Polymorphism in Molecular Crystals

JOEL BERNSTEIN

Department of Chemistry
Ben-Gurion University of the Negev

CLARENDON PRESS • OXFORD
2002

OXFORD
UNIVERSITY PRESS
Great Clarendon Street, Oxford OX2 6DP
Oxford University Press is a department of the University of Oxford.
It furthers the University's objective of excellence in research, scholarship,
and education by publishing worldwide in
Oxford New York
Auckland Bangkok Buenos Aires Cape Town Chennai
Dar es Salaam Delhi Hong Kong Istanbul Karachi Kolkata
Kuala Lumpur Madrid Melbourne Mexico City Mumbai Nairobi
São Paulo Shanghai Taipei Tokyo Toronto
Oxford is a registered trade mark of Oxford University Press
in the UK and in certain other countries
Published in the United States
by Oxford University Press Inc., New York

First published 2002
Reprinted 2002

A catalogue record for this book is available from the British Library
Library of Congress Cataloging in Publication Data
Bernstein, Joel.
Polymorphism in molecular crystals / Joel Bernstein.
(IUCr monographs on crystallography; 14)
Includes index.
1. Polymorphism (Crystallography) 2. Molecular crystals. I. Title. II. International
Union of Crystallography monographs on crystallography; 14.
QD951.B57 2002 548'.3—dc21 2001047556
ISBN 0 19 850605 8
Printed in Great Britain
on acid-free paper by
T.J. International Ltd, Padstow

7

Polymorphism of pharmaceuticals

After discovery of the first cases of polymorphism with dramatic differences in biological activity between two forms of the same drug . . . no pharmaceutical manufacturer could neglect the problem. (Borka 1991)

There are many mysteries of nature that we have not yet solved. Hurricanes, for example continue to occur and often cause massive devastation. Meteorologists cannot predict months in advance when and with what velocity a hurricane will strike a specific community. Polymorphism is a parallel phenomenon. We know that it will probably happen. But not why or when. Unfortunately, there is nothing we can do today to prevent a hurricane from striking any community or polymorphism from striking any drug. (Sun 1998)

7.1 Introduction

The increasing awareness and importance of polymorphism in the past 30 years or so is perhaps nowhere more evident than in the field of pharmaceuticals (Bavin 1989). The landmark chapters of Buerger and Bloom (1937) and McCrone (1965) did not place any special emphasis on pharmaceutical materials. One outstanding exception was the book of Kofler and Kofler (1954), whose authors were members of an academic department of pharmacognosy (Webster: the branch of pharmacology that treats or considers the natural and chemical history of unprepared medicines). The seminal paper on the subject of polymorphism of pharmaceuticals was the review of Haleblian and McCrone (1969), which set the scope and the standards for many subsequent works. The literature on the polymorphism of pharmaceuticals is now best described as vast. A multiauthored monograph has appeared covering various aspects of the subject (Brittain 1999*b*), along with major sections of other books (Byrn 1982; Byrn *et al.* 1999), and an ever increasing number of reviews (Haleblian 1975; Kuhnert-Brandstätter 1975; Bouche and Draguet-Brughmans 1977; Giron 1981; Burger 1983; Threlfall 1995; Streng 1997; Caira 1998; Yu *et al.* 1998; Winter 1999; Vippagunta *et al.* 2001) covering various aspects of polymorphism as related directly to problems in the pharmaceutical field and/or pharmaceutical compounds, including some of the economic and intellectural property implications (Henck *et al.* 1997). Therefore, it would be foolhardy to attempt to present a comprehensive review of the subject here. Rather, in keeping with the general philosophy of this book, the aim is to provide a general introduction to the subject, with sufficient examples to demonstrate the points raised, and commensurate relevant references for the reader to seek further details and information.

7.2 Occurrence of polymorphism in pharmaceuticals

7.2.1 *Drug substances*

The development of a new drug from a promising lead compound to a marketed product is a long and expensive process, with odds of success estimated at 1 in 10 000 (Yevich 1991). The strict quality control requirements and the intellectual property implications of the drug industry lead to thorough and intensive investigations of the formation and properties of solid substances intended for the use in pharmaceutical formulations, both active ingredients and excipients. These efforts, often extending over long periods of time and with many potential experimental and environmental variables, can create conditions that can lead to the appearance of polymorphic forms, intentionally or serendipitously. While it may not be surprising that many pharmaceutically important materials have been found to be polymorphic, or that any particular compound may turn out to be polymorphic, every compound is essentially a new situation, and the state of our knowledge and understanding of the phenomenon of polymorphism is still such that we cannot predict with any degree of confidence if a compound will be polymorphic, prescribe how to make possible (unknown) polymorphs, or predict what their properties might be (Beyer *et al.* 2001).

