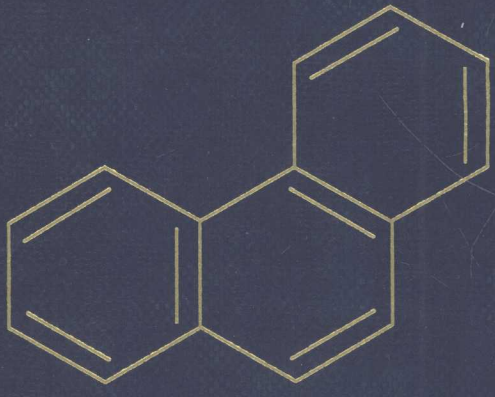
Analytical Profiles of Drug Substances and Excipients

VOLUME 21



Edited by
Harry G. Brittain

Analytical Profiles of Drug Substances and Excipients

Volume 21

Edited by

Harry G. Brittain

Bristol-Myers Squibb
Pharmaceutical Research Institute
New Brunswick, New Jersey

Founding Editor

Klaus Florey

ACADEMIC PRESS, INC.
Harcourt Brace Jovanovich, Publishers
San Diego New York Boston London Sydney Tokyo Toronto

Academic Press Rapid Manuscript Reproduction

Academic Press, Inc.
1250 Sixth Avenue, San Diego, California 92101-4311

United Kingdom Edition published by
Academic Press Limited
24–28 Oval Road, London NW1 7DX

International Standard Serial Number: 0099-5428

International Standard Book Number: 0-12-260821-6

PRINTED IN THE UNITED STATES OF AMERICA
92 93 94 95 96 97 BC 9 8 7 6 5 4 3 2 1

AFFILIATIONS OF EDITORS AND CONTRIBUTORS

Mohammad A. Abounassif, Pharmaceutical Chemistry Department, College of Pharmacy, King Saud University, Riyadh 11451, Saudi Arabia

Abdul Fattah A. A. Afify, Department of Pharmacognosy, College of Pharmacy, King Saud University, Riyadh 11451, Saudi Arabia

Iqbal Ahmad, Pharmaceutical Chemistry Department, Faculty of Pharmacy, University of Karachi, Karachi 75270, Pakistan

Tauqir Ahmad, Department of Pharmaceutical Chemistry, Faculty of Pharmacy, University of Karachi, Karachi 75270, Pakistan

Abdullah A. Al-Badr, Pharmaceutical Chemistry Department, College of Pharmacy, King Saud University, Riyadh 11451, Saudi Arabia

Fahad J. Al-Shammary, Clinical Laboratory Sciences Department, College of Applied Medical Sciences, King Saud University, Riyadh 11433, Saudi Arabia

Silvia Alessi-Severini, Faculty of Pharmacy and Pharmaceutical Sciences, University of Alberta, Edmonton, Alberta T6G 2N8, Canada

Syed Laik Ali, Zentrallaboratorium Deutscher Apotheker, 6236 Eschborn, Germany

Adnan A. Badwan, The Jordanian Pharmaceutical Manufacturing Company, Naor, Jordan

Gary Barbera, Bristol-Myers Squibb, Pharmaceutical Research Institute, New Brunswick, New Jersey 08903

Gerald S. Brenner, Merck Sharp & Dohme Research Laboratories, West Point, Pennsylvania 19486

Glenn A. Brewer, Bristol-Myers Squibb, Pharmaceutical Research Institute, New Brunswick, New Jersey 08903

Harry G. Brittain, Bristol-Myers Squibb, Pharmaceutical Research Institute, New Brunswick, New Jersey 08903

Marvin A. Brooks, Merck Sharp & Dohme Research Laboratories, West Point, Pennsylvania 19486

Robert A. Carr, Faculty of Pharmacy and Pharmaceutical Sciences, University of Alberta, Edmonton, Alberta T6G 2N8, Canada

Owen I. Corrigan, School of Pharmacy, University of Dublin, Dublin 4, Ireland

Ronald T. Coutts, Faculty of Pharmacy and Pharmaceutical Sciences, University of Alberta, Edmonton, Alberta T6G 2N8, Canada

Joseph D. DeMarco, Merck Sharp & Dohme Research Laboratories, West Point, Pennsylvania 19486

Joseph DeVincentis, Bristol-Myers Squibb, Pharmaceutical Research Institute, New Brunswick, New Jersey 08903

Humeida A. El-Obeid, Pharmaceutical Chemistry Department, College of Pharmacy, King Saud University, Riyadh 11451, Saudi Arabia

Dean K. Ellison, Merck Sharp & Dohme Research Laboratories, West Point, Pennsylvania 19486

Klaus Florey, Bristol-Myers Squibb Company, Lawrenceville, New Jersey 08543

George A. Forcier, Central Research Division, Pfizer, Inc., Groton, Connecticut 06340

