## **Polymorphism**

in the Pharmaceutical Industry

Edited by Rolf Hilfiker



WILEY VCH Varlag CombH S. Ca. KCaA



1

### **Contents**

D	7/1/

#### List of Contributors XVII

1	Relevance of Solid-state Properties for Pharmaceutical Products Rolf Hilfiker, Fritz Blatter, and Markus von Raumer
1.1	Introduction 1
1.2	Drug Discovery and Development 4
1.3	Bioavailability of Solids 6
1.4	Phases of Development and Solid-state Research 7
1.4.1	Salt Selection 8
1.4.2	Polymorph Screening 9
1.4.3	Crystallization Process Development 12
1.4.4	Formulation 13
1.4.5	Method Development 14
1.5	Solid-state and Life Cycle Management 15
1.6	Conclusions 15
	References 17
2	Thermodynamics of Polymorphs 21
	Sachin Lohani and David J. W. Grant
2.1	Introduction 21
2.2	Structural Origin of Polymorphism 22
2.3	Thermodynamic Theory of Polymorphism 22
2.4	Thermodynamic Relationship Between Polymorphs:
	Enantiotropy and Monotropy 24
2.4.1	Energy–Temperature Diagrams 24
2.4.2	Pressure–Temperature Diagrams 28
2.4.3	Inversion of Polymorphic Behavior 30



۷I	Contents	
•	2.5	Rules to Predict Thermodynamic Relationships Between Polymorphs 31
	2.5.1	Heat of Transition Rule 31
	2.5.2	Heat of Fusion Rule 31
	2.5.3	Entropy of Fusion Rule 32
	2.5.4	Heat Capacity Rule 32
	2.5.5	Density Rule 33
	2.5.6	Infrared Rule 33
	2.6	Relative Thermodynamic Stabilities of Polymorphs 33
	2.7	Crystallization of Polymorphs 34
	2.7.1	Nucleation of Polymorphs 34
	2.8	Introduction to Solvates and Hydrates 37
	2.8.1	Thermodynamics of Hydrates 37
	2.9	Summary 40
		References 41
	3	Characterization of Polymorphic Systems Using Thermal Analysis 43 Duncan Q. M. Craig
	3.1	Introduction – Scope of the Chapter 43
	3.2	Use of Differential Scanning Calorimetry for the Characterization
	J.2	of Polymorphs 44
	3.2.1	Principles of DSC in the Context of Polymorphism 44
	3.2.2	Examples of the Uses of DSC: Characterization of Drugs, Excipients and Dosage Forms 49
	3.2.3	Further Uses of DSC 54
	3.3	Combined Approaches 58
	3.3.1	Multi-instrument Approaches 58
	3.3.2	Thermal and Crystallographic Studies 63
	3.3.3	Interfaced Techniques 65
	3.4	Additional Thermal Methods for the Study of Polymorphism 67
	3.4.1	Thermogravimetric Analysis 67
	3.4.2	Thermal Microscopy 68
	3.4.3	Heat of Solution Studies 69
	3.4.4	Modulated Temperature DSC 70
	3.4.5	High-speed DSC 72
	3.4.6	Microthermal Analysis 73
	3.4.7	Thermally Stimulated Current 74
	3.5	Conclusions 76
		References 77



Contents	VII
----------	-----

4	Joseph W. Lubach and Eric J. Munson
4.1	Introduction 81
4.1.1	Basics of Solid-state NMR 82
4.2	Applications 82
4.2.1	Identification 82
4.2.2	Selectivity 84
4.2.3	Mobility and Dynamics 85
4.2.4	Quantitation of Forms 86
4.3	Conclusions 92 References 92
5	Vibrational Spectroscopic Methods in Pharmaceutical Solid-state Characterization 95 John M. Chalmers and Geoffrey Dent
5.1	Introduction 95
5.2	Mid-infrared, Raman and THz Spectroscopy:
	Basic Comparison of Theory, Instrumentation and Sampling 97
5.2.1	Basic Theory 97
5.2.2	Instrumentation Brief 100
5.2.3	Sampling 104
5.2.3.1	Raman Sampling 104
5.2.3.2	Mid-infrared Sampling 105
5.2.3.3	THz Spectroscopy Sample Presentation 109
5.3	Changes of State and Solid-state Effects on Infrared and
	Raman Spectra 110
5.3.1	Introduction 110
5.3.2	Spectra of Gases, Liquids and Solutions 110
5.3.3	Hydrogen Bonding 111
5.3.4	Amine Salts (including Amino Acids) 114
5.3.5	Solids 115
5.3.6	Polymorphism 117
5.3.7	Enantiomers and Racemates 118
5.3.8	Tautomerism 119
5.3.9	Summary 119
5.4	Examples and Applications 119
5.4.1	Polymorphism 120
5.4.2	Hydration/Drying 126
5.4.3	Quantitative Analysis and Process Monitoring 128
5.4.4	Tablets 130
5.5	Closing Remarks 135



