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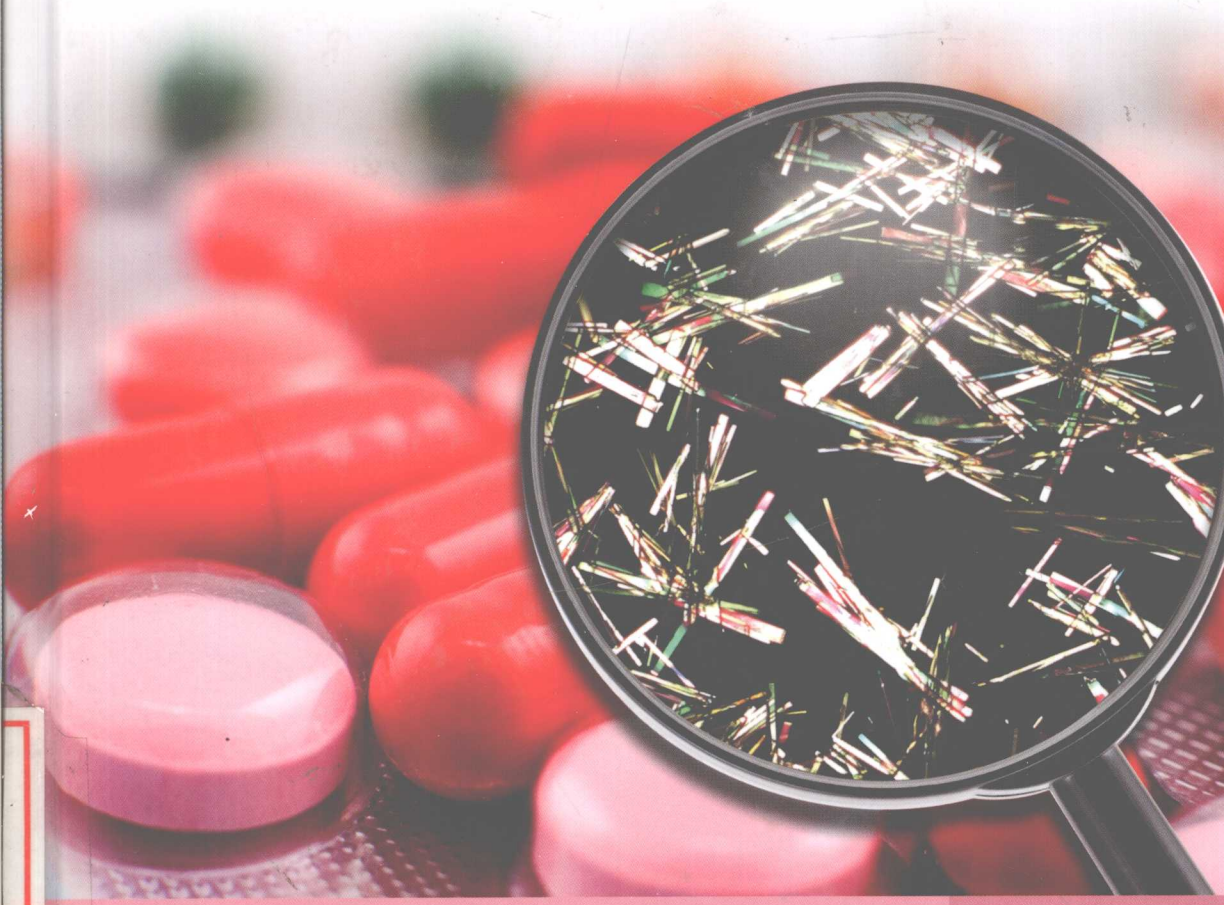
Solid State Characterization of Pharmaceuticals



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Solid State Characterization of Pharmaceuticals

Editors

RICHARD A. STOREY

AstraZeneca R&D, Macclesfield, UK

INGVAR YMÉN

AstraZeneca R&D, Södertälje, Sweden

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List of Contributors

Milan D. Antonijevic, School of Science, University of Greenwich at Medway, Chatham Maritime, UK

Susan Barker, School of Pharmacy, University of East Anglia, Norwich, UK

Howell Edwards, Bradford University, Bradford, UK

Paul Gabbott, PETA Solutions and Thermal Instruments Ltd, Aylesbury, UK

Simon Gaisford, School of Pharmacy, University of London, London, UK

Bertrand Gellie, European Patent Office, Pure and Applied Organic Chemistry, Munich, Germany

Chris J. Gilmore, WestCHEM, Department of Chemistry, University of Glasgow, Glasgow, UK

Jerry Y. Y. Heng, Department of Chemical Engineering, Imperial College London, London, UK

Andrew Hills, Pfizer Global R&D, Sandwich, UK

Claire Johnson, European Patent Office, Pure and Applied Organic Chemistry, Munich, Germany

Shen Luk, Molecular Profiles, Nottingham, UK

Clive Roberts, University of Nottingham, UK

Gary Nichols, Pfizer Global R&D, Sandwich, UK

Andrew O'Neil, School of Pharmacy and Chemistry, Kingston University, London, UK

Sarah L. Price, University College London, London, UK

Louise S. Price, University College London, London, UK

Ron J. Roberts, AstraZeneca R&D, Macclesfield, UK

Mark Saunders, Kuecept Ltd, Hengoed, UK

Richard Storey, AstraZeneca R&D, Macclesfield, UK

Thomas Weisbrod, European Patent Office, Pure and Applied Organic Chemistry, Berlin, Germany