Robert T. Foster, Faculty of Pharmacy and Pharmaceutical Sciences, University of Alberta, Edmonton, Alberta T6G 2N8, Canada

Lee T. Grady, The United States Pharmacopeia, Rockville, Maryland 20852

Dominic P. Ip, Merck Sharp & Dohme Research Laboratories, West Point, Pennsylvania 19486

Fakhreddin Jamali, Faculty of Pharmacy and Pharmaceutical Sciences, University of Alberta, Edmonton, Alberta T6G 2N8, Canada

Eric C. Jensen, Lilly Research Laboratories, Eli Lilly and Company, Indianapolis, Indiana 46285

Michael J. Kaufman, Merck Sharp & Dohme Research Laboratories, West Point, Pennsylvania 19486

David J. Mazzo, Department of Analytical & Physical Chemistry, Rhône-Poulenc Rorer Recherche-Development, 92165 Antony Cedex, France

Michael J. McLeish, School of Pharmaceutical Chemistry, Victorian College of Pharmacy, Monash University, Parkville, Victoria 3052, Australia

Mohammad Saleem Mian, Pharmaceutical Chemistry Department, College of Pharmacy, King Saud University, Riyadh 11451, Saudi Arabia

Neelofur Abdul Aziz Mian, Clinical Laboratory Sciences Department, College of Applied Medical Sciences, and Department of Pharmacognosy, College of Pharmacy, King Saud University, Riyadh 11433, Saudi Arabia

Ann W. Newman, Bristol-Myers Squibb, Pharmaceutical Research Institute, New Brunswick, New Jersey 08903

Caitriona M. O'Driscoll, School of Pharmacy, University of Dublin, Dublin 4, Ireland

Mahmoud Al Omari, The Jordanian Pharmaceutical Manufacturing Company, Naor, Jordan

Franco M. Pasutto, Faculty of Pharmacy and Pharmaceutical Sciences, University of Alberta, Edmonton, Alberta T6G 2N8, Canada

Thomas W. Rosanske, Marion Merrell Dow, Inc., Kansas City, Kansas 64134

Charles M. Shearer, Wyeth-Ayerst Research, Rouses Point, New York 12979

Delores J. Sprankle, Lilly Research Laboratories, Eli Lilly and Company, Indianapolis, Indiana 46285

K. Usmanghani, Department of Pharmacognosy, Faculty of Pharmacy, University of Karachi, Karachi 75270, Pakistan

G. Michael Wall, Alcon Laboratories, Inc., Fort Worth, Texas 76134

Timothy J. Wozniak, Eli Lilly and Company, Lilly Corporate Center, Indianapolis, Indiana 46285

Muhammad B. Zughul, Department of Chemistry, Faculty of Science, University of Jordan, Amman, Jordan

PREFACE

The profiling of drug compounds as to their physical and analytical characteristics has been the focus of the preceding twenty volumes in the *Analytical Profiles* series, and the need for this information is as important today as it was when the series was first initiated. The compilation of concise summaries of physical and chemical data, analytical methods, routes of compound preparation, degradation pathways, and the like, is a vital function to both academia and industry. Under the editorship of Klaus Florey, the *Analytical Profiles* has met this need over its twenty year history.

With the publication of Volume 21, the editorship has been assumed by Harry Brittain. The focus of the chapters will remain unchanged, but the scope of the *Analytical Profiles* series has expanded to include profiles of excipient materials, and this has led to a modification of the series title. The series will henceforth be known as the *Analytical Profiles of Drug Substances and Excipients*. The first excipient profile (anhydrous lactose) appeared in Volume 20, and a profile on titanium dioxide is included in the present volume.

The success of the series will continue to be based on the contributions of the chapter authors, and on the quality of their work. We seek profiles of new drug compounds as they come to markets but we also wish to profile important older compounds that have escaped attention thus far. A complete list of available candidates can be obtained from the editor by any prospective author. We look forward to hearing from new and established authors and to working with the pharmaceutical community on the *Analytical Profiles of Drug Substances and Excipients*.

Harry G. Brittain
Editor

Klaus Florey
Founding Editor

CONTENTS

ACETOHEXAMIDE

Abdullah A. Al-Badr and Humeida A. El-Obeid

Pharmaceutical Chemistry Department

College of Pharmacy

King Saud University

Riyadh, Saudi Arabia

CONTENTS

ACETOHEXAMIDE

1. DESCRIPTION

1.1 Nomenclature

1.1.1 Chemical Names

4-Acetyl-N-[(cyclohexylamino)carbonyl]benzenesulfonamide
1-[(*p*-Acetylphenyl)sulfonyl]-3-cyclohexylurea.
3-Cyclohexyl-1-(*p*-acetylphenylsulfonyl)urea.
N-(*p*-Acetylbenzylsulfonyl)-N -cyclohexylurea.

