytical tools for the characterization of amorphous solid dispersions, prediction of long term stability, evolving suitable dissolution methods particularly addressing supersaturation kinetics, as well as regulatory aspects germane to amorphous solid dispersion formulations and technologies are also extensively covered.

This volume explores technologies on the horizon, such as supercritical fluid processing, mesoporous silica, KinetiSol®, and the use of non-salt forming organic acids and amino acids for the stabilization of amorphous systems. It presents a comprehensive overview of the theory and practice of amorphous solid dispersions in overcoming the challenges associated with poorly soluble drugs, and it includes practical examples based on commercially successful products using different manufacturing technologies and stabilization strategies. *Amorphous Solid Dispersions* provides pharmaceutical scientists with up-to-date knowledge on amorphous solid dispersions that will further enhance their ability to handle more challenging molecules and will pave the way for future innovation to bring cutting-edge therapeutics to patients in need.

Sincerely
Navnit Shah
Harpreet Sandhu
Duk Soon Choi
Hitesh Chokshi
A.Waseem Malick

Acknowledgement

The editors want to thank all the individuals who provided scientific input and critique as well as offered valuable changes and suggestions. These contributions truly enhanced the quality of the book. We acknowledge and express our sincere and deep appreciation for their efforts.

It is hard to express our gratitude in words to Hoffmann-La Roche Inc. for supporting high quality research and creating an atmosphere that was conducive to exploring new ideas and innovation. The inspirational and collaborative environment enabled us to pursue original research and contribute to the advancement of amorphous systems. These efforts led to cutting edge innovations that in turn enabled development of effective new medicines. None of this would have been possible if it were not for the dedication and enormous effort of many outstanding scientists from the Pharmaceutical and Analytical R&D Department, strong partnership of scientists from other disciplines as well as unwavering management support. In reality, getting these differentiated medicines to the patients in need is the true inspiration for writing this book.

We do not have enough words to express our earnest thanks to all the authors and co-authors for accepting our request for contributing to this effort and most importantly for providing high quality contents to enable the timely completion of the book. We are highly appreciative of their patience in responding to our numerous requests throughout this process. It indeed has been a privilege to work with people of such high scientific caliber and integrity.

We want to express our sincere thanks to Springer for the invitation for writing this book. Our special thanks to Ms. Carolyn Honour and Ms. Sarah McCabe for their valuable suggestions, helpful comments and especially for putting up with our slight tardiness in completion of the book.

The editors want to acknowledge the valuable contributions of Mr. Dinesh Shah and Dr. Martin Infeld for reviewing documents and providing constructive comments for enhancing the quality of the book. Our thanks to Ms. Lisa Mitchell for handling the logistics and all the support for arranging the book contents, formatting, preparing tables, and valuable edits. A special thank you to Ms. Vicky Pacholec for keeping us together during challenging times.

Most importantly, our heartfelt thanks are owed to our families. Our spouses, Gita, Farooq, Kwanghee, Sonal and Aneeza and our children for their patience and sacrifice during the last two years, for tolerating our long hours away from them and encouraging us to undertake this mission. Without their support, the timely completion of this book would not have been possible.

Sincerely
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Part I
ASD Introduction