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Formulating Poorly Water Soluble Drugs

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Preface

High-throughput screening (HTS) methodologies for lead identification in drug discovery were developed in the 1980s to enable the utilization of advances in genomics and combinatorial chemistry. Since their advent, HTS methodologies have developed rapidly and have been widely adopted in the pharmaceutical industry. Consequently, the number of potential drug candidates indentified by HTS has steadily increased over the past two decades. The HTS approach tends to identify leads with high-molecular weight and lipophilicity, and, consequently, poor water solubility. As more and more leads are identified by HTS, poorly water-soluble drug candidates are emerging from drug discovery with greater frequency. The problem of poor solubility has therefore become pervasive in the pharmaceutical industry recently, with percentages of poorly water-soluble compounds in development pipelines reaching as high as 80–90% depending on the therapeutic area.

Drug dissolution is a necessary step to achieve systemic exposure that ultimately leads to binding at the biological target to elicit the therapeutic effect. Poor water solubility hinders dissolution and therefore limits drug concentration at the target site, often to an extent that the therapeutic effect is not achieved. This can be overcome by increasing the dose; however, it may also lead to highly variable absorption that can be detrimental to the safety and efficacy profile of the treatment. In these cases, solubility enhancement is required to improve exposure, reduce variability, and, ultimately, improve the drug therapy. It is therefore understood that in modern pharmaceutical development, solubility-enhancement technologies are becoming critical to rendering viable medicines from the growing number of insoluble drug candidates.

A pharmaceutical scientist's approach toward solubility enhancement of a poorly water-soluble molecule typically includes detailed characterization of the compounds physiochemical properties, solid-state modifications, advanced formulation design, nonconventional process technologies, advanced analytical characterization, and specialized product performance analysis techniques. The scientist must also be aware of the unique regulatory considerations pertaining to the nonconventional approaches often utilized for poorly water-soluble drugs. One faced with the challenge of developing a drug product from a poorly soluble compound must possess at minimum a working knowledge of each of the above-mentioned facets and

detailed knowledge of most. In light of the magnitude of the growing solubility problem to drug development, this is a significant burden especially when considering that knowledge in most of these areas is relatively new and continues to develop. There are numerous literature resources available to pharmaceutical scientists to educate and provide guidance toward formulations development with poorly water-soluble drugs; however, a single, comprehensive reference is lacking. Furthermore, without access to a vast journal library, the detailed methods used to implement these approaches are not available. The objective of this book is therefore to consolidate within a single text the most current knowledge, practical methods, and regulatory considerations pertaining to formulations development with poorly water-soluble molecules.

The volume begins with an analysis of the various challenges faced in the delivery of poorly water-soluble molecules according to the route of administration, i.e., oral, parenteral, pulmonary, etc. This chapter provides understanding of the formulation strategies that one should employ depending on the intended route of administration. Chapter 2 covers analytical techniques most pertinent to poorly water-soluble drugs with regard to preformulation, formulation characterization, and in vitro performance assessment. Solid-state approaches to overcoming solubility limitations are discussed in Chapter 3. This chapter presents an in-depth review of the solubility benefits obtained via conversion of drug crystals to salts, cocrystals, metastable polymorphs, and amorphous forms. When such solid-state approaches are not viable, particle-size reduction of the stable crystalline form is perhaps the next most straightforward option. In Chapter 4, mechanical particle-size reduction technologies are described, providing a comprehensive discussion of traditional and advanced milling techniques commonly used to increase surface area and improve dissolution rates.