Daryl R. Williams, Department of Chemical Engineering, Imperial College London, London, UK and Surface Measurement Systems Limited, London, UK

Ingvar Ymén, AstraZeneca R&D, Södertälje, Sweden

Xian-Ming Zeng, TEVA Branded Pharmaceutical Products R&D, Inc., Miami, USA

About the Editors

Dr Richard Storey is Principal Scientist, Pharmaceutical Development at AstraZeneca R&D, Macclesfield (Richard.a.storey@astrazeneca.com). He is a pharmacist who completed his PhD in Crystallization and Materials Science in 1997 at the University of Bradford. He then moved to the supercritical fluid crystallization SME, Bradford Particle Design, investigating the potential applications of this new technology. In 1998 he moved to Pfizer Global R&D and worked on solid form selection of new pharmaceutical molecules with a specific focus on the use of high throughput screening of solid forms. In 2003 Richard moved to AstraZeneca in Macclesfield where he has held roles in both management and scientific areas in solid state selection and materials science with a specific focus on the role of material properties on process performance. Richard is also the treasurer and board member of the Academy of Pharmaceutical Sciences of Great Britain.

Dr Ingvar Ymén is Principal Scientist at AstraZeneca R&D, Medicines Development, Physical Science, 151 85 Södertälje Sweden (ingvar.ymen@astrazeneca.com). He obtained his PhD in Inorganic Chemistry and Crystallography on metal-organic compounds in 1983 at the University of Lund. He then moved to Norsk Hydro Fertilizers and Explosives, where he held scientific as well as managerial positions from 1984 to 1992. There he did scientific work on heterogeneous equilibrium, including polymorphism, crystallization and reaction controlling of ammonium nitrate-containing compounds. By determining and exploring binary, ternary and quarternary phase diagrams, together with mass and energy balances, he also designed and implemented stable, continuous, large-scale, granulation and prilling processes for fertilizers and explosives. In 1992, he moved to Astra to work as a solid state scientist and became manager of the Solid State Analysis Team in Södertälje in 1995, a position he held until 2003, when he returned to a purely scientific position as principal scientist. He has remained in this role and is today involved in research on heterogeneous equilibrium, especially towards crystallization, polymorphism and salt screening. As of today he has been working in the field of heterogeneous equilibrium for more then 30 years.

Preface

Drug products are, in an overwhelming number of cases, produced as solid materials – for example, as tablets or granules in capsules. Even when formulated as liquids, the active pharmaceutical ingredient (API) is still usually produced as a solid prior to the final dissolution. During the development of a pharmaceutical formulation, knowledge of the physical properties of pharmaceutical materials – the APIs, the raw materials and the process intermediates for the API production, as well as the excipients and other chemicals for formulation – can help mitigate risks and offer opportunities for improved delivery. Knowledge of material properties is essential in a large number of activities when substances are brought in and out of the solid state, either as singular entities or as mixtures. Investigations into the effects of processes on materials present are termed 'solid-state work' and can have an effect during crystallization, dissolution, milling, drying, mixing, granulation, tableting, and so forth. Materials used in and obtained from these processes need to be characterized in a number of different ways, depending on what type of information is desired and on the properties of the material. For a solid-state scientist it is quite important to know which method of characterization to use for a particular material, how to design and run the instruments and how to use and evaluate the data from each technique. Unfortunately there is, to our knowledge, nowhere where a full academic education in pharmaceutical solid-state science is given; hence there is a continuous need for literature in this field.

One solid-state activity of special importance is the selection of the most suitable solid form of the API. This is a key solid-state process for successful scale-up and launch. Usually, a crystalline solid is desired because it provides an ideal solid for development due to its reproducible properties, such as solubility, and because it provides an excellent purification method during manufacture.

The form selection involves initial trials to crystallize the free form of the API, followed by salt-, co-crystal- and polymorph screening. Finally, the different solid phases obtained must be put on a thermodynamic stability scale so that the risks of future processing can be assessed without undesired surprises. It is critical that the correct solid form is selected for development as changes late in development and even in launch can affect the bioavailability of the API and hence its performance on dosing.

Solid form selection requires input from a wide number of disciplines including crystallization, stability assessment, biopharmaceutics, materials science and formulation, using a wide range of techniques, including high-throughput screening and computer predictions, for a successful nomination. Eventually, after the final selection has been made, patents covering some or perhaps all of the solid forms obtained during the selection work must be written.

Due to the importance of the different types of 'solid-state work' noted above, specifically the form selection, this book has been compiled to provide the reader with a single reference point. It incorporates an introduction to the crystalline state, a wide range of techniques for the

assessment of solid forms and chapters on their prediction, as well as the applicability of solid forms for patenting.

We hope that this book will provide the reader with a full toolbox for solid-state characterization and that the reader will have as much pleasure reading it as we have had producing it.

Richard A. Storey
Ingvar Ymén

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