1.1.2 Generic Names

Acetohexamide, Acetohexamidum

1.1.3 Trade Names

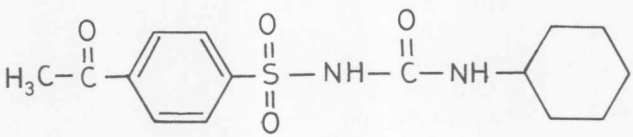
Cyclamide, Dimelin, Dimelor, Dymelor, Gamadiabet, Metaglucina, Ordimel, Tsiklamid.

1.2 Formulae

1.2.1. Empirical

$C_{15}H_{20}N_2O_4S$

1.2.2 Structural



1.2.3 CAS No.

[968-81-0]

1.3 Molecular Weight

324.42 (1)

1.4 Elemental Composition

C 55.54%, H 6.21%, N 8.64%, O 19.73%, S 9.89% (1).

1.5 Appearance

A white, crystalline powder; odorless or almost odorless (2).

2. PHYSICOCHEMICAL PROPERTIES

2.1 Melting Range

Crystals from 90% aqueous ethanol melt between 188-190° (3). Crystals from dilute ethanol melt between 175-177 (4).

2.2 Solubility

Soluble in pyridine, slightly soluble in alcohol and chloroform. Insoluble in water and ether (1).

2.3 Polymorphism

The literature reports indicate that acetohexamide exists as more than one polymorphic forms (5-15). Girgis-Takla and Chroneos (5) prepared acetohexamide polymorphs A and B by heating the drug (1 gm) with glacial acetic acid or chloroform respectively, before crystallization at 105° and room temperature respectively. While acetohexamide polymorph A showed a melting range of 180°-183°, the acetohexamide polymorph B melted at 183°-185°. Differential scanning calorimetry and IR spectroscopy showed that crystals of polymorph B were converted to polymorph A by grinding. Accordingly, these results indicate that any identification test utilizing grinding may fail to identify the two polymorphs. In their physico-chemical studies on the polymorphism of acetohexamide, Kuroda *et al* (6) obtained three polymorphs of acetohexamide by recrystallization from different solvents. These are form I, form II and $CHCl_3$-II. Although the X-ray diffraction patterns, IR spectra and differential scanning calorimeter curves of the $CHCl_3$-II polymorph were identical with those of polymorph II, the $CHCl_3$-II type contained a $CHCl_3$ molecule which could not be removed by normal drying condition. Polymorph $CHCl_3$-II seemed to be unsuitable for medicinal use. Form II is 1.2 times more soluble than form I.

Burger (7) characterized the three polymorphic modifications of acetohexamide by thermomicroscopy, differential scanning calorimetry and IR spectroscopy. The solubility behavior of the three modifications of the drug in butanol and buffer solutions is described and discussed in relation to thermodynamics and pharmacological parameters such as bioavailability from tablets and USP XIX dissociation test. Mueller and Lagas (8) have confirmed the existence and characterized two polymorphic forms of acetohexamide using differential scanning calorimetry, thermogravimetric analysis, scanning electron microscopy as well as IR, NMR and X-ray analysis. The study has pointed to the unsuitability of phosphate buffer solution which is sometimes prescribed for use in the dissolution tests of the drug since the salt of the drug crystallizes out during the test. In another study (9) the same authors reported that form I decomposed during melting and form II melted at 180° and then recrystallized to form I. At a heating rate of 10°/minute melting points of 193.6° and 180.5° were found for forms I and II, respectively. No morphological differences were observed between the two forms. In solubility and dissolution rate studies in sodium potassium buffer, potassium acetohexamide crystallized exhibiting a lower solubility than acetohexamide. In this respect, form II was transferred to potassium acetohexamide more quickly than form I.

Yokoyama *et al* (10) calculated the thermodynamic values of forms I and II of acetohexamide from solubility measurements. The transition temperature and the heat of transition were 154° and 230 cal/mole, respectively. It is found that the polymorphic forms of acetohexamide did not affect its bioavailability when *in vivo* absorption studies of form I & II were carried out in beagle dogs. The preparation of four crystalline modifications of acetohexamide was reported (11). Their thermograms, IR spectra, X-ray diffraction and solubility are also reported. Two of the forms reverted to the most stable form on storage in solution.

