

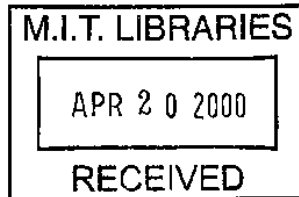
Polymorphism in Pharmaceutical Solids

edited by
Harry G. Brittain
Discovery Laboratories, Inc.
Milford, New Jersey



MARCEL DEKKER, INC.

NEW YORK • BASEL



RS201
S57
P64
1999

ISBN: 0-8247-0237-9

This book is printed on acid-free paper.

Headquarters

Marcel Dekker, Inc.
270 Madison Avenue, New York, NY 10016
tel: 212-696-9000; fax: 212-685-4540

Eastern Hemisphere Distribution

Marcel Dekker AG
Hutgasse 4, Postfach 812, CH-4001 Basel, Switzerland
tel: 44-61-261-8482; fax: 44-61-261-8896

World Wide Web

<http://www.dekker.com>

The publisher offers discounts on this book when ordered in bulk quantities. For more information, write to Special Sales/Professional Marketing at the headquarters address above.

Copyright © 1999 by Marcel Dekker, Inc. All Rights Reserved.

Neither this book nor any part may be reproduced or transmitted in any form or by any means, electronic or mechanical, including photocopying, microfilming, and recording, or by any information storage and retrieval system, without permission in writing from the publisher.

Current printing (last digit):

10 9 8 7 6 5 4 3 2 1

PRINTED IN THE UNITED STATES OF AMERICA

4

Structural Aspects of Hydrates and Solvates

Kenneth R. Morris

*Purdue University
West Lafayette, Indiana*

I. PHARMACEUTICAL IMPORTANCE OF CRYSTALLINE HYDRATES	126
II. HYDRATE THERMODYNAMICS	130
A. Classical Higuchi/Grant Treatment	130
B. Similarities and Differences Between Polymorphs and Hydrates	132
C. Hydrogen Bonding in Hydrates	135
III. CLASSIFICATION OF HYDRATES	141
A. Class 1: Isolated Site Hydrates	142
B. Class 2: Channel Hydrates	145
C. Class 3: Ion Associated Hydrates	155
IV. DEHYDRATION/HYDRATION KINETICS	161
A. Dehydration and Hydrate Class	162
B. Impact of Particle Size and Morphology	163

125

V. BEHAVIOR OF HYDRATES DURING PROCESSING, HANDLING, AND STORAGE	167
A. Processing Induced Transitions	167
B. Transitions in the Final Product	173
C. Kinetics of Transformation	177
VI. SUMMARY	178
REFERENCES	179

I. PHARMACEUTICAL IMPORTANCE OF CRYSTALLINE HYDRATES

The potential pharmaceutical impact of changes in hydration state of crystalline drug substances and excipients exists throughout the development process. The behavior of pharmaceutical hydrates has become the object of increasing attention over the last decade, primarily due (directly or indirectly) to the potential impact of hydrates on the development process and dosage form performance. Substances may hydrate/dehydrate in response to changes in environmental conditions, processing, or over time if in a metastable thermodynamic state [1].

It may not be practical or possible to maintain the same hydrate isolated at the discovery bench scale synthesis during scale-up activities for a hydrated compound. The choice of counterions to produce a more soluble salt form may also be dictated by the extent and type of hydration observed for a given salt and/or by the moisture level that may be safely accommodated by the dosage form [2].

The physicochemical stability of the compound may raise issues during preformulation. Some hydrated compounds may convert to an amorphous form upon dehydration and some may become chemically labile. This is true of cephadrine dihydrate that dehydrates to become amorphous and undergoes subsequent oxidation. Other compounds may convert from a lower to a higher state of hydration yielding

forms with lower solubility. In any case, the resulting "new" forms would represent unique entities that, depending on the dosage form, might have to be maintained throughout the manufacturing process and in the clinic and would impact on the regulatory status of the compound. Most often this demands that the form (usually crystalline) be identified and characterized with respect to handling conditions during the early pre-IND stage of the development process.

As dosage form development proceeds, changes in hydration state can result in variable potencies depending on handling conditions during weighing steps, the kinetics of the hydration/dehydration process, and the environmental conditions during processing. Differences in powder flow can result from changes in crystal form and/or morphology that may accompany the hydration/dehydration process. This can affect content uniformity in solid processing either in the mixing process or during transfer to other processing equipment such as tablet presses. Aqueous granulation, particle size reduction, film coating, and tablet compression all provide opportunities to "trap" a compound in a metastable form that may "relax" to a more stable form at some unpredicted point in the life of a dosage form. Alternately, a kinetically favored but thermodynamically unstable form may be converted during these processes to a more stable and less soluble form.

During and after manufacturing, moisture from the environment or that sealed in the package may redistribute throughout the dosage form and change the hydration state(s). These changes can, in turn, visit the negative consequences discussed above for the bulk drug on the dosage form. These can be manifest as changes in tablet/capsule dissolution rates (and perhaps bioavailability), changes in lyophile reconstitution times, tablet capping, chemical instability, discoloration, and more. Of course, the potential for changes in hydration state also exists for many pharmaceutical excipients (such as lactose or magnesium stearate).

Such problems are typically magnified as both synthetic and dosage form production is scaled up. This may be caused by solvent limitations, heat transfer differences in production equipment, changes in raw materials and/or raw material suppliers, changes in processing times, and time and control constraints on product storage, to name a few.

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.