There have been a few attempts to compile instances of polymorphism in pharmaceutically important materials. Since even the definition of what comprises 'pharmaceutically important materials' is itself subject to debate it is difficult to judge how comprehensive such compilations might be. However, generally they serve as useful references and are given here. One of the first organized attempts at such a compilation for steroids, sulphonamides and barbiturates was by Kuhnert-Brandstätter (1965) (see also Kuhnert-Brandstätter and Martinek 1965). Much of those data may be found in her subsequent book (Kuhnert-Brandstätter 1971), which also contains a compilation of many of the thermal studies of pharmaceutical compounds that revealed polymorphic behaviour. Numerous additional reports of studies by the Innsbruck school of polymorphic pharmaceutical compounds (using thermomicroscopy and IR spectroscopy) have appeared in the literature since the middle 1960s; many of those have been listed by Byrn *et al.* (1999). Borka and Haleblian (1990) compiled a list of over 500 references to reports of polymorphism in over 470 pharmaceutically important compounds.[1] This was shortly followed (Borka 1991) by a review of polymorphic substances included in Fasciculae 1–12 of the European Pharmacopoeia (EP), including a comparison of melting points in the EP and the original literature. The latter review was subsequently updated in 1995 by including EP entries for Fasciculae 13–19 (Borka 1995).

Griesser and Burger (1999) compiled the information regarding 559 polymorphic forms, solvates (including hydrates) of drug solids at 25 °C in the 1997 edition of

[1] Dr Borka has communicated with this author that he and Dr Haleblian did not receive galley proofs of this paper, which unfortunately contains 'numerous printing errors'. The list of errata actually contains 48 of them. Even with that cautionary note, it is a useful compilation.

the EP. They also noted that of the 10 330 compounds in the 1997 edition Merck Index only 140 (1.4 per cent) are specifically noted as polymorphic, 540 (5 per cent) are noted as hydrates and 55 (0.5 per cent) have been specified as solvates. These numbers reflect a failure to report or to include these phenomena rather than representative statistics, and may suggest the current state of awareness of polymorphism on the part of compilers of such compendia and reference works.

A survey by this author of the 1 October 2000 release of the CSD (~225 000 entries) yielded 6353 hits for the qualifier 'form', 1045 hits for the qualifier 'phase' 528 hits for the qualifier 'polymorph', 201 hits for the qualifier 'modification', 28 342 hits for the qualifier 'solvate' and 21 132 hits for the qualifier 'hydrate'. Of course, the last two numbers give no indication of whether the materials are polymorphic and none of these statistics indicate the instances for which the structures of more than one form have been determined. The data for hydrates and solvates from the CSD may be considered quite reliable, since molecules of solvation are usually positively identified in the course of a crystal structure determination. The frequency of polymorphs, however, is likely to be underestimated, since many crystal structures of polymorphic systems, or what later are discovered to be polymorphic systems, are reported without making note of that fact. If the structure of only one member of a polymorphic family has been reported, then there may not be any reference to the polymorphism in the CSD. References to drugs discovered prior to 1971 that form solvates have been compiled, along with a separate summary of the thermomicroscopic behaviour of drug hydrates by Byrn *et al.* (1999).

Because of the rather select nature of the sample set and the distinct possibility that not all forms are always reported caution must be exercised in drawing conclusions from such statistical surveys. Nevertheless, according to Griesser and Burger (1999) there may be some apparent tendencies which should be monitored as data continue to accumulate: polymorphism seems to be more common for compounds with molecular weight below 350; polymorphism seems to be more common for compounds with low solubility in water; for organic salts, the formation of hydrates appears to be more common among larger molecules; organic solvates appear to be more common among neutral compounds with higher molecular weights.

7.2.2 *Excipients*

Pharmaceutical formulations contain the active drug ingredient(s) as well as excipients that serve a variety of purposes: fillers, stabilizers, coatings, drying agents, etc. As solid materials excipients exhibit varying degrees of crystallinity, from the highly crystalline calcium hydrogen phosphate to nearly amorphous derivatives of cellulose. These materials can also exhibit polymorphism which may influence their performance in the formulation. Giron (1995, 1997) has listed many of the excipients that are known to exhibit a number of forms (polymorphs, solvates and amorphous). They include many of those that are widely used: lactose, sorbitol, glucose, sucrose, magnesium stearate, various calcium phosphates and mannitol (Burger *et al.* 2000).

DOCKET ALARM

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.