Oftentimes, modification of the API form is not possible and particle-size reduction fails to appreciably increase the dissolution rate owing to the inherent solubility limitation of the stable crystalline polymorph. In these cases, a noncrystalline approach is necessary; perhaps the most straightforward noncrystalline approach is a solution-based formulation. Solution-based approaches are covered by Chapters. 5–7 where liquid formulation technologies for poorly water-soluble drugs are presented. Chapter 5 provides a review of solution systems for oral delivery whereby the molecule is dissolved in a suitable nonaqueous vehicle. The chapter discusses the various vehicles available for such systems as well as options for conversion to a final dosage form. Chapter 6 reviews techniques for overcoming compound solubility challenges in developing liquid formulations for parenteral administration, which is of particular relevance as the number and complexity of cancer therapeutics continue to increase. Advanced liquid formulations for oral delivery, self-emulsifying systems, are discussed in Chapter 7. These systems are advancements over traditional solution formulations in that the formulation droplet size formed on contact with GI fluids can be controlled through rational formulation design. Controlling droplet size to the micro- or nanometer scales has been shown to produce significant enhancements in drug absorption.

In many cases, poorly water-soluble compounds also exhibit limited solubility in vehicles suitable for oral liquid formulations. In these cases (assuming all other previously mentioned options are not viable), an amorphous formulation approach is often necessary. The design of amorphous formulations presents numerous challenges, which much of the latter half of this book (Chapters 8–12) aims to address. These chapters describe the importance of appropriate preformulation studies, formulation design, process selection, as well as considerations specific to the selected process technology. In Chapter 8, a structured, rational approach toward the development of optimized amorphous solid dispersion formulations is presented. Specific emphasis is given to critical preformulation studies, identification of the best excipient carrier system, optimization of drug loading, and process technology selection. Chapter 9 provides a comprehensive guide to the application of hot-melt extrusion technology for the formulation of poorly water-soluble drugs. This chapter provides a detailed overview of the process technology as well as formulation design considerations specific to hot-melt extrusion applications. Spray drying is the subject of Chapter 10, again emphasizing the process technology and formulation development specific to spray drying. Particular focus is given to the development of amorphous spray-dried dispersions owing to its industrial relevance to the production of viable products containing poorly water-soluble drugs. Chapter 11 teaches cryogenic technologies whereby nanostructured particles and amorphous solid dispersions are formed by rapid freezing technologies. The chapter discusses different cryogenic process technologies, formulation design considerations, and downstream processing options. Precipitation technologies for the production of engineered particles and solid dispersions are covered in Chapter 12. Various solvent/antisolvent techniques are discussed along with formulation design principles, particle recovery techniques, and key process design considerations.

Emerging technologies relevant to the formulation of poorly water-soluble drugs are discussed in Chapter 13. These are technologies that have begun to appear in the literature and elsewhere in recent years that exhibit promise, but have yet to mature. Finally, in Chapter 14 regulatory considerations specific to drug products of poorly water-soluble compounds are presented. It is the aim of this chapter to educate formulation scientists regarding unique regulatory aspects to consider for solubility-enhancement approaches, i.e., solid-state modifications, particle-size reduction, lipid/solution formulations, and amorphous solid dispersions. This chapter also provides a unique review of case studies for marketed products that employ these solubility-enhancement approaches, highlighting the principal regulatory concerns for each case.

This volume is intended to provide the reader with a breadth of understanding regarding the many challenges faced with the formulation of poorly water-soluble drugs as well as in-depth knowledge in the critical areas of development with these compounds. Further, this book is designed to provide practical guidance for overcoming formulation challenges toward the end goal of improving drug therapies with poorly water-soluble drugs. Enhancing solubility via formulation intervention is a unique opportunity in which formulation scientists can enable drug therapies by creating viable medicines from seemingly undeliverable molecules. With the ever-increasing number of poorly water-soluble compounds entering development,

the role of the formulation scientist is growing in importance. Also, knowledge of the advanced analytical, formulation, and process technologies as well as specific regulatory considerations related to the formulation of these compounds is increasing in value. Ideally, this book will serve as a useful tool in the education of current and future generations of scientists, and in this context contribute toward providing patients with new and better medicines.

The editors sincerely thank all contributors for their dedication toward achieving the vision of this book. It is thanks only to your knowledge and efforts that it was accomplished.

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