References 136

VIII	II   Contents		
•	6	Crystallography for Polymorphs 139 Philippe Ochsenbein and Kurt J. Schenk	
	6.1	Introduction 139	
	6.2	Solving Difficult Crystal Structures with Parallel Experiments 140	
	6.3	Atropisomers and Desmotropes 144	
	6.4	Salts 148	
	6.5	Influence of Solvents 149	
	6.6	Isolation of a Furtive Species 153	
	6.7	Mizolastine Polymorphs 154	
	6.8	Solid Solutions 157	
	6.9	Structures from Powder Data 160	
	6.10	"Behind Every Structure There is a Crystal" 164 References 165	
	7	Light Microscopy 167 Gary Nichols	
	7.1	Introduction 167	
	7.2	Why Use a Light Microscope to Study Solid-state Properties? 168	
	7.3	Polarizing Light Microscope 169	
	7.4	Photomicrography 170	
	7.5	Specimen Preparation 171	
	7.5.1	Permanent and Temporary Mounts 172	
	7.5.1.1	Permanent Mounts 172	
	7.5.1.2	Temporary Mounts 173	
	7.5.2	Preparation of Temporary Mounts 173	
	7.5.3	Examination of Tablets 173	
	7.6	Observations Using Polarized Light Microscopy 174	
	7.6.1	Polarized Light 174	
	7.6.2	Crystal Studies with Plane Polarized Light 175	
	7.6.3	Crystal Studies with Crossed Polarizers 177	
	7.6.3.1	Interference Colors 177	
	7.6.3.2	Extinction 179	
	7.6.3.3	Interference Figures 181	
	7.6.3.4	Compensator Plates 183	
	7.6.3.5	Use of Circularly Polarized Light 183	
	7.6.4	Crystallinity 184	
	7.7	Refractive Index 186	
	7.7.1	Measuring Refractive Indices 187	
	7.7.2	The Becke Test 188	
	7.7.3	Dispersion Staining 188	
	7.8	Particle Size 189	
	7.9	Particle Shape 190	
	7.10	Comparing Powder Samples 194	



# DOCKET A L A R M

# Explore Litigation Insights



Docket Alarm provides insights to develop a more informed litigation strategy and the peace of mind of knowing you're on top of things.

## **Real-Time Litigation Alerts**



Keep your litigation team up-to-date with **real-time** alerts and advanced team management tools built for the enterprise, all while greatly reducing PACER spend.

Our comprehensive service means we can handle Federal, State, and Administrative courts across the country.

## **Advanced Docket Research**



With over 230 million records, Docket Alarm's cloud-native docket research platform finds what other services can't. Coverage includes Federal, State, plus PTAB, TTAB, ITC and NLRB decisions, all in one place.

Identify arguments that have been successful in the past with full text, pinpoint searching. Link to case law cited within any court document via Fastcase.

## **Analytics At Your Fingertips**



Learn what happened the last time a particular judge, opposing counsel or company faced cases similar to yours.

Advanced out-of-the-box PTAB and TTAB analytics are always at your fingertips.

#### API

Docket Alarm offers a powerful API (application programming interface) to developers that want to integrate case filings into their apps.

#### **LAW FIRMS**

Build custom dashboards for your attorneys and clients with live data direct from the court.

Automate many repetitive legal tasks like conflict checks, document management, and marketing.

#### **FINANCIAL INSTITUTIONS**

Litigation and bankruptcy checks for companies and debtors.

### **E-DISCOVERY AND LEGAL VENDORS**

Sync your system to PACER to automate legal marketing.