Solid dispersion of acetohexamide was studied by Graf *et al* (12-14) using different polymers and various ratios. Coprecipitates of acetohexamide with polyethylene glycol (PEG 6000) were prepared by the solvent method with ethanol (crystalline form I) or with chloroform (crystalline form III). Phase diagrams

of form I-PEG and form III-PEG coprecipitates were of the peritectic type and the molecular compounds were formed in the ratio of 1 mole of acetohexamide to 4 moles of PEG. The eutectic temperature, eutectic composition and the end of melting of the two binary system were, however, different (12). Both the solubility and the solution rate were increased by PEG. Similar results were obtained by substituting poly(vinylpyrrolidone) (PVP) for PEG (13). Also, coprecipitates of acetohexamide-PVP (in ethanol) containing drug concentrations of 60% or more showed the same X-ray diffraction pattern as that of form I. Increasing the PVP concentration (> 55%) did not show any crystal behavior in the X-ray analysis. In another report Graf *et al* (14) described the methods of preparation and the effect of the solvents on the acetohexamide-PVP coprecipitates. They were obtained from ethanol or chloroform by evaporating the solvent at room temperature, under vacuum or by spray drying. Changing the solvent and/or its evaporation rate affected the polymorphic form, the crystallinity and the solution rate of acetohexamide in coprecipitates containing less than 70% PVP.

Kassem *et al* (15) studied the enhancement of the rate of release of acetohexamide from its tablets by the formation of solid dispersions with each of four water-soluble polymers prepared in different ratios. The polymers were rated in the order of decreasing release rates as follows: PEG 6000, PVP, hydroxypropylmethylcellulose, methylcellulose.

2.4 Thermal Analysis

The heat of fusion and melting point of acetohexamide were done using DuPont TA 9900 on the DSC- unit at a temperature range indicated in the thermogram (Figure 1). Sample is done in duplicate and the average of the value is reported as follows:

ΔH_f = 63.7 kJ/mole Purity = 99.82% T_m = 187.45 C

2.5 X-ray Powder Diffraction

The X-ray powder diffraction pattern of acetohexamide was determined using Philips full automated X-ray diffraction spectrogoniometer equipped with PW1730/10

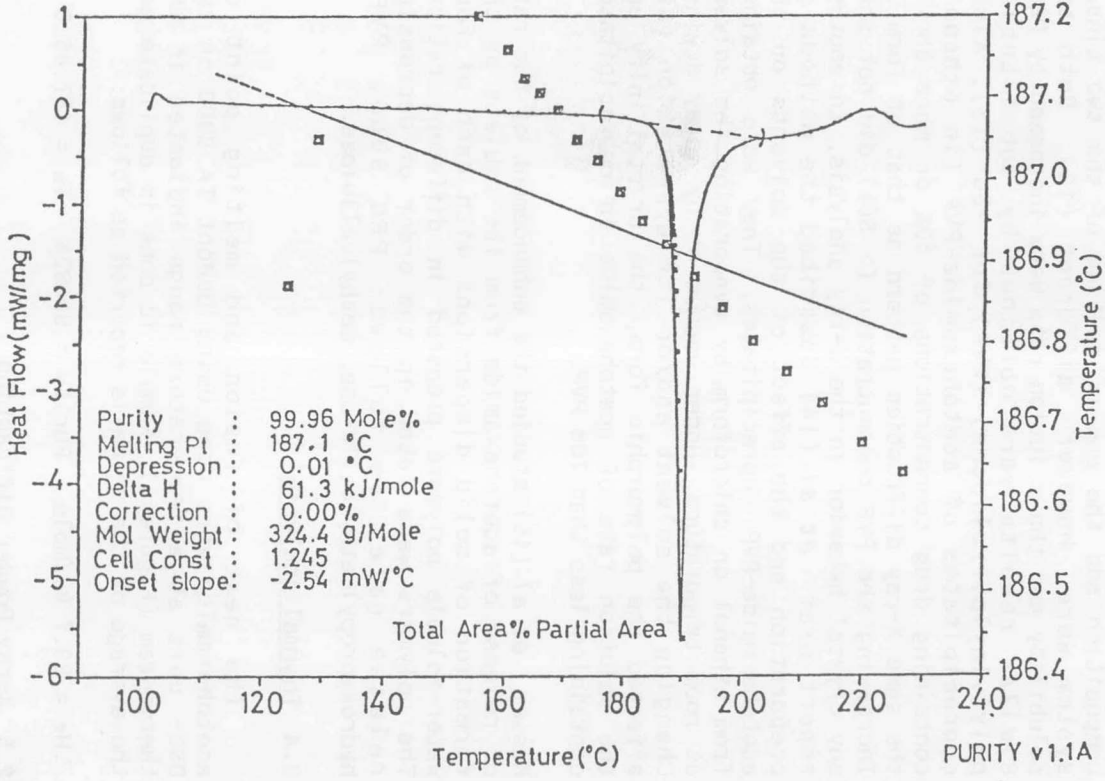


Figure 1. Thermal curve of acetohexamide.