

Preface

Polymorphism, a term derived from the Greek words for “much/many” (poly, πολύ) and “form” (morphē, μορφή), is used in disciplines as diverse as linguistics, computer science, biology, genetics, and crystallography. In the life sciences industry, two completely different types of polymorphism play a major role: polymorphisms in DNA sequence and polymorphs of crystalline substances. In the former, great strides are being made using polymorphisms in their DNA sequence to predict an individual’s susceptibility to disease and response to drugs, making it possible to design and select appropriate drugs. In the latter, the polymorphic form of a drug substance or excipient can have a profound impact on a spectrum of aspects, such as biological action, production, formulation and intellectual property protection. This book deals exclusively with the polymorphs of solids, covering not only polymorphs in the narrow sense, i.e., different crystalline forms of the same molecular entity, but also other solid-state forms relevant to industry, such as solvates, salts, and the amorphous form.

Interest in the solid-state properties of drugs has grown tremendously in recent decades as can be seen, for example, by the numerous conferences and workshops organized by various scientific and commercial institutions. This interest is well deserved. Anyone who has worked in the field for some time can point to examples where insufficient understanding of solid-state properties has led to serious setbacks. Problems encountered range from the sudden unexpected inability to produce reliably a form that has been used for pivotal clinical studies and is the basis for registration documents to variations in the drug product properties due to seemingly random changes of the solid form during processing or storage. Conversely, a thorough understanding of solid-state properties can create opportunities, which are increasingly being exploited for the benefit of both the company and the patient. Not only can patent protection be broadened or prolonged, and production made more efficient and cheaper, but the properties of the drug can also be improved to the advantage of the patient.

Increasing recognition of the importance of polymorphism to the life sciences industry has generated a great deal of interest and the field has been evolving rapidly. Given the pace of recent developments, an update is both useful and timely. This book discusses the whole breadth of the subject, covering all relevant aspects of solid-state issues for the pharmaceutical industry. It should act as a manual and a guideline for scientists dealing with solid-state issues, and

serve both as an introduction to people new to the field and as a source for experts to round off their knowledge. It also provides valuable information for scientists working in other areas where solid-state issues are important, such as animal health, agrochemical, and specialty chemical industries.

Chapters are organized according to the following aspects of polymorphism: relevance, tools, properties, practical approaches, and legal issues. Chapter 1 discusses the relevance of solid-state forms in the pharmaceutical industry and makes recommendations on how best to approach solid-state issues. Chapter 2, on the thermodynamics of polymorphs, provides the theoretical tools needed to understand solid-state behavior. Chapters 3 to 7 give detailed descriptions, instructions, and hints on how to characterize solids, since solid-state behavior can only be understood after thorough characterization. Such an understanding is crucial to making the right decisions at key stages of drug development and production. Chapters 8 to 10 highlight the properties and importance of solid-state forms that are not included in the narrow definition of polymorphism, namely, solvates, hydrates and the amorphous form. Essential practical aspects for development scientists are described in Chapters 11 to 13, which deal with identifying relevant polymorphs, finding optimal salts and controlling solid-state behavior during processing. The last two chapters discuss legislative aspects of solid-state properties. Often, solid-state forms can be protected by patents, which may create significant financial benefits. Chapter 14 outlines the principles of intellectual property protection and provides relevant examples. Finally, since the solid form can have an impact on the safety and efficacy of drugs, Chapter 15 explains regulatory issues in connection with solid-state behavior. Rules, based on scientific considerations, are elucidated.

The broad range of topics discussed in this text, from thermodynamics to legal issues, emphasizes the complexity of the subject. It also demonstrates that the challenges and opportunities connected with solid-state properties can only be addressed successfully through an integral approach that considers all these aspects.

The strength of this volume lies in the quality of its contributions. My sincere thanks go to every author for the excellent standard of their submissions and their engaged cooperation. The balance of contributions from industry, academia and government highlights the far-reaching importance of the subject. From a personal perspective, I very much appreciated the fact that after developing the concept for this book and inviting authors to submit chapters on specific themes, colleagues willingly agreed to do so despite their very busy schedules. Finally, I thank Wiley-VCH for recognizing the timeliness of such a volume and Dr. Elke Maase and Dr. Bettina Bems for an enjoyable collaboration in the preparation of this book.

Basel, January 